UNIVERSITY OF COLOGNE

Immune Checkpoint Inhibitors for the Treatment of Adult Solid Cancer Patients in the Palliative 1st Line Setting

Proposal for Additions and Expansion of Indications
Application to the 2025 Update of the WHO Model Lists of Essential Medicines

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WHO Collaborating Centre on Evidence Synthesis and Evaluation of Novel Cancer Therapies

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Section 1: Summary statement of the proposal

This application proposes the addition of the six immune checkpoint inhibitors (ICIs) atezolizumab, cemiplimab, dostarlimab, durvalumab, ipilimumab, and tremelimumab to the complementary list of the EML as well as the extension of the indications for nivolumab and pembrolizumab which are currently listed as therapeutic alternatives for the treatment of malignant melanoma. This proposal covers 26 pairings of ICIs and indications pertaining to adult solid cancer patients who are treated in the palliative first-line setting.

Cancer and its treatment are becoming increasingly relevant in the context of a growing and aging world population. With an estimated 20 million new cases of cancer and 9.7 million deaths from cancer in 2022, cancer is a major global health threat and has a huge economic impact due to costs of care, premature mortality, and lost productive life years. Given the projected global population growth and ageing trends, and assuming stable cancer incidence rates, more than 35 million new cancer cases are expected to occur in 2050, marking a 77% increase from the estimate for 2022 [1]. The proportion of patients presenting with advanced-stage cancers at initial diagnosis remains substantial, especially in low- and middle-income countries.

The advent of ICIs in the past decade has led to a paradigm shift in oncology, providing significant (long-term) survival benefits and durable responses in patients with advanced solid tumours compared to traditional therapies like chemotherapy. In the absence of other EML-listed treatment options for some indications covered by this proposal, listing ICIs for these indications could enhance the availability of effective and safe therapies for cancer patients with unmet medical needs. However, ICIs are associated with considerable immune-mediated and financial toxicity, warranting a nuanced understanding of which cancer types and patient groups are most likely to benefit from the novel treatment.

This application is unique in its form, as it systematically encompasses one of the largest and fastest-growing groups of pharmaceutical agents in medical oncology, covering various cancer entities since the introduction of chemotherapy in the field, potentially demonstrating a class effect.

Section 2: Consultation with WHO technical departments

Lorenzo Moja, Technical Officer, EML (Essential Medicines List) Secretariat

Section 3: Other organizations consulted and/or supporting the submission

- Cochrane Evidence Synthesis Unit (ESU) Germany/UK
- Cochrane Haematology
- Institute of Public Health, University of Cologne, Cologne, Germany
- Department I of Internal Medicine, University Hospital of Cologne, Cologne Germany

Section 4: Key information summary for the proposed medicines

Immune checkpoint inhibitors*

Pembrolizumab		
INN	pembrolizumab	
ATC code	L01FF02	
Indications	(A)	First-line palliative treatment combination with chemotherapeutic partner (e.g., nab-paclitaxel, paclitaxel, or gemcitabine-carboplatin) for locally recurrent, unresectable or metastatic triple-negative breast cancer with PD-L1 expression of CPS ≥ 10
	(B)	First-line palliative treatment combination with paclitaxel, cisplatin or carboplatin for persistent, recurrent, or metastatic cervical cancer with PD-L1 expression of CPS ≥ 1
	(C)	First-line palliative treatment (monotherapy) for MSI-H/dMMR metastatic colorectal cancer
	(D)	First-line palliative treatment combination with fluoropyrimidine- and platinum-based chemotherapy for locally advanced unresectable or metastatic squamous cell carcinoma of the oesophagus with PD-L1 expression of CPS ≥ 10
	(E)	First-line palliative treatment combination with fluoropyrimidine- and platinum-containing chemotherapy for locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma with PD-L1 expression of CPS ≥ 1
	(F)	First-line palliative treatment combination with axitinib or lenvatinib for advanced renal cell carcinoma
	(G)	First-line palliative treatment combination with platinum chemotherapy and pemetrexed for non-squamous cell NSCLC without driver mutations
	(H)	First-line palliative treatment combination with carboplatin and either paclitaxel or nab-paclitaxel for metastatic squamous NSCLC without driver mutations
	(I)	First-line palliative treatment (monotherapy) for metastatic NSCLC with PD-L1 expression TPS ≥ 50% without driver mutations
	(J)	First-line palliative treatment (monotherapy) for advanced (unresectable or metastatic) melanoma
	(K)	First-line palliative treatment combination with fluoropyrimidine- and platinum-based chemotherapy for metastatic or unresectable recurrent head and neck squamous cell carcinoma with PD-L1 expression of CPS ≥ 1
ICD-11 codes	(A)	2C6Z Malignant neoplasms of breast, unspecified
	(B)	2C77 Malignant neoplasms of cervix uteri
	(C)	2B93 Malignant neoplasms of large intestine, site unspecified
	(D)	2B70.1 Squamous cell carcinoma of oesophagus
	(E)	2B70.0 Adenocarcinoma of oesophagus 2B71.0 Adenocarcinoma of oesophagogastric junction 2B72.0 Adenocarcinoma of stomach
	(F)	2C90 Malignant neoplasms of kidney, except renal pelvis
	(G)	2C25.Y Other specified malignant neoplasms of bronchus or lung
	(H)	2C25.2 Squamous cell carcinoma of bronchus or lung
	(I)	2C25.Y Other specified malignant neoplasms of bronchus or lung
	(J)	2C30 Melanoma of skin
	(K)	2B6E.0 Squamous cell carcinoma of other or ill-defined sites in the lip, oral cavity or pharynx 2C23.10 Squamous cell carcinoma of larynx, glottis

Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	25mg/mL in 4mL vial	Yes	No

Nivolumab		
INN	nivolumab	
ATC code	L01FF01	
Indications	(A)	First-line palliative treatment as monotherapy or in combination with ipilimumab for advanced (unresectable or metastatic) melanoma
	(B)	First-line palliative treatment combination with ipilimumab for intermediate/poor-risk advanced renal cell carcinoma
	(C)	First-line palliative treatment combination with ipilimumab and two cycles of platinum-based chemotherapy for metastatic NSCLC without driver mutations
	(D)	First-line palliative treatment combination with ipilimumab for unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with PD-L1 expression TC ≥ 1%
	(E)	First-line palliative treatment combination with fluoropyrimidine- and platinum-based chemotherapy for unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with PD-L1 expression TC ≥ 1%
	(F)	First-line palliative treatment combination with fluoropyrimidine- and platinum-based chemotherapy for HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma with PD-L1 expression and combined positive score (CPS) ≥ 5
ICD-11 codes	(A)	2C30 Melanoma of skin
	(B)	2C90 Malignant neoplasms of kidney, except renal pelvis
	(C)	2C25.Y Other specified malignant neoplasms of bronchus or lung
	(D)	2B70.1 Squamous cell carcinoma of oesophagus
	(E)	2B70.1 Squamous cell carcinoma of oesophagus
	(F)	2B70.0 Adenocarcinoma of oesophagus

* ICIs and partnering agents are listed by number of selected indications

	2B71.0 Adenocarcinoma of oesophagogastric junction 2B72.0 Adenocarcinoma of stomach		
Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	10mg/mL in 4mL vial 10mg/mL in 10mL vial 10mg/mL in 12mL vial 10mg/mL in 24mL vial	Yes	No

Durvalumab

INN	durvalumab	
ATC code	L01XC28	
Indications	(A)	First-line palliative treatment in combination with tremelimumab and platinum-based chemotherapy of metastatic NSCLC without driver mutations
	(B)	First-line palliative treatment in combination with gemcitabine and cisplatin of unresectable or metastatic biliary tract cancer
	(C)	First-line palliative treatment as monotherapy or in combination with tremelimumab of advanced or unresectable hepatocellular carcinoma
ICD-11 codes	(A)	2C25.Y Other specified malignant neoplasms of bronchus or lung
	(B)	2C12.1 Malignant neoplasm of intrahepatic bile ducts 2C13 Malignant neoplasms of gallbladder 2C14 Malignant neoplasms of proximal biliary tract, cystic duct 2C15 Malignant neoplasms of biliary tract, distal bile duct
	(C)	2C12.0 Malignant neoplasm of liver

Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	50 mg/mL in 2.4mL vial 50 mg/mL in 10mL vial	Yes	No

Atezolizumab

INN	atezolizumab	
ATC code	L01FF05	
Indications	(A)	First-line treatment (monotherapy) of metastatic NSCLC without driver mutations and a PD-L1 expression ≥ 50% in tumour cells (TC) or ≥ 10% tumour-infiltrating immune cells (IC)
	(B)	First-line treatment of advanced or unresectable hepatocellular carcinoma in combination with bevacizumab
ICD-11 codes	(A)	2C25.Y Other specified malignant neoplasms of bronchus or lung
	(B)	2C12.02 Hepatocellular carcinoma of liver

Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	840 mg / 14 mL vial 1200 mg / 20 mL vial	Yes	No

Cemiplimab

INN	cemiplimab	
ATC code	L01XC33	
Indications	(A)	First-line palliative treatment (monotherapy) of locally advanced or metastatic NSCLC without driver mutations and a PD-L1 expression TC ≥ 50%
	(B)	First-line palliative treatment in combination with platinum-based chemotherapy of locally advanced or metastatic NSCLC without driver mutations and a PD-L1 expression TC ≥ 1%
ICD-11 codes	(A)	2C25.Y Other specified malignant neoplasms of bronchus or lung
	(B)	2C25.Y Other specified malignant neoplasms of bronchus or lung

Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	50 mg/mL in 7 mL vial	Yes	No

Dostarlimab

INN	dostarlimab
ATC code	L01FF07
Indications	First-line palliative treatment in combination with carboplatin and paclitaxel for dMMR/MSI-H primary advanced or recurrent endometrial cancer
ICD-11 codes	2C76 Malignant neoplasms of corpus uteri

Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	50 mg/mL in 10mL vial	Yes	No

Partnering immune-checkpoint inhibitors

Ipilimumab

INN	ipilimumab	
ATC code	L01XC11	
Indications	(A)	First-line palliative treatment in combination with nivolumab of advanced (unresectable or metastatic) melanoma
	(B)	First-line palliative treatment in combination with nivolumab of intermediate/poor-risk advanced renal cell carcinoma
	(C)	First-line palliative treatment in combination with nivolumab and two cycles of platinum-based chemotherapy of metastatic NSCLC without driver mutations
	(D)	First-line palliative treatment in combination with nivolumab of unresectable abvanced, recurrent or metastatic oesophageal squamous cell carcinoma with PD-L1 expression TC ≥ 1%
ICD-11 codes	(A)	2C30 Melanoma of skin
	(B)	2C90 Malignant neoplasms of kidney, except renal pelvis
	(A)	2C25.Y Other specified malignant neoplasms of bronchus or lung
	(B)	2B70.1 Squamous cell carcinoma of oesophagus

Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	5 mg/mL in 10 mL vial 20 mg/mL in 40 mL vial	Yes	No

Tremelimumab

INN	tremelimumab	
ATC code	L01FX20	
Indications	(A)	First-line palliative treatment in combination with durvalumab of advanced or unresectable hepatocellular carcinoma
	(B)	First-line palliative treatment in combination with durvalumab and platinum-based chemotherapy of metastatic NSCLC without driver mutations
ICD-11 codes	(C)	2C12.0 Malignant neoplasm of liver
	(D)	2C25.Y Other specified malignant neoplasms of bronchus or lung

Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	20 mg/mL in 1.25 mL vial 20 mg/mL in 15 mL vial	Yes	No

Partnering antiangiogenic agents

Bevacizumab

INN	bevacizumab	
ATC code	L01FG01	
Indications	(A)	First-line treatment of advanced or unresectable hepatocellular carcinoma in combination with atezolizumab
ICD-11 codes	(A)	2C12.02 Hepatocellular carcinoma of liver

Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	25 mg/mL in 4 mL vial 25 mg/mL in 16 mL vial	Yes	No

Axitinib

INN	axitinib	
ATC code	L01EK01	
Indications	(A)	First-line palliative treatment combination with pembrolizumab for advanced renal cell carcinoma
ICD-11 codes	(A)	2C90 Malignant neoplasms of kidney, except renal pelvis

Dosage forms	**Strength**	**EML**	**EMLc**
Oral film-coated tablet	1 mg 3 mg 5 mg	Yes	No

Lenvatinib

INN	lenvatinib	
ATC code	L01XE29	
Indications	(A)	First-line palliative treatment combination with pembrolizumab for advanced renal cell carcinoma
ICD-11 codes	(A)	2C90 Malignant neoplasms of kidney, except renal pelvis

Dosage forms	**Strength**	**EML**	**EMLc**
Oral hard capsule	4 mg 10 mg	Yes	No

Partnering chemotherapeutic agents

Cisplatin

INN	cisplatin			
ATC code	L01XA01			
Indications	(A)	First-line palliative treatment combination with fluoropyrimidine and pembrolizumab or nivolumab for locally advanced unresectable or metastatic squamous cell carcinoma of the oesophagus		
	(B)	First-line palliative treatment combination with fluoropyrimidine and pembrolizumab or nivolumab for locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma		
	(C)	First-line palliative treatment in combination with gemcitabine and durvalumab of unresectable or metastatic biliary tract cancer		
ICD-11 codes	(A)	2B70.1 Squamous cell carcinoma of oesophagus		
	(B)	2B70.0 Adenocarcinoma of oesophagus 2B71.0 Adenocarcinoma of oesophagogastric junction 2B72.0 Adenocarcinoma of stomach		
	(C)	2C12.1 Malignant neoplasm of intrahepatic bile ducts 2C13 Malignant neoplasms of gallbladder 2C14 Malignant neoplasms of proximal biliary tract, cystic duct 2C15 Malignant neoplasms of biliary tract, distal bile duct		
Dosage forms	**Strength**		**EML**	**EMLc**
Concentrate for solution for infusion	1 mg/mL in vials of 10 mL, 20 mL, 50 mL, 100 mL		Yes	No

5-fluorouracil

INN	fluorouracil			
ATC code	L01BC02			
Indications	(A)	First-line palliative treatment combination with platinum and pembrolizumab or nivolumab for locally advanced unresectable or metastatic squamous cell carcinoma of the oesophagus		
	(B)	First-line palliative treatment combination with platinum and pembrolizumab or nivolumab for locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma		
ICD-11 codes	(A)	2B70.1 Squamous cell carcinoma of oesophagus		
	(B)	2B70.0 Adenocarcinoma of oesophagus 2B71.0 Adenocarcinoma of oesophagogastric junction 2B72.0 Adenocarcinoma of stomach		
Dosage forms	**Strength**		**EML**	**EMLc**
Concentrate for solution for infusion	50 mg/mL in vial		Yes	No

Carboplatin

INN	carboplatin		
ATC code	L01XA02		
Indications	First-line palliative treatment in combination with paclitaxel and dostarlimab for dMMR/MSI-H primary advanced or recurrent endometrial cancer		
ICD-11 codes	2C76 Malignant neoplasms of corpus uteri		
Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	10 mg/mL in vials of 5 mL, 15 mL, 45 mL, 60 mL	Yes	No

Oxaliplatin

INN	oxaliplatin		
ATC code	L01XA03		
Indications	First-line palliative treatment combination with fluoropyrimidine and pembrolizumab or nivolumab for locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma		
ICD-11 codes	2B70.0 Adenocarcinoma of oesophagus 2B71.0 Adenocarcinoma of oesophagogastric junction 2B72.0 Adenocarcinoma of stomach		
Dosage forms	**Strength**	**EML**	**EMLc**
Powder or concentrate for solution for infusion	50 mg vial powder, 100 mg vial powder, 5 mg/mL in vials of 10 mL, 20 mL, 40 mL	Yes	No

Capecitabine

INN	capecitabine		
ATC code	L01BC06		
Indications	First-line palliative treatment combination with platinum and pembrolizumab or nivolumab for locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma		
ICD-11 codes	2B70.0 Adenocarcinoma of oesophagus 2B71.0 Adenocarcinoma of oesophagogastric junction 2B72.0 Adenocarcinoma of stomach		

Dosage forms	Strength	EML	EMLc
Oral film-coated tablet	150 mg 500 mg	Yes	No

Gemcitabine			
INN	gemcitabine		
ATC code	L01BC05		
Indications	First-line palliative treatment in combination with cisplatin and durvalumab of unresectable or metastatic biliary tract cancer		
ICD-11 codes	2C12.1 Malignant neoplasm of intrahepatic bile ducts 2C13 Malignant neoplasms of gallbladder 2C14 Malignant neoplasms of proximal biliary tract, cystic duct 2C15 Malignant neoplasms of biliary tract, distal bile duct		
Dosage forms	**Strength**	**EML**	**EMLc**
Powder for solution for infusion	200 mg vial powder 1000mg vial powder	Yes	No

Paclitaxel			
INN	paclitaxel		
ATC code	L01CD01		
Indications	First-line palliative treatment in combination with carboplatin and dostarlimab for dMMR/MSI-H primary advanced or recurrent endometrial cancer		
ICD-11 codes	2C76 Malignant neoplasms of corpus uteri		
Dosage forms	**Strength**	**EML**	**EMLc**
Concentrate for solution for infusion	6 mg/mL in vial	Yes	No

Section 5: Listing as individual medicine

This application relates to the inclusion of ICIs and partnering antiangiogenic or chemotherapeutic agents in the form of **individual medicine listings** for the palliative first-line treatment of various adult solid cancers.
We propose listing medicines individually due to possible within-class differences for some ICIs in light of limited therapeutic equivalency data and partly due to limited research data in the proposed treatment settings for some ICIs.

Herein, and in the context of medical oncologic cancer treatments, we use the terms “palliative (oncologic) treatment” and “palliative setting” exclusively to distinguish them from the curative, i.e., the neoadjuvant or adjuvant treatment settings (12). Therefore, it should not be interpreted as synonymous with “palliative care”, for example, at the end of life, which aims to preserve and improve quality of life and alleviate suffering irrespective of life-prolongation. We understand palliative chemo- or immunotherapy, including targeted therapies, as any medical drug intervention aimed at inhibiting cancer growth. Such therapies intend to prolong life by halting further tumour expansion or spreading in advanced, locally extensive, metastasised or relapsed disease, where patients are not eligible for curative surgery or radiation therapy.
In the following tables, we present drugs proposed for addition to the EML for each separate indication (i.e., cancer subtype). The choice of drugs and indications was based on a structured prioritisation framework and resulting evidence reviews, detailed further in Section 8.

We must emphasise that owing to the nature of the prioritisation, the choice of proposed additions does not imply the ineffectiveness of other drugs within the pharmacological class in the proposed indications and settings. Consequently, inferences can only be made for the drugs and drug pairings selected for the proposed indications. Furthermore, in choosing treatment regimens presented in each box below, we aimed to emphasise treatment protocols, including medicines currently listed on the EML, albeit in some instances not for the proposed indication. This meant, for example, in NSCLC, omitting regimens that included pemetrexed or nab-paclitaxel (both not included in the EML), or in the case of biliary tract cancer, listing gemcitabine and cisplatin (on the EML but not for the proposed indication). If a partnering drug of the regimen was instrumental to its overall treatment effect (i.e., it cannot be substituted or omitted), we included them regardless of their EML status and proposed their addition. Please refer to section 6 for details on treatment alternatives currently included in the Model List for each indication.

Table 1 presents a summary of proposed indications and drug pairings.

Table 1. *Summary of proposed indication and drug pairings for listing on the EML*

Proposed indications			Proposed drugs	ICIs						ICI-partner*		AAA-partner†			CTx-partner‡							
				Pembrolizumab	Nivolumab	Durvalumab	Cemiplimab	Atezolizumab	Dostarlimab	Ipilimumab (+ nivolumab)	Tremelimumab (+ durvalumab)	Bevacizumab (+ atezolizumab)	Lenvatinib (+ pembrolizumab)	Axitinib (+ pembrolizumab)	Cisplatin	Carbopatin	Oxaliplatin	5-fluorouracil	Capecitabine	Gemcitabine	Paclitaxel	Total
Organ system	Cancer entity	Cancer subentity																				
Respiratory	NSCLC	Oncogenic-driver wild-type non-small cell lung cancer with ≥ 50%§ PD-L1 expression		■			■	■														3
		Oncogenic-driver wild-type non-small cell lung cancer, irrespective of PD-L1 expression		■	■	■	■			■	■											6
	HNSCC	Head and neck squamous cell carcinoma with ≥ 1% PD-L1 expression (CPS)		■																		1
Integumentary	MEL**	Malignant melanoma, irrespective of PD-L1 expression								■												3
Urinary	RCC	Renal cell carcinoma, irrespective of PD-L1 expression		■	■					■			■	■								5
Hepatobiliary	HCC	Hepatocellular carcinoma, irrespective of PD-L1 expression				■		■			■	■										4
	BTC	Biliary tract cancer, irrespective of PD-L1 expression				■									■					■		3
Digestive	OESCC	Oesophageal squamous cell carcinoma (PD-L1 ≥ 1%)			■					■					■			■				4
		Oesophageal squamous cell carcinoma (PD-L1 ≥ 10%)		■	■					■					■			■				5
	GC/GOJ	HER-2 negative, gastric/gastro-oesophageal junction adenocarcinoma (PD-L1 ≥ 1%)		■											■		■	■	■			5
		HER-2 negative, gastric/gastro-oesophageal junction adenocarcinoma (PD-L1 ≥ 5%)		■	■										■		■	■	■			6
	CRC	Colorectal cancer with mismatch-repair protein deficiency (dMMR/MSI-H)		■																		1
Female reproductive	TNBC	Triple-negative breast cancer with ≥ 10% PD-L1 expression (CPS)		■																		1
	CC	Cervical cancer with ≥ 1% PD-L1 expression (CPS)		■																		1
	EC	Endometrial carcinoma with mismatch-repair protein deficiency (dMMR/MSI-H)							■							■					■	3
			Total	10	5	3	2	2	1	5	2	1	1	1	5	1	2	4	2	1	1	

Abbreviations: *NSCLC – non-small cell lung cancer, HNSCC – head and neck squamous cell carcinoma, MEL – malignant melanoma, RCC – renal cell carcinoma, HCC – hepatocellular carcinoma, BTC – biliary tract cancer, OESCC – oesophageal squamous cell carcinoma, GC/GOJ – gastric and gastro-oesophageal junction adenocarcinoma, CRC – colorectal carcinoma, TNBC – triple-negative breast cancer, CC – cervical cancer, EC – endometrial carcinoma*

* ICI-partner: proven efficacy data for the proposed indication and setting exists only with the corresponding ICI-partner (i.e., ipilimumab + nivolumab and tremelimumab + durvalumab)

† AAA-partner (antiangiogenic agent): proven efficacy data for the proposed indication and setting exists only with the corresponding AAA-partner (i.e., bevacizumab + atezolizumab, lenvatinib + pembrolizumab, axitinib + pembrolizumab)

‡ CTx-partner (chemotherapeutic agent): proven efficacy data for the proposed indication and setting exists only with the corresponding CTx-partner

§ Specifications for the types of PD-L1 measurement (TPS, TC, IC, CPS, TAP) are covered in the corresponding sections of the report

** Pembrolizumab and nivolumab were included in the Model List for the proposed indication in 2019. This pertains to the listing of ipilimumab in combination with nivolumab

Proposed indication and ICI-containing treatment pairings

Pembrolizumab [L01FF02]; cemiplimab [L01XC33]; atezolizumab [L01FF05]	
Indication	**Oncogenic-driver wild-type non-small cell lung cancer with ≥ 50% PD-L1 expression (TPS or TC ≥ 50%)**
Treatment type	Monotherapy

Pembrolizumab [L01FF02]; cemiplimab [L01XC33]; ipilimumab [L01XC11]; nivolumab [L01FF01]; tremelimumab [L01FX20]; durvalumab [L01XC28]	
Indication	**Oncogenic-driver wild-type non-small cell lung cancer, irrespective of PD-L1 expression**
Treatment type	Combination therapy
Regimen(s)	ICI mono- or PD-(L)1/CTLA-4-inhibitor combination therapy + platinum-based doublet chemotherapy
Protocol(s)	
Pembrolizumab + platinum (cisplatin or carboplatin) + paclitaxel *Cemiplimab + platinum (cisplatin or carboplatin) + paclitaxel* *Durvalumab + tremelimumab + platinum (cisplatin or carboplatin) + paclitaxel or gemcitabine* *Ipilimumab + nivolumab + carboplatin + paclitaxel*	

Pembrolizumab [L01FF02]	
Indication	**Head and neck squamous cell carcinoma with ≥ 1% PD-L1 expression (CPS ≥ 1)**
Treatment type	Combination therapy
Regimen(s)	Pembrolizumab + platinum (cisplatin or carboplatin) + 5-fluorouracil

Pembrolizumab [L01FF02]; ipilimumab [L01XC11]; nivolumab [L01FF01]; axitinib [L01EK01]; lenvatinib [L01EX08]	
Indication	**Renal cell carcinoma, irrespective of PD-L1 expression**
Treatment type	Combination therapy
Regimen(s)	Antiangiogenic-immune checkpoint inhibitor combination or PD-L1/CTLA-4-inhibitor combination
Protocol(s)	
Ipilimumab + nivolumab *Pembrolizumab + axitinib* *Pembrolizumab + lenvatinib*	

Pembrolizumab [L01FF02]	
Indication	**Cervical cancer with ≥ 1% PD-L1 expression (CPS ≥ 1)**
Treatment type	Combination therapy
Regimen(s)	Pembrolizumab + platinum (cisplatin or carboplatin) + paclitaxel

Pembrolizumab [L01FF02]	
Indication	**Triple-negative breast cancer with ≥ 10% PD-L1 expression (CPS ≥ 10)**
Treatment type	Combination therapy
Regimen(s)	Pembrolizumab + carboplatin + paclitaxel or gemcitabine

Pembrolizumab [L01FF02]	
Indication	**Colorectal cancer with mismatch-repair protein deficiency (dMMR/MSI-H)**
Treatment type	Monotherapy
Regimen(s)	Pembrolizumab + carboplatin + paclitaxel or gemcitabine

Pembrolizumab [L01FF02]; cisplatin [L01XA01]; oxaliplatin [L01XA03]; 5-fluorouracil [L01BC02]; capecitabine [L01BC06]	
Indication	**HER-2 negative, gastric/gastro-oesophageal junction adenocarcinoma with ≥ 1% PD-L1 expression (CPS ≥ 1)**
Treatment type	Combination therapy
Regimen(s)	Pembrolizumab + platinum- and fluoropyrimidine based chemotherapy
Protocol(s)	
Pembrolizumab + platinum (cisplatin or oxaliplatin) + fluoropyrimidine (5-fluorouracil or capecitabine)	

Pembrolizumab [L01FF02]; nivolumab [L01FF01]; cisplatin [L01XA01]; oxaliplatin [L01XA03]; 5-fluorouracil [L01BC02]; capecitabine [L01BC06]	
Indication	**HER-2 negative, gastric/gastro-oesophageal junction adenocarcinoma ≥ 5% PD-L1 expression (CPS ≥ 5)**
Treatment type	Combination therapy
Regimen(s)	ICI + platinum- and fluoropyrimidine based chemotherapy
Protocol(s)	
Pembrolizumab + platinum (cisplatin or oxaliplatin) + fluoropyrimidine (5-fluorouracil or capecitabine) *Nivolumab + oxaliplatin + fluoropyrimidine (5-fluorouracil or capecitabine)*	

Nivolumab [L01FF01]; ipilimumab [L01XC11]	
Indication	**Oesophageal squamous cell carcinoma with ≥ 1% PD-L1 expression (CPS ≥ 1)**
Treatment type	Combination therapy
Regimen(s)	Nivolumab + ipilimumab or platinum-based doublet chemotherapy
Protocol(s)	
Nivolumab + cisplatin + 5-fluorouracil *Ipilimumab + nivolumab*	

Nivolumab [L01FF01]; ipilimumab [L01XC11]; pembrolizumab [L01FF02]; cisplatin [L01XA01]; 5-fluorouracil [L01BC02]	
Indication	**Oesophageal squamous cell carcinoma with ≥ 10% PD-L1 expression (PD-L1 ≥ 10)**
Treatment type	Combination therapy
Regimen(s)	PD-L1/CTLA-4 combination or ICI + platinum-based doublet chemotherapy
Protocol(s) *Nivolumab + cisplatin + 5-fluorouracil* *Ipilimumab + nivolumab* *Pembrolizumab + cisplatin + 5-fluorouracil*	

Durvalumab [L01XC28]; atezolizumab [L01FF05]; tremelimumab [L01FX20]; bevacizumab [L01FG01]	
Indication	**Hepatocellular carcinoma, irrespective of PD-L1 expression**
Treatment type	Combination therapy
Regimen(s)	PD-1/CTLA-4 combination, antiangiogenic-ICI combination, monotherapy
Protocol(s) *Atezolizumab + bevazicumab* *Tremelimumab + durvalumab* *Durvalumab*	

Durvalumab [L01XC28]; cisplatin [L01XA01]; gemcitabine [L01BC05]	
Indication	**Biliary tract cancer, irrespective of PD-L1 expression**
Treatment type	Combination therapy
Regimen(s)	Durvalumab + cisplatin + gemcitabine

Dostarlimab [L01FF07]; carboplatin [L01XA02]; paclitaxel [L01CD01]	
Indication	**Endometrial carcinoma with mismatch-repair protein deficiency (dMMR/MSI-H)**
Treatment type	Combination therapy
Regimen(s)	Dostarlimab + carboplatin + paclitaxel

Ipilimumab [L01XC11]	
Indication	**Malignant melanoma, irrespective of PD-L1 expression**
Treatment type	Combination therapy
Regimen(s)	Ipilimumab + nivolumab

Section 6: Information supporting the public health relevance

Global disease burden

Cancer causes nearly one in three premature deaths from noncommunicable disease (NCD) and is its leading cause in 57 countries [2]. Following trends, by the end of the century, it may surpass cardiovascular disease as its primary cause globally [2]. Recent analyses of the GLOBOCAN database estimated that the year 2022 saw 20 million new cancer cases and 9.7 million cancer deaths [1]. In 2050, the number of incident cases will likely reach 35 million, an increase of 77% [1]. Since demographic transitions are a crucial driver of the cancer burden, the absolute increase in cancer cases is predicted to be greatest in countries with high and very high Human Development Indices (HDI) [1], i.e., countries with higher incomes according to the World Bank Classification, and generally higher aged population. However, relative increases will be highest in medium and low HDI countries, with increases of nearly 100% and 142%, respectively [1]. This more rapid increase in cancer cases, in conjunction with the disproportionally high cancer death burden of those countries, with low- and middle-income countries (LMICs) accounting for 70.6% of all cancer deaths [3, 4], projects a substantial worsening of the already existing global inequality in cancer care as a consequence. **Figure 1** illustrates the projected incidence and death rates of cancer based on IARC data categorised by income classes.

Palliative disease setting

Reasons for the high mortality/incidence ratio (70% vs 60%) in LMICs are manifold, including late-stage presentation, barriers to healthcare access, low availability and prohibitively high prices of cancer medicines [4-6]. While prevention, early detection and early diagnosis of cancer undoubtedly represent cornerstones of effective cancer care improvement campaigns in LMICs, data from high-income countries (HICs), like the United States (SEER database) [7], illustrate that the proportion of advanced-stage at first presentations remains substantial (**Figure 3**), and is also part of the phenotype of some cancers, that grow aggressively, spread early but do not cause easily noticeable symptoms until advanced disease stages. Consequently, a holistic approach is necessary to reduce the cancer burden effectively, which includes improvements in the availability, access and affordability of disease-stage-appropriate care in the form of medical oncologic treatments and palliative care measures.

Higher quality, reliable epidemiologic data, particularly regarding cancer incidence categorisation by disease stages at presentation, are oftentimes lacking for LMICs [5]. Varying demographics, populations and risk factors linked to the occurrence of cancers influence their incidence rates in different countries and regions, as evidenced by global cancer statistics reports [8]. It is beyond the scope of this report to model the potential population reach of the intervention of ICI-based treatment in the palliative first-line setting for each prioritised indication in a region-specific manner. However, notwithstanding the factors leading to over- and underestimation, we calculated a crude estimate of the proportion of cancer patients who would potentially be eligible for and substantially benefit from ICI-based treatments based on GLOBOCAN data on cancer incidence and SEER database information on stage distribution (**Figure 2**). Based on this calculation, about 12.2% of all cancer patients combined would be eligible for palliative first-line treatments that incorporate ICIs in their regimens. Given that lung cancer, as illustrated, frequently occurs at advanced stages and constitutes a significant share of

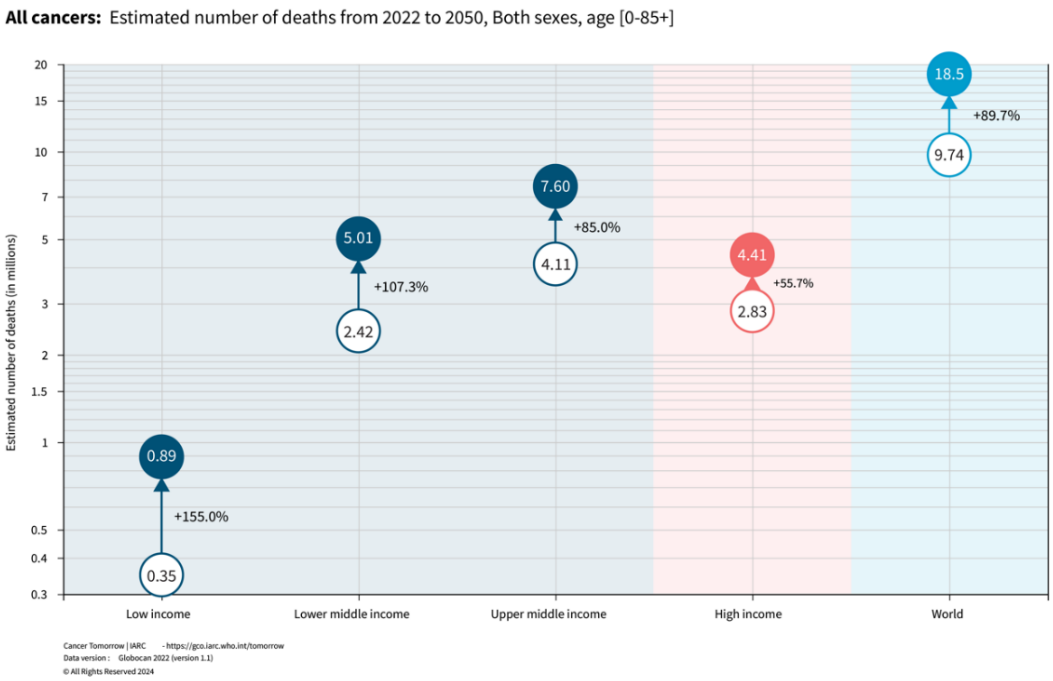


Figure 1. *Projections of cancer deaths in 2050 by income category*

total cancer cases, it is not surprising that it accounts for over half of all projected ICI uses.

Immune checkpoint inhibitors

Since the approval of the first ICI, ipilimumab, in 2011, ICIs have gained critical relevance in the treatment of several malignancies, especially solid tumours. A defining feature of ICIs is their potential to elicit long-lasting responses in patients with metastatic disease which distinguishes them from other classes of antineoplastics [9]. Unlike cytotoxic treatment regimens that directly attack and destroy rapidly dividing cells, ICIs modulate the host immune system to effectively target tumour cells [10]. While ICIs enhance tolerability of anti-cancer treatment for certain populations, at the same time they introduce a unique spectrum of immune-mediated adverse events [9]. ICIs are monoclonal antibodies which target specific receptors and ligands in immune regulation, including cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), programmed cell death ligands 1 and 2 (PD-L1/PD-L2), and lymphocyte activation gene 3 protein (LAG-3). ICIs considered as candidates during prioritisation for this application include ipilimumab and tremelimumab as CTLA-4 inhibitors, PD-1 inhibitors comprise nivolumab, pembrolizumab, cemiplimab, dostarlimab and tislelizumab, PD-L1 inhibitors comprise atezolizumab, avelumab and durvalumab, and relatlimab represents a LAG-3 inhibitor. However, avelumab, the only LAG-3 inhibitor relatlimab, and tislelizumab have not been prioritised. CTLA-4 regulates the intensity of T cell activation through inhibiting the function of the T cell co-stimulatory receptor CD28, PD-1 reduces cytokine secretion and cell proliferation by disrupting the CD28 co-stimulatory pathway, and PD-L1 inhibits migration and proliferation of T cells by binding to negative regulators of T cell activation like PD-1 and B7.1 (CD80) [11]. Hence, the engagement of these receptors limits the immune system's antitumour activity through distinct pathways and at different stages of the immune response. Immune checkpoint inhibition with CTLA-4, PD-L1, and PD-1 inhibitors thus inactivates the negative immune regulatory activity of the named receptors and ligands, and enhances the immune system's antitumour activity through modulation of distinct pathways and at different stages of the immune response.

Proposed treatment and patient characteristics

- Palliative 1st line treatment setting of cancer in advanced, locally extensive, metastasised or relapsed disease, where patients are not eligible for curative surgery or radiation therapy
- Patients with good overall performance status, i.e., ECOG 0-1 or Karnofsky (≥70%), adequate organ function, absence of autoimmune disease requiring systemic treatment, and without infectious diseases like HIV, tuberculosis or signs of active hepatitis B or C

Target population and current EML treatment alternatives

In the following subsection, apart from the proposed indications and treatment regimens for inclusion, we provide listings of medicines currently included in the EML for the proposed indications identified through search queries of the electronic EML [12]. Since listings of drugs on the EML are for individual drugs rather than treatment regimens, please note that we do not claim completeness of possible polychemotherapy combinations as EML-listed alternatives but aim to provide representative treatment examples for the proposed indications.

NON-SMALL CELL LUNG CANCER

Proposed indication(s)

(A) Non-small cell lung cancer without oncogenic driver mutations, irrespective of PD-L1 expression

(B) Non-small cell lung cancer without oncogenic driver mutations with high PD-L1 expression (≥50%)

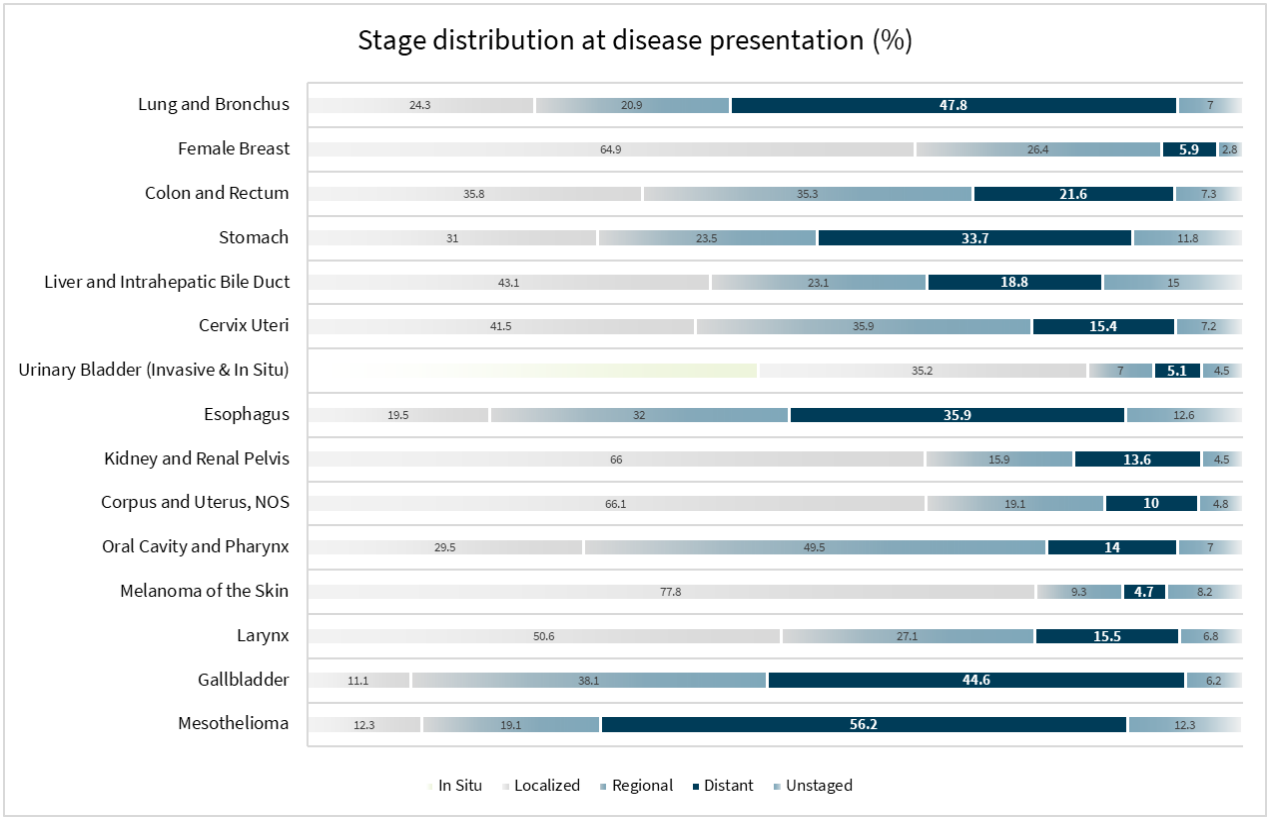


Figure 3. *Cancer stage distribution according to SEER database data (search date: 21.06.2024)*

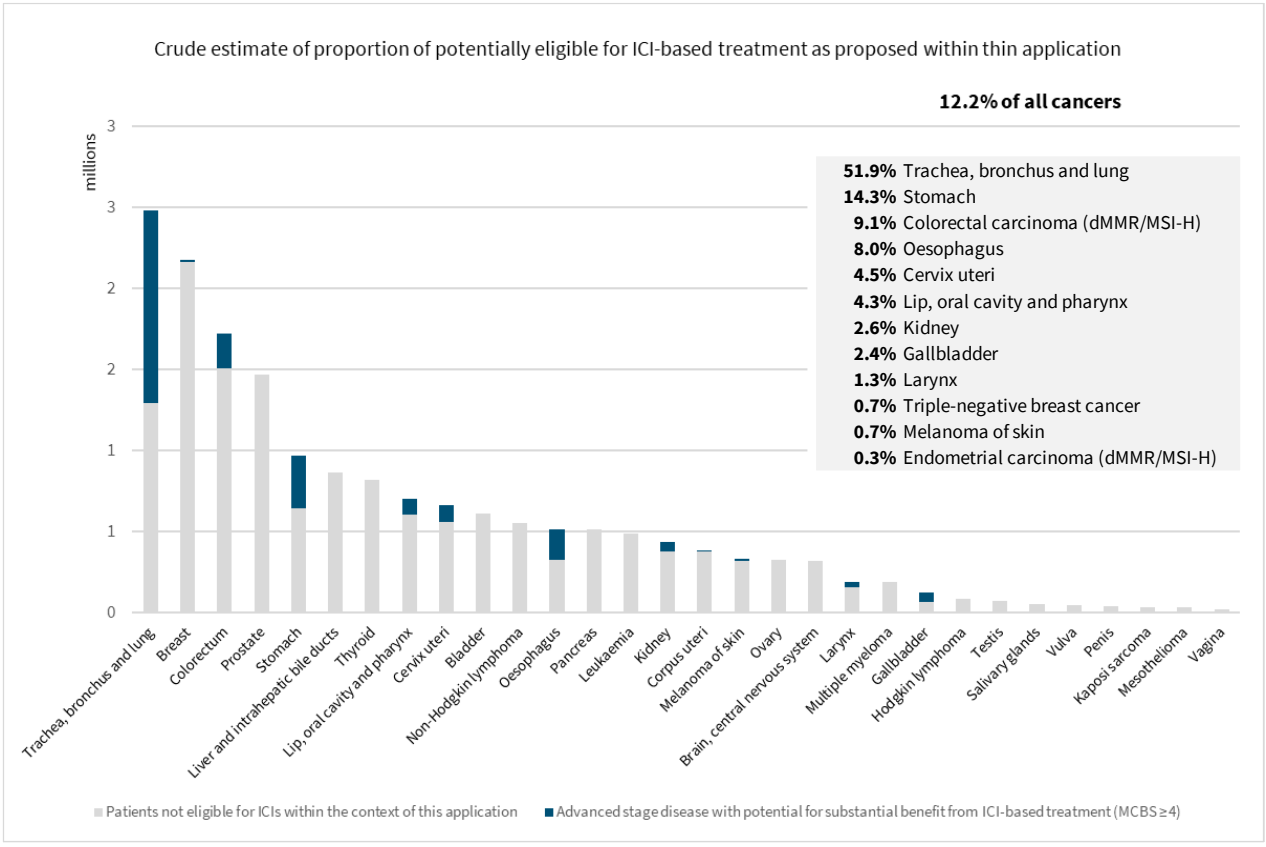


Figure 2. *Crude estimate patient eligibility for ICI-based treatment*

Proposed ICI-/combination regimens

(A) Pembrolizumab + platinum compound (carboplatin or cisplatin) + paclitaxel
Cemiplimab + platinum compound (carboplatin or cisplatin) + paclitaxel
Durvalumab + tremelimumab + platinum compound (carboplatin or cisplatin) + paclitaxel
Durvalumab + tremelimumab + platinum compound (carboplatin or cisplatin) + gemcitabine
Ipilimumab + nivolumab + carboplatin + paclitaxel

(B) Atezolizumab monotherapy
Cemiplimab monotherapy
Pembrolizumab monotherapy

Alternative medicines currently included on the EML

(A, B, C) Platinum compound (carboplatin or cisplatin) + paclitaxel
Platinum compound (carboplatin or cisplatin) + gemcitabine
Gemcitabine + vinorelbine or docetaxel

Head and neck squamous cell carcinoma

Proposed indication(s)

(A) Head and neck squamous cell carcinoma with PD-L1 expression (≥1%)

Proposed ICI-/combination regimens

(A) Pembrolizumab + platinum compound (carboplatin or cisplatin) + 5-fluorouracil

Alternative medicines currently included on the EML

(A) Platinum compound (carboplatin or cisplatin) + 5-fluorouracil

Renal cell carcinoma

Proposed indication(s)

(A) Clear cell renal cell carcinoma, irrespective of PD-L1 expression

Proposed ICI-/combination regimens

(A) Pembrolizumab + axitinib
Pembrolizumab + lenvatinib
Ipilimumab + nivolumab

Alternative medicines currently included on the EML

(A) –
(B)

Hepatocellular carcinoma

Proposed indication(s)

(A) Hepatocellular carcinoma, irrespective of PD-L1 expression

Proposed ICI-/combination regimens

(A) Atezolizumab + bevazicumab
Durvalumab
Durvalumab + tremelimumab

Alternative medicines currently included on the EML

(A) –

Biliary tract cancer

Proposed indication(s)

(A) Biliary tract cancer, irrespective of PD-L1 expression

Proposed ICI-/combination regimens

(A) Durvalumab + cisplatin + gemcitabine

Alternative medicines currently included on the EML

(A) –

Oesophageal squamous cell carcinoma

Proposed indication(s)

(A) Oesophageal squamous cell carcinoma with PD-L1 expression (≥1%)
(B) Oesophageal squamous cell carcinoma with PD-L1 expression (≥10%)

Proposed ICI-/combination regimens

(A) Ipilimumab + nivolumab
Nivolumab + cisplatin + 5-fluorouracil

(B) Ipilimumab + nivolumab
Nivolumab + cisplatin + 5-fluorouracil
Pembrolizumab + cisplatin + 5-fluorouracil

Alternative medicines currently included on the EML

(A) –
(B) –

Gastric and gastro-oesophageal junction adenocarcinoma

Proposed indication(s)

(A) HER-2 negative gastric or gastro-oesophageal junction adenocarcinoma with PD-L1 expression (≥1%)
(B) HER-2 negative gastric or gastro-oesophageal junction adenocarcinoma with PD-L1 expression (≥5%)

Proposed ICI-/combination regimens

(A) Pembrolizumab + platinum compound (cisplatin or oxaliplatin) + fluoropyrimidine (5-fluorouracil or capecitabine)

(B) Pembrolizumab + platinum compound (cisplatin or oxaliplatin) + fluoropyrimidine (5-fluorouracil or capecitabine)
Nivolumab + oxaliplatin + fluoropyrimidine (5-fluorouracil or capecitabine)

Alternative medicines currently included on the EML

(A) –
(B) –

Colorectal carcinoma

Proposed indication(s)

(A) Colorectal carcinoma with mismatch-repair protein deficiency (dMMR/MSI-H)

Proposed ICI-/combination regimens

(A) Pembrolizumab

Alternative medicines currently included on the EML

(A) Oxaliplatin + fluoropyrimidine (5-fluorouracil or capecitabine)
Irinotecan + fluoropyrimidine (5-fluorouracil or capecitabine)
Monotherapy with fluoropyrimidine (5-fluorouracil or capecitabine)

Cervical cancer

Proposed indication(s)

(A) Cervical carcinoma with PD-L1 expression (≥1%)

Proposed ICI-/combination regimens

(A) Pembrolizumab + carboplatin + paclitaxel

Alternative medicines currently included on the EML

(A) Platinum compound (cisplatin or carboplatin) + paclitaxel

Endometrial cancer

Proposed indication(s)

(A) Endometrial carcinoma with mismatch-repair protein deficiency (dMMR/MSI-H)

Proposed ICI-/combination regimens

(A) Pembrolizumab + carboplatin + paclitaxel

Alternative medicines currently included on the EML

(A) -

Malignant melanoma

Proposed indication(s)

(A) Malignant melanoma, irrespective of PD-L1 expression

Proposed ICI-/combination regimen

(A) Ipilimumab + nivolumab

Alternative medicines currently included on the EML

(A) ICI monotherapy with pembrolizumab or nivolumab

Triple-negative breast cancer

Proposed indication(s)

(A) Triple-negative breast cancer with PD-L1 expression (≥10%)

Proposed ICI-/combination regimens

(A) Pembrolizumab + carboplatin + paclitaxel or gemcitabine

Alternative medicines currently included on the EML

(A) Either alone or in combination: taxanes (paclitaxel or docetaxel), carboplatin, doxorubicin, vinorelbine, capecitabine

Section 7: Treatment details

Dosage, regimen, and administration details

All immune-checkpoint inhibitors proposed for inclusion are administered intravenously and can generally be given in an outpatient treatment setting, depending on the regimen, including partnering drugs (e.g., chemotherapy).

None of the drugs SmPCs state requirements for co-medications, but, in particular corticosteroids or immunosuppressants should be avoided before starting ICIs due to their potential interference with the drug's pharmacodynamic activity and efficacy. However, if corticosteroids are part of an immunochemotherapeutic regimen, their co-administration as antiemetic prophylaxis or prevention of, for instance, infusion reactions, as premedication is permitted. Compared to chemotherapeutics, ICIs have a low risk of emetogenicity. Thus, no primary preventative antiemetic medication is required. Infusion reactions caused by ICIs are rare, ranging from 0.2 to 5.8% [13]. Management of infusion-related reactions should be according to severity and follow established standard operating procedures. In case of lower-grade reactions (grade 1-2 reaction), and continuation of the infusion is considered, the infusion rate should be decreased and patients closely monitored. Subsequent treatment doses should be given under close monitoring, and the need for premedication with antipyretics and antihistamines should be evaluated. In the case of grade 3-4 infusions-related reactions, aside from the appropriate emergency measures, including the administration of corticosteroids, treatment with the ICI should permanently be discontinued.

Dec Given their mechanism of action as monoclonal antibodies and the absence of a cytotoxic payload, leading to their classification as non-irritants [14, 15], the administration of ICIs via peripheral venous access is generally considered safe. Nevertheless, extravasation should be avoided.

Even though regulatory approval in some indications only exists for treatment combinations rather than single agents, the following tables present treatment specifics for each treatment component individually. Medicines already listed on the EML are not included.

Pembrolizumab [16]			
Day	**Dose**	**Route**	**Administration details**
1	200mg (fixed dose) 400mg (fixed dose)	IV	In 100 mL NaCl 0.9% over 30 min
Premedication	NaCl 0.9%, 500mL IV		
Cycle frequency	Every 3 weeks (200mg dose) Every 6 weeks (400mg dose)		
Duration	Until disease progression, intolerable toxicity or up to 2 years		
Notes	If given in combination with other agents, always administered first At the start of treatment, a 3-weekly dosing regimen is preferred for better observation of drug tolerability		

Nivolumab [17]			
Day	**Dose**	**Route**	**Administration details**
1	1 or 3mg/kg 240mg (fixed dose) 360mg (fixed dose) 480mg (fixed dose)	IV	In 100 mL NaCl 0.9% over 30 min
Premedication	NaCl 0.9%, 500mL IV		
Cycle frequency	Together with ipilimumab, depending on the entity - Every 3 weeks for 4 cycles (1mg/kg), followed by maintenance with a fixed dose (see below) - Every 3 weeks for 4 cycles (3mg/kg), followed by maintenance with a fixed dose (see below) - Every 3 weeks (360mg dose) until progression (OESCC) Every 2 weeks (240mg dose) Every 4 weeks (480mg dose)[18]		

Duration	Until disease progression, intolerable toxicity or up to 24 months
Notes	CAVE: depending on the cancer entity (OESCC, MEL, RCC, NSCLC), different combinations of ipilimumab/nivolumab are used

Ipilimumab [19]

Day	Dose	Route	Administration details
1	1mg/kg 3mg/kg	IV	In 100 mL NaCl 0.9% over 30 min
Premedication	NaCl 0.9%, 500mL IV		
Cycle frequency	Together with nivolumab, depending on the entity - Every 6 weeks (1mg/kg) until progression (OESCC, NSCLC) - Every 3 weeks (1mg/kg) for 4 cycles (RCC) - Every 3 weeks (3mg/kg) for 4 cycles (MEL)		
Duration	Up to 4 cycles		
Notes	CAVE: depending on the cancer entity, different combinations of ipilimumab/nivolumab are used		

Atezolizumab [20]

Day	Dose	Route	Administration details
1	840mg (fixed dose) 1200mg (fixed dose)	IV	In 250 mL NaCl 0.9% over 1h (If well tolerated, subsequent doses over 30 min are possible)
Premedication	NaCl 0.9%, 500mL IV		
Cycle frequency	Every 2 weeks (840mg) Every 3 weeks (1200mg)		
Duration	Until disease progression, intolerable toxicity		
Notes	If together with bevacizumab at dose of 1200mg IV every 3 weeks		

Cemiplimab [21]

Day	Dose	Route	Administration details
1	350mg (fixed dose)	IV	In 100 mL NaCl 0.9% over 30 min
Premedication	NaCl 0.9%, 500mL IV		
Cycle frequency	Every 3 weeks		
Duration	Until disease progression, intolerable toxicity or up to 2 years		

Durvalumab [22]

Day	Dose	Route	Administration details
1	1500mg (fixed dose) 20mg/kg (weight-adjusted)	IV	In 250 mL NaCl 0.9% over 1 hour
Premedication	NaCl 0.9%, 500mL IV		
Cycle frequency	Every 3 weeks during combination regimens, thereafter every 4 weeks		
Duration	Until disease progression, intolerable toxicity		
Notes	Dose adjustment based on patient's body weight (at 20mg/kg if < 30kg)		

Tremelimumab [23]

Day	Dose	Route	Administration details
1	75mg (fixed dose) 300mg (fixed dose) 4mg/kg (< 30 kg) 1mg/kg (< 30 kg)	IV	Over 60 min
Premedication	NaCl 0.9%, 500mL IV		
Cycle frequency	HCC: - 300mg (single dose), if less than 30kg at 4mg/kg NSCLC: - 75mg (4x three-weekly, then single dose at week 16, if less than 30kg at 1mg/kg		
Duration	HCC: single dose NSCLC: 5 doses total		
Notes	Dose adjustment based on patient's body weight Only given in regimens together with durvalumab		

Dostarlimab [24]

Day	Dose	Route	Administration details
1	500mg for 1-4 cycles 1000mg for 5-n cycles	IV	In 100 mL NaCl 0.9% over 30 min
Premedication	NaCl 0.9%, 250mL IV		
Cycle frequency	Every 3 weeks for 1-4 cycles, every 6 weeks for 5-n cycles		
Duration	Until disease progression, intolerable toxicity		

Axitinib [25]

Day	Dose	Route	Administration details
1-28	5mg (starting dose)	PO	taken independently of meals
Cycle frequency	2 times a day, at 12-hour intervals		
Duration	Until disease progression, intolerable toxicity		

Notes	Monitoring for TKI-specific adverse events and AE-driver dose adjustments, refer to SmPC CAVE: CYP-interactions

Lenvatinib [26]			
Day	**Dose**	**Route**	**Administration details**
1-21	20mg (starting dose)	PO	2x10mg capsules, taken daily at the same time
Cycle frequency	Daily		
Duration	Until relapse, intolerable toxicity		
Notes	Monitoring for TKI-specific adverse events and AE-driver dose adjustments, refer to SmPC CAVE: CYP-interactions Dose reduction levels: First dose reduction: 14mg PO once daily Second dose reduction: 10mg PO once daily Third dose reduction: 8mg PO once daily Good blood pressure control is mandatory before lenvatinib treatment		

Bevacizumab [27]			
Day	**Dose**	**Route**	**Administration details**
1	15mg/kg	IV	In 100 mL NaCl 0.9%, 1st administration over 90min, 2nd administration over 60min, from 3rd administration over 30min or infusion duration according to tolerance
Cycle frequency	Every 3 weeks		
Duration	Until disease progression, intolerable toxicity		
Notes	Monitoring for proteinuria and hypertension; refer to SmPC for details		

Diagnostic requirements

Several assays and scoring systems are available to quantify PD-L1 expression, which can be used as a biomarker to predict the response to PD-1 and PD-L1 inhibitors. For many ICI indications, regulatory approvals are restricted to patients whose tumours and tumour microenvironments exhibit PD-L1 expression above specific yet arbitrarily set thresholds as determined by the immunohistochemical assays and scoring systems used in the pivotal randomised controlled trials. While for tumours with high PD-L1 expression levels, the exact threshold for positivity may be less critical, for tumours with lower PD-L1 expression levels, precise thresholds are of higher relevance because the difference between PD-L1 positive and negative, or even positivity at different cut-offs may impact the likelihood of outcome improvements. Among the most established PD-L1 expression scoring methods are the Tumour Proportion Score (TPS), Combined Positive Score (CPS), Tumour Cell Score (TC), and Immune Cell Score (IC). TPS evaluates the percentage of viable tumour cells that exhibit partial or complete PD-L1-staining relative to all viable tumour cells. In contrast, CPS evaluates the number of viable tumour and immune cells (lymphocytes and macrophages) that exhibit PD-L1-staining relative to all viable tumour cells. TC is equivalent to TPS per definition, and IC refers to the proportion of the tumour and tumour microenvironment occupied by PD-L1-positive immune cells [28]. Equivalence data verifying the interchangeability of scoring methods (i.e., TPS and CPS) are mostly lacking. For single entities, including non-small cell lung cancer and head and neck squamous cell carcinoma, the predictive value of CPS and TPS is equal [29, 30]. Beyond that, in the context of this review, immunohistochemistry (IHC) testing is required to identify mismatch repair (dMMR) or microsatellite instability-high (MSI-H) status in patients with colorectal and endometrial cancers.

Table 2 provides an overview of indications, their associated immunohistochemistry testing requirements, and threshold criteria.

Table 2. *PD-L1 testing requirements across cancer entities*

Cancer entity	Immune checkpoint inhibitor(s)	Immunohistochemistry testing	Threshold/status
NSCLC	Pembrolizumab	PD-L1 Tumour Proportion Score (TPS)	≥ 50%
	Cemiplimab		
	Atezolizumab	PD-L1 Tumour Cell (TC) or Immune Cell (IC) expression	≥ 50% (TC) ≥ 10% (IC)
	Pembrolizumab + chemotherapy	None	–
	Cemiplimab + chemotherapy		
	Ipilimumab + nivolumab + chemotherapy		
	Durvalumab + tremelimumab + chemotherapy		
HNSCC	Pembrolizumab + chemotherapy	PD-L1 Combined Positive Score (CPS)	≥ 1
Melanoma	Ipilimumab + nivolumab	None	–
RCC	Ipilimumab + nivolumab	None	–
	Pembrolizumab + lenvatinib or axitinib		
HCC	Atezolizumab + bevacizumab	None	–
	Durvalumab		
	Durvalumab + tremelimumab		
BTC	Durvalumab + chemotherapy	None	–
OESCC	Pembrolizumab + chemotherapy	PD-L1 Combined Positive Score (CPS)	≥ 10
	Nivolumab + chemotherapy	PD-L1 Tumour Cell/Tumour Proportion Score (TC/TPS)	≥ 1%
	Ipilimumab + nivolumab		
Gastric, GOJ	Pembrolizumab + chemotherapy	PD-L1 Combined Positive Score (CPS)	≥ 1

	Nivolumab + chemotherapy	PD-L1 Combined Positive Score (CPS)	≥ 5
CRC	Pembrolizumab	PD-L1: none	–
		MMR/MSI	dMMR or MSI-H
TNBC	Pembrolizumab + chemotherapy	PD-L1 Combined Positive Score (CPS)	≥ 10
CC	Pembrolizumab + chemotherapy	PD-L1 Combined Positive Score (CPS)	≥ 1
EC	Dostarlimab + chemotherapy	PD-L1: none	–
		MMR/MSI	dMMR or MSI-H

Adverse event screening and treatment monitoring

Adverse events related to immunotherapy are notably distinct from those resulting from chemotherapy and other cancer treatments. Consequently, it is crucial to establish thorough screening protocols and maintain vigilance to facilitate the early detection and effective management of these events. Due to their pharmacodynamics, ICIs lead to the downregulation of checkpoints that essentially block the body's immune response, raising the risk of mistakenly targeting healthy tissue and leading to autoimmune phenomena. The most common immune-related adverse events (irAE) are cutaneous irAE, colitis, pneumonitis, hepatitis and endocrinopathies like thyroiditis or adrenal insufficiency [31-33]. However, a variety of organ systems may be affected. Importantly, the occurrence of such immune-related adverse events, unlike chemotherapy, does not follow a clearly predictable pattern but may occur with the first dose and has also been documented up to a year after treatment has been discontinued [34]. Their treatment, in broad terms, apart from considerations regarding the discontinuation or merely halting ICI therapy, is analogous to treating autoimmune diseases, i.e., immunosuppression. The choice of immunosuppression depends on the severity, the organ systems affected, and the symptomatic response. Addressing the management of irAEs individually is beyond the scope of this application. For information regarding their grade-appropriate management, please refer to the respective guideline recommendations [35-37].

Screening recommendations for irAE and baseline testing prior to the initiation of ICIs vary considerably in terms of their extent and the choice of investigations. These selections are influenced not only by patient factors such as pre-existing conditions and comorbidities but also by treatment specifics that may affect the likelihood of adverse event occurrence, such as the use of doublet-ICI therapy versus monotherapy, or the administration of concomitant chemotherapy, targeted therapies, or monoclonal antibodies. The table below offers an overview of testing requirements, compiled from recommendations and publications by medical oncology societies regarding the monitoring of patients undergoing immunotherapy [33, 35-39]. It is important to note that these guidelines are primarily based on expert consensus rather than robust evidence supporting their necessity. In instances of suspected or likely irAE, further autoimmune and organ-specific diagnostics should be considered on a case-by-case basis.

		Before treatment initiation	Prior to each cycle ‡
Blood laboratory diagnostics			
Haematology		FBC with differential	FBC with differential
Chemistry	Kidney/Electrolyte	Na, K, Ca, bicarbonate, creatinine, eGFR, BUN	Na, K, creatinine, eGFR, BUN
	Liver/pancreas	Total bilirubin, ALP, AST, ALT, GGT, (Amylase, lipase)	Total bilirubin, ALP, AST, ALT, (GGT)
	Cardiac/muscle	CK, Troponin*, Nt-pro-BNP*	CK, (Nt-pro-BNP, troponin)
	Inflammatory markers	CRP, (ESR)	-
	Glucose metabolism	Blood glucose, (HbA1c)	Blood glucose
	Lipid metabolism	(Lipid panel)	-
	Iron metabolism	(Ferritin)	-
	Protein diagnostics	Albumin	-
Endocrinology	Thyroid	TSH, T4	TSH and FT4 every 4-6 weeks, T3 (as indicated)
	Adrenal	ACTH*, cortisol	-
	Gonadal	(FSH, LH)	
Coagulation		(PT, PTT, INR, Fibrinogen)	-
Infectious disease		Hepatitis B, C and HIV (other serologic tests depending on endemic situation), CMV (in preexisting diarrhea)	-
Autoimmunity		If pre-existing autoimmune disease	-
Non-blood laboratory diagnostics			
Stool		Urine dipstick	Urine dipstick (every 3-6 months)
Urine		(Stool calprotectin)	-
Apparative diagnostics			
Cardiac		ECG, echocardiography*	-
Pulmonary		(Spirometry), (DLCO*)	-

In () not uniformly recommended
** if pre-existing organ disease or at risk of organ specific toxicity*
‡ provided no clinical suspicion of irAE or laboratory abnormalities dictate otherwise

Section 8: Review of evidence for benefits and harm

Summary of available evidence for comparative effectiveness and safety

Review objective

Based on the prioritised selection of eight ICIs and twelve cancer entities, we conducted multiple systematic reviews of RCTs, comparing ICI-based treatments with the established, entity-specific treatment standard in the palliative first-line setting. Four patient-relevant outcomes were predefined and evaluated: overall survival, progression-free survival, quality of life, and higher-grade adverse events (CTCAE ≥ 3).

Summary of evidence

Evidence from relevant RCTs was systematically gathered for ICIs atezolizumab, cemiplimab, dostarlimab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and tremelimumab. The cancer entities subject to our analyses include NSCLC, HNSCC, MEL, RCC, HCC, and OESCC. GC/GOJ, CRC, TNBC, CC and EC.

Across indications, the largest body of evidence proving a beneficial effect for multiple ICI-based treatments was identified for oncogenic-driver wild-type NSCLC. While survival benefits could be seen for treatment protocols that combine ICIs with other oncologic drugs or prescribe ICIs only as monotherapy, additional benefits from significant reductions of higher-grade adverse events were only noted for ICI monotherapy. Quality of life improvements, even though statistically significant in several trials, only reached a level of clinically noticeable difference (i.e., minimal clinically important difference) in the case of pembrolizumab monotherapy for NSCLC with high PD-L1 expression or colorectal carcinoma with dMMR/MSI-H, and the combination of dostarlimab with chemotherapy in endometrial carcinoma with dMMR/MSI-H. However, due to relatively low participant numbers in studies of cancers with mismatch-repair protein deficiency, the certainty in the body of evidence was low for this outcome.

A frequent reason for downgrading the certainty of evidence regarding the overall survival estimate in multiple studies, and in particular cancer entities where ICIs are firmly established as later-line treatment options, was that a substantial number of trial participants receiving the control treatment were subsequently treated with ICIs upon progression. Assuming, within the context of this EML application, that ICIs are not a widely available treatment option for patients means that, in this regard, the evidence is indirect, raising concerns that the effect estimate potentially underestimates the true effect. High numbers of treatment switching, exceeding 30% of included participants, were noted, particularly in trials of NSCLC, RCC, and dMMR/MSI-H cancers of the colorectum and endometrium.

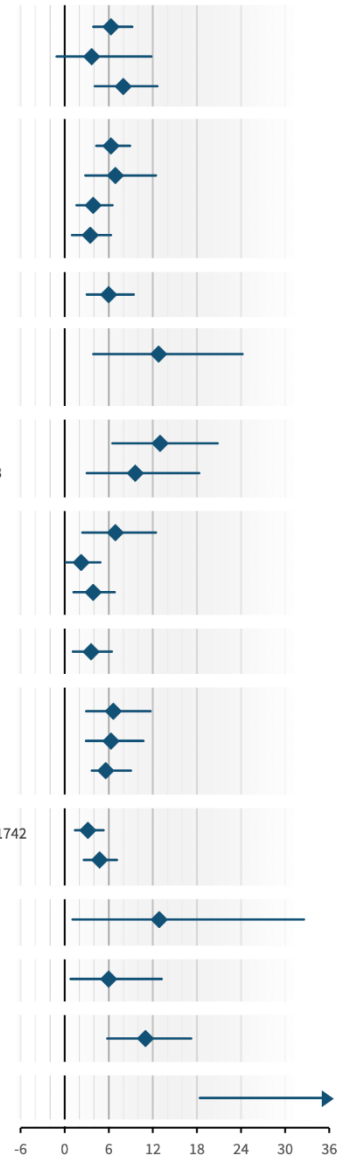
Applicability and interchangeability

Due to the selective nature of participant inclusion in efficacy studies, the generalisability of the data is limited and applies only to patients with good overall performance status and relatively few comorbidities. Concerned with the pharmacodynamics of immunotherapy, patients with a history of autoimmune disease and infectious diseases such as HIV, hepatitis B, C, or tuberculosis were excluded from study participation. Consequently, the evidence provided does not apply to these cohorts of patients underrepresented in trials.

Evidence from analyses within the included studies suggests that the beneficial effects of ICIs may be lost if patients do not meet certain PD-L1 expression thresholds or MSI status requirements. While subgroup analyses may be prone to overfitting and reduced statistical power, these limitations still restrict the transferability of findings to broader cancer populations across entities.

Most ICIs approved for prioritised indications were supported only by single studies, and we did not plan for comparisons of different ICI regimens. Thus, considering the limitations of cross-study comparisons, our reviews do not provide information on the interchangeability of different regulatory-approved ICI-containing treatment regimens. Nevertheless, findings from three-armed studies included in the review and studies on ICIs not gaining approval for immunogenic tumours identified outside the review process imply intra-class differences that limit their interchangeability.

COMPARISONS WITH STANDARD OF CARE (SoC)	TOTAL № OF PARTICIPANTS IN STUDIES	MEDIAN OS GAIN (MONTHS)	BASELINE RISK FOR MEDIAN OS [1]	ICI IN CONTROL [2]	NNT (n; CI) FOR OS (AT 2 YEARS)	NNH (n; CI) FOR AE (CTCAE ≥ 3)	LIKELIHOOD BEING HELPED OR HARMED (LHH) BEST | BASE | WORST	QoL (MCID)	OVERALL CERTAINTY OF EVIDENCE
NSCLC (PD-L1 TC/TPS 50%)									
Pembrolizumab monotherapy	904		12.2	31.5%	7 [5 to 10] ↑	-5 [-4 to -7] ↓	NC [+] | NC [+] | NC [+]	↑	●●○○ Low*
Atezolizumab monotherapy	280		13.9	34.7%	11 [5 to ∞ to -33] NS	-9 [-4 to ∞ to 8] NS [5]	NC [+] | NC [+] | NC [-]		●●○○ Low*
Cemiplimab monotherapy	712		13.7	56.0%	6 [4 to 11] ↑	-17 [-8 to ∞ to 100] NS	NC [+] | NC [+] | 9.0		●●○○ Low*
NSCLC (irrespective of PD-L1 expression)									
Pembrolizumab-based treatment	1298		12.3	55.5%	7 [5 to 9] ↑	20 [10 to ∞ to -100] NS	NC [+] | 3.0 | 1.1		●●●○ Moderate*
Cemiplimab-based treatment	466		12.9	15.0%	6 [4 to 14] ↑	8 [4 to 50] ↑	12.8 | 1.3 | 0.3		●●●○ Moderate
Ipilimumab/nivolumab-based treatment	719		11.0	29.6%	9 [6 to 20] ↑	10 [6 to 50] ↑	2.8 | 0.9 | 0.3		●●○○ Low*
Durvalumab/tremelimumab-based treatment	675		11.7	33.2%	11 [7 to 33] ↑	33 [9 to ∞ to -25] NS	NC [+] | 3.0 | 0.3		●●○○ Low*
HNSCC (PD-L1 CPS ≥ 1)									
Pembrolizumab-based treatment	477		10.6	25.2%	7 [5 to 13] ↑	50 [11 to ∞ to -25] NS	NC [+] | 7.5 | 0.9		●●●○ Moderate*
Malignant melanoma									
Ipilimumab/nivolumab vs ICI monotherapy	1133		28.4	NA	8 [5 to 33] ↑	3 [2 to 4] ↑	2.9 | 0.5 | 0.1		●●●○ Moderate
Ipilimumab/nivolumab vs BRAF/MEK inhibitors	138		Not reached	52.2%	13 [6 to ∞ to -14] NS	8 [3 to ∞ to -33] NS	NC [+] | 0.6 | NC [-]		●○○○ Very low*
Renal cell carcinoma									
Ipilimumab/nivolumab	1178		36.9	44.0%	11 [8 to 20] ↑	-7 [-4 to ∞ to 33] NS	NC [+] | NC [+] | 1.7		●●○○ Low*
Pembrolizumab-based treatement	1573		46.9	54.0%	20 [13 to 50] ↑	14 [8 to 50] ↑	4.0 | 0.7 | 0.2		●●○○ Low*
Hepatocellular carcinoma									
Atezolizumab-based treatment	501		13.4	26.0%	7 [5 to 17] [6] ↑	14 [6 to ∞ to -50] NS	NC [+] | 2.1 | 0.4		●○○○ Very low
Durvalumab monotherapy [3]	778		13.8	23.4%	20 [9 to ∞ to -100] NS	-6 [-5 to -11] ↓	NC [+] | NC [+] | 0.1		●●○○ Low
Durvalumab/tremelimumab-based treatment [3]	782		13.8	23.4%	11 [7 to 33] ↑	-50 [-13 to ∞ to 17] NS	NC [+] | NC [+] | 0.5		●●●○ Moderate
Biliary tract cancer									
Durvalumab-based treatment	685		11.3	7.0%	11 [7 to 33] [6] ↑	-100 [-14 to ∞ to 20] NS	NC [+] | NC [+] | 0.6		●●●○ Moderate
Oesophageal squamous cell caricnoma									
Pembrolizumab-based treatment (CPS ≥ 10)	286		8.8	9.0%	5 [3 to 11] ↑	33 [11 to ∞ to -50] NS	NC [+] | 6.3 | 1.0		●●○○ Low
Nivolumab-based treatment (TC/TPS ≥ 1%) [4]	315		9.1	15.9%	6 [4 to 13] ↑	8 [5 to 25] ↑	6.5 | 1.4 | 0.4		●●○○ Low*
Ipilimumab/nivolumab (TC/TPS ≥ 1) [4]	315		9.1	15.9%	7 [4 to 17] ↑	-25 [-10 to ∞ to 25] NS	NC [+] | NC [+] | 1.5		●●○○ Low*
Gastric cancer and GOJ adenocarcinoma									
Pembrolizumab-based treatment (CPS ≥ 1)	1742		11.3	9.0%	13 [8 to 25] ↑	17 [8 to 100] ↑	13.0 | 1.3 | 0.3		●○○○ Very low
Nivolumab-based treatment (CPS ≥ 5)	955		11.1	8.0%	8 [6 to 13] ↑	6 [5 to 10] ↑	1.7 | 0.8 | 0.3		●●○○ Low
Colorectal cancer (dMMR/MSI-H)									
Pembrolizumab monotherapy	307		36.7	59.0%	10 [5 to ∞ to -100] [6] NS	-5 [-3 to -8] ↓	NC [+] | NC [+] | 0.1	↑	●●○○ Low*
Triple-negative breast cancer (CPS ≥ 10)									
Pembrolizumab-based treatment	323		16.1	NR	9 [5 to 50] ↑	25 [9 to ∞ to -33] NS	NC [+] | 2.8 | 0.2		●●○○ Low
Cervical cancer (CPS ≥ 1)									
Pembrolizumab-based treatment	548		16.5	NR	6 [4 to 9] ↑	14 [7 to 100] ↑	24.0 | 2.6 | 0.7		●●●○ Moderate
Endometrial carcinoma (dMMR/MSI-H)									
Dostarlimab-based treatment	118		31.4	38.5%	4 [3 to 7] ↑	8 [5 to 25] ↑	8.5 | 2.3 | 0.6	↑	●●○○ Low*



Abbreviations: NNT – number needed to treat, NNH – number needed to harm, LHH – likelihood of being helped or harmed, SoC – standard of care, OS – overall survival, AE – adverse events, QoL – quality of life, MCID – minimal clinically important difference, NA – not applicable, NR – not reported, NS – not statistically significant, NC – not calculable.

Explanations: NNT and NNH indicate the number of patients required for one to benefit from ICI-based treatment versus SoC (OS at 2 years) or to experience additional harm (higher-grade AEs, CTCAE ≥ 3). The LHH (or NNH/NNT ratio) reflects the balance between benefits and toxicity, showing the likelihood of experiencing OS versus higher-grade AEs. An LHH of 1 indicates equal likelihood, while values above 1 suggest an n-times higher chance of the favourable outcome. The LHH is presented as the base-case scenario (middle column, from point estimates) and as best-case (left column: NNH upper CI/NNT lower CI) and worst-case (right column: NNH lower CI/NNT upper CI) scenarios. If both NNT and NNH indicate likely benefit (i.e., NNT positive and NNH negative, or vice versa), trade-offs cannot be calculated, likewise if NNT or NNH CIs are not statistically significant. In such cases, the LHH direction is indicated with NC[+] or NC[-]. Calculations were performed without assuming differential outcome importance (i.e., same value placed on OS gain as on avoidance of AEs).

[1] The baseline risk (in months) is derived from reported risks in comparator arms of trials. [2] ICI in control refers to the proportion of patients in comparator groups of trials who, upon disease progression, subsequently received ICIs. [3,4] Information comes from single 3-armed trials with the same comparator arm. [5] Atezolizumab monotherapy in NSCLC represents the only study including older, less fit participants. Subgroup analysis favours the intervention regarding higher-grade AEs in younger, fitter populations. [6] OS timepoints differ: Atezolizumab-based treatment in HCC: 1.5 years, durvalumab-based treatment in BTC: 1 year, pembrolizumab in CRC: 3 years

* The certainty of evidence is downgraded due to indirectness and concerns that the effect estimate may not truly represent the effect, given patients' exposure to ICIs in subsequent treatment lines, which may lead to potential underestimation.

Methods

Sequential prioritisation of ICI-containing treatments and indications

Systematic reviews ordinarily aim to assess the risks and benefits of one treatment versus another to provide an unbiased, comprehensive assessment of the available literature while neither being invested in showing the superiority nor inferiority of one or the other. However, in that regard, the objective of an EML application differs. Although EML applicants should unquestionably present the evidence for harms and benefits following systematic review standards in a conscientious and unbiased manner, the goal of the EML application at large is to build a case for the inclusion of new medicines, pharmacological drug classes, or indications. Within this context, systematic evidence synthesis should target disease settings and medicines with reasonable certainty in their proven benefit. However, it must be stressed that following such an approach, as done within this application, inevitably leads to a positive outcome bias. Consequently, only inferences about indications and drug-class representatives prioritised for EML application can be made. This does not imply their' or other drug-class agents' ineffectiveness in other disease or treatment settings.

Various ICIs are approved for use across cancers at different stages and treatment settings. Depending on the tumours' immunobiology, in line with concepts of precision medicine and multimodality in cancer treatment, ICIs are used alone as monotherapy or as part of disease-specific treatment regimens, combined with targeted, cytotoxic or antibody therapies.
To identify ICI-containing treatment regimens, settings, and cancer entities best suited for application to the model list, aiming for the highest potential impact, we predefined and followed a prioritisation framework based on the following presuppositions (**Figure 4**):

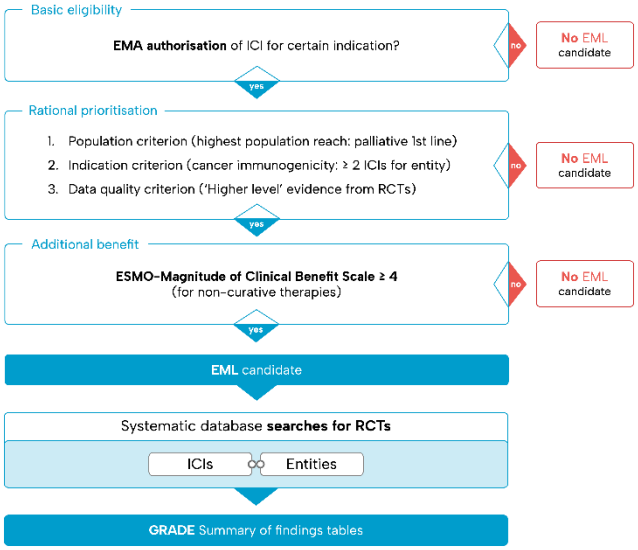


Figure 4. *Prioritisation framework*

1. REGULATORY AGENCY APPROVAL

In a first step, we systematically searched the European Medicines Agency's (EMA) drug database to identify all EMA-approved ICIs and listed indications for use.

2. POPULATION REACH

The second prioritisation step entailed selecting a treatment setting (e.g., curative adjuvant/neoadjuvant or palliative 1st-, 2nd-, or 3rd-line) most suitable for further exploration based on the highest available evidence and potential population reach. Three determining factors governed the choice of the palliative first-line treatment setting.

a. The nature of stepwise drug development, particularly in oncology, dictates that early-phase drug trials are conducted at later lines of treatment, i.e., after failure and disease progression under preceding therapies with proven benefit. Thus, only in case of sufficient additional value does drug exploration gradually move towards earlier palliative and curative treatment settings. With such advancement in treatment lines comes an escalation of trial phases, which translates into the inclusion of larger sample sizes, ultimately contributing to a more robust evidence base.

b. While second or later lines of therapy suggest a multitude of treatment options, the number of patients who could potentially benefit and who are eligible to receive treatment declines considerably with every line of therapy due to death or decline in overall health from disease and treatment complications, quality of complication management, and available resources.

c. The disease stage at diagnosis differs among cancer entities and is affected by extrinsic and intrinsic factors. Extrinsic factors that contribute to the presentation of late-stage advanced disease include the implementation of cancer screening programmes, health literacy, and access to healthcare. Intrinsic factors include idiosyncrasies of some cancer entities, which, for example, have the propensity to early metastasis or late presentation. Cumulatively, this accounts for a significant proportion of cancer patients only arriving at a diagnosis in an already advanced and incurable cancer setting.

3. MAGNITUDE OF CLINICAL BENEFIT

The Magnitude of Clinical Benefit Scale (MCBS) for solid tumours and hematologic malignancies is a tool constructed by the European Society of Medical Oncology (ESMO) in collaboration with the European Haematological Association (EHA), intending to reduce inequity of access to high-value cancer treatments and aid impact-oriented resource allocation decisions [40-43]. According to the ESMO-MCBS scoring system in the non-curative setting, a score of 4 or 5 indicates a significant benefit of the medication or treatment regimen and should prompt swift consideration for reimbursement and cost-effectiveness evaluation. As a result, incorporating the MCBS assessment into our prioritisation scheme meant that we would only consider ICIs or ICI-based treatments that scored four or higher.

Search strategy and selection criteria

An experienced information specialist (IM) constructed search strategies based on the prioritised selection of cancer entities and ICI-/combination pairings. Searches for randomised controlled trials (RCTs) were conducted in MEDLINE (OvidSP) and the Cochrane Central Register of Controlled Trials (CENTRAL). We used the Cochrane RCT classifier to increase the screening precision. No language restrictions were applied. The detailed search strategies are in the appendix.

Due to their high level of evidence and ability to control for confounding, we considered only RCTs for inclusion. Trials were eligible if they compared ICIs alone or in combination (with each other or treatment standard) with the established standard of care treatment (SoC) in the palliative first-line cancer setting. We excluded studies that evaluated only disease maintenance. Studies in the curative treatment setting (i.e., adjuvant and neoadjuvant therapy) and studies of later palliative treatment lines (i.e., 2nd, 3rd, or 4th line therapy) were also excluded. Restrictions concerning the cancer type resulted from the prioritisation framework described above. We broadly defined standard treatment as any chemo-, antibody-, or targeted therapy established in the palliative first-line treatment setting before the approval of ICI-containing regimes for each specific cancer entity or subentity. In case of uncertainty about the established SoC and trials' eligibility concerning the comparator treatment, we consulted guideline publications and clinical experts. Two researchers (MG, JS, AW, MC) screened at least 20% of records in parallel. Following the rapid review methodology and provided there was sufficient interrater agreement (Cohen's kappa > 0.8), single screening of the remainder of the records continued. Conflicts arising during title, abstract, or full-text screening were resolved by discussion. The data flow of the trial selection was summarised in PRISMA flowcharts.

Outcome selection

We prioritised four main patient-relevant outcomes.

- **Overall survival (OS)** (death from any cause, measured from randomisation to time of death; time-to-event outcome)
- **Progression-free survival (PFS)** (disease progression or death from any cause, whichever comes first, composite outcome from randomisation until the occurrence of the event; time-to-event outcome)
- **Health-related quality of life (QoL)** (measured using validated tools; continuous outcome)
- **Adverse events (CTCAE ≥ 3) irrespective of treatment attribution** (number of people with an event; dichotomous outcome)

If QoL was assessed using more than one measurement instrument, we prioritised data extraction from instruments that derived an overall health score and were applied most frequently across trials. Consequently, this led to the following priority ranking:

1. Global health score/quality of life (GHS/QoL) as measured by the European Organisation for Research and Treatment of Cancer Quality and Life Questionnaire-C30 (EORTC QLQ-C30)
2. The total score of the European Quality of Life 5 Dimensions Instrument (EQ-5D) or Functional Assessment of Cancer Therapy – General (FACT-G)
3. Disease-specific quality-of-life measurement instruments

If HR-QoL was reported at more than one time point, we extracted data from the time point with the longest follow-up and the most overlap with other included studies. If both change scores and final scores were reported, we chose to extract change scores to represent changes more closely in quality of life over time.

Data collection and analysis

Single reviewers (MC, MG, JS, AW) performed data extraction and risk of bias assessment, which were divided based on disease entity. Extractions were undertaken using a prepiloted form. A second reviewer verified key outcome extractions and the risk of bias judgements [44, 45]. The Cochrane Risk of Bias Tool 1.0 was used for risk of bias assessment [46]. Disagreements concerning extractions or bias judgement were resolved through discussion among reviewers. We regarded each study rather than individual study reports of the same study as the unit of interest. In extracting data, we collected information from reports with the most complete dataset for each outcome and the longest median length of follow-up.

Measures of treatment effect

For time-to-event outcomes (OS, PFS), we extracted hazard ratios (HRs) and corresponding confidence intervals (CIs) provided from the most recent and complete publications of trials. If meta-analysis of time-to-event outcomes was possible, we used the inverse variance method and random effects model to arrive at pooled estimates of the effect. Adverse events with CTCAE ≥ 3, irrespective of treatment attribution, were addressed as dichotomous outcomes, calculating risk ratios (RR) and CIs via the Mantel-Haenszel method. Results of QoL assessments were extracted and analysed as continuous outcomes, using the mean difference (MD) with 95% CIs. For QoL outcomes reported in studies of the same comparison but with different scales, we planned to analyse data using the standardised mean difference (SMD). However, as only single studies could be identified for most indications and reporting GHS/QoL was common, we did not resort to SMD for analysis.

Summary of findings tables

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to assess the certainty of the evidence in an outcome-centric manner [47].

Target population

In this review, and within the context of the EML application, we defined the target population as individuals for whom ICIs would not be readily available. That is, treatment regimens and subsequent treatment lines do not include the use of ICIs. We considered this perspective when assigning a certainty rating to the evidence regarding each preselected outcome.

Target intervention

By choosing only approved drug regimens with substantial benefits for comparisons, the prioritisation framework, by design, introduced publication bias, necessitating the avoidance of comparisons that combine multiple ICIs as the target intervention. To mitigate this risk, we systematically analysed and presented data solely at the level of individual ICIs or ICI-containing regimens for prioritised cancer entities.

Thresholds for effect size and imprecision

Determining thresholds for effect sizes and imprecision ratings is a topic of ongoing debate. Ideally, only drugs that demonstrate a meaningful improvement in overall survival and show a substantial benefit are added to the EML [48]. With this goal in mind, we have established upper and lower thresholds to denote appreciable benefit and harm for relative effects at 0.75 and 1.25, which reflect these criteria. These cut-offs are derived from early GRADE guidance on rating imprecision [49]. Ratings concerning the QoL outcome were mainly dictated by the defined minimal clinically important difference (MCID) for each instrument. For EORTC QLQ-C30, this difference was set at 10 [50].

Absolute effects of survival outcome

To increase the informative value of our evidence presentation in the summary of findings tables we presented the absolute effect for overall survival in two ways:

- Difference in survival (percentage of people surviving) at a specific timepoint
- Difference in median survival (length of median survival months)

For both data presentation modes, we utilised the HRs and corresponding CIs on survival, whether derived from individual studies or meta-analyses, to calculate the anticipated absolute effect estimate. This calculation was based on the reported proportion of study participants surviving at specific time points (e.g., at 2 years) and the median OS reported in the trials. As a result, estimates of survival benefits that were not based on meta-analyzed data may have varied slightly from the survival differences reported in trials. However, further steps to identify causal explanations were only taken if these discrepancies clearly fell outside the calculated CI.

EXPLORATORY BENEFIT-HARM COMPARISON

The likelihood of being helped or harmed serves as an indirect measure of effect size that balances beneficial and harmful outcomes. It has been utilised to analyse benefit-harm trade-offs in recent reviews of cancer medicines [51-53]. The LLH is a ratio derived from the number needed to treat (NNT) for a beneficial outcome and the number needed to harm (NNH) for a harmful outcome. In our case, the beneficial outcome chosen was OS gain at two years, while higher-grade adverse events (CTCAE ≥ 3) represented the harmful outcome. An LLH of 1 indicates an equal likelihood of either the harmful or beneficial outcome occurring, while values above 1 suggest an n-times higher chance of the favourable outcome. We presented the LLH as the base-case scenario using the point estimates of NNT and NNH. Additionally, we calculated the best- and worst-case scenarios by using the upper confidence interval (CI) of the NNT for OS gain and the lower CI of NNH for higher-grade adverse events to establish the worst-case scenario, and vice versa for the best-case scenario. The NNT and NNH estimates were derived from the anticipated absolute effects, calculated based on the baseline risk and relative effect measures. If both NNT and NNH suggest a likely benefit or harm (i.e., NNT is positive and NNH is negative and vice versa), trade-offs cannot be calculated; this is also true if the NNT or NNH confidence intervals are not statistically significant. In such cases, we noted only the direction of the LLH. The calculations for LLH were performed without assuming differential importance of outcomes, meaning the same weight was assigned to OS gain to avoid higher-grade adverse events.

Reporting

While analyses and data were compiled into separate summary of findings tables for all prioritised indication and ICI pairings, and included informative statements about effect size and certainty of evidence [54], due to feasibility concerns, more detailed reporting was only conducted for eight entities: NSCLC, HNSCC, MEL, BTC, OESCC, CRC, EC and CC.

For RCC, HCC, GC/GOJ and TNBC, please refer to their respective summary of findings tables data summaries.

Results

Prioritisation

1. Regulatory agency approval

By applying filters (a. remove all filters, b. authorised, c. medicines, d. antineoplastic agents, e. monoclonal antibodies, f. antineoplastic and immunomodulating agents, g. human, h. MeSH terms: cancer, carcinoma, neoplasms), we found 223 entries by searching EMA's Medicine Finder on April 4th, 2024. We identified 11 immune checkpoint inhibitors (atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, ipilimumab, nivolumab, pembrolizumab, tislelizumab, tremelimumab, relatlimab) for further review. Next, the ICI's product information documents were screened to identify their indicated use, revealing 76 EMA approvals of ICI-containing treatment regimens for 21 cancer indications.

2. Population reach: Palliative 1st line treatment setting

Of identified approvals, 11 were in the curative (neo)adjuvant setting, 44 in the palliative 1st line treatment setting and 19 for later treatment lines. Exclusions also entailed approvals specifically for the maintenance setting. Please refer to the appendix for a detailed listing of approvals.

3. ESMO-Magnitude of Clinical Benefit Score ≥ 4

Lastly, we evaluated the prioritised approvals for the palliative 1st line cancer treatment against ESMO-MCBS Scorecards, to identify treatments with a substantial benefit (i.e., with a score of 4 or 5). This was done via ESMO's MCBS Scorecards register [55], including 29 approvals for evidence review. ***Table 1*** summarises the ICI/-combination treatment and indication pairings with substantial benefit scores selected for systematic searches and reviews. The detailed justificatory selection process is provided in the document appendix, while **Figure 5** illustrates the prioritisation flow through a Sankey diagram.

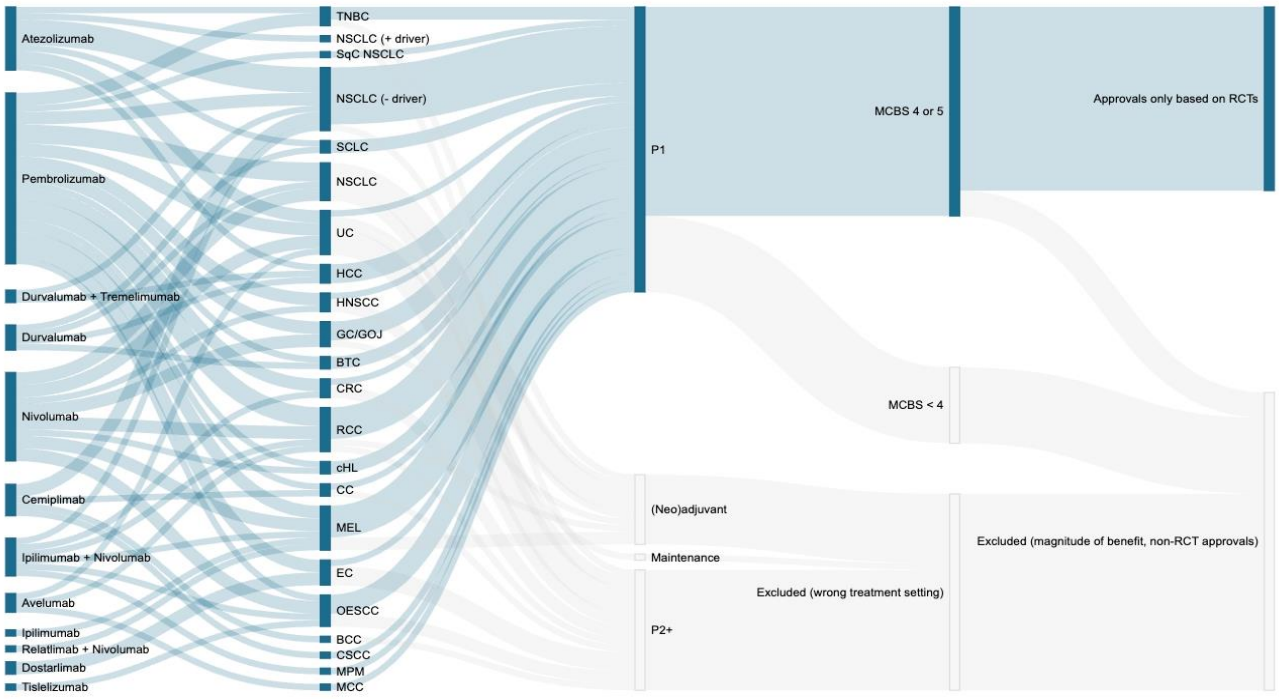


Figure 5. *Sankey diagram of prioritisation flow*

Abbreviations: *TNBC – triple-negative breast cancer, NSCLC (+ driver) – non-small cell lung cancer with driver mutations, NSCLC (- driver) – non-small cell lung cancer without driver mutations, SqC NSCLC – squamous cell non-small cell lung cancer, SCLC – small cell lung cancer, UC – urothelial carcinoma, HCC – hepatocellular carcinoma, HNSCC – head and neck squamous cell carcinoma, GC/GOJ – gastric cancer and gastro-oesophageal junction adenocarcinoma, BTC – biliary tract cancer, CRC – colorectal carcinoma, RCC – renal cell carcinoma, cHL – classic Hodgkin lymphoma, CC – cervical cancer, MEL – malignant melanoma, EC – endometrial carcinoma, OESCC – oesophageal squamous cell carcinoma, BCC – basal cell carcinoma of the skin, CSCC – cutaneous squamous cell carcinoma, MPM – malignant pleural mesothelioma, MCC – Merkel cell carcinoma, P1 – palliative first-line treatment setting, P2+ – palliative second- and later line treatment setting, MCBS – ESMO magnitude of clinical benefit scale, RCT – randomised controlled trial*

Search

We developed multiple search strategies for single cancer entities and ICIs. Every search was built equally, encompassing a search string with search terms for the cancer entity (e.g., endometrial carcinoma) and a search string containing the prioritised ICI(s) (e.g., dostarlimab). Due to relevant overlaps between some cancer entities, these diseases were grouped and a joint search was conducted (e.g., oesophageal squamous cell carcinoma and gastric, gastro-oesophageal junction and oesophageal adenocarcinoma). The systematic search strategies were applied in the CENTRAL and MEDLINE databases from July through August 27th, 2024. Alongside this EML application, a systematic review was performed on the efficacy and safety of ipilimumab combined with nivolumab as palliative first-line therapy across various cancer types (PROSPERO: CRD42024548061), providing relevant trials and reports. Hence, the combination of ipilimumab and nivolumab was omitted from searches conducted for this EML application. **Figure 6** summarises the record and screening flow across all conducted searches and identified studies and reports per disease entity.

The detailed search strategies can be found in the document's appendix.

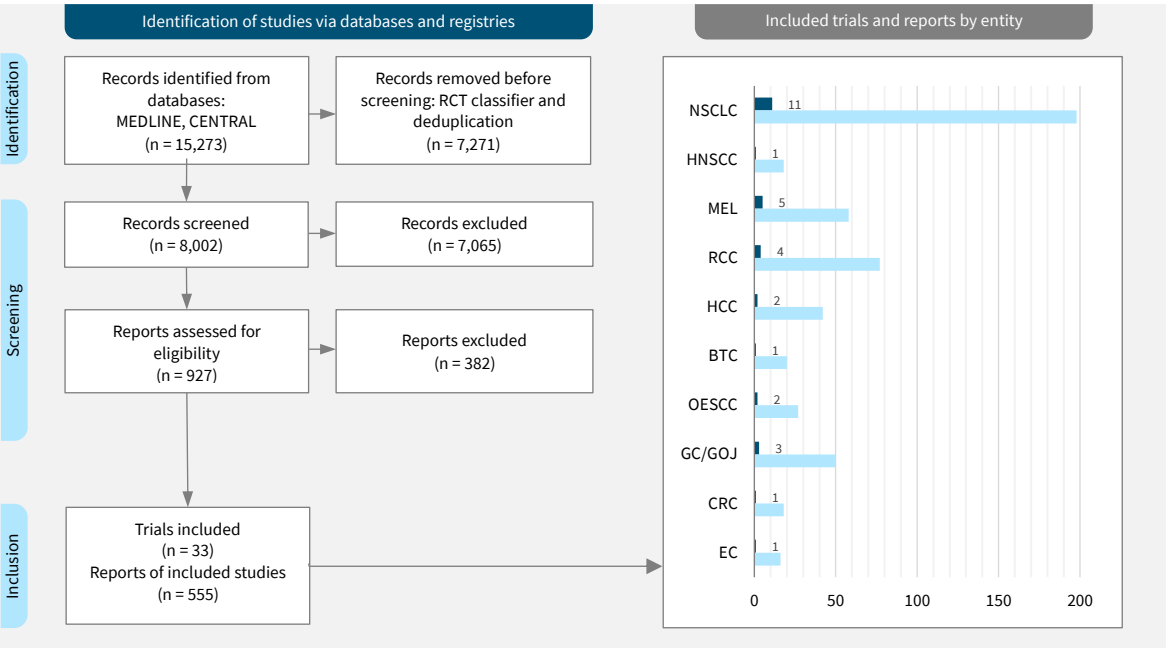


Figure 6. *PRISMA flow diagram across all conducted searches*

Lung cancer

Prioritisation and search results

Our search of the EMA drug registry for ICIs in lung cancer identified 20 approvals for seven different ICI-class drugs. After the exclusion of approvals in the adjuvant, neoadjuvant and palliative later-line settings (i.e., progressive disease after at least one palliative treatment line), 12 approvals for the palliative first-line setting remained. Eight met the MCBS ≥ 4 criterion and were thus considered for further evaluation via systematic review. Two ICIs, namely atezolizumab and durvalumab, both in combination with etoposide and a platinum-chemotherapeutic, are approved for small-cell lung carcinoma in the palliative first-line setting. However, not reaching the required clinical benefit score, they were excluded. Similarly, ipilimumab combined with nivolumab failed to achieve the necessary margin in malignant pleural mesothelioma (not shown in the table below). Consequently, only approvals for non-small cell lung cancer, without oncogenic driver mutations like EGFR or ALK1, met our prioritisation criteria. Going forward, approved ICIs and indications could be grouped into two categories: ICI monotherapy for high PD-L1 expression and ICI plus chemotherapy combination, irrespective of the PD-L1 expression status. The table below provides information on approved indications, highlighting prioritised treatment regimens and reasons for exclusion.

PRIORITISATION

ICI/-combination	Setting	Diagnostic requirement	Treatment details	MCBS-Score	RCT	LTS
Atezolizumab	A	PD-L1 ≥ 50%	Monotherapy	A	Yes	–
Atezolizumab	P1	NR	Atezolizumab + platinum-based CTx + bevacizumab	3	Yes	–
Atezolizumab	P1	NR	Atezolizumab + platinum-based CTx	3	Yes	–
Atezolizumab	P1	≥ 50% (TC), ≥ 10% (IC)	Monotherapy	5	Yes	–
Atezolizumab	P2	NR	Monotherapy	5	Yes	–
Atezolizumab	P1	NR	Atezolizumab + carboplatin + etoposide	3	Yes	–
Cemiplimab	P1	PD-L1 ≥ 50%	Monotherapy	4	Yes	–
Cemiplimab	P1	PD-L1 ≥ 1%	Cemiplimab + platinum-based CTx	4	Yes	–
Durvalumab	A	PD-L1 ≥ 1%	Monotherapy	4	Yes	–
Durvalumab	P1	NR	Durvalumab + cisplatin/carboplatin + etoposide	3	Yes	–
Durvalumab + tremelimumab	P1	NR	Durvalumab + tremelimumab + platinum-based CTx	4	Yes	–
Ipilimumab + nivolumab	P1	NR	Ipilimumab + nivolumab + platinum-based CTx	4	Yes	–
Nivolumab	P2	NR	Monotherapy	5	Yes	–
Nivolumab	N	PD-L1 ≥ 1%	Nivolumab + platinum-based CTx	A	Yes	–
Pembrolizumab	N	NR	Pembrolizumab + platinum-based CTx	A	Yes	–
Pembrolizumab	A	NR	Monotherapy	A	Yes	–
Pembrolizumab	P2	PD-L1 ≥ 1%	Monotherapy	5	Yes	–
Pembrolizumab	P1	PD-L1 ≥ 50%	Monotherapy	5	Yes	✓
Pembrolizumab	P1	NR	Pembrolizumab + platinum-based CTx	4	Yes	✓
Pembrolizumab	P1	NR	Pembrolizumab + platinum-based CTx	4	Yes	✓

Reason for exclusion (red colour); LTS – long-term survival benefit as reported by ESMO-MCBS Scorecard based on PFS and/or OS outcomes (not defined as a prioritisation criterion)

Based on this selection, we developed a search strategy encompassing search terms for non-small cell lung cancer and ICIs that qualified for inclusion. The search conducted in the CENTRAL and MEDLINE databases yielded 3285 records. After deduplication and applying the Cochrane RCT classifier, 1771 remained. The concurrently performed systematic review supplied relevant trials and reports on the safety and efficacy of ipilumumab/nivolumab-based regimens. Hence, the combination of ipilimumab and nivolumab was omitted from the entity-specific search strategy. **Figure 7** depicts the information flow in form of a PRISMA diagram.

Monotherapy

Included studies and participants

For a detailed description of the studies, see the Characteristics of Included Studies table. Here, we provide a brief overview.

For the three ICIs, atezolizumab, cemiplimab, and pembrolizumab, approved as monotherapy treating NSCLC without oncogenic driver mutations (EGFR, ALK) and high PD-L1 expression, we included a total of five studies. For atezolizumab monotherapy (IMpower 110, IPSOS) and pembrolizumab monotherapy (Keynote-024, Keynote-042) two studies each met inclusion criteria [56-63]. For cemiplimab, only one study was identified (EMPOWER-Lung 1) [64-66].

All five studies were global, multicentre, unblinded phase 3 RCTs, comparing ICI monotherapy with the established treatment standard in NSCLC, apart from IPSOS, which was conducted in a patient setting where no clearly established treatment standard

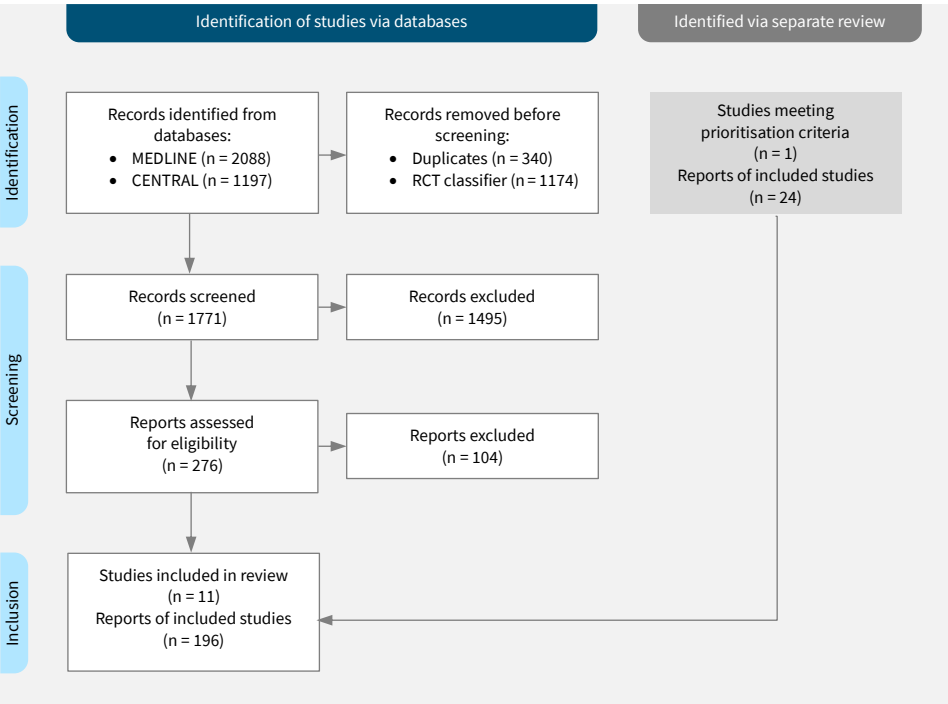


Figure 7. *PRISMA flow diagram: NSCLC*

exists. In all studies, patients with either squamous or non-squamous tumour cell histology were eligible for inclusion as long as they were negative for EGFR and ALK driver mutations. In EMPOWER-Lung 1, ROS1 was also mentioned as a targetable mutation that would exclude patients in the event of positivity. Studies varied with respect to PD-L1 expression as an eligibility criterion. In IPSOS, participant inclusion was not limited by PD-L1 expression. For IMpower 110 and Keynote-042 a PD-L1 expression of at least 1%, i.e., TC or IC higher than 1% and TPS ≥ 1%, respectively, was required. EMPOWER-Lung 1 and Keynote-024 considered only participants with PD-L1 TPS ≥ 50% eligible for inclusion. For the measurement of the PD-L1 status, different IHC assays were used. The age cut-off for all studies was set at 18 years without an upper limit. Regarding comorbidities and performance status, all studies, apart from IPSOS, were restrictive, only allowing trial participation in case of an ECOG performance status of 0-1, with sufficient organ function. IPSOS was a trial conducted specifically in patients with an ECOG performance status of 2 or higher or performance status of 0 or 1 but an age equal to or higher than 70 with significant comorbidities or contraindications to platinum-chemotherapy. Other exclusion criteria, equal to all trials, were a history of HIV, active HBV, HCV or latent tuberculosis or a history of autoimmune disease requiring systemic treatment. In addition, in EMPOWER-Lung 1, only people with smoking history were eligible for inclusion. Aside from IPSOS, where the comparator treatments were single-agent chemotherapies like vinorelbine or gemcitabine per investigator's choice, ICI monotherapy was compared to a doublet chemotherapeutic regimen containing either cisplatin or carboplatin, coupled with pemetrexed, paclitaxel or gemcitabine. Pemetrexed containing doublet-regimens were only reserved for patients with non-squamous NSCLC histology.

All studies stratified the randomisation based on the histologic subtype (squamous vs. non-squamous histology). In Keynote-024, Keynote-042 and IMpower 110, patients were additionally stratified based on their performance status (ECOG 0 vs ECOG 1). The pembrolizumab studies (Keynote-024, Keynote-042) and the cemiplimab study (EMPOWER-Lung 1) were further stratified based on geographic regions (Europe, Asia or East Asia and non-East Asia). In studies permitting the inclusion of patients with lower PD-L1 expression (Keynote-042, IMpower 110, IPSOS), expression levels were included as stratification variables.

Pembrolizumab

Across the pembrolizumab studies (Keynote-024, Keynote-042), 904 participants with PD-L1 expression of TPS ≥ 50% underwent stratified randomisation, with 453 receiving pembrolizumab monotherapy and 451 the comparator treatment. Across studies, the median age was 63-65 years. Notably, the proportion of female participants was higher in Keynote-024 than in Keynote-042 (38.7% vs 30.5%). Differences could also be noted with respect to the smoking status and histological features of patients. While the proportion of patients who were never smokers was around 20% in Keynote-042, in Keynote-024, this proportion was lower and differed between intervention and comparison, being 3.2% and 12.6%, respectively. Additionally, while non-squamous cell NSCLC was the predominant histologic subtype in both studies, their participant proportion varied nearly by a fifth (81.6 vs 63.1%). The proportion of participants across trials with brain metastases was around 6%, although slightly higher in the intervention group of Keynote-024 (11.7%). The length of follow-up was similar, reaching the five-year mark in both studies, with a weighted median follow-up of 60.7 months.

Atezolizumab

In the atezolizumab studies (IMpower 110, IPSOS), a total of 280 patients with high PD-L1 expression, either by tumour or invading immune cells, were randomised to receive atezolizumab monotherapy or the treatment standard (157 vs 123 participants). Expectedly, considering different eligibility criteria, participants in IPSOS were, on average, around ten years older than in IMpower 110. The median age of participants in IMpower 110, resembled the median age distribution of other ICI monotherapy studies, lying between 63 to 65 years. In IPSOS, three-fourths of patients had a performance status of ECOG 2 and higher, and thus, would not have

been eligible for inclusion in IMpower 110, or any other ICI monotherapy study identified, for that matter. Of note, only a small proportion of participants in IPSOS, 50 and 25 participants receiving atezolizumab and standard of care, contributed to the analysis. While in IPSOS, participants with smoking history were equally distributed among the intervention and comparator groups but not reported for the PD-L1 subgroup, the proportion of never-smokers in the atezolizumab monotherapy arm in IMpower 110 was slightly higher than the standard of care arm (8.4 vs 15.3%). The longest median follow-up reported in IMpower 110 and IPSOS publications were 31.3 and 41 months, respectively, with a weight-adjusted pooled median of 35.6 months.

Cemiplimab

EMPOWER-Lung 1 included 710 participants based on PD-L1 testing results and randomised them to intervention and comparator treatment. Following a review of diagnostic analysis inconsistencies, retesting of samples revealed that around 20% of trial participants were misclassified as having tumours that express PD-L1 TPS ≥ 50%. Analysis was provided for both the intention-to-treat (ITT) population and participants reclassified as high PD-L1 expressors. The characteristics of included participants did not show any significant baseline differences between the ITT and reclassified population. Apart from IPSOS, compared to other studies investigating ICI monotherapy, a higher proportion of patients with squamous cell histology was observed in EMPOWER-Lung 1, around 44%, as opposed to 17.9% to 38%. In IPSOS, the proportion of patients with squamous cell histology was similarly as high as in EMPOWER-Lung 1. In addition, while the proportion of female participants was 26.2% to 40.3% in other ICI monotherapy studies, EMPOWER-Lung 1 only included 14.6% female patients. The longest median follow-up reported in EMPOWER-Lung 1 publications was 37 months.

All studies were funded by their subsequent investigational drug-producing pharmaceutical companies. The pembrolizumab trials (Keynote-024, Keynote-042) were funded by Merck Sharp & Dohme LLC, atezolizumab (IMpower 110, IPSOS) by Hoffmann-La Roche and cemiplimab (EMPOWER-Lung 1) by Regeneron Pharmaceuticals and Sanofi.

Interventions and comparisons

All three ICIs were administered intravenously on day one of every three-week cycle at fixed doses: atezolizumab at 1200 mg (IMpower 110, IPSOS), cemiplimab at 350 mg (EMPOWER-Lung 1), and pembrolizumab at 200 mg (Keynote-024, Keynote-042). Comparator treatments except in IPSOS, which only included participants not eligible for platinum-based polychemotherapy, built on combinations of either cisplatin or carboplatin partnered with gemcitabine, paclitaxel or pemetrexed, depending on the underlying histology. Participants in IPSOS received as comparator treatments single-agent chemotherapy of gemcitabine intravenously or vinorelbine, intravenously or orally, at three-weekly or four-weekly cycles, according to relevant local guidelines and Summary of Product Characteristics (SmPC), until disease progression. Polychemotherapy in IMpower 110, EMPOWER-Lung 1, Keynote-024 and Keynote-042 was given for four to six three-week cycles. Depending on the regimen composition, cisplatin was administered at 75 or 100 mg/m^2 body surface area (BSA) and carboplatin at AUC 5 to 6 mg/mL/min. The platinum compound was either combined with pemetrexed at 500 mg/m^2, provided the tumour was of non-squamous cell origin, with paclitaxel at 200 mg/m^2, or with gemcitabine at either 1000 mg/m^2 or 1250 mg/m^2.

In the interventional treatment arms, ICIs were continued until disease progression, unacceptable toxicity or up to 35 or 36 treatment cycles, in the case of pembrolizumab and cemiplimab, respectively, which adds up to around two years. In the atezolizumab trials (IMpower 110, IPSOS), no maximum number of treatment cycles was defined. Patients with non-squamous cell NSCLC receiving comparator treatment were allowed to receive pemetrexed as maintenance. Treatment beyond radiological disease progression, as assessed by RECIST v1.1, was permitted in atezolizumab and cemiplimab trials, trying to account for the possibility of pseudoprogression. In EMPOWER-Lung 1, the option of adding chemotherapy upon progression while continuing to receive cemiplimab was introduced per protocol amendment. The authors of Keynote-024 did not specify treatment beyond progression in their protocol for pembrolizumab. Continuous treatment following only radiological progression was allowed in Keynote-042, provided that confirmatory scans indicating progression were conducted at least four weeks thereafter.

Outcomes of interventions

Apart from Keynote-042, which did not plan to assess quality of life outcomes, our prespecified outcomes of interest were assessed in all studies either as primary or secondary endpoints. Overall survival was the primary endpoint in IPSOS and Keynote-042 and was promoted to be included as a primary endpoint in EMPOWER-Lung 1 and IMpower 110 by protocol amendment after the studies were already ongoing. In Keynote-024, the primary endpoint was PFS by independent review, and in EMPOWER-Lung 1 and IMpower 110 PFS was planned by investigator assessment, listing PFS by independent review only as a secondary outcome. Assessments of quality of life aspects were planned using the EORTC QLQ-C30 measure with the addition of the LC13 extension in all studies. IMpower 110, IPSOS and Keynote-024 also planned further assessments using the EQ-5D instrument. Considering our predefined analysis plan for quality-of-life outcomes, reporting in identified publications on the endpoint was only sufficient for further analysis in the case of Keynote-024 and EMPOWER-Lung 1.

Risk of bias

The risk of bias in included studies is summarised in the risk of bias section of the data summary.

Allocation (selection bias)

The cited randomisation methods appeared to be adequate in all included studies, using variants of interactive voice response systems or interactive web response systems. The baseline criteria of included participants in trials did not show substantial differences between randomised groups. In Keynote-024 and IMpower 110 a discrepancy between smoking statuses could be noted, but considering the number of participants included and randomisation not being stratified by smoking history, this difference may have resulted by chance. Consequently, we judged the risk of selection bias as low.

Blinding (performance bias and detection bias)

All five included studies utilised an open-label design. Therefore, we assessed the risk of performance and detection bias as low for the objective outcomes OS and PFS, provided that data from blinded independent central radiological reviews was utilised and reported for PFS. We considered the risk of bias as high for safety and quality of life outcomes, which, due to their partially subjective nature, are susceptible to bias.

Incomplete outcome reporting (attrition bias)

The participant flow was reported adequately in all five studies. All patients were included in the survival analyses, and nearly all were included in the safety analysis. Thus, the risk of attrition bias was judged as low for these outcomes. Completion rates and quality of life assessment compliance were reported adequately in Keynote-024 publications and were around 80% at measuring time points in both treatment arms. Therefore, we rated the risk of attrition bias as low. IMpower 110 cited a completion rate of more than 80% at most visits. However, similar to EMPOWER-Lung 1 publications, where a high completion rate throughout the study period was reported, more detailed information was lacking, which is why we judged the risk of bias to be unclear for both studies regarding quality-of-life outcomes. In IPSOS a differential missingness of data could be noted, with lower completion numbers for questionnaires in the comparator arm. To which extent these were missing by design remained unclear, leading to a judgement of unclear risk of attrition bias.

Selective reporting (reporting bias)

The trial protocols were accessible for all studies included, and apart from the quality of life in studies of atezolizumab (IMpower 110, IPSOS), predefined outcomes of interest were adequately reported. Although initially, EMPOWER-Lung 1 and IMpower 110 only promoted OS from a secondary to a primary outcome after studies were ongoing, we did not interpret this change to affect the bias judgement. IMpower 110 and Keynote-024 also included participants with PD-L1 tumours or tumour-invading immune cells at lower expression rates. Clear specification of subgroup analyses based on high PD-L1 expression (i.e., TPS ≥ 50 in Keynote-024 and TC3 or IC3 in IMpower 110) were only provided after interim analyses had been conducted, according to the trials' respective registry entry histories. Nevertheless, considering that randomisation was stratified based on the degree of PD-L1 expression, we judged the risk of reporting bias to be low.

Effects of interventions

See the summary of findings tables: Pembrolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression; Atezolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression; Cemiplimab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression

Pembrolizumab

Overall survival

ICI monotherapy with pembrolizumab in NSCLC patients without sensitising driver mutations and high PD-L1 expression likely results in a large increase in overall survival, compared to polychemotherapy in the palliative first-line setting (HR 0.66 [95% CI, 0.57 to 0.76]; 2 studies, 904 participants; moderate-certainty evidence; Analysis 1.1). This translates to a survival benefit of 15.2% (10.1 to 20.3% more) at two years and 11.9% (7.4 to 16.9% more) at five years. Compared to chemotherapy, pembrolizumab monotherapy leads to a 6.3 months longer median survival (3.9 to 9.2 months more), based on the calculation of survival differences using the hazard ratio and baseline risk estimate of 12.2 months, derived from the pooled median OS with control treatment in Keynote-024 and Keynote-042. However, considering that 66% (Keynote-024) and 23% (Keynote-042) of trial participants receiving the comparator treatment subsequently received ICI therapy upon progression, the treatment effect might be underestimated; thus, we downgraded for indirectness.

Progression-free survival

Compared to polychemotherapy, pembrolizumab may increase progression-free survival (HR 0.66 [95% CI, 0.39 to 1.12]; 2 studies, 904 participants; low-certainty evidence; Analysis 1.2). At one year follow-up, this leads to a 14.6% PFS advantage (3.6 fewer to 33.4% higher) of pembrolizumab over chemotherapy. The certainty of evidence was downgraded for inconsistency and imprecision. The high degree of statistical heterogeneity with an I-squared of 91%, prompting us to downgrade for inconsistency, resulted from confidence intervals for PFS in trials barely overlapping. Since both point estimates and confidence intervals were predominantly on the same side of the null-effect line, and considering the limited reliability of I-squared with fewer trial numbers, as observed in this case, we conducted a meta-analysis nonetheless. Imprecision resulted from the confidence interval crossing both the lines of null effect at one and appreciable benefit at 0.75.

Health-related quality of life

Quality of life was only assessed in Keynote-024 using the EORTC QLQ-C30 and QLQ-LC13 module checklists. The completion rate at 15 weeks was 72% and 62% in the intervention and control groups, respectively, with a compliance rate of 84% and 79% (i.e., the proportion of participants who completed questionnaires of those expected to do so). Of the 154 and 150 participants included in the survival analysis, 150 and 147 from the pembrolizumab monotherapy and chemotherapy groups were included in the calculation of the change from baseline to 15 weeks in global health score/quality of life (GHS/QoL). The mean difference of least-squares mean change scores for GHS/QoL crossed the threshold of minimal clinically important difference (MCID) at 10, favouring pembrolizumab (MD 7.85 [95% CI, 2.51 to 13.19]; 1 study; 297 participants; low-certainty evidence; Analysis 1.3). Therefore, compared to SoC, pembrolizumab monotherapy may slightly increase the GHS/QoL at 15 weeks. Due to concerns of imprecision and risk of bias, the certainty of the evidence was downgraded to low.

Adverse events

Adverse events graded as CTCAE ≥ 3 and irrespective of treatment attribution were only reported for all participants included in Keynote-042 (i.e., including participants with PD-L1 expression less than 50%). Pembrolizumab monotherapy probably results in a large reduction in adverse events compared to polychemotherapy (RR 0.49 [95% CI, 0.37 to 0.66]; 2 studies, 1555 participants; moderate certainty evidence; Analysis 1.4). Considering a baseline risk of 43.4% in absolute terms, this translates to 22.1% fewer (27.3 to 14.8% fewer) individuals being affected by adverse events (CTCAE ≥ 3) with pembrolizumab monotherapy than with platinum-based doublet chemotherapy. We downgraded the certainty in the evidence due to the risk of detection and performance bias resulting from the open-label trial design in both studies. Even though adverse events in Keynote-042 were only reported for the entire ITT population and not for the subgroup of high PD-L1 expressors, we did not downgrade for indirectness. This was due to considerations of ICI pharmacodynamics and the absence of a clearly established link between tumour PD-L1 expression and the occurrence of immune-mediated adverse events.

Atezolizumab

Overall survival

Atezolizumab monotherapy, compared to chemotherapy, may increase overall survival slightly in oncogenic-driver wild-type NSCLC with high PD-L1 expression (HR 0.79 [95% CI, 0.54 to 1.09]; 2 studies, 280 participants; low-certainty evidence; Analysis 1.5). In

absolute numbers and based on a baseline risk of 30% survival at two years, this leads to 8.6% more patients (3.1 fewer to 22.2% more) surviving with atezolizumab monotherapy than with chemotherapy alone and a prolongation of median survival of 3.7 months (1.1 fewer to 11.8 months more). The certainty of the evidence was downgraded for imprecision resulting from the pooled estimates crossing the line of no effect and the line of appreciable benefit at 0.75. Further downgrading of the evidence certainty resulted from considerable therapy switching, with 34.7% of patients receiving ICIs in the comparator group of IMpower 110 upon progression, leading to a potential underestimation of the effect. Neither the testing for subgroup differences nor the testing for heterogeneity showed a significant difference between the two studies, so we did not downgrade for inconsistency.

Progression-free survival

Compared to chemotherapy, atezolizumab may increase progression-free survival (HR 0.63 [95% CI, 0.48 to 0.84]; 2 studies, 280 participants; low-certainty evidence; Analysis 1.6). At one year, 16% more people (5.7 to 25.9% more) are alive without disease progression if treated with atezolizumab as opposed to chemotherapy. In both studies, the outcome assessment was not performed by blinded independent review but was investigator-assessed. Moreover, the confidence interval of the pooled estimate crossed the line of appreciable benefit at 0.75, which, together with the relatively small sample size, led to concerns regarding insufficient power; thus, we downgraded for study limitations and imprecision.

Health-related quality of life

While publications of both studies (IMbrave 110, IPSOS) provide information regarding some quality of life aspects [58, 67], change scores of GHS/QoL measured by EORTC QLQ-C30 were only reported graphically in the supplement of the IPSOS publication and only for the entire ITT population. Consequently, this outcome was not further evaluated following our predefined reporting requirements.

Adverse events

Adverse events CTCAE ≥ 3, regardless of treatment attribution, were only reported in both studies for the entire ITT population (i.e., irrespective of the level of PD-L1 expression by tumour or tumour-invading immune cells). Overall, atezolizumab monotherapy, compared to chemotherapy, may result in little to no difference in adverse events (CTCAE ≥ 3) (RR 0.81 [95% CI, 0.54 to 1.22]; 2 studies, 996 participants; low-certainty evidence; Analysis 1.7). In absolute numbers, this translates to 10.9% fewer patients treated with atezolizumab monotherapy experiencing adverse events (26.4% fewer to 12.6% more). Considering the wide confidence interval and open-label trial design, we downgraded for imprecision and risk of bias. Substantial heterogeneity was introduced by varying patient populations in the included studies and was reflected statistically by an I-squared of 90% in the meta-analysis. The evidence, therefore, suggests that while the intervention of atezolizumab monotherapy may lead to fewer adverse events (CTCAE ≥ 3) in younger, overall fitter patients (i.e., ECOG 0-1, fewer comorbidities), this advantage may be lost in the elderly/unfit population. Since this heterogeneity could plausibly be explained, we did not downgrade for inconsistency.

Cemiplimab

Overall survival

Cemiplimab monotherapy probably results in a large increase in overall survival compared to chemotherapy in the first-line palliative treatment of NSCLC with high PD-L1 expression, without targetable oncogenic driver mutations (HR 0.63 [95% CI, 0.52 to 0.77]; 1 study, 712 participants; moderate-certainty evidence; Analysis 1.8). In absolute terms, this means a 16.7% higher survival (9.6 to 23.1% more) at two years, a 16.6% (9.3 to 23.6% more) higher survival at three years and a median OS advantage of 8 months more (4.1 to 12.6 months more), based on the calculation of survival differences using the hazard ratio and baseline risk estimate in the comparator treatment arm, which was at 13.7 months median OS. Notably, 56% of participants receiving the comparator treatment, upon progression, subsequently received ICIs, which, considering the target population of patients to whom ICIs would not be available, leads to indirectness and potential underestimation of the treatment effect; thus, we downgraded the evidence for indirectness.

Progression-free survival

In comparison to platinum-based doublet chemotherapy, cemiplimab monotherapy likely results in a large increase in PFS (HR 0.56 [95% CI, 0.47 to 0.67]; 1 study, 712 participants; moderate-certainty evidence; Analysis 1.9). At a follow-up of one year, 16.1% more (10.2 to 22.3 more) trial participants receiving cemiplimab monotherapy were alive and did not experience disease progression, as opposed to participants receiving polychemotherapy. However, with the open-label trial design and potential deviations due to contextual bias, the evidence was downgraded for study limitations.

Health-related quality of life

A total quality of life score was calculated and assessed using the EORTC QLQ-C30's GHS/QoL domain. At one-year follow-up, cemiplimab likely results in little to no difference in GHS/QoL compared to chemotherapy (MD 5.03 [95% CI, 2.11 to 7.96]; 1 study, 563 participants; moderate-certainty evidence; Analysis 1.10). Even though a statistically significant difference could be shown in the study, the mean difference did not reach the MICD of 10. The open-label trial design and subjective nature of the outcome led to an increased risk of bias, which caused us to downgrade the evidence.

Adverse events

Cemiplimab monotherapy may reduce adverse events (CTCAE ≥ 3), irrespective of treatment attribution slightly, when compared to SoC chemotherapy (RR 0.89 [95% CI, 0.76 to 1.03]; 1 study, 699 participants; low-certainty evidence; Analysis 1.11). In absolute terms, higher-grade AEs (CTCAE ≥ 3) are experienced by 5.7% fewer (12.4 fewer to 1.5% more) patients receiving cemiplimab monotherapy as opposed to chemotherapy. The open-label trial design with the potential for detection and performance bias and the inclusion of the null effect prompted us to downgrade for study limitations and imprecision.

Evidence discussion

Summary of main results

The evidence shows that ICI monotherapy with pembrolizumab, atezolizumab, or cemiplimab improves overall survival in patients with NSCLC without oncogenic driver mutations but high PD-L1 expression in the palliative first-line setting compared to chemotherapy. We did not identify RCTs directly comparing ICIs to one another, and our analysis plan did not encompass conducting indirect comparisons. Nevertheless, important clinical heterogeneity in trials and the distribution of potential effect modifiers would make ranking ICIs in order of effectiveness problematic. This, in particular, not only refers to the striking difference of participant characteristics in IPSOS compared to other studies but also pertains to more subtle variances like the exclusion of non-smokers in EMPOWER-Lung 1, which might not

only have led to a higher proportion of patients with squamous cell histology but also a lower proportion of female trial participants being included. In all studies, ICIs led to a reduction in the occurrence of adverse events (CTCAE ≥ 3) compared to chemotherapy. However, data from one atezolizumab trial (IPSOS), which included generally older and less fit NSCLC patients, showed that adverse event differences might be less pronounced in this patient population. Quality of life improvements, as measured by the GHS/QoL, were shown for both pembrolizumab and cemiplimab, yet only the former also reached MCID.

The LHH, counterbalancing the OS gains with the occurrence of higher-grade adverse events (AE CTCAE ≥ 3), not assuming differential outcome importance, based on the point estimate of anticipated absolute effects could not be calculated for pembrolizumab, as both showed improvements with pembrolizumab monotherapy vs chemotherapy, even if accounting for worst-case scenarios (i.e., lower CI for OS, and upper CI for higher-grade AE). Similarly, for both cemiplimab and atezolizumab, no LHH could be calculated based on the point estimates of absolute OS gain and higher-grade AEs. Consequently, LHH for the best-case scenarios were not calculable. In the worst-case scenarios, cemiplimab would be 9.09 times more likely to improve survival at two years than cause additional harm (AE CTCAE ≥ 3) compared to chemotherapy. The worst-case scenario for atezolizumab, considering confidence intervals for both overall survival and higher-grade AE crossed the null-effect line, is that the choice of atezolizumab over chemotherapy is more likely to cause harm by both raising the number of people experiencing higher-grade AEs and leading to worse survival at two years when compared to chemotherapy (not assuming differential outcome importance). However, if the data from IPSOS is not included, considering the heterogeneity of trial participants, treatment tolerance concerning AEs favours atezolizumab.

The certainty of evidence across comparisons was rated as low to moderate. The reasons for downgrading were concerns of detection and performance bias in all included studies due to the open-label trial design and subjective nature of safety and quality of life outcomes, at least in part. Furthermore, we downgraded for indirectness, particularly in the case of OS, since a considerable proportion of patients in comparator arms received ICIs upon progression, which might have led to an underestimation of the effect. This is particularly relevant since the review's defined target population consists of patients to whom ICIs were assumed unavailable as a treatment option.

Overall completeness and applicability of evidence

PD-L1 expression and mutational dependence

Three of the included studies also investigated the effect of ICI monotherapy in patients with lower PD-L1 expressions (Keynote-042, IMpower 110, IPSOS). Neither Keynote-042 nor IMpower 110 showed a statistically significant survival benefit for ICI monotherapy with atezolizumab or pembrolizumab if participants with high PD-L1 expression were excluded. This points to the assumption that the subgroup of patients with high PD-L1 expression is the main driver of the benefit. However, since our initial search of the EMA register in May 2024, the EMA approved atezolizumab monotherapy as first-line therapy for use in patients, irrespective of their PD-L1 expression, who are ineligible for platinum-chemotherapy based on the IPSOS trial.

Generalizability of data for other patient populations or settings

Our search and analysis focused exclusively on the first-line palliative treatment setting for patients without sensitising mutations in EGFR or ALK. As evident from the prioritisation table listing EMA's ICI approvals, monotherapy is utilised in both the curative adjuvant setting and later palliative treatment lines following the failure of chemotherapy or targeted therapies. Both atezolizumab and pembrolizumab are approved for these settings as monotherapies [16, 20] based on phase II/III and III RCTs [68-71].

We limited our search and review to findings of RCTs only, as the study design, so we did not search for real-world evidence or non-randomised clinical trials assessing the safety and efficacy in other patient populations. Therefore, except for atezolizumab, the applicability of the evidence for ICI monotherapy provided herein is mainly restricted to patients with good performance status (ECOG 0-1), relatively few comorbidities, without chronic infectious diseases like HIV, latent tuberculosis or active hepatitis B or C. Moreover, the results presented are not transferable to patients with a recent history of systemic treatment requiring autoimmune diseases. Furthermore, since patients without a smoking history were excluded from the study, it is questionable to which extent cemiplimab can be used in such circumstances. Concerning atezolizumab, although it was evaluated in a population of patients with worse performance status and higher levels of frailty, the results of the meta-analysis are not representative of this particular cohort with regard to OS and PFS due to their relatively low contributing weight. Lastly, as ICIs are approved for NSCLC with driver mutations (EGFR, ALK, ROS1) only after the failure of targeted therapies, given that all studies included in this review considered only patients without such mutations eligible, the evidence presented applies solely to NSCLC without sensitising mutations.

Agreements and disagreements with other studies

Other ICIs and contradictory findings

Since our initial search of the EMA register, apart from the earlier mentioned inclusion of atezolizumab for patients ineligible for platinum-based therapy, no additional ICIs have been authorised for use as monotherapy in the palliative first-line setting.

We conducted a pragmatic search of MEDLINE via PubMed to identify studies of ICI monotherapy or ICI-doublets with published results for NSCLC in the palliative first-line setting, comparing them to established SoC regimens that did not lead to EMA approval or were not approved yet. In doing so, we identified one study on avelumab (JAVELIN Lung 100; a phase III study), two for the combination of ipilimumab/nivolumab (CheckMate 227, eNERGY; both phase III studies), two studies evaluating tremelimumab/durvalumab, one of which also investigates durvalumab monotherapy (NEPTUNE, MYSTIC; both phase III studies), and one additional study of durvalumab monotherapy (PEARL; a phase III study). [72-78]. All three studies evaluating ICI monotherapy either with avelumab or durvalumab although numerically indicating longer survival with the intervention, did not prove a statistically significant OS benefit for patients with high PD-L1 expression (defined as TC ≥ 80% in JAVELIN Lung 100, TC ≥ 50% in MYSTIC and TC ≥ 25% in PEARL). For the combination of tremelimumab/durvalumab, neither NEPTUNE nor the MYSTIC study could prove a statistically significant survival benefit. However, results for the subgroup of patients with high PD-L1 expression were only available from the MYSTIC trial. The two studies investigating the combination of ipilimumab/nivolumab differed from one another in that eNERGY, similarly to IPSOS, was conducted in patients with ECOG performance status of 2 or higher or aged ≥ 70 years but were deemed fit for a carboplatin-based doublet, while CheckMate 227 only included participants with ECOG ≤ 1. In neither study was PD-L1 expression an eligibility criterion. In Checkmate 227, a statistically significant benefit was observed for patients with PD-L1 ≥ 1% and patients with PD-L1 ≥

50% regarding OS. However, since patients were only stratified based on PD-L1 expression in general but not the degree of PD-L1 expression, this might have affected the resulting subgroup analysis, limiting their interpretability. In addition, the authors noted a violation of the proportional hazard assumption, which is why the presented effect estimates might be misinterpreted. According to the ESMO-MCBS, the combination of ipilimumab/nivolumab appears to show substantial benefit, denoted by a score of four as a treatment regimen in patients with PD-L1 ≥ 1% expression. While approval was granted by the FDA for this regimen, it was not included by the EMA, which is why the prioritisation framework did not capture it. The eNERGY trial was stopped early after an interim analysis showed no survival benefit in the intervention group over chemotherapy. With only eleven participants included in the study who had PD-L1 expression ≥ 50%, the interpretative strength of results for this subgroup is very limited.

Conclusion

Immune-checkpoint inhibitors as monotherapy used in the first-line palliative treatment of NSCLC without oncogenic-driver mutations and high PD-L1 expression likely result in considerable survival benefits, even at long-term, less higher-grade adverse events and a tendency for better quality of life, when compared to chemotherapy. As evident from the analysed studies, this effect, however, depends on carefully considering patients' eligibility for treatment and PD-L1 expression status. Accounting for the effect of treatment switching, with patients receiving ICIs upon progression if the first-line treatment was chemotherapy, leads to less certainty in the presented effect estimates but raises the certainty in the benefit of the intervention. Nevertheless, considering that other ICIs, apart from the preselected agents for this review, failed to prove a statistically significant superiority over chemotherapy, this points to intra-class differences limiting their interchangeability.

Immunochemotherapy

Included studies and participants

For a detailed description of studies, see the Characteristics of included studies tables. Here, we provide a brief overview.

Four ICI-based treatment combinations met our prioritisation criteria. Thereof, two were combinations of a single ICI, pembrolizumab or cemiplimab, together with platinum-based chemotherapy, and two were ICI doublets of PD-(L)1/CTLA-4 partnerings together with chemotherapy, namely ipilimumab/nivolumab and durvalumab/tremelimumab. For these, we found a total of six studies fitting our criteria. Aside from pembrolizumab-based combinations, for which we identified three eligible studies, Keynote-021 [79, 80], Keynote-189 [81-83], and Keynote-407 [84-86], only one RCT for each other ICI-based combination therapy qualified for further inclusion: EMPOWER-Lung 3 for cemiplimab-based combinations [87-89], CheckMate 9LA for ipilimumab/nivolumab-based treatment [90-92], and durvalumab/tremelimumab regimens were studied in POSEIDON [93, 94].

All five studies were global multicentre phase 3 RCTs, except for Keynote-021, which was a phase 1/2 RCT. Three studies were conducted with double-blinding, comparing ICI-based regimens to an active chemotherapeutic backbone and placebo. Studies investigating ICI-doublets, i.e., POSEIDON and CheckMate 9LA had an open-label design. Keynote-021 was unblinded as well. All studies followed the same basic structure of comparing the addition of an ICI or ICI-doublet to platinum-based chemotherapy with platinum-based chemotherapy without an immunotherapeutic partner. In all studies, only patients with an ECOG performance status of 0-1, adequate organ function and relatively few comorbidities not precluding platinum-based chemotherapy were eligible for participation. Patients with active or a history of systemic treatment requiring autoimmune diseases, a history of HIV or active hepatitis B or C were excluded. Prerequisites concerning the tumour type were negative molecular tests for driver mutations in EGFR and ALK, with the addition of ROS1 in EMPOWER-Lung 3. In Keynote-407, which was conducted exclusively in NSCLC with squamous cell histology, considering the rare co-occurrence of driver mutations, molecular aberration testing was not mandated. The other two pembrolizumab studies only included non-squamous cell NSCLC participants. In studies of other ICIs, participants with either histology were eligible. In none of the trials did inclusion rely on the PD-L1 expression status. Age limits were uniformly set at 18 years, without an upper age cut-off. Eligibility criteria regarding smoking status and CNS metastases were similar in all studies. Participants with CNS metastases could be included, provided radiological stability after treatment and corticosteroids have been tapered out. Studies including both, participants with squamous and non-squamous histology stratified their randomisation accordingly. Stratification in all studies was based on PD-L1 tumour expression as either above or below 1%. The exception was POSEIDON, where participants were stratified by PD-L1 levels above or below 50%, and EMPOWER-Lung 3, which grouped participants into categories of less than 1%, 1-50%, and 50% or higher. Further stratification criteria based on the choice of chemotherapeutic agents: cisplatin vs carboplatin in Keynote-189 and the choice of the taxane agent in Keynote-407. Additional criteria were smoking status in Keynote-189 and sex in CheckMate 9LA.

Pembrolizumab-based treatment combinations were studied in 1298 participants in total (Keynote-021, Keynote-189, Keynote-407), cemiplimab-based regimens in 466 patients, and ICI-doublet additions to platinum-chemotherapy in 719 participants and 675 participants in CheckMate 9LA and POSEIDON respectively. Across studies, the median age of participants was approximately 64 years. In terms of the gender distribution of trial participants, a significant variance was observed across studies. For instance, EMPOWER-Lung 3 included only 16.1% female patients, whereas Keynote-021 had the most female patients, with 60.9% across the treatment arms of cohort G1. However, when combining all three pembrolizumab studies—bearing in mind that trial entry was histology-selective—the proportion of female participants averages out at 33.3%, thus aligning more closely with the proportion of female participants in CheckMate 9LA at 30% and 23.4% in POSEIDON. Concerning the distribution of histologic subtypes, the proportion of patients with squamous cell histology ranged from 31% in CheckMate 9LA to 43.1% in pembrolizumab studies combined. Never-smokers were evenly distributed across studies, ranging from 7.3% in Keynote-407 to 25% in Keynote-021, mirroring expected findings regarding tumour cell histology. Between-group differences of more than 10% were noted regarding smoking history in Keynote-021, of 25% vs 14% in the intervention and comparator arms, respectively. The proportion of participants with brain metastases ranged from 7.8% in Keynote-407 to 17.5% in Keynote-189.

The longest reported median length of follow-up in trial publications was for Keynote-189 (at 64.6 months) and POSEIDON (at 63.4 months). The median follow-up length in EMPOWER-Lung 3 was only 28.4 months. However, the study was closed early due to proven survival benefit by the independent data monitoring committee (IDMC).

The pharmaceutical industry funded all studies: Merck Sharp & Dohme LLC funded the pembrolizumab trials (Keynote-021, Keynote-407, Keynote-189); Regeneron Pharmaceuticals and Sanofi funded the cemiplimab study (EMPOWER-Lung 3); Bristol Myers Squibb funded the study on ipilimumab/nivolumab combination regimens (CheckMate 9LA); and AstraZeneca funded the durvalumab/tremelimumab study (POSEIDON).

Interventions and comparisons

The chemotherapeutic regimen administered to participants in both the intervention and comparator arms was consistent across studies, utilising a platinum-based backbone, with either cisplatin at 75 mg/m² or carboplatin AUC 5 to 6, paired with a histology-specific chemotherapeutic agent: pemetrexed at 500 mg/m² for non-squamous histology only, gemcitabine at 1000 to 1250 mg/m², paclitaxel at 200 mg/m², or nab-paclitaxel at 100 mg/m². All treatments were given in three-week cycles on day 1, except for gemcitabine, which was administered on days 1 and 8 of each cycle, and nab-paclitaxel, which was given on days 1, 8, and 15. Except for CheckMate 9LA, where the number of chemotherapeutic cycles in the intervention arm was reduced to two, immunochemotherapy was administered for a total of four to six cycles across the studies. In all studies, pemetrexed maintenance was mandated or chosen by investigators every three to four weeks after completing polychemotherapy. In contrast to CheckMate 9LA, where the option of pemetrexed maintenance was limited to participants in the comparator arm, those receiving verum therapy could also receive pemetrexed maintenance concurrently, provided they had a non-squamous tumour cell histology.

Outcomes of interventions

While varying in being addressed as primary or secondary outcomes, all studies reported OS and PFS by independent review and published data on safety analyses. Quality of life assessments were mainly published separately. Aside from Keynote-021, which did not plan to address quality of life, and POSEIDON, which only reported quality of life as a time-to-event outcome, i.e., the time to deterioration, and did not report change scores from baseline, reporting on the outcome was sufficient to be included in further analysis.

Risk of bias

The risk of bias in included studies is summarised in the corresponding document section.

Allocation (Selection bias)

All studies used an Interactive Response System or interactive Web Response System to randomise participants. While there were slight differences in baseline characteristics between the intervention and control arms of studies, these were observed in studies with a relatively small number of participants or in those where randomisation was not stratified by these factors, suggesting that they could have occurred by chance. Consequently, we judged the risk of selection bias as low in all studies.

Blinding (Performance bias and detection bias)

Regardless of blinding, considering the objective nature of OS and the independent review of progression for PFS across all studies, we deemed the risk of performance and detection bias for these outcomes to be low. However, as quality of life assessment and adverse event reporting and recording are partly subjective and prone to bias, we rated bias as high for the open-label studies of Keynote-021, CheckMate 9LA, and POSEIDON.

Incomplete outcome reporting (Attrition bias)

The participant flow was adequately reported in all studies. Regarding safety and survival outcome analysis, no relevant attrition was noted; therefore, we rated the risk of bias as low for all studies. Compliance rates for completing PRO questionnaires were above 80% in CheckMate 9LA, EMPOWER-Lung 3, and Keynote-407, so we rated the risk of attrition bias as low for these studies. In POSEIDON, compliance data indicated significant attrition; consequently, we judged the risk of bias as high. Although compliance in Keynote-189 was sufficient up to week twelve, a drop was observed, which was more pronounced in the comparison group, suggesting differential attrition. Thus, we rated this risk of attrition bias as unclear.

Selective reporting (reporting bias)

The trial protocols were accessible for all studies, and the predefined outcomes of interest were reported adequately, which led us to assess the risk of reporting bias as low for all studies.

Effects of interventions

See the summary of findings tables: Pembrolizumab-based treatment compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression; Cemiplimab-based treatment compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression; Ipilimumab/nivolumab-based treatment vs SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression; Durvalumab/tremelimumab-based treatment vs SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression

Pembrolizumab-based treatment regimens

Overall survival

Pembrolizumab-based treatment regimens in NSCLC without EGFR or ALK driver mutations, irrespective of their PD-L1 expression, likely increase overall survival compared to polychemotherapy in the palliative first-line treatment setting (HR 0.66 [95% CI, 0.58 to 0.74]; 3 studies, 1298 participants; moderate-certainty evidence; Analysis 2.1). This benefit was observed for both patients with non-squamous and squamous histology, with the analysis results showing no significant heterogeneity (I-squared of 0%) or a notable subgroup effect. This translates to a survival benefit of 15.1% more individuals surviving at two years (11 to 19.6% more) and 12.1% at five years (8.3 to 16.5% more). Calculating the median OS difference based on the pooled hazard ratio and baseline risks in the control arms reveals a 6.3 month (4.3 to 6.9 months more) longer median OS with treatment integrating ICIs than without. However, considering that more than half of patients receiving control treatment upon progression received ICIs, the effect may be underestimated; therefore, we downgraded for indirectness.

Progression-free survival

Treatment with pembrolizumab-based combination regimens in NSCLC, irrespective of PD-L1 expression, results in a large increase in progression-free survival compared to polychemotherapy only (HR 0.55 [95% CI, 0.48 to 0.64]; 3 studies, 1298 participants; high-

certainty evidence; Analysis 2.2). At one year follow-up, this leads to 21.4% more (15.9 to 26.3% more) people surviving without disease progression.

Health-related quality of life

Quality of life was assessed using the EORTC QLQ-C30 and QLQ-LC13 at different intervals across two studies. Pembrolizumab-based treatment may result in little to no difference in GHS/QoL at a median of 19.3 weeks, based on no significant difference in least-squares mean changes scores from baseline (MD 5.00 [95% CI, 2.13 to 7.87]; 2 studies, 1156 participants; moderate-certainty evidence; Analysis 2.3). Considering the proportion of participants excluded from analysis and potential attrition bias, we downgraded the evidence for risk of bias.

Adverse events

Grade ≥ 3 adverse events according to CTCAE were observed in 5.2% more (ranging from 0 to 10.3% more) participants receiving pembrolizumab-containing treatment compared to those not receiving an ICI. Pembrolizumab-based immunochemotherapy may result in little to no difference in higher-grade adverse events when compared to chemotherapy (RR 1.08 [95% CI, 1.00 to 1.16]; 3 studies, 1286 participants; moderate-certainty evidence; Analysis 2.4). We downgraded the certainty in the evidence due to imprecision.

Cemiplimab-based treatment regimens

Overall survival

Cemiplimab-containing treatment regimens likely increase overall survival compared to standard of care in NSCLC, irrespective of PD-L1 expression (HR 0.65 [95% CI, 0.51 to 0.82]; 1 study, 466 participants; moderate-certainty evidence; Analysis 2.5). This translates to an estimated 15.7% more individuals surviving at two years (7.2 to 24.3% more), and a median OS increase of 6.9 months (2.8 to 12.4 months more), based on a baseline risk of 12.9 months. We downgraded the certainty of evidence for imprecision as the confidence interval crossed the threshold of appreciable benefit at 0.75. Considering that only 15% of participants received ICIs upon progression in the control arm, the certainty of evidence was not downgraded for indirectness. A potential reason for this comparatively low proportion was that the trial was stopped early.

Progression-free survival

Treatment with cemiplimab-based regimens results in a large increase in PFS compared to chemotherapy only (HR 0.55 [95% CI, 0.44 to 0.68]; 1 study, 466 participants; high-certainty evidence; Analysis 2.6). In absolute terms, this leads to an estimated 20.5% more people surviving without disease progression (12.8 to 28.7% more) at one year. We did not downgrade the certainty in the evidence for this outcome.

Health-related quality of life

Cemiplimab-based treatment may result in little to no difference in GHS/QoL compared to chemotherapy in oncogenic-driver wild-type NSCLC at 24 months from baseline (MD 0.61 [95% CI, -2.23 to 3.45]; 1 study, 466 participants; high-certainty evidence; Analysis 2.7). We did not downgrade the certainty of evidence for this outcome.

Adverse events

Grade ≥ 3 adverse events were observed in 12.2% more (1.9 to 25.4% more) participants receiving cemiplimab-containing treatment compared to those receiving the comparator treatment (RR 1.39 [95% CI, 1.06 to 1.81]; 1 study, 465 participants; moderate-certainty evidence; Analysis 2.8). Consequently, cemiplimab-based regimens are likely to increase the incidence of higher-grade adverse events, regardless of treatment attribution, in comparison to chemotherapy alone. The certainty of the evidence was downgraded to moderate due to imprecision, as the confidence interval was wide and crossed the line of appreciable harm at 1.25, resulting in uncertainty about the effect size.

Ipilimumab/nivolumab-based treatment regimens

Overall survival

Ipilimumab/nivolumab combined with two cycles of platinum-based doublet chemotherapy likely increases overall survival (OS) compared to chemotherapy alone (HR 0.74 [95% CI, 0.63 to 0.87]; 1 study, 719 participants; low-certainty evidence; Analysis 2.9). In absolute terms, this translates to 10.9% more individuals surviving at 2 years (ranging from 5 to 16.8% more) and 8.5% more at 5 years (from 3.7 to 13.9% more), with a median OS increase of 3.9 months (1.6 to 6.5 months more). The certainty of the evidence was low due to indirectness, with 36% of patients in the control arm receiving subsequent immunotherapy, which may have underestimated the effect. Additionally, imprecision was noted, as the confidence interval crossed the threshold for appreciable benefit at 0.75.

Progression-free survival

Regimens containing ipilimumab and nivolumab likely increase progression-free survival compared to standard of care (HR 0.70 [95% CI, 0.59 to 0.83]; 1 study, 719 participants; moderate-certainty evidence; Analysis 2.10). At one year, this results in an estimated 12.3% more patients alive without disease progression (ranging from 6.2 to 18.5% more). The certainty of the evidence was downgraded due to imprecision, as the confidence interval crosses the line of appreciable benefit at 0.75.

Health-related quality of life

Quality of life outcomes were assessed using different outcome measures. Following the prioritisation of outcome measures for QoL assessment, the LCSS 3-IGI scale was selected, for which change scores from baseline were presented up until two years of follow-up. Compared to treatment regimens without ICI, the addition of ipilimumab/nivolumab may result in little to no difference in quality of life, as measured by the LCSS 3-IGI scale (MD 4.7 [95% CI, -3.26 to 12.66]; 1 study, 646 participants; moderate-certainty evidence; Analysis 2.11). Because of the potential risk of performance and detection bias, the certainty of the evidence for the outcome was downgraded to moderate.

Adverse Events

Ipilimumab/nivolumab-based treatment regimens may slightly increase the number of people experiencing higher-grade AEs (CTCAE ≥ 3) compared to chemotherapy (RR 1.21 [95% CI, 1.05 to 1.40]; 1 study, 707 participants; low-certainty evidence; Analysis 2.12). In absolute numbers, this leads to 9.8% more people experiencing higher-grade AEs (2.3 to 18.7% more). The certainty of evidence was downgraded to low due to imprecision, with the confidence interval crossing the line of appreciable harm at 1.25 and due to the risk of detection and performance bias, considering the open-label trial design.

Durvalumab/tremelimumab-based treatment regimens

Overall survival

Treatment regimens featuring the durvalumab/tremelimumab doublet may slightly increase OS compared to chemotherapy without ICIs (HR 0.77 [95% CI, 0.65 to 0.92]; 1 study, 675 participants; low-certainty evidence; Analysis 2.13). This results in

an additional 9.2% patient survival (2.8 to 15.4% higher) at 2 years and 5.8% at 5 years (1.6 to 10.6% higher). The median OS, based on a baseline risk of 11.7 months, derived from the control group of POSEIDON, is increased by 3.5 months (1 to 6.3 months more). The low certainty in the evidence arises from indirectness, given that over 30% of control patients received ICIs upon disease progression, which may underestimate the effect, and imprecision, as the confidence interval crosses the threshold for appreciable benefit at 0.75.

Progression-free survival

Durvalumab/tremelimumab-containing regimens likely increase PFS compared to chemotherapy only (HR 0.72 [95% CI, 0.60 to 0.86]; 1 study, 675 participants; moderate-certainty evidence; Analysis 2.14). At one year, this translates to an additional 10% more patients achieving PFS (4.3 to 16.4% more). The certainty of the evidence for this outcome was downgraded due to imprecision.

Health-related quality of life

Although patient-reported outcomes and quality of life were assessed within the trial, results of global or total scores were not reported as mean change from baseline score and thus not addressed further within this review.

Adverse Events

Compared to chemotherapy alone, durvalumab/tremelimumab-including combinations may result in little to no difference in grade 3 or higher adverse events (RR 1.05 [95% CI, 0.92 to 1.21]; 1 study, 664 participants; moderate-certainty evidence; Analysis 2.15). The absolute difference was 2.7% more individuals experiencing such adverse events (4.3 fewer to 11.3% more) if receiving the ICI doublet. The decrease in the certainty of evidence resulted from the open-label trial design, which potentially introduced detection and performance bias.

Evidence discussion

Summary of main results

The combination of chemotherapy with single ICIs such as pembrolizumab or cemiplimab, or with ICI doublets like ipilimumab/nivolumab or durvalumab/tremelimumab leads to various degrees of survival benefit, ranging from slight to moderate when compared to treatment regimens that do not include ICIs in the palliative first-line treatment of NSCLC without driver mutations and regardless of PD-L1 expression. However, at the same time, evidence suggests a slight increase in the occurrence of higher-grade adverse events if ICIs are added. Across studies, quality of life, as measured by global health assessment scales or disease-specific instruments did not appear to be substantially worsened or improved when comparing ICI-based regimens to chemotherapy alone.

Counterbalancing higher-grade AEs and OS gains via calculation of the LHH, not assuming differential outcome importance, pembrolizumab-containing treatment is 3.0 times more likely to improve survival at 2 years than cause higher-grade AEs (CTCAE ≥ 3) (worst-case scenario: 1.1x, i.e., as likely; best-case scenario: not estimable because the lower AE boundary crosses the null effect line) when compared to chemotherapy only. Cemiplimab-based treatments in the same setting are 1.3 times more likely to improve 2-year survival than increase the number of people experiencing higher-grade AEs (worst-case scenario: 3.3 times more likely harmed by experiencing higher-grade AEs than helped by improvement of survival at 2 years; best-case scenario: 12.8 times more likely helped by improved survival at 2 years than experiencing additional higher-grade AEs) compared to chemotherapy. Treatment with ipilimumab/nivolumab-based regimens is 0.9 times more likely to increase survival at two years than cause additional harm (worst-case scenario: 3.3 times more likely harmed; best-case scenario: 2.8 times more likely helped) when compared to chemotherapy. Combinations involving durvalumab and tremelimumab are 3.0 times more likely to improve survival at two years compared to chemotherapy, rather than causing additional harm in the form of additional higher-grade adverse events (worst-case scenario: 3.3x more likely to experience harm by additional higher-grade AEs than have improvements in survival at 2 years; best-case scenario: not estimable because the lower boundary crosses the null effect line).

Across comparisons and outcomes, the certainty of evidence was rated as low to high. Particularly regarding the overall survival outcome, the reason for downgrading was indirectness, which resulted from a substantial proportion of trial participants in control arms receiving ICIs upon progression. Assuming improvement of outcomes with ICIs, this switching of treatments upon progression might have led to an underestimation of the effect size. Further reasons for downgrading were the imprecision of the effect estimates, their confidence intervals, and the risk of detection and performance bias in open-label trials for safety and QoL outcomes.

Overall completeness and applicability of evidence

PD-L1 expression and mutational dependence

Participant eligibility for study entry was independent of their tumour's PD-L1 expression status across all evaluated studies for this indication. Nevertheless, due to the stratification of participants in all studies based on varying PD-L1 expression levels, subgroup analyses were conducted in all but Keynote-021, owing to its small sample size. In addition to analyses across different PD-L1 expression levels, subgroup analyses were also performed by histological type. In CheckMate-9LA, POSEIDON, and EMPOWER-Lung 3, which included both patients with squamous cell and non-squamous cell tumour histologies, subgroup analyses revealed statistically significant findings favouring ICI-based treatment in all studies except for the subgroup of patients with squamous cell histology in POSEIDON. PD-L1 subgroup analyses were categorised as PD-L1 < 1%, PD-L1 ≥ 1%, PD-L1 1-50%, PD-L1 < 50%, and PD-L1 ≥ 50%, with slight variations across studies. The most consistent reporting was available for the PD-L1 ≥ 50% and PD-L1 < 1% subgroups. In most studies, statistical significance favoured ICI-based treatment in the subgroup of patients with PD-L1 ≥ 50%, apart from CheckMate 9LA. In most studies, subgroup analyses for PD-L1 < 1% did not demonstrate statistical significance for overall survival, except in CheckMate 9LA and Keynote-189. This was particularly true for EMPOWER-Lung 3, which potentially has also led to slight differences in the approval texts by the EMA and FDA, as the former only approved the regimen for patients with PD-L1 ≥ 1%. Overall, the evidence from the included studies implies a dependence of the beneficial effect of ICIs on PD-L1 positivity. However, as demonstrated in CheckMate 9LA, where counterintuitively, the subgroup analysis in patients with PD-L1 ≥ 50% was negative, while other subgroups reached statistical significance, their interpretability is limited by the loss of statistical power.

Generalisability of data for other patient populations or settings

In addition to its use in the palliative first-line setting, immunochemotherapy with nivolumab or pembrolizumab is also approved in the curative, neoadjuvant setting based on results

from CheckMate 816, CheckMate 77T and Keynote-671 [95-97], which are all phase III RCTs.

Since our review was limited to RCTs, and the eligibility criteria of the included studies were narrowly defined, the generalisability and applicability of the findings are restricted to patients with oncogenic-driver wild-type NSCLC, a good performance status, an ECOG of 0 or 1, few comorbidities, no chronic viral or bacterial infections, and those able to tolerate platinum-based doublet chemotherapy. Importantly, considering that patients with a history of autoimmune disease were excluded from enrolment, the data cannot be applied to this cohort. Since we did not identify studies investigating immunochemotherapy in the palliative first-line setting for patients regardless of their driver mutational status, apart from those with squamous cell histology, no generalisations regarding treatment effects in patients with NSCLC of non-squamous histology can be made, remaining agnostic of their driver mutation status.

Agreements and disagreements with other studies

Other ICIs and contradictory findings

During prioritisation, we excluded treatment regimens involving atezolizumab from further review as they did not satisfy the defined ESMO-MCBS threshold. Nevertheless, several studies examining atezolizumab in combination with a platinum-based doublet, with or without the addition of bevacizumab (IMpower 130, IMpower 131, IMpower132, IMpower 150, IMpower 151), led to the regulatory approval of such regimens in the palliative first-line treatment setting [98-102]. However, OS outcomes varied across studies in that no statistically significant survival benefit could be observed in three of the trials. A similar case was observed with nivolumab-based regimens, without ipilimumab. While in CheckMate 227, no significant difference in overall survival was noted in patients with non-squamous histology compared to chemotherapy, the TASUKI-52 study observed a significant improvement in survival [103, 104]. Although both studies were phase III trials, they differed in that the experimental regimen in TASUKI-52 additionally included bevacizumab and had all study sites located in East Asia, unlike the global distribution of sites in CheckMate 227. Durvalumab, given without its CTLA-4 inhibiting partner alongside SoC in the POSEIDON trial, did not achieve a statistically significant improvement in survival, similar to nivolumab and ipilimumab in the CheckMate 227.

The pragmatic search, conducted to identify studies of ICI and chemotherapy combinations in the palliative first-line setting of NSCLCs, not part of our review's search strategies, identified two phase III studies comparing different ICI-based regimens to one another, namely pembrolizumab with ipilimumab/nivolumab (NIPPON) and pembrolizumab with dostarlimab (PERLA) [105, 106]. In both studies, similar efficacy regarding overall survival was noted. However, in NIPPON, a higher number of adverse events were noted with the ipilimumab/nivolumab plus chemotherapy than with the pembrolizumab-chemotherapy combination.

Since our initial search of the EMA register, three additional ICI-based combination regimens were approved and, according to our predefined criteria, would have qualified for further review, considering an ESMO-MCBS of 4 or higher. These include approvals for tislelizumab together with a platinum-based doublet in squamous and non-squamous cell NSCLC and sugemalimab in addition to a platinum-based doublet in oncogenic driver-negative NSCLC.

Conclusion

The combination of ICIs with chemotherapy in the treatment of NSCLC without driver mutations and regardless of PD-L1 expression likely increases overall survival, even in the long term, based on median follow-ups across most of the included studies of around five years. However, a tendency to a higher occurrence of adverse events poses a risk, which dictates a careful patient selection. Similar to studies of ICI monotherapy in NSCLC, a substantial number of participants who received control treatment switched to ICIs upon progression, which introduced indirectness and uncertainty in the point estimate, which, assuming a beneficial impact, might have led to an underestimation. With agents like durvalumab or nivolumab, without their CTLA-4 partners not showing survival gains, the interchangeability of ICIs in this indication is questionable.

Combined with the small number of trials per comparison and varying participant characteristics, cross-study comparisons are of limited value and preclude ranking regimens by efficacy.

Head and neck squamous cell carcinoma

Prioritisation and search results

We identified three EMA approvals for two ICIs in the treatment of squamous cell carcinoma of the head and neck: pembrolizumab and nivolumab. Thereof, only one, namely pembrolizumab met our prioritisation criteria of being investigated in the palliative first-line treatment setting and having an MCBS of 4 or higher. The other two approvals were for pembrolizumab and nivolumab, both in the palliative second-line, as monotherapy.

PRIORITISATION

ICI/-combination	Setting	Diagnostic requirement	Treatment details	MCBS-Score	RCT	LTS
Pembrolizumab	P1	NR	Pembrolizumab + CTx	4	Yes	–
Pembrolizumab	P2	50%	Monotherapy	3	Yes	–
Nivolumab	P2	NR	Monotherapy	5	Yes	–

Reason for exclusion (red colour); LTS – long-term survival benefit as reported by ESMO-MCBS Scorecard based on PFS and/or OS outcomes (not defined as a prioritisation criterion)

A search strategy building on search terms for pembrolizumab and head and neck squamous cell carcinoma was constructed by the information specialist. The search conducted in the MEDLINE and CENTRAL databases yielded a total of 1047 record hits. Following deduplication and use of the Cochrane RCT classifier, 540 records were screened for relevant reports. After title and abstract screening 39 reports underwent full-text screening. Two studies were excluded, not meeting our predefined criteria, investigating pembrolizumab monotherapy in the palliative first-line setting: Keynote-669 [107] and ELDORANDO [108]. Only one study, Keynote-048 (NCT02358031) was consequently included for further analysis [109-112].

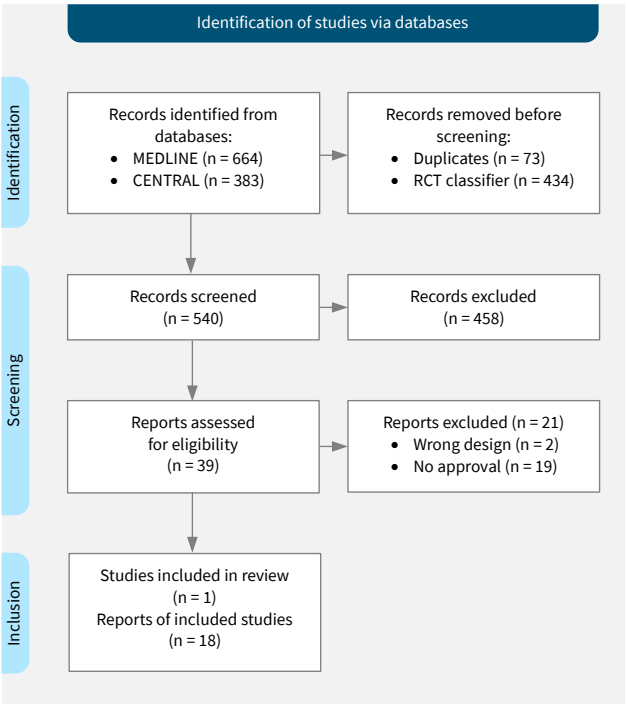


Figure 8. *PRISMA flow diagram: HNSCC*

Included studies and participants

For a detailed description of the study, see the Characteristics of included studies. Here, we provide a brief overview.

Keynote-048 was a phase 3, three-armed, open-label multicentre trial that investigated pembrolizumab monotherapy or pembrolizumab combined with either cisplatin or carboplatin and 5-fluorouracil comparing it to the EXTREME regimen of platinum-chemotherapy combined with 5-fluorouracil and cetuximab. Key eligibility criteria of the study were a primary tumour location of either in the oropharynx, oral cavity, larynx or hypopharynx, an age of 18 years or older, an ECOG performance status of 0 or 1, and adequate organ function. Pateints with progressive disease within six months of curatively intended systemic therapy, need for systemic corticosteroid therapy, untreated or active CNS metastases, an active autoimmune disease, requiring systemic therapy within the last two years, a history of HIV or active hepatitis B or C were excluded.

A total of 882 participants underwent randomisation, stratified based on PD-L1 expression as higher or lower than 50%, their HPV status and performance status. Of those, 301 received pembrolizumab monotherapy, 281 pembrolizumab and chemotherapy, and 300 were allocated to reiceive the standard of care comparator treatment. The median age of participants across treatment arms was 61.3 years, with a female proportion of 16.7%. PD-L1 expression CPS ≥ 1 was equally distributed in intervention and comparator arms, found in approximately 85% of participants. The main tumour location was the oropharynx with 38-40%. HPV p16 positivity was seen in 21-22% of participants and a similar proportion of patients included were never-smokers. No substantial between-group differences in patient characteristics could be noted. Considering that only the pembrolizumab-chemotherapy combination satisfied our inclusion criteria, data extraction solely focused on the comparison of pembrolizumab-chemotherapy to cetuximab-chemotherapy.

The longest median follow-up reported was 45 months for OS and 11.9 months for PFS across treatment arms.

The study was funded by Merck Sharp & Dohme LLC.

Interventions and comparisons

Pembrolizumab was given intravenously at 200mg on day one of each 3 weeks cycle together with cisplatin at 100 mg/m^2 or carboplatin AUC 5 and 5-fluorouracil at 1000 mg/m^2/day continuous infusion from day one to four.
Patients in the comparator arm received the same chemotherapy backbone, but instead of pembrolizumab received cetuximab at 400 mg/m^2 at first dose, followed by 250 mg/m^2 at weekly intervals.

Treatment was planned for a maximum of six cycles, followed by continuation of pembrolizumab for up to 35 cycles. Cetuximab was continued until disease progression or unacceptable toxicity.

Outcomes of interventions

All prespecified outcomes of interest were planned to be assessed in Keynote-048 as primary outcomes (PFS by blinded independent central reivew) or secondary outcomes (OS, safety analysis – adverse events, mean change from baseline GHS/QoL) and reported in different trial publications. Further PRO assessments in Keynote-048 were planned as exploratory outcomes using the PROMs of EORTC QLQ-C30, EQ-5D, and EORTC QLQ-H&N35. Upon a protocol amendment, while the study was ongoing OS was promoted to a co-primary outcome. Another noticeable change was the inclusion of analyses by different PD-L1 expression level subgroups.

Risk of bias

The risk of bias in included studies is summarized in the respective section.

Allocation (selection bias)

Adequate randomisation methods were used in Keynote-048, employing an interactive voice and web response system. No significant differences in participant baseline characteristics were noted that could not be attributable to chance. Therefore, we judged the risk of selection bias to be low.

Blinding (performance bias and detection bias)

In Keynote-048, adequate methods of allocation were used. Bias risk derived from the open-label design was judged as low for the objective outcomes of OS and PFS since radiological response was assessed by a blinded independent central review (BICR). The unblinded study design led to a judgement of high risk of performance and detection bias for quality of life and safety assessment.

Incomplete outcome reporting (attrition bias)

The participant flow was adequately reported in Keynote-048 without suggesting a significant incompleteness of data for safety and survival outcomes. An intention-to-treat analysis was performed; thus, we judged the risk of attrition bias to be low. For quality of life outcomes, although completion rates of questionnaires were similar between the pembrolizumab-chemotherapy and cetuximab-chemotherapy groups at week 15, adherence, while reported as ≥ 79%, it is unclear to what extent non-differential data missingness affected the outcome. Therefore, we assessed the quality of life outcome as unclear regarding attrition bias.

Selective reporting (reporting bias)

The trial protocol was accessible, and the predefined outcomes of interest were adequately reported. However, considering that stratification was based on high vs low PD-L1 expression and analysis based on PD-L1 CPS ≥ 1 was introduced by protocol amendment, it is unclear to which extent these changes resulted from knowledge of the results. Since the proportion of participants with PD-L1 CPS < 1 was relatively small, we judged the risk of reporting bias as unclear.

Effects of interventions

See the summary of findings: Pembrolizumab-based treatment compared to SoC in HNSCC with PD-L1 expression

Overall survival

Pembrolizumab-chemotherapy, compared to cetuximab-chemotherapy in HNSCC with PD-L1 expression (CPS ≥1), likely results in a large increase in overall survival (HR 0.64 [95% CI, 0.53 to 0.78]; 1 study, 477 participants; moderate-certainty evidence; Analysis 3.1.). In absolute terms, this translates to a 15% higher survival at 2 years (25 to 39% more) and 12% more at 3 years (15 to 27% more). The median OS was 6 months longer (3 to 9.4 months more) with the pembrolizumab-based treatment. The moderate certainty resulted from a downgrade for indirectness because 25.2% of the control group received subsequent ICIs upon disease progression, which may have underestimated the effect.

Progression-free survival

Compared to SoC, pembrolizumab-containing treatment may result in little to no difference in progression-free survival (HR 0.82 [95% CI, 0.67 to 1.00]; 1 study, 477 participants; low-certainty evidence; Analysis 3.2.). The low certainty rating resulted from very serious imprecision due to the CI crossing both the null-effect line and the line of appreciable benefit.

Health-related quality of life

Pembrolizumab-chemotherapy likely results in little to no difference in GHS/QoL scores at 15 weeks, compared to cetuximab-chemotherapy (MD 0.4 [95% CI, -3.8 to 4.6]; 1 study, 527 participants; moderate-certainty evidence; Analysis 3.3.). The certainty in the evidence was downgraded due to the open-label trial design and the risk of performance and detection bias.

Adverse events

Pembrolizumab-containing treatment in HNSCC likely results in little to no difference in the number of people experiencing adverse events (CTCAE ≥ 3) compared to SoC (RR 1.02 [95% CI, 0.95 to 1.10]; 1 study, 563 participants; moderate-certainty evidence; Analysis 3.4.). The moderate certainty is due to a downgrade in the risk of detection and performance bias, considering the open-label trial design and subjectivity of the outcome, at least in part.

Evidence discussion

Summary of main results

Pembrolizumab combined with chemotherapy in the palliative first-line setting for HNSCC likely increases overall survival compared to the standard of care of cetuximab combined with chemotherapy in patients eligible for platinum-based chemotherapy with good performance status and organ function. However, the evidence does not indicate any improvement in quality of life or a higher incidence of severe adverse events, for which there is likely little to no difference.

Assessing benefit-harm trade-offs, not assuming differential importance of outcomes, treatment with a pembrolizumab-based regimen is 7.5 times more likely to improve OS at 2 years than cause additional harm in the form of higher-grade AEs compared to standard of care. Considering that there was no statistically significant difference with respect to people experiencing higher-grade AEs, the best-case scenario was not calculable. In the worst-case scenario, treatment with pembrolizumab-chemotherapy is 0.9 times as likely to improve survival than cause additional harm.

The overall certainty of evidence across outcomes was low to moderate, with downgrading due to the risk of performance and detection bias, due to the open-label trial design, imprecision, particularly regarding the outcome of PFS and indirectness, which affected the OS outcome, considering that at least a quarter of

patients in the control arm received ICIs upon disease progression, which, assuming not accessible to the target population within the context of this review, might lead to an underestimation of the effect.

Overall completeness and applicability of evidence

PD-L1 expression and mutational dependence

Study entry in Keynote-048 was possible, irrespective of the tumour's PD-L1 status. Despite the risk of lack of power, the subgroup analysis revealed that patients with CPS < 1 did not profit from a pembrolizumab-based regimen, only reaching statistical significance for OS in the subgroups with CPS 1-19 and ≥ 20 [113]. Consequently, the response to pembrolizumab-based treatments in HNSCC appears to depend on the PD-L1 expression of the tumour. Similar findings, were observed in subgroup analyses of patients receiving pembrolizumab monotherapy, in the second interventional arm of Keynote-048, where a statistically significant survival advantage was only noted patients with a PD-L1 expression of CPS ≥ 20 [113].

Generalisability of data for other patient populations or settings

Apart from the palliative first-line setting, pembrolizumab is approved in HNSCC for patients who progress after platinum-based chemotherapy, i.e. in the second-line of therapy, provided they have a PD-L1 expression of CPS ≥ 50%, following results of Keynote-040 [114]. In the curative setting, together with chemoradiotherapy, pembrolizumab did not reach its primary outcome of event-free survival in Keynote-412 [115]. Eligibility criteria in trials were restrictive, only including participants with good performance status (ECOG 0-1) and relatively few, comorbidities, particularly with regard to preexisting autoimmune diseases or immunodeficiencies. Consenquently, the herein presented findings can only be applied to this subset of patients. However, we did identify a study that was conducted in patients who are cisplatin-ineligible, either due to an ECOG of 2 or GFR of less than 60 mL/min, investigating pembrolizumab monotherapy as a treatment option, for whom no significant differences with respect to OS or PFS were detected, although favouring the intervention with regard to the safety profile [116].

Agreements and disagreements with other studies

Other ICIs and contradictory findings

Since our initial search of the EMA drug register, no new ICIs were approved for HNSCC, excluding nasopharyngeal carcinoma. Apart from pembrolizumab, approvals exist for nivolumab monotherapy in the palliative second-line after progression on platinum-chemotherapy [117]. For nivolumab, approval is however not restricted by PD-L1 expression. Performing a pragmatic search of MEDLINE via PubMed to identify studies of ICI use in the palliative first-line setting of HNSCC that did not lead to regulatory approval, we identified studies comparing nivolumab plus ipilimumab and durvalumab or durvalumab plus tremelimumab to the EXTREME regimen (CheckMate 651 and KESTREL; both phase 3 studies) [118, 119]. In both instances, no statistically significant improvement compared to the treatment standard could be shown with regard to overall survival. Overall, this indicates lack of intra-class interchangeability.

Malignant melanoma

Prioritisation and search results

As of May 2024, we have identified seven EMA approvals for four ICIs concerning the indication of malignant melanoma: ipilimumab, nivolumab, pembrolizumab, and relatlimab. No additional approvals were identified from an update search in January 2025. Of the seven approvals, four approvals were in the palliative first-line setting and met the MCBS ≥ 4 criterion, but only one approval was considered for further systematic review. This was justified in nivolumab and pembrolizumab already being listed on the WHO EML, and ipilimumab having been used as comparator treatment in the studies which the previous listing was based on.

PRIORITISATION

ICI/-combination	Setting	Diagnostic requirement	Treatment details	MCBS-Score	RCT	LTS
Ipilimumab	P1	NR	Monotherapy	4	Yes	✓
Ipilimumab + nivolumab	P1	NR	Ipilimumab + nivolumab	4	Yes	✓
Nivolumab	P1	NR	Monotherapy	4	Yes	✓
Nivolumab	A	NR	Monotherapy	A	Yes	–
Relatlimab + nivolumab	P1	PD-L1 TC < 1%	Relatlimab + nivolumab	3	Yes	–
Pembrolizumab	P1	NR	Monotherapy	4	Yes	✓
Pembrolizumab	A	NR	Monotherapy	A	Yes	–

Reason for exclusion (red colour); LTS – long-term survival benefit as reported by ESMO-MCBS Scorecard based on PFS and/or OS outcomes (not defined as a prioritisation criterion); P1 = palliative first-line, A = adjuvant

For this selection, the comprehensive search strategy has been adopted from the previously mentioned systematic review on ipilimumab plus nivolumab conducted in conjunction with this EML application. The systematic search, using search terms related to ipilimumab and nivolumab, identified 5,013 entries in the CENTRAL and MEDLINE databases as well as the ClincialTrials.gov and WHO ICTRP registries. After deduplication and application of the Cochrane RCT classifier, 2,508 potential records across cancer entities remained. Restricting these results to RCTs in patients with malignant melanoma and applying the full inclusion and exclusion criteria as predefined for this EML application, 47 records of five studies were eligible for inclusion. During the full-text screening, eight studies with results and one ongoing study (SWOG S2000, NCT04511013) were excluded with reasons:

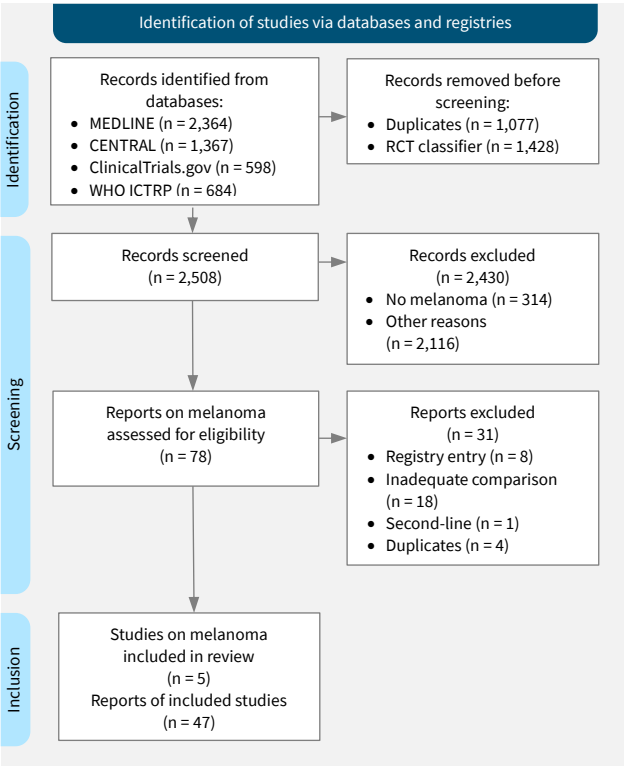


Figure 9. *PRISMA flow diagram: MEL*

- ABC-X (NCT03340129): inadequate comparison (effect of adding concurrent stereotactic radiosurgery investigated)
- CheckMate 038 (NCT01621490): wrong population (patients were pretreated in the metastatic setting)
- CheckMate 511 (NCT02714218): inadequate comparison (dosing trial)
- EBIN (NCT03235245): inadequate comparison (effect of adding encorafenib/binimetinib investigated)
- INITIUM (NCT04382664): inadequate comparison (effect of adding UV1 vaccine investigated)
- NCT02339571: inadequate comparison (effect of adding sargramostim investigated)
- NIBIT-M2 (NCT02460068): inadequate comparison (the chemotherapeutic agent fotemustine is outdated in melanoma treatment)
- RadVax (NCT03646617): inadequate comparison (effect of adding hypofractionated radiation therapy investigated)

Included studies and participants

For a detailed description of the studies, see the Characteristics of included studies. Here, we provide a brief overview.

ABC was a phase 2, open-label, multicentre, two-arm RCT comparing the combination of ipilimumab and nivolumab to nivolumab alone. An additional non-randomised cohort including patients with poor prognostic factors was excluded from this review. Patients were eligible irrespective of PD-L1 and BRAF V600 mutational status, were 18 years or older, had an ECOG performance status of 0 to 2, and had melanoma brain metastases without prior localized treatment for brain metastases. Randomisation was stratified by site [120, 121].

CheckMate 067 was a phase 3, double-blind, multicentre, three-arm RCT comparing the combination of ipilimumab and nivolumab to placebo and individual monotherapy with ipilimumab or nivolumab, respectively. Patients were eligible irrespective of PD-L1 and BRAF V600 mutational status, were aged 18 years or older, had an ECOG performance status of 0 or 1, and had histologically

confirmed unresectable stage III or stage IV melanoma without active brain or leptomeningeal metastases. Randomisation was stratified by BRAF V600 mutational status, metastasis stage and tumour cell PD-L1 expression [122, 123].

CheckMate 069 was a phase 2, double-blind, multicentre, two-arm RCT comparing the combination of ipilimumab and nivolumab to ipilimumab monotherapy and placebo. Patients were eligible irrespective of PD-L1 and BRAF V600 mutational status, were aged 18 years or older, presented with an ECOG performance status of 0 or 1, and had histologically confirmed unresectable stage III or stage IV melanoma without active brain or leptomeningeal metastases. Randomisation was stratified by BRAF V600 mutational status [124, 125].

DREAMseq/EA6134 was a two-stage, phase 3, open-label, multicentre, two-arm RCT determining the optimal sequence of ICI therapy and BRAF/MEK inhibitor therapy. In the first stage, representing the palliative first-line setting, the combination of ipilimumab and nivolumab was compared to dabrafenib and trametinib. BRAF V600 mutation-positive patients with unresectable stage III or stage IV melanoma were eligible irrespective of PD-L1 expression, were 18 years or older, had an ECOG performance status of 0 or 1, and were free from active and definitive CNS metastases. Randomisation was stratified by ECOG performance status and LDH elevation [126, 127].

SECOMBIT was a two-stage, phase 2, open-label, multicentre, non-comparative, three-arm RCT determining the optimal sequence of ICI therapy and BRAF/MEK inhibitor therapy. In the first stage, representing the palliative first-line setting, the combinations of ipilimumab and nivolumab and of encorafenib and binimetinib were investigated. A third arm investigating BRAF/MEK inhibitors followed by ipilimumab/nivolumab in the first-line setting until first progression of disease was excluded because the administration of BRAF/MEK inhibitors and ICIs within one line of therapy was not of interest for this review. BRAF V600-mutated patients with unresectable stage III or stage IV melanoma were eligible irrespective of PD-L1 expression, were aged 18 years or older, had an ECOG performance status of 0 or 1, and were free from active and definitive CNS metastases. Randomisation was stratified by the number of involved tumour sites and LDH elevation [128].

The weighted-adjusted median follow-up across studies was 34.4 months from randomisation.

Across studies, 1,537 patients underwent randomisation, with 639 patients being randomised to the combination of ipilimumab and nivolumab, and 898 patients to one of the control treatment regimens. Of all randomised patients, 346 receiving ipilimumab and nivolumab and 422 receiving standard of care harboured a BRAF V600 mutation. While the ABC trial included patients with asymptomatic melanoma brain metastases (N = 45), the vast majority of patients included in this review were free from melanoma metastases to the central nervous system.

Bristol Myers Squibb, the pharmaceutical company producing ipilimumab and nivolumab, provided funding for all studies. The SECOMBIT trial was additionally supported by grants from Array Biopharma Inc./Pfizer, and in DREAMseq study medications (BRAF/MEK inhibitors) were provided by Novartis.

Interventions and comparisons

Across studies, ipilimumab was administered at a dose of 3 mg/kg and nivolumab at a dose of 1 mg/kg on day one of four three-week cycles. Subsequently, patients received nivolumab 3 mg/kg on day one of two-week cycles. Treatment was continued for a total duration of up to two years of nivolumab administration, until disease progression, the development of unacceptable toxic events, or withdrawal of consent.

The intervention was compared to individual monotherapy with ipilimumab 3 mg/kg on day one of four three-week cycles (CheckMate 067 and CheckMate 069), to individual monotherapy with nivolumab 3 mg/kg on day one of two-week cycles (ABC and CheckMate 067), to the BRAF/MEK inhibitor combination dabrafenib 150 mg twice daily and trametinib 2 mg once daily (DREAMseq), and to the BRAF/MEK inhibitor combination encorafenib 450 mg once daily and binimetinib 45 mg twice daily (SECOMBIT). In the CheckMate 067 and CheckMate 069 trials, patients received matching placebo in addition to ICI monotherapy. Nivolumab was administered for a maximum duration of two years. Treatments were continued until disease progression, the development of unacceptable toxic events, or withdrawal of consent.

Outcomes of interventions

Overall survival was planned and assessed as a primary outcome in CheckMate 067, DREAMseq and SECOMBIT, as a secondary outcome in the ABC trial, and as an exploratory outcome in CheckMate 069. Primary outcomes in the ABC and CheckMate 069 trials were the intracranial response rate in patients with melanoma brain metastases and the objective response rate in BRAF wild-type melanoma patients, respectively. Progression-free survival as determined by investigators was planned and assessed as a primary outcome in CheckMate 067, as a secondary outcome in ABC and DREAMseq, and as an exploratory outcome in SECOMBIT. Progression-free survival, as determined by independent central radiologic review, was assessed as a secondary outcome in CheckMate 069. Quality of life outcomes were planned and assessed as secondary or exploratory outcomes in the trials ABC, CheckMate 067, CheckMate 069 and DREAMseq using the patient-reported outcome measures EORTC QLQ-C30, EORTC QLQ-BN20, EQ-5D and PROMIS-29. Safety outcomes were assessed and reported in all five trials.

Risk of bias

The risk of bias in included studies is summarised in the corresponding section.

Allocation (selection bias)

The randomisation methods used in CheckMate 067, CheckMate 069 and DREAMseq were adequate, using permuted blocks within each stratum implemented by an interactive voice response system or the web-based Oncology Patient Enrolment Network (OPEN), respectively. Patients in SECOMBIT were randomised in a 1:1:1 ratio, but the methods of randomisation and allocation concealment were not further specified. Randomisation was inadequate in the ABC trial due to initial non-random assignment of the first six patients and subsequent randomisation in a 30:24 ratio using the biased coin method. In ABC, the allocation was web-based and concealed from staff, investigators and patients until the initiation of treatment. Baseline characteristics were balanced between the intervention and control groups within trials, except for the ABC trial in which a higher proportion of patients in the intervention group (n = 14, 40%) than in the control group (n = 5, 20%) had more than four brain metastases, and for the SECOMBIT trial in which a slightly higher proportion of patients in the intervention group presented with high-risk characteristics (concretely, elevated LDH levels, M1c staging and higher number of metastatic sites). These considerations prompted us to rate CheckMate 067, CheckMate 069 and DREAMseq at low risk of

selection bias, SECOMBIT at an unclear risk of bias and ABC at a high risk of bias.

Blinding (performance bias and detection bias)

CheckMate 067 and CheckMate 069 were double-blind placebo-controlled trials with blinding of participants, investigators, site staff and the sponsor team and were therefore judged at low risk of performance and detection bias for all outcomes. ABC, DREAMseq and SECOMBIT were open-label trials and were judged at low risk of performance and detection bias for overall survival, for low risk of performance and high risk of detection bias for progression-free survival, and at high risk of performance and detection bias for quality of life and safety outcomes.

Incomplete outcome reporting (attrition bias)

The participant flow in all five trials was reported adequately. Except for the ABC and SECOMBIT trials, all and nearly all randomised patients were included in the survival and safety analyses, respectively. In ABC and SECOMBIT, a modified ITT analysis was conducted, including patients who received at least one dose of the study drug. Risk of attrition bias was rated to be low for survival and safety outcomes in CheckMate 067, CheckMate 069 and DREAMseq, as well as for safety outcomes of ABC and SECOMBIT, and was rated to be unclear for survival outcomes of ABC and SECOMBIT. For the quality-of-life assessment in the CheckMate 067 trial, which was selected for analysis because it was the most comprehensive and had the longest follow-up across included melanoma trials, a completion rate of questionnaires over 50% through week 55 was reported. This raised some concerns, and hence the risk of attrition bias was rated to be unclear.

Selective reporting (reporting bias)

The original trial protocol was accessible for all but the ABC trial. Predefined outcomes of interest were adequately reported in the CheckMate 067, CheckMate 069 and DREAMseq trial publications, leading to a low risk of reporting bias rating in these trials. Although intended according to the protocol, there is no indication of the collection or publication of quality-of-life data in the SECOMBIT trial, leading to an overall rating of unclear reporting bias. Overall progression-free survival (intracranial and/or extracranial) was reported selectively in the ABC trial, resulting in an unclear risk of bias rating.

Effects of interventions

Due to significant heterogeneity of the comparator treatments and participant characteristics across studies, evidence synthesis was split into two parts, and the comparisons of ipilimumab/nivolumab to ICI monotherapy and to BRAF/MEK inhibitors were considered separately. Results for the comparison of ipilimumab/nivolumab to ICI monotherapy are based on the ABC, CheckMate 067, and CheckMate 069 trials, and results for the comparison to BRAF/MEK inhibitors are based on the DREAMseq and SECOMBIT trials.

See the summary of findings: 1) Ipilimumab/nivolumab compared to ICI monotherapy for malignant melanoma, and 2) Ipilimumab/nivolumab compared to BRAF/MEK-inhibitors for BRAF V600-mutant malignant melanoma.

Overall survival

Ipilimumab/nivolumab, compared to individual monotherapy with ipilimumab or nivolumab, likely increases overall survival in malignant melanoma treated in the palliative first-line setting (HR 0.68 [95% CI, 0.50 to 0.93]; 3 studies; 1,133 participants; moderate-certainty evidence; Analysis 4.1.) [120, 122, 124]. In absolute terms, this translates to a survival benefit of 12.1% (2.4% to 20.1% more) at two years and of 14.0% (2.7% to 24.1% more) at five years. CheckMate 067 is listed twice in the forest plot because both the comparison of ipilimumab/nivolumab to ipilimumab monotherapy and to nivolumab monotherapy, respectively, were included. We accounted for double counting of the patients in the intervention group by increasing the standard error of both comparisons [129, 130]. The median overall survival with SoC, weighted across nivolumab and ipilimumab monotherapy, was 28.4 months [122]. Calculating the median overall survival difference using the hazard ratio and baseline risk estimate from the comparator arms led to a 12.8 months (3.9 months to 24.2 months more) survival benefit for patients receiving the intervention. Notably, the median overall survival using the pooled hazard ratio underestimates the actual median overall survival reported in the relevant trial publication [122]. Due to the hazard ratio's wide confidence interval, crossing the defined appreciable effect at 0.75, we downgraded for imprecision. Moderate heterogeneity (I^2 = 58%, P = 0.07) was observed which can be explained through the inclusion of two different ICI monotherapies as SoC therapy.

The evidence is very uncertain about the effect of ipilimumab/nivolumab compared to BRAF/MEK inhibitors on overall survival in BRAF V600-mutant malignant melanoma in the palliative first-line setting (HR 0.73 [95% CI, 0.42 to 1.27]; 1 study; 138 participants; very low-certainty evidence; Analysis 4.2.) [128]. In absolute terms, this corresponds to a survival benefit of 8.0% (7.1% fewer to 18.4% more) at two years and of 9.8% (8.3% fewer to 23.2% more) at three years. The median overall survival was reached neither in the control nor intervention group and therefore no difference in the median overall survival could be calculated. Given that the study design included a planned cross-over of the control group patients to ipilimumab/nivolumab in case of disease progression, and 36 of 69 (52.2%) patients actually having received subsequent ICIs, we downgraded for indirectness because the effect of ipilimumab/nivolumab was potentially underestimated. Further, a downgrade by two levels was justified because of the small number of events and the wide confidence interval crossing both the line of appreciable benefit and appreciable harm.

Progression-free survival

Ipilimumab/nivolumab, compared to individual monotherapy with ipilimumab or nivolumab, may increase progression-free survival in melanoma patients treated in the first-line setting (HR 0.50 [95% CI, 0.31 to 0.82]; 2 studies; 1,087 participants; low-certainty evidence; Analysis 4.3.) [122, 124]. After two years of follow-up this results in a progression-free survival advantage of 25.0% (7.0% to 40.3% more). The certainty of the evidence was each downgraded by one level for imprecision, as the confidence interval crosses the line of defined appreciable benefit at 0.75, and for inconsistency, as considerable heterogeneity was observed which likely results from the inclusion of different comparator treatment regimens (I^2 = 88%, P = 0.0003).

In both trials investigating the optimal sequence of ipilimumab/nivolumab and BRAF/MEK inhibitors, no comparative results were reported for progression-free survival. The pooled two-year survival rates, as assessed by investigators who were aware of the intervention, based on two studies including 403 participants were 40.1% with ipilimumab/nivolumab and 23.9% with BRAF/MEK inhibitors [126, 128]. The evidence is very uncertain about the intervention's effect on progression-free survival because the point estimates in the narrative synthesis are not precise, there was risk of performance and detection bias due to the trials' open-label design, and inconsistency was observed in the two-year progression-free survival rates between trials.

Health-related quality of life

Quality of life outcomes were planned and assessed as secondary or exploratory outcomes in the trials ABC, CheckMate 067, CheckMate 069 and DREAMseq using the patient-reported outcome measures EORTC QLQ-C30, EORTC QLQ-BN20, EQ-5D, and PROMIS-29. Nevertheless, quality of life data from different RCTs could not be pooled due to insufficient reporting, heterogeneity of utilised measurement instruments and remarkable differences in the length of observation across trials. Herein, EORTC QLQ-C30 results from CheckMate 067 were the most comprehensive and, therefore, used for analysis. The questionnaire was administered at weeks 1 and 5 of each six-week cycle for the first six months and once every six weeks thereafter. Completion rates were ≥ 50% at any assessment. Of the 945 patients included in survival analysis, 758 patients were also available for global quality of life analysis. Approximately 55 weeks from baseline, i.e., 43 weeks after completion of protocol-compliant ipilimumab therapy and during nivolumab maintenance therapy, the difference in global health score/quality of life (GHS/QoL) between ipilimumab/nivolumab and ICI monotherapy using least-squares mean change scores did not cross the threshold of minimal clinically important difference of 10 (MD −1.08 [95% CI, −3.44 to 1.28]); Analysis 4.4.) [123]. Two studies with smaller sample sizes and shorter follow-up, also utilising EORTC QLQ-C30 support this finding [121, 125]. Accordingly, ipilimumab/nivolumab likely preserves GHS/QoL in patients with malignant melanoma. The evidence was rated to be of moderate certainty, considering the risk of attrition bias from moderate to low questionnaire completion rates.

Adverse events

Since adverse events of any cause could not be meta-analysed for melanoma, we had to rely on treatment-related adverse events. Ipilimumab/nivolumab, compared to ICI monotherapy with ipilimumab or nivolumab, results in a large increase in adverse events graded as CTCAE ≥ 3 in patients with malignant melanoma treated in the first-line setting (RR 2.37 [95% CI, 2.03 to 2.77]; 3 studies; 1,137 participants; high-certainty evidence; Analysis 4.5.) [120, 122, 124]. The baseline risk for adverse events with one of the comparator ICI monotherapies was 24.9%. Adverse events were encountered by 34.1% more (25.6% to 44.1% more) participants treated with ipilimumab/nivolumab.

Ipilimumab/nivolumab, compared to BRAF/MEK inhibitors, may slightly increase adverse events graded as CTCAE ≥ 3 in patients with BRAF V600-mutant malignant melanoma treated in the first-line setting (RR 1.26 [95% CI, 0.94 to 1.69]; 2 studies; 394 participants; low-certainty evidence; Analysis 4.6.) [126, 128]. The baseline risk for adverse events with BRAF/MEK inhibitors was 48.2%. Adverse events were encountered by 12.5% more (2.9% fewer to 33.3% more) participants treated with ipilimumab/nivolumab.

Evidence discussion

Summary of main results

When compared to ICI monotherapy with ipilimumab or nivolumab, respectively, the combination of ipilimumab/nivolumab shows promising results in the treatment of patients with malignant melanoma treated in the palliative first-line setting, based on the three presented trials. The ICI doublet likely increases overall survival, probably increases progression-free survival, and likely maintains quality of life. However, the ICI doublet results in a large increase in adverse events of CTCAE grade ≥ 3 compared to ICI monotherapy. In absolute terms, combining the ICIs ipilimumab and nivolumab for the treatment of malignant melanoma is 2.0 times (worst case scenario: 10 times; best case scenario: 0.3 times) more likely to cause additional harm in the form of adverse events of CTCAE grade ≥ 3 than to lead to a survival benefit (12.1% at two years) when compared to ICI monotherapy (NNT/NNH ratio; not assuming differential outcome importance).

The evidence is uncertain about the effect of ipilimumab/nivolumab on outcomes in BRAF V600-mutant melanoma patients compared to BRAF/MEK inhibitors in the palliative first-line setting, based on the two presented studies. It may increase overall survival and progression free survival, but the evidence on survival outcomes is very uncertain, and adverse events of CTCAE grade ≥ 3 may be encountered slightly more often. In absolute terms, administering ipilimumab/nivolumab in the treatment of BRAF V600-mutant melanoma is 1.7 times more likely (no meaningful worst and best case scenarios could be calculated because of negative NNT and positive NNH, and vice versa) to cause additional harm in the form of adverse events of CTCAE grade ≥ 3 than leading to a survival benefit (8.0% at two years) when compared to BRAF/MEK inhibitor therapy (NNT/NNH ratio; not assuming differential outcome importance).

Quality of evidence

For the comparison with ICI monotherapy, we rated the certainty of evidence as low to high, depending on the respective outcome. Reasons for downgrading were imprecision and inconsistency due to heterogeneity of the comparator treatments (ipilimumab or nivolumab monotherapy) as well as risk of attrition bias for GHS/QoL.

For the comparison with BRAF/MEK inhibitors we rated the certainty of evidence as very low to low. Reasons for downgrading included imprecision, risk of performance and detection bias due to the open-label design of the trials, and inconsistency of results. Moreover, we downgraded for indirectness, recognising the cross-over of patients with progressive disease after BRAF/MEK inhibitors to the intervention treatment, and the review's target population to whom the ICI doublet ipilimumab/nivolumab was presumed to be unavailable.

Overall completeness and applicability of evidence

PD-L1 expression and mutational dependence

There is no requirement for a specific PD-L1 expression or presence of a certain mutation in the population of interest (i.e., advanced or metastatic malignant melanoma) resulting from the EMA approval of ipilimumab/nivolumab for melanoma or our prioritisation framework. PD-L1 expression and BRAF V600-mutational status were investigated as prognostic markers in the RCTs included in this review, not suggesting the restriction to certain subgroups.

Generalizability of data for other patient populations or settings

The approval of ipilimumab for melanoma in 2011 marked the first approval of an ICI for an oncologic indication. Hence, with regard to ICIs, particularly ipilimumab and nivolumab, both as monotherapy and in combination, malignant melanoma is a highly studied entity with a substantial body of research. Nevertheless, since this review is limited to RCTs, we did not search for real-world evidence or non-randomised clinical trials assessing the drugs' safety and efficacy in other patient populations or settings. The ICI doublet is not approved by EMA for palliative second- or later lines of therapy or, unlike nivolumab monotherapy, for the adjuvant treatment of completely resected melanoma. As a consequence, the applicability of the evidence provided herein is confined to preselected subset of patients treated in the palliative first-line setting with good performance status (ECOG 0–1) and relatively few comorbidities, particularly no systemic autoimmune diseases

requiring treatment. Notably, results from the ABC, and additionally from the NIBIT-M2 trial which was excluded from this review due to the utilisation of an outdated comparator (fotemustine), indicate safety and efficacy of ipilimumab/ nivolumab in patients with asymptomatic melanoma brain metastases [120, 131].

AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEWS

Other ICIs and contradictory findings

Since the initial EMA register search, no further ICIs for the indication of malignant melanoma were approved for the palliative first-line or any other setting. As of January 2025, four ICIs held approval for melanoma treatment (ipilimumab, nivolumab, pembrolizumab and relatlimab). Performing a pragmatic search of MEDLINE via PubMed, one RCT of an ICI which is currently not EMA approved could be identified that compared the ICI-based treatment regimen to established SoC in the palliative first-line setting. In the phase 3 study (NCT00257205) patients with treatment-naive, unresectable stage IIIc or IV melanoma were randomly assigned to receive tremelimumab (15 mg/kg once every 90 days) or physician's choice of SoC chemotherapy (temozolomide or dacarbazine). Tremelimumab did not lead to a statistically significant survival benefit, but increased adverse events in patients with advanced melanoma.

Biliary tract cancer

Prioritisation and search results

Our search identified two EMA approvals for two ICIs concerning the indication of biliary tract carcinoma: durvalumab and pembrolizumab, both approved for the palliative first-line setting. Only one, durvalumab, showed a MCSB of 4 and was considered for systematic review, while pembrolizumab was rated with a MCBS of 1 and was thus excluded from our evaluation.

Durvalumab was approved in combination with chemotherapy in form of cisplatin and gemcitabine.

PRIORITISATION

ICI/-combination	Setting	Diagnostic requirement	Treatment details	MCBS-Score	RCT	LTS
Durvalumab	P1	NR	Durvalumab + CTx	4	Yes	-
Pembrolizumab	P1	NR	Pembrolizumab + CTx	1	Yes	–

Reason for exclusion (red colour); LTS – long-term survival benefit as reported by ESMO-MCBS Scorecard based on PFS and/or OS outcomes (not defined as a prioritisation criterion)

Based on the prespecified selection process, a search strategy including search terms for durvalumab and biliary tract carcinoma was developed. The search identified 930 records in the CENTRAL and MEDLINE databases (search date: 26/07/2024). Deduplication and application of the Cochrane RCT classifier resulted in 502 potentially eligible hits. Of these, 458 were excluded during title and abstract screening, and an additional number of 25 reports during full-text screening. The 20 remaining reports all addressed the trial TOPAZ-1 (NCT03875235) [132, 133].

Included studies and participants

For a detailed description of the study, see the Characteristics of included studies. Here, we provide a brief overview.

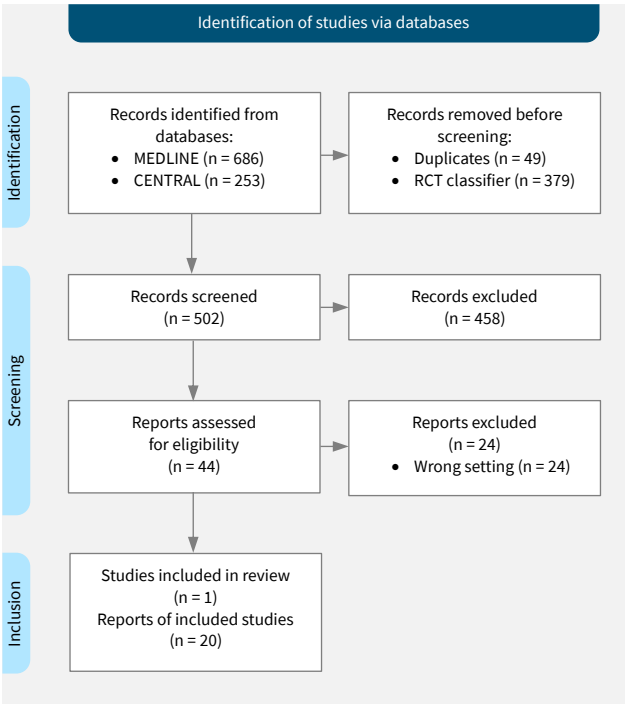


Figure 10. *PRISMA flow diagram: BTC*

TOPAZ-1 was a phase 3, double-blind, multicentre RCT comparing the combination of durvalumab with gemcitabine and cisplatin to placebo, gemcitabine and cisplatin. Eligible individuals were 18 years or older and suffered from histologically confirmed unresectable advanced or metastatic biliary tract cancer, including cholangiocarcinoma and gallbladder carcinoma. Participants had unresectable or metastatic disease at their initial diagnosis or recurrent disease at over 6 months after surgery with curative attempt or completion of adjuvant chemo and/or radiotherapy. Further criteria for inclusion were an ECOG performance status of 0 or 1.

Overall, 685 patients underwent randomization. Of those, 341 were allocated to the experimental treatment and 344 to control treatment. No substantial between-group differences were reported, with a median age of participant of 64 years and a proportion of 49.6% of female participants. Most participants (56%) suffered from intrahepatic cholangiocarcinoma, had initially unresectable disease (80%) as compared to recurrent disease (20%), and had metastatic disease (86%) as compared to locally advanced disease (14%). The long term survivors analysis set included 88 participants initially allocated to the experimental group and 65 individuals initially allocated to the comparator group and also included a majority of participants with initially unresectable disease (63%) in difference to initially recurrent disease (38%), and had initially metastatic disease (84%) as compared to locally advanced disease (16%).

The longest median follow-up reported was 16.8 months (95% CI, 14.8 to 17.7) in the durvalumab group and 15.9 months (95% CI, 14.9 to 16.9) in the control group.

AstraZeneca funded the trial.

Interventions and comparisons

Durvalumab was administered intravenously at a dose of 1500mg in combination with gemcitabine at 1000 mg/m^2 and cisplatin at 25 mg/m^2 body-surface area on day one of eight 21-day cycles. Durvalumab was administered on day one and the chemotherapy agents at day one and eight. Patients who were allocated to the comparator treatment followed the same schedule and drug regimen, but instead of durvalumab received placebo infusions. After completion of gemcitabine and cisplatin, 1500 mg of durvalumab or placebo monotherapy was administered once every four weeks.

Outcomes of interventions

The prespecified primary outcome of TOPAZ-1 was overall survival. Secondary outcomes included progression-free survival, the overall response rate and the duration of response. Participant reported outcomes, in particular quality of life outcomes, were published separately.

Risk of bias

The risk of bias in included studies is summarized in the respective section.

Allocation (selection bias)

Randomization in TOPAZ-1 was performed centrally based on an interactive voice and web response system and adequately concealed. No notable baseline and post-baseline imbalances not attributable to chance were reported for the overall population so that we rated the risk of selection bias as low.

Blinding (performance bias and detection bias)

The trial was performed in a double-blind fashion, with placebo for the active agent in the control arm. As investigators and patients were masked to study treatment, we rated the risk of performance and detection bias as low.

Incomplete outcome reporting (attrition bias)

The participant flow in TOPAZ-1 was reported adequately. A large proportion of participants was included in the efficacy analysis, with less than 6% of individuals discontinuing the study for patient related reasons. This happened balanced between arms. For the safety analyses, a large proportion of the full analysis set was available. We rated the risk of attrition bias for these outcomes as low. Since a considerable number of individuals was not included in the quality of life analysis set, we rated the risk of attrition bias for this outcome as high.

Selective reporting (reporting bias)

The trial protocol was accessible and the predefined outcomes of interest were adequately reported so that we rated the study as having a low risk of reporting bias.

Effects of interventions

See summary of findings: Durvalumab-based treatment regimen compared to SoC for biliary tract cancer

Overall survival

The durvalumab-based treatment regimen, compared to chemotherapy only in biliary tract carcinoma treated in the palliative first-line setting, likely leads to a slight improvement in overall survival (HR 0.76 [95% CI, 0.63 to 0.91]; 1 study; 685 participants; moderate-certainty evidence; Analysis 7.1). In absolute terms, this translates to a survival benefit of 9.4% (3.3% to 14.8% more) and 9.8% (3.3% to 16.1% more) at 12 and 18 months, respectively. Median overall survival with chemotherapy alone was 11.3 months. Calculating the median overall survival difference using the hazard ratio and baseline risk estimate from the comparator arm led to a 3.6 months (1.1 to 6.4 more) survival benefit for patients receiving the intervention.
Because the relative effect estimates confidence interval crossed the line of an appreciable benefit (75%) and the evidence consisted of a single trial only, we downgraded the overall evidence for imprecision. Overall, a relatively small proportion of 7% of control participants who experienced disease progression subsequently received ICIs.

Progression-free survival

Compared to SoC, the durvalumab-based treatment strategy likely results in an increase in progression-free survival (HR 0.75 [95% CI, 0.63 to 0.89]; 1 study; 685 participants; moderate-certainty evidence; Analysis 7.2). At one year follow-up, this leads to a progression-free survival advantage of 6.1% (2.2% to 11.0% more). Given that the relative effect crossed the defined line of appreciable benefit and because the evidence consisted of a single trial only, we downgraded the evidence for imprecision.

Health-related quality of life

Quality of life was assessed using the EORTC QLQ-C30 checklist at different intervals. Of the 685 patients included in survival analyses, 646 were evaluated in the global quality of life outcome analysis. At a median of 9.9 months from baseline, the difference in global health score/quality of life (GHS/QoL) from baseline using least-squares mean change scores was comparable between the intervention group and the group with chemotherapy alone (MD 0.88 [95% CI, 1.8 fewer to 3.65], Analysis 7.3). Durvalumab-based treatment may result in little to no difference in GHS/QoL in biliary tract carcinoma patients. Due to the proportion of individuals excluded from the quality-of-life analysis, we downgraded the certainty of evidence for attrition bias resulting in a moderate-certainty evidence rating.

Adverse events

Adverse events graded as CTCAE ≥ 3 were reported for 680 of 685 participants included in the TOPAZ-1 trial and were encountered by 1.6% fewer (7.1 fewer to 4.8 more) receiving chemotherapy plus durvalumab as opposed to chemotherapy without ICI (RR 0.98 [95% CI, 0.91 to 1.06]; 1 study, 680 participants; low-certainty evidence; Analysis 7.4). The baseline risk of adverse events with the comparator treatment was 79.2%. We did not downgrade our certainty in this outcome. In effect, the durvalumab-based treatment strategy likely results in little to no difference in adverse events of CTACE grade 3 or higher as compared to chemotherapy alone in individuals with biliary tract carcinoma.

Evidence discussion

Summary of main results

When compared to chemotherapy alone, the combination of durvalumab with gemcitabine and cisplatin shows a slight increase in overall survival, based on a single study with 685 participants. However, the evidence does not indicate any substantial improvements with regard to quality of life or adverse events of CTCAE grade ≥ 3.

In balancing benefits and harm, only the worst-case scenario was calculable, since higher-grade AEs did not reach a statistically significant difference, with both base-case and best-case scenarios suggesting an overall improvement. In the worst-case scenario durvalumab-based treatment would be 0.6 times as likely to result in survival improvement at one year than additional occurrence of higher-grade adverse events (NNT/NNH ratio; not assuming differential outcome importance).

Quality of evidence

We rated the certainty of evidence as moderate to high. Reasons for downgrading mainly included concerns over imprecision.
About 7% of individuals initially allocated to the control group received ICIs in the course of the study.

Overall completeness and applicability of evidence

PD-L1 expression and mutational dependence

Participants were enrolled in the TOPAZ-1 trials irrespective of the PD-L1 expression-level of their biliary tract carcinomas. Also, the EMAs approval of the drug in the here addressed palliative first-line setting is independent of the PD-L1 expression of the target tumors. TOPAZ-1 reports consistent findings for overall survival across the assessed patient subgroups, including patients with

tumors high >1% PD-L1 tumor area expression as well as with low (<1%) PD-L1 expression.

Generalizability of data for other patient populations or settings

Apart from TOPAZ-1, we did not identify published RCTs investigating the use of durvalumab in biliary tract carcinoma.
Since our review is limited to RCTs, we did not search for real-world evidence nor non-randomised clinical studies assessing the drug's safety and efficacy in other patient populations. Consequently, the applicability of the evidence provided herein is confined to a preselected subset of patients with good performance statuses (ECOG 0-1) who have relatively few comorbidities.

Agreements and disagreements with other studies

Other ICIs and contradictory findings

Pembrolizumab is another ICI approved for the treatment of biliary tract carcinoma. In difference to durvalumab, pembrolizumab, received an MCBS-Score of 1 and was therefore formally excluded from this application which defined an MCBS score of 3 or high for eligibility. The Keynote-966 trial, which compared treatment with pembrolizumab in combination with gemcitabine and cisplatin with gemcitabine and cisplatin alone for individuals with advanced biliary tract carcinoma, also points towards slight improvements in overall survival and progression-free survival with ICI based treatment with comparable rates of adverse events [134].

Yet, the shown benefits are lesser than in the here discussed TOPAZ-1 trial comparing durvalumab. Longer term follow-up results from the trial are currently only published in abstract form but indicate that the benefits with pembrolizumab are sustained at a similar level as the primary analysis underlying the MCSB rating of 1 [135].

Oesophageal squamous cell carcinoma

Prioritisation and search results

As of May 2024, we have identified seven EMA approvals for four ICIs concerning the indication of oesophageal squamous cell carcinoma (OESCC): ipilimumab, nivolumab, pembrolizumab, and tislelizumab. Two additional approvals were identified from an update search in January 2025: toripalimab and an extension of the indication for tislelizumab. Of the five EMA approvals initially identified, three approvals were in the palliative first-line setting and met the ESMO MCBS ≥ 4 criterion, and were therefore considered for further systematic review.

PRIORITISATION

ICI/-combination	Setting	Diagnostic requirement	Treatment details	MCBS-Score	RCT	LTS
Ipilimumab + nivolumab	P1	PD-L1 ≥ 1%	Ipilimumab + nivolumab	4	Yes	–
Nivolumab	P1	PD-L1 ≥ 1%	Nivolumab + CTx	4	Yes	–
Nivolumab	P2	NR	Monotherapy	3	Yes	–
Pembrolizumab	P1	PD-L1 CPS ≥ 10	Pembrolizumab + CTx	4	Yes	–
Tislelizumab	P2	NR	Monotherapy	4	Yes	–

Reason for exclusion (red colour); LTS – long-term survival benefit as reported by ESMO-MCBS Scorecard based on PFS and/or OS outcomes (not defined as a prioritisation criterion)**;** P1 = palliative first-line, P2 = palliative second-line; A = adjuvant

Based on this prioritisation, a search strategy combining the PICO for oesophageal squamous cell carcinoma with the PICO for gastric, gastro-oesophageal junction and oesophageal adenocarcinoma was developed. Reports pertaining to ipilimumab plus nivolumab were identified via the concurrently performed systematic review (PROSPERO: CRD42024548061). The search in the MEDLINE and CENTRAL databases yielded 1,589 entries. After deduplication and application of the Cochrane RCT classifier 772 records were screened, and ultimately 27 reports of two studies were eligible for inclusion. Figure **11** depicts the PRISMA diagram of information flow in the screening and selection process. One study was excluded with reasons:

- CRUCIAL (NCT03437200): Inadequate comparison (nivolumab combined with chemoradation is no established standard of care for the population of interest) and the study was terminated early

Included studies and participants

For a detailed description of the study, see the Characteristics of included studies. Here, we provide a brief overview.

Keynote-590 was a phase 3, double-blind, placebo-controlled, two-arm RCT comparing pembrolizumab combined with chemotherapy to placebo plus chemotherapy in patients with advanced oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer. Our analyses were restricted to the subgroup of patients with OESCC. Patients were eligible regardless of PD-L1 expression, were aged 18 years or older, had measurable disease per RECIST version 1.1, and presented with an ECOG performance status of 0 or 1. Randomisation was stratified by geographical region (Asia vs. non-Asia), histology (OESCC vs. adenocarcinoma), and performance status. For this review, only the subgroup of OESCC patients with PD-L1 expression CPS ≥ 10 was relevant considering the prioritisation framework. The longest median follow-up reported was 22.6 months from randomisation across treatment arms.

Overall, 749 patients underwent randomisation in Keynote-590, with 373 patients being randomised to pembrolizumab plus chemotherapy and 376 patients to placebo plus chemotherapy. Of those, 143 patients in each group had OESCC with a PD-L1 expression of CPS ≥ 10. Baseline characteristics were not reported separately for the OESCC PD-L1 CPS ≥ 10 population, but were generally well balanced in the ITT population.

CheckMate 648 was a phase 3, open-label, multicentre, three-arm RCT comparing ipilimumab/nivolumab and nivolumab plus chemotherapy, respectively, with chemotherapy alone. Patients had unresectable, advanced, recurrent or metastatic histologically confirmed OESCC or oesophageal adenosquamous cell carcinoma, were eligible regardless of PD-L1 expression, were at least 18 years old, and presented with an ECOG performance status of 0 or 1. Stratification of patients into respective arms was based on their tumour cell PD-L1 expression status (≥ 1% vs. < 1% or indeterminate), region (East Asia vs. rest of Asia vs. rest of the world), ECOG performance status and number of organs with metastases (≤1 vs. ≥2). For this review, only the subgroup of patients with PD-L1 expression ≥ 1% in the CheckMate 648 trial was relevant considering the prioritisation framework. The longest median follow-up reported was 39.6 months from randomisation across treatment arms.

Overall, 970 patients underwent randomisation in CheckMate 648, with 321 patients being randomised to nivolumab plus chemotherapy, 325 patients to ipilimumab/nivolumab, and 324 patients to chemotherapy alone. Of those, 158 patients receiving nivolumab plus chemotherapy, 158 patients receiving ipilimumab/nivolumab, and 156 patients receiving chemotherapy alone had a tumour cell PD-L1 expression ≥ 1%. Notably, the percentage of patients with PD-L1 TC ≥ 1% who had metastatic disease in the nivolumab plus chemotherapy group was 14% and 11% higher than in the ipilimumab/nivolumab and chemotherapy alone group, respectively. However, no substantial between-group differences were reported and all other reported baseline characteristics were well balanced across treatment arms.

MSD, a subsidiary of Merck, the pharmaceutical company producing pembrolizumab, funded the Keynote-590 trial, and Bristol Myers Squibb, in collaboration with Ono Pharmaceutical, the pharmaceutical companies producing ipilimumab and nivolumab, funded the CheckMate 648 trial.

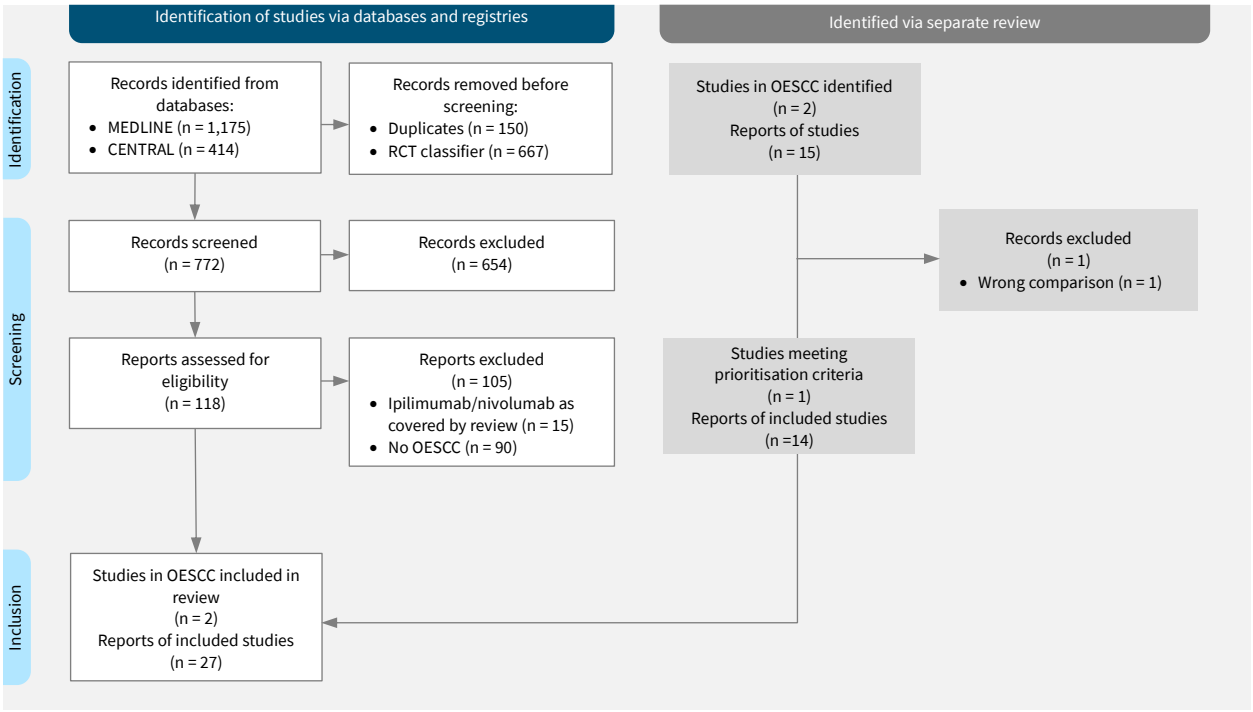


Figure 11. PRISMA flow diagram: OESCC

Interventions and comparisons

Pembrolizumab was administered at a dose of 200 mg on day one of three-week cycles combined with 5-fluorouracil 800 mg/m^2/ day on days one through five and cisplatin 80 mg/m^2 on day one (for a maximum of six cycles) of three-week cycles in Keynote-590. Treatment was continued until completion of 35 cycles, disease progression, unacceptable toxicity, illness, physician's or patient's decision to withdraw, non-compliance or complete response.

The nivolumab-based treatment regimen in CheckMate 648 consisted of nivolumab 240 mg on day one of two-week cycles for up to two years in combination with fluorouracil 800 mg/m^2/day on days one through five and cisplatin 80 mg/m^2 on day one of four-week cycles. Treatment was continued until progression, unacceptable toxicity or withdrawal of consent.

Subjects allocated to ipilimumab/nivolumab in CheckMate 648 received ipilimumab at dose of 1 mg/kg on day one of six-week cycles combined with nivolumab at a dose of 3 mg/kg on day one of two-week cycles. Treatment continued for up to two years, disease progression, unacceptable toxicity or withdrawal of consent.

Patients allocated to the comparator group in the Keynote-590 trial received the same platinum-based chemotherapy regimen as the intervention group, but instead of the experimental agent pembrolizumab they received saline placebo.

Outcomes of interventions

Overall survival and progression free-survival were planned and assessed as primary efficacy outcomes in Keynote-590 and CheckMate 648. In both trials, progression-free survival was planned to be assessed by blinded independent central review, but was changed to investigator-assessed in the double-blind Keynote-590 trial because of higher than expected discordance which led to a higher than expected censoring of progression-free survival events. In Keynote-590, quality of life was assessed as a secondary efficacy outcome using the EORTC QLQ-C30 and the EORTC oesophageal module QLQ-OES18, and was assessed as an exploratory outcome using EQ-5D. In CheckMate 648, quality of life was evaluated as an exploratory outcome using the disease-specific questionnaire FACT-Esophageal (FACT-E) and EQ-5D. Safety outcomes were assessed in both trials.

Risk of bias

The risk of bias in included studies is summarised in the corresponding section.

Allocation (selection bias)

The randomisation method used in Keynote-590 was adequate and relied on an interactive voice response system. Baseline characteristics were not reported separately for the OESCC PD-L1 CPS ≥ 10 population, but were generally well balanced in the ITT population.

The randomisation method used in CheckMate 648 was adequate and relied on web-based interactive response technology. No notable imbalances in the baseline characteristics were reported in the overall population. However, in the PD-L1 ≥ subgroup, the percentage of patients with metastatic disease at trial entry was higher and the percentage of patients with distant recurrent disease was lower in the nivolumab plus chemotherapy arm, while this distribution was reversed in the ipilimumab/ nivolumab and chemotherapy only arms.

Blinding (performance bias and detection bias)

Keynote-590 was a double-blind, placebo-controlled trial in which patients, investigators, and site staff were masked to group assignment and PD-L1 biomarker status. Therefore, the trial was judged to be at low risk of performance and detection bias for all outcomes.

CheckMate 648 was an open-label trial that used blinded independent central review for the assessment of progression-free survival. Therefore, the trial was judged to be at low risk of performance and detection bias for overall survival and

progression-free survival, and to be at high risk of performance and detection bias for adverse events and health-related quality of life.

Incomplete outcome reporting (attrition bias)

The participant flow was reported adequately in both trials. All and nearly all randomised patients were included in the survival and safety analyses, respectively. Risk of attrition bias was rated to be high in Keynote-590 because approximately 10% of patients in each arm left the study based on the patient's or physician's decision. For the quality of life assessment, completion rates were high (≥ 97%) up to week 18, but decreased thereafter. As analyses were limited to week 18, no further downgrade for attrition was justified for the outcome quality of life.

Risk of attrition bias was rated to be unclear in CheckMate 648 because drop-out was unbalanced and at medium level for the chemotherapy only arm due to a higher percentage of patients withdrawing consent (ipilimumab/nivolumab 0.9%; nivolumab plus chemotherapy 3.4%; chemotherapy only 6.2%). Completion rates of the FACT-E questionnaire were not reported in detail in the CheckMate 648 trial, but 90% of patients completed at least the baseline and one follow-up questionnaire, and were included in the patient-reported outcome analysis population. We judged a high risk of bias rating not to be warranted.

Selective reporting (reporting bias)

In absence of the first version of the Keynote-590 trial protocol, there was high risk of reporting bias, considering multiple changes of the outcomes and analysis populations. All outcomes that are relevant for this review were reported, but the ClinicalTrials.gov record history suggests that the OESCC PD-L1 CPS ≥ 10 subgroup has not been prespecified.

The original trial protocol was accessible for CheckMate 648, and predefined outcomes of interest were adequately reported. Hence, we rated the trial to be at low risk of reporting bias.

Effects of interventions

See summary of findings: Pembrolizumab-based treatment regimens compared to SoC for OESCC with PD-L1 CPS ≥ 10; Nivolumab-based treatment regimens compared to SoC for OESCC with PD-L1 ≥ 1% expression; Ipilimumab/nivolumab compared to SoC for OESCC with PD-L1 ≥ 1% expression.

Overall survival

Pembrolizumab-based regimens, compared to platinum-based doublet chemotherapy, may increase overall survival in patients with unresectable advanced or metastatic OESCC with PD-L1 CPS ≥ 10 treated in the palliative first-line setting (HR 0.57 [95% CI, 0.43 to 0.75]; 1 study; 286 participants; low-certainty evidence; Analysis 8.1.). In absolute terms, this translates to a survival benefit of 18.9% more (9.1% to 29.2% more) at two years. The median overall survival in the control group with chemotherapy alone was 8.8 months [136]. Calculating the median overall survival difference using the hazard ratio and baseline risk estimate from the comparator arm led to a 6.6 months (2.9 months to 11.7 months more) survival benefit for patients receiving the intervention. There was serious risk of attrition bias because approximately 10% of patients left the study because of patient or physician decision in each arm and risk of type II error due to the low sample size. Hence, we downgraded for risk of bias and imprecision considering the wide confidence interval crossing the line of appreciable benefit at 0.75.

Nivolumab-based regimens, compared to platinum-based doublet chemotherapy, may increase overall survival in patients with unresectable advanced or metastatic OESCC with a tumour cell PD-L1 expression ≥ 1% treated in the palliative first-line setting (HR 0.59 [95% CI, 0.46 to 0.76]; 1 study; 315 participants; low-certainty evidence; Analysis 8.2.). In absolute terms, this translates to a survival benefit of 16.6% more (8.0% to 25.7% more) at two years and 15.7% more (7.4% to 24.7% more) at three years, respectively. The median overall survival in the control group with chemotherapy alone was 9.1 months [137]. Calculating the median overall survival difference using the hazard ratio and baseline risk estimate from the comparator arm led to a 6.3 months (2.9 months to 10.7 months more) survival benefit for patients receiving the intervention. Considering that 15.9% of all randomised control group patients who experienced disease progression subsequently received ICIs, which could lead to an underestimation of the effect, and the suggested imbalance in trial withdrawals due to deviations from the intended treatment in the open-label design, a downgrade by one level in total for indirectness and risk of bias was justified. We downgraded for imprecision for the risk of type II error due to the low sample size and a wide confidence interval that crosses the line of appreciable benefit at 0.75.

Ipilimumab/nivolumab, compared to platinum-based doublet chemotherapy, may increase overall survival in patients with unresectable advanced or metastatic OESCC with a tumour cell PD-L1 expression ≥ 1% treated in the palliative first-line setting (HR 0.62 [95% CI, 0.48 to 0.80]; 1 study; 315 participants; low-certainty evidence; Analysis 8.3.). In absolute terms, this translates to a survival benefit of 14.9% more (6.3% to 24.1% more) at two years and 14.0% more (5.8% to 23.1% more) at three years, respectively. The median overall survival in the control group with chemotherapy alone was 9.1 months [137]. Calculating the median overall survival difference using the hazard ratio and baseline risk estimate from the comparator arm led to a 5.6 months (3.7 months to 9.0 months more) survival benefit for patients receiving the intervention. Considering that 15.9% of all randomised control group patients who experienced disease progression subsequently received ICIs, which could lead to an underestimation of the effect, and the suggested imbalance in trial withdrawals due to deviations from the intended treatment in the open-label design, a downgrade by one level in total for indirectness and risk of bias was justified. We downgraded for imprecision for the risk of type II error due to the low sample size and a wide confidence interval that crosses the line of appreciable benefit at 0.75.

Progression-free survival

Pembrolizumab-based regimens, compared to platinum-based doublet chemotherapy, may increase progression-free survival in patients with OESCC with PD-L1 CPS ≥ 10 treated in the first-line setting (HR 0.53 [95% CI, 0.40 to 0.60]; 1 study; 286 participants; low-certainty evidence; Analysis 8.4.). After two years of follow-up, this results in a progression-free survival advantage of 13.4% (9.9% to 22.7% more). We downgraded the certainty for risk of attrition bias because approximately 10% of patients left the study in each arm, and for imprecision due to the small sample size and risk of type II error.

Nivolumab-based regimens, compared to platinum-based doublet chemotherapy, likely increase progression-free survival as assessed by blinded independent central review in patients with unresectable advanced or metastatic OESCC with a tumour cell PD-L1 expression ≥ 1% treated in the palliative first-line setting (HR 0.67 [95% CI, 0.51 to 0.89]; 1 study; 315 participants; moderate-certainty evidence; Analysis 8.5.). After one year of follow-up, this results in a progression-free survival advantage of 11.4% (2.9% to 20.9% more). Certainty of evidence was downgraded for imprecision because of a wide confidence interval that crosses the

line of appreciable benefit at 0.75 and for risk of type II error due to low sample size.

Ipilimumab/nivolumab, compared to platinum-based doublet chemotherapy, may result in little to no difference in progression-free survival as assessed by blinded independent central review in patients with unresectable advanced or metastatic OESCC with a tumour cell PD-L1 expression ≥ 1% treated in the palliative first-line setting (HR 1.04 [95% CI, 0.79 to 1.36]; 1 study; 315 participants; low-certainty evidence; Analysis 8.6.). After one year of follow-up, this results in a progression-free survival disadvantage of 0.9% (2.9% fewer to 6.2% more). Certainty of evidence was downgraded by two levels for imprecision because of a very wide confidence interval that crosses both the line of null-effect and of appreciable harm at 1.25, as well as for risk of type II error due to low sample size.

Health-related quality of life

The quality of life analysis for pembrolizumab-based regimens is based on EORTC QLQ-C30 results from the Keynote-590 study. Results were reported separately for the OESCC PD-L1 CPS ≥ 10 population [138]. Questionnaires were completed electronically by the patients before all other study procedures one day 1 of the three-week treatment cycles. Of the 286 patients with OESCC PD-L1 CPS ≥ 10 included in survival analyses, 274 patients were also evaluable for global quality of life outcome analysis. At 18 weeks from baseline, approximately after six cycles of pembrolizumab and chemotherapy, there was little to no difference in global health score/quality of life (GHS/QoL) using least-squares mean change scores between the intervention and control group, not crossing the threshold of minimal clinically important difference of 9.5 (MD –1.95 [95% CI, –7.72 to 3.82]; 1 study; 274 participants; low-certainty evidence; Analysis 8.7.). Thus, pembrolizumab-based regimens may have little to no effect on GHS/QoL in OESCC patients with PD-L1 CPS ≥ 10. Due to general attrition of patients from the study, and the imprecision of the change score, we downgraded by one level for risk of bias and imprecision each, resulting in a low certainty evidence rating.

In CheckMate 648, quality of life was assessed using the disease-specific Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaire and the single generic item “I am bothered by the side effects of treatment” (GP5 item of FACT-G). Because no comprehensive generic patient-reported outcome measure was applied in this trial and results were not reported separately for the PD-L1 ≥ 1% subgroup, our assessment was based on FACT-E results for the whole trial population irrespective of PD-L1 expression status. Assessments were conducted prior to procedures on the first day of cycles one, two, and three, and every six weeks thereafter.

For nivolumab-based regimens the difference in quality of life from baseline through week 49 using least-squares mean change scores indicated slightly improved quality of life with nivolumab and chemotherapy than with chemotherapy alone, not crossing the threshold of minimal clinically important difference of 9.5 (MD 3.44 [95% CI, –0.03 to 6.91]; 1 study; 522 participants; moderate-certainty evidence; Analysis 8.8.). Thus, nivolumab-based regimens likely result in little to no difference in quality of life of patients with OESCC. Even though numerical quality of life data were not reported separately for the PD-L1 ≥ 1% subgroup, the trial authors state that results were similar for all randomised patients and the PD-L1 ≥ 1% subgroup, and there is no apparent reason to assume the contrary. We downgraded for risk of performance and detection bias due to the trial’s open-label design, resulting in a moderate-certainty rating.

For ipilimumab/nivolumab the difference in quality of life from baseline through week 49 using least-squares mean change scores indicated slightly improved quality of life with the ICI doublet than with chemotherapy alone not crossing the threshold of minimal clinically important difference of 9.5 (MD 1.91 [95% CI, –1.70 to 5.51]; 1 study; 529 participants; moderate-certainty evidence; Analysis 8.9.). Thus, ipilimumab/nivolumab likely results in little to no difference in quality of life of patients with OESCC. Even though numerical quality of life data were not reported separately for the PD-L1 ≥ 1% subgroup, the trial authors state that results were similar for all randomised patients and the PD-L1 ≥ 1% subgroup, and there is no apparent reason to assume the contrary. We downgraded for risk of performance and detection bias due to the trial’s open-label design, resulting in a moderate-certainty rating.

Adverse events

First-line pembrolizumab plus chemotherapy, as compared to placebo plus chemotherapy, may result in little to no difference in adverse events CTCAE grade ≥ 3 in patients with OESCC with CPS ≥ 10 (RR 1.03 [95% CI, 0.97 to 1.10]; 1 study; 740 participants; low-certainty evidence; Analysis 8.10.). The baseline risk for adverse events with chemotherapy alone was 83.2% [136]. Adverse events were encountered by 2.5% more (2.5% fewer to 8.3% more) participants treated with pembrolizumab plus chemotherapy. We downgraded the certainty of evidence for imprecision because of a wide confidence interval that crosses the line of appreciable harm, and for risk of attrition bias because around 10% of patients in each arm left the study on the patient’s or physician’s decision.

The addition of nivolumab to chemotherapy in the first line of therapy, as compared to chemotherapy alone, may increase adverse events CTCAE grade ≥ 3 in patients with OESCC with PD-L1 ≥ 1% (RR 1.33 [95% CI, 1.11 to 1.61]; 1 study; 614 participants; low-certainty evidence; Analysis 8.11.). The baseline risk for adverse events with chemotherapy alone was 36.5% [137]. Adverse events were encountered by 12.0% more (4.0% to 22.3% more) participants treated with nivolumab plus chemotherapy. We downgraded the certainty of evidence for imprecision because of a wide confidence interval that crosses the line of appreciable harm. Only treatment-related adverse events, which include a subjective judgement of treatment-relatedness, were reported in CheckMate 648. In conjunction with the trial’s open-label design, which poses a risk of performance and detection bias, we further downgraded. Overall, the certainty of evidence for the effect of nivolumab-based regimens on adverse events was rated to be low.

First-line ipilimumab/nivolumab, as compared to chemotherapy alone, may reduce adverse events CTCAE grade ≥ 3 in patients with OESCC (RR 0.91 [95% CI, 0.73 to 1.13]; 1 study; 626 participants; low-certainty evidence; Analysis 8.12.). The baseline risk for adverse events with chemotherapy alone was 36.5%. Adverse events were encountered by 3.3% fewer (9.9% fewer to 4.7% more) participants treated with ipilimumab/nivolumab. We downgraded the certainty of evidence for imprecision because of a wide confidence interval that crosses the line of null-effect and appreciable benefit. Only treatment-related adverse events, which include a subjective judgement of treatment-relatedness, were reported in CheckMate 648. In conjunction with the trial’s open-label design, which poses a risk of performance and detection bias, we further downgraded. Overall, the certainty of evidence for the effect of ipilimumab/nivolumab on adverse events was rated to be low.

Evidence discussion

Summary of main results

When compared to platinum-based doublet-chemotherapy, the combination of an ICI with platinum-based doublet chemotherapy or with a second ICI shows promising results in the treatment of patients with advanced or metastatic OESCC in the first-line setting, based on the two presented trials.

Pembrolizumab-based treatment regimens may increase overall and progression-free survival, and may result in little to no difference in global health score/quality of life and adverse events CTCAE grade ≥ 3 in OESCC with PD-L1 CPS ≥ 10. In absolute terms, pembrolizumab combined with chemotherapy is 6.3 times more (worst case scenario: 1.0 times; best case scenario: no calculation possible because of negative NNH and positive NNT) likely to lead to a survival benefit (18.9% more at two years) than to cause additional harm in the form of adverse events of CTCAE grade ≥ 3 compared to chemotherapy alone (NNT/NNH ratio; not assuming differential outcome importance).

Nivolumab-based treatment regimens may increase overall survival, likely increase progression-free survival, and likely result in little to no difference in health-related quality of life in OESCC with a PD-L1 expression ≥ 1%. However, nivolumab combined with chemotherapy may increase adverse events of CTCAE grade ≥ 3 compared to chemotherapy alone. In absolute terms, combining nivolumab with chemotherapy in OESCC is 1.4 times (worst case scenario: 0.4 times; best case scenario: 6.5 times) more likely to lead to a survival benefit (16.6% at two years) than to cause additional harm in the form of adverse events of CTCAE grade ≥ 3 compared to chemotherapy alone (NNT/NNH ratio; not assuming differential outcome importance).

Ipilimumab/nivolumab may increase overall survival, may result in little to no difference in progression-free survival, likely result in little to no difference in health-related quality of life, and may reduce adverse events CTCAE grade ≥ 3 in OESCC with PD-L1 TC ≥ 1%. The calculation of a meaningful NNT/NNH ratio was not possible because of a negative NNH combined with a positive NNT in the base and best case scenarios. In the base case scenario, the survival benefit amounts to 14.9% at two years. In the worst case scenario, ipilimumab/nivolumab is 1.5 times more likely to lead to a survival benefit than to cause additional harm.

Quality of evidence

Certainty of the evidence was rated to be low for pembrolizumab-based regimens, and was rated to be low to moderate for nivolumab-based regimens and ipilimumab/nivolumab. Reasons for downgrading included concerns over insufficient power and imprecision, indirectness from treatment switching, risk of performance bias due to CheckMate 648's open-label design, and risk of attrition bias.

Overall completeness and applicability of evidence

PD-L1 expression and mutational dependence

Although our prioritisation framework dictated the population of interest (i.e., OESCC patients with a TC PD-L1 expression ≥ 1% [ipilimumab/nivolumab or nivolumab plus chemotherapy] or CPS ≥ 10 [pembrolizumab]), all three ICI regimens have also shown statistically significant improvements in overall survival in the overall study populations of Keynote-590 and CheckMate 648 irrespective of PD-L1 expression status. The evidence presented herein is not restricted to patients with a certain mutational profile.

Generalizability of data for other patient populations or settings

Apart from Keynote-590, we did not identify published RCTs investigating pembrolizumab for palliative first-line treatment of OESCC. Pembrolizumab is not EMA approved for second-line treatment, and evidence from the phase 3 Keynote-181 study suggests no statistically significant improvements in overall survival with pembrolizumab as second-line treatment in OESCC compared to standard of care chemotherapy with paclitaxel, docetaxel, or irinotecan [139]. Likewise, we did not identify other published RCTs investigating nivolumab or ipilimumab/nivolumab for palliative first-line treatment of OESCC. Nivolumab monotherapy is EMA approved for unresectable advanced, recurrent or metastatic OESCC after prior fluoropyrimidine- and platinum-based combination chemotherapy based on the phase 3 ATTRACTION-3 trial which showed statistically significant and clinically meaningful improvement in overall survival compared to chemotherapy as second-line treatment [140].

Since our review is limited to RCTs as the study design, we did not search for real-world evidence nor non-randomised clinical trials assessing the drugs' safety and efficacy in other patient populations. Consequently, the applicability of the evidence provided herein is confined to a preselected subset of OESCC patients with good performance statuses (ECOG 0 to 1) who have relatively few comorbidities, particularly no systemic treatment-requiring autoimmune diseases.

Agreements and disagreements with other studies or reviews

Other ICIs and contradictory findings

Since the initial EMA register search, further PD-1 inhibitors for the indication of OESCC in the palliative first-line setting were approved. These were tislelizumab in combination with platinum-based chemotherapy in patients with OESCC whose tumours express PD-L1 with a TAP score ≥ 5%, and toripalimab in combination with cisplatin and paclitaxel in patients with OESCC irrespective of PD-L1 expression. For neither of the new indications long-term survival criteria were met as per their ESMO-MCBS scorecards which relied on overall survival data from the respective trials [141, 142]. Notably, the ESMO-MCBS scorecard for the tislelizumab first-line regimen in OESCC was based on results of the PD-L1 TAP ≥ 10% group because in the RATIONALE-306 trial OS was not formally tested using the 5% threshold set in the EMA approval for tislelizumab.

Performing a pragmatic search of MEDLINE via PubMed, no further RCTs of ICIs, currently not EMA approved for the indication but comparing ICI-based treatment regimens to established treatment standards for the palliative first-line treatment of OESCC, could be identified.

Colorectal carcinoma

Prioritisation and search results

As of August 2024, we have identified two EMA approvals for a single ICI, pembrolizumab, concerning the indication of microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) colorectal carcinoma. One of respective approvals was in the palliative first-line setting and met the ESMO MCBS ≥ 4 criterion to be considered further for systematic review. Recently, past our systematic search, EMA has recommended the approval of the combination of ipilimumab and nivolumab as an ICI-based strategy for the treatment of metastatic MSI-H/dMMR colorectal cancer in the palliative first- and second line treatment.

PRIORITISATION

ICI/-combination	Setting	Diagnostic requirement	Treatment details	MCBS-Score	RCT	LTS
Pembrolizumab	P1	dMMR/MSI-H	Monotherapy	4	Yes	✓
Pembrolizumab	P2	dMMR/MSI-H	Monotherapy			

Reason for exclusion (red colour); LTS – long-term survival benefit as reported by ESMO-MCBS Scorecard based on PFS and/or OS outcomes (not defined as a prioritisation criterion)

The search strategy developed from this selection, utilising search terms related to colorectal carcinoma and pembrolizumab, identified 840 entries in the CENTRAL and MEDLINE databases through the search performed on August 7th, 2024. After deduplication and applying the Cochrane RCT classifier, 424 potential records remained. Of these, 18 records met the inclusion criteria. All of which were reports of the Keynote 177 (NCT02563002) trial [143]. No RCTs were identified for exclusion during the full-text screening.

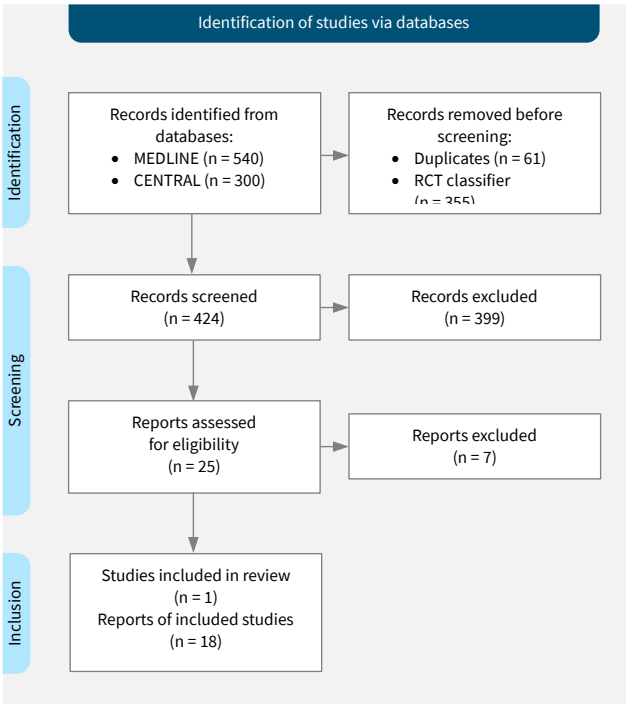


Figure 12. *PRISMA flow diagram: CRC*

Included studies and participants

For a detailed description of the study, see the Characteristics of included studies table. Here, we provide a brief overview.

Keynote 177 was a phase 3, open-label, multicentre, two-arm RCT comparing pembrolizumab monotherapy to chemotherapy alone or in combination with an EGFR or VEGF inhibitor, depending on the chosen standard of care chemotherapeutic regimen. Adult patients with locally confirmed dMMR or MSI-H stage IV colorectal carcinoma were eligible irrespective of their PD-L1 expression status. Further criteria for inclusion were an ECOG performance status of 0 or 1, adequate organ function and the absence of autoimmune disease requiring systemic treatment within the preceding two years apart from hormone substitution therapy.

Overall, 307 individuals were randomised: 153 to the intervention and 154 to the comparator group. No substantial differences in the baseline characteristics between-groups were reported. The median age of participants was 63 years (IQR, 50 to 73).

The longest reported median follow-up was 44.5 months (IQR, 39.7 to 49.8) from randomisation.

Merck Sharp & Dohme, the pharmaceutical company producing pembrolizumab, funded the trial.

Interventions and comparisons

Pembrolizumab was administered intravenously at a dose of 200 mg on day one of three-week cycles.

Control group participants received one of the following standard chemotherapy regimens: mFOLFOX6, mFOLFOX6 + bevacizumab (5 mg/kg IV on day one of each two-week cycle), mFOLFOX6 + cetuximab (400 mg/m2 IV over two hours then 250 mg/m^2 over one hour weekly in each two-week cycle), FOLFIRI, FOLFIRI + bevacizumab (5 mg/kg IV on day one of each two-week cycle) or FOLFIRI + cetuximab (400 mg/m^2 IV over two hours then 250 mg/m^2 over one hour weekly in each two-week cycle).

Participants with disease progression under control chemotherapy could cross-over and receive pembrolizumab for up to 35 cycles, i.e., approximately two years.

Outcomes of interventions

The primary outcomes of the Keynote 177 trial were overall survival and centrally assessed progression-free survival (PFS). Relevant secondary of exploratory outcomes included quality of life, overall response rate (ORR), adverse events and study treatment discontinuation due to adverse events.

Risk of bias

The risk of bias in included studies is summarised in the corresponding section.

ALLOCATION (SELECTION BIAS)

The randomisation method of Keynote was 177 adequate and randomisation was performed centrally using an interactive voice

response system or integrated web response system. Baseline characteristics seemed adequately balanced between groups.

Blinding (performance bias and detection bias)

The trial was performed in an open-label fashion. Due to the overall robustness of the outcome OS towards performance and detection bias, the respective risk of bias in these domains was low. However, due to the open-label nature of the trial, the risk of performance bias for other outcomes such as PFS, quality of life and adverse events was increased, including, but not limited to, patient reported outcomes.

Throughout follow-up, the trial conductors reported that 36% (56/145) of participants in the control chemotherapy group received pembrolizumab after confirmed disease progression. Furthermore, 35 control participants received other forms of checkpoint inhibitor immunotherapy, leading to an overall control cross-over rate of 59% in reference to the control intention to treat population.

Incomplete outcome reporting (attrition bias)

The participant flow in Keynote 177 was reported adequately. All patients were included in the survival analyses, and nearly all were included in the safety analysis. The proportion of trial participants included in the quality of life assessments was large. We rated the risk of attrition bias as low for all outcomes.

Selective reporting (reporting bias)

The trial protocol was accessible, and the predefined outcomes of interest were adequately reported. We rated the study as having a low risk of bias.

Effects of interventions

See summary of findings: Pembrolizumab compared to SoC for dMMR/MSI-H colorectal carcinoma.

Overall survival

Treatment with pembrolizumab monotherapy compared to chemotherapy in colorectal carcinoma with dMMR/MSI-H treated in the palliative first-line setting, may increase in overall survival (HR 0.74 [95% CI, 0.53 to 1.03]; 1 study, 307 participants; low-certainty evidence; Analysis 10.1.). In absolute terms, this translates to a survival benefit of 9.8% (1 fewer to 19.2 more) at three years. With SoC the median overall survival was 36.7 months [143]. Calculating the median overall survival difference using the hazard ratio and baseline risk estimate from the comparator arm led to a a 12.89 months higher (1.07 lower to 32.55 higher) survival benefit for patients receiving pembrolizumab.
We downgraded for serious imprecision, because the confidence interval of relative effect included an appreciable benefit of the intervention, but also crossed the line of null effect, and because the available evidence consisted of a single trial with a limited sample size only.

Progression-free survival

Compared to chemotherapy, pembrolizumab monotherapy may increase progression-free survival (HR 0.59 [95% CI, 0.45 to 0.79]; 1 study, 307 participants; low-certainty evidence; Analysis 10.2.). At three years of follow-up this leads to an increase in median progression-free survival by 18.4% more (8.5 more to 26.5 more) as compared to a median of 39.0% with chemotherapy. Given that the confidence interval of the relative effect crossed the appreciable effect and a risk of performance and detection bias in the included trial, we downgraded the evidence for imprecision and study limitations resulting in a low certainty of evidence for the outcome.

Health-related quality of life

Quality of life was assessed using the EORTC QLQ-C30 checklist. 292 of 307 (95%) participants were included in global quality of life outcome analysis. At 18 weeks, the mean difference in global health score/quality of life (GHS/QoL) from baseline using least-squares mean change scores was 8.96 points higher (4.24 more to 13.69 more) with pembrolizumab than with chemotherapy only (Analysis 10.3.). Thus, treatment with pembrolizumab may increase the GHS/QoL. We rated the certainty in the evidence as low. Given that the confidence interval of the relative effect crossed the appreciable effect, and a risk of performance and detection bias in the included trial, we downgraded the evidence for imprecision and study limitations.

Adverse events

Overall, 77.6% of participants treated with control chemotherapy experienced adverse events of CTCAE grade 3 or higher. In the pembrolizumab monotherapy arm, 21.7% fewer (30.3 fewer to 11.6 fewer) individuals experienced such events (RR 0.72 [95% CI, 0.61 to 0.85]; 1 study, 296 participants; low-certainty evidence; Analysis 10.4.). Overall, the treatment strategy based on pembrolizumab may reduce adverse events of grade 3 or higher as compared to chemotherapy. We rated the certainty on the evidence as low because the confidence interval of the relative effect crossed the appreciable effect and a risk of performance and detection bias in the included trial.

Evidence discussion

Summary of main results

When compared to chemotherapy, pembrolizumab monotherapy shows promising results in the first-line palliative treatment of metastatic colorectal carcinoma patients with dMMR/MSI-H, based on a single study with 307 participants (Keynote 177). It may increase OS and improve HR-QoL, while it may also lead to a reduction in adverse events of CTCAE grade ≥ 3.

No likelihood of being helped or harmed was calcuable for the base and best case scenarios of the treatment of metastatic colorectal cancer dMMR/MSI-H based on the point estimates of absolute OS gain and higher-grade AEs because of a negative NNH and positive NNT. In the worst case scenario, pembrolizumab monotherapy is 0.08 times more likely to lead to a survival benefit (1% lower survival at three years) than causing additional harm in the form of adverse events CTCAE grade ≥ 3 when compared to chemotherapy regimens (NNT/NNH ratio; not assuming differential outcome importance).

Quality of evidence

We rated the certainty of evidence as low for all assessed outcomes. Reasons for downgrading included concerns over imprecision. Furthermore, we downgraded for a risk of performance bias and detection bias for all outcomes except OS.

Overall completeness and applicability of evidence

Generalizability of data for other patient populations or settings

The great majority of metastatic colorectal cancer that are treated are microsatellite stable (MSS). Unfortunately, previous studies have failed to demonstrate a benefit with immune checkpoint inhibitor-based treatment, in particular monotherapy, for individuals with MSS metastatic colorectal cancer patients that is comparable to the benefits seen in patients with the dMMR/MSI-H subtype. Combination treatments to overcome this treatment gap are currently being evaluated. Nevertheless, the here presented

results are applicable to dMMR/MSI-H metastatic colorectal cancers only [144, 145].

AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES

Other ICIs

After the systematic search for this application was performed, another trial on immune checkpoint inhibitor-based palliative first-line treatment of dMMR/MSI-H metastatic colorectal cancer (CheckMate 8HW, NCT04008030) was published. This trial compares the combination of ipilimumab and nivolumab to chemotherapy and shows promising results with regard to overall survival, progression-free survival and a reduction in adverse events with the ICI doublet. Although we did not formally include this trial in our application, together with the herein presented results for pembrolizumab based on the Keynote 177 trial, it may point towards a possible positive class effect of ICIs in the first-line palliative treatment of dMMR/MSI-H metastatic colorectal cancer [146].

Endometrial carcinoma

Prioritisation and search results

As of May 2024, we have identified four EMA approvals for two ICIs concerning the indication of endometrial carcinoma: dostarlimab and pembrolizumab. Thereof, only one approval was in the palliative first-line treatment setting and met the MCBS ≥ 4 criterion to be considered further for systematic review.

PRIORITISATION

ICI/-combination	Setting	Diagnostic requirement	Treatment details	MCBS-Score	RCT	LTS
Dostarlimab	P2	dMMR/MSI-H	Monotherapy	3	No	–
Dostarlimab	P1	dMMR/MSI-H	Dostarlimab + CTx	4	Yes	✓
Pembrolizumab	P2	dMMR/MSI-H	Monotherapy	3	No	–
Pembrolizumab	P2	NR	Pembrolizumab + lenvatinib	4	Yes	–

Reason for exclusion (red colour); LTS – long-term survival benefit as reported by ESMO-MCBS Scorecard based on PFS and/or OS outcomes (not defined as a prioritisation criterion)

The search strategy developed from this selection, utilising search terms related to dMMR/MSI-H endometrial carcinoma and dostarlimab, identified 93 entries in the CENTRAL and MEDLINE databases. After deduplication and applying the Cochrane RCT classifier, 48 potential records remained. Of these, 16 records met the inclusion criteria. All of which were reports of the RUBY study (NCT03981796) [147-150]. No studies were identified for exclusion during the full-text screening.

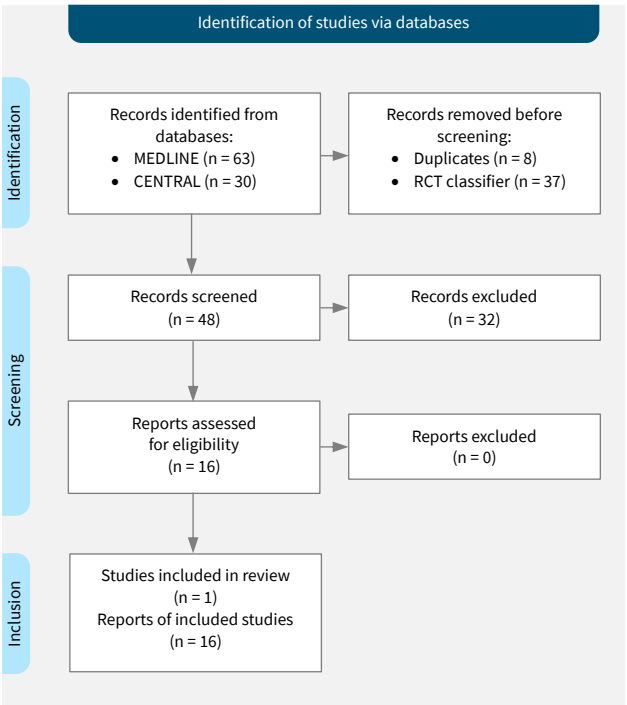


Figure 13. *PRISMA flow diagram: EC*

Included studies and participants

For a detailed description of the study, see the Characteristics of included studies table. Here, we provide a brief overview.

RUBY was a phase 3, double-blind, multicentre RCT comparing the combination of dostarlimab with carboplatin and paclitaxel to placebo, carboplatin, and paclitaxel. Patients were eligible irrespective of their MMR/MSI status, were 18 years or older and had primary stage III or IV disease or a first recurrence of endometrial cancer but at least six months after completing neo-adjuvant/adjuvant treatment if having received systematic therapy. Further criteria for inclusion were an ECOG performance status of 0 or 1, adequate organ function and the absence of autoimmune disease requiring systemic treatment within the preceding two years apart from hormone substitution therapy. Stratification of patients into respective arms was based on their MMR/MSI status, prior pelvic radiotherapy, and disease status (i.e., recurrent disease, primary stage III or IV).

Overall, 494 patients underwent randomisation. Of those, 53 receiving verum treatment and 65 receiving placebo harboured a deficient MMR protein or were MSI-high. Notably, the proportion of patients over 65 was slightly higher in the control arm than in the intervention arm. However, no substantial between-group differences were reported. Approximately half of the included patients were in the recurrent disease setting, with more than 80 percent having an endometrioid histologic subtype.

The longest median follow-up reported was 36.6 months from randomisation.

GlaxoSmithKline, the pharmaceutical company producing dostarlimab, funded the RUBY trial.

Interventions and comparisons

Dostarlimab was administered intravenously at a dose of 500mg in combination with carboplatin AUC5 and paclitaxel 175mg/m2 body-surface area on day one of six three-week cycles. Thereafter, chemotherapy was discontinued, and the administration interval of dostarlimab widened to six-week cycles and a dose of 1000mg. Treatment was continued for a maximum of three years, disease progression, toxic events, or death. Patients who were allocated to the comparator treatment followed the same schedule and drug regimen, but instead of dostarlimab, they received placebo infusions.

Outcomes of interventions

All prespecified outcomes of interest were planned and assessed in RUBY as secondary outcomes (PFS assessed by BICR, OS, QoL, and safety), with the primary outcome of the study being PFS (progression recorded by RECIST v1.1) based on investigator assessment. Patient-reported outcome measures used for quality-of-life outcomes assessment were EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-EN24.

Risk of bias

The risk of bias in included studies is summarised in the corresponding section.

Allocation (selection bias)

The randomisation method of RUBY was adequate and relied on an interactive web-based response system. No notable baseline imbalances were reported for the overall population. However, in patients with dMMR/MSI-H tumours, the proportion aged over 65 was 11% higher in the comparator arm than in the intervention arm, prompting us to evaluate the trial as having an unclear risk of bias. Given the small number of participants, this discrepancy might have occurred by chance.

Blinding (performance bias and detection bias)

RUBY was a double-blind placebo-controlled study, with participants, investigators, study staff, and the sponsor study team blinded. Therefore, we judged the risk of detection and performance bias as low for all prioritised outcomes.

Incomplete outcome reporting (attrition bias)

The participant flow in RUBY was reported adequately. All patients were included in the survival analyses, and nearly all were included in the safety analysis. For the quality of life assessment, a questionnaire completion rate of over 94 percent at the chosen time points was reported. Therefore, we rated the risk of attrition bias as low for all outcomes.

Selective reporting (reporting bias)

The trial protocol was accessible, and the predefined outcomes of interest were adequately reported. Since the protocol included a prespecified subgroup analysis for patients with dMMR/MSI-H tumours, we rated the study as having a low risk of bias.

Effects of interventions

See summary of findings: Dostarlimab-based treatment regimens compared to SoC for dMMR/MSI-H endometrial carcinoma.

Overall survival

Dostarlimab-based treatment regimens, compared to chemotherapy only, in endometrial carcinoma with dMMR/MSI-H treated in the palliative first-line setting, likely result in a large increase in overall survival (HR 0.32 [95% CI, 0.17 to 0.63]; 1 study, 118 participants; low-certainty evidence; Analysis 11.1.). In absolute terms, this translates to a survival benefit of 26.3% (13.1 to 33.5 more) and 32.0% (15.3 to 41.6 more) at two and three years, respectively. With SoC the median overall survival was 31.4 months. In the intervention arm of RUBY, the median overall survival has not been reached yet [149]. Calculating the median overall survival difference using the hazard ratio and baseline risk estimate from the comparator arm led to a 66.7 months (18.4 to 153.3 more) survival benefit for patients receiving the intervention. Considering the small sample size, introducing beta error could potentially result in overestimating the effect. On the other hand, 38.5% of participants who experienced disease progression subsequently received ICIs, which could lead to an underestimation; therefore, we downgraded for imprecision and indirectness.

Progression-free survival

Progression-free survival was planned as both a primary and secondary endpoint while differing in the assessment by investigators or by blinded independent central review (BICR). Herein, considering its lower risk for bias, BICR assessments were used. Compared to SoC, the combination of carboplatin/paclitaxel with dostarlimab likely results in a large increase in progression-free survival (HR 0.28 [95% CI, 0.16 to 0.59]; 1 study, 118 participants; moderate-certainty evidence; Analysis 11.2.). At one year follow-up this leads to a progression-free survival advantage of 43% (25 more to 55.4 more). Given the small sample size, we downgraded the evidence for imprecision.

Health-related quality of life

Quality of life was assessed using the EORTC QLQ-C30 and QLQ-EN24 module checklists were reported specifically for the dMMR/MSI-H subset of patients [150], at different intervals (baseline, cycle 7 and cycle 13) with completion rates, above 94%. Of the 118 patients included in survival analyses, 115 were also evaluable for global quality of life outcome analysis. At the seventh cycle of treatment, i.e., following the prescribed treatment protocol, after completion of chemotherapy and entry into maintenance, approximately 19 weeks from baseline, the difference in global health score/quality of life (GHS/QoL) from baseline using least-squares mean change scores was higher with the intervention than with chemotherapy only, crossing the threshold of minimal clinically important difference of 10 (MD 9.38 [95% CI, 5.45 to 13.31]; Analysis 11.3.). Thus, dostarlimab-based treatment likely increases the GHS/QoL in endometrial cancer patients with dMMR/MSI-H. Due to the small sample size and imprecision of the change score, we downgraded by two for imprecision, resulting in a low certainty evidence rating.

Adverse events

Adverse events graded as CTCAE ≥ 3 were only reported for all participants included in the RUBY trial and were encountered by 12% more (3.6 to 21.7 more) receiving chemotherapy plus dostarlimab as opposed to chemotherapy without ICI (RR 1.20 [95% CI, 1.06 to 1.36]; 1 study, 487 participants; low-certainty evidence; Analysis 11.4.). The baseline risk of adverse events with the comparator treatment was 60.2%. While we did not downgrade the certainty of the evidence for including patients with pMMR/MSS, we downgraded it for indirectness potentially resulting from a longer treatment exposure in the intervention arm in patients who did respond to therapy. Consequently, dostarlimab-based treatment in endometrial carcinoma with dMMR/MSI-H may increase the number of experienced adverse events with CTCAE ≥ 3 slightly.

Evidence discussion

Summary of main results

When compared to chemotherapy alone, the combination of dostarlimab with paclitaxel and carboplatin shows promising results in the treatment of endometrial cancer patients with dMMR/MSI-H, based on the presented study. It likely results in a large increase in overall survival and probable improvements in quality of life. However, it may slightly increase adverse events of CTCAE grade ≥ 3.

In absolute terms, integrating dostarlimab in the treatment of endometrial carcinoma with dMMR/MSI-H is 2.67 times (worst case scenario: 0.71 times; best case scenario: 14 times) more likely to lead to a survival benefit (32% higher survival at three years) than causing additional harm in the form of adverse events CTCAE grade ≥ 3 when compared to chemotherapy alone (NNT/NNH ratio; not assuming differential outcome importance).

QUALITY OF EVIDENCE

We rated the certainty of evidence as low to moderate. Reasons for downgrading included concerns over insufficient power and imprecision. Furthermore, we downgraded for indirectness, considering subsequent treatment with ICIs in patients with progressive disease after chemotherapy alone and the review's target population to whom ICIs were assumed unavailable.

OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

PD-L1 expression and mutational dependence

Although our prioritisation framework dictated the population of interest (i.e., endometrial carcinoma with dMMR/MSI-H), dostarlimab has also shown statistically significant improvements in overall survival in the subset of endometrial carcinoma patients with pMMR/MSS in RUBY [148, 149]. Thus, in an update, EMA extended the indication for dostarlimab-based treatment to include pMMR/MSS patients in the palliative first-line setting.

Generalizability of data for other patient populations or settings

Apart from RUBY, we did not identify published RCTs investigating the use of dostarlimab in endometrial carcinoma. Regulatory approval of second-line use of dostarlimab monotherapy in dMMR/MSI-H endometrial carcinoma was based on a single-arm study after progression following platinum-containing chemotherapy [151].

Since our review is limited to RCTs as the study design, we did not search for real-world evidence nor non-randomised clinical trials assessing the drug's safety and efficacy in other patient populations. Consequently, the applicability of the evidence provided herein is confined to a preselected subset of patients with good performance statuses (ECOG 0-1) who have relatively few comorbidities, particularly no systemic treatment-requiring autoimmune diseases.

AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES

Other ICIs and contradictory findings

Since the initial EMA register search, further ICIs for the indication of endometrial carcinoma in the palliative first-line setting, including for pMMR/MSS alongside dMMR/MSI, were approved. These were durvalumab, in combination with carboplatin and paclitaxel, followed by maintenance with either durvalumab or durvalumab plus olaparib, depending on the MMR/MSI status, and pembrolizumab, combined with the same chemotherapeutic backbone of carboplatin and paclitaxel. In both cases, long-term survival criteria were met as per their ESMO-MCBS scorecards, which relied on PFS data from the respective trials [152, 153].

Performing a pragmatic search of MEDLINE via PubMed, further RCTs of ICIs, currently not EMA approved for the indication but comparing ICI-based treatment regimens to established treatment standards in the palliative first-line setting before the introduction of ICIs (i.e., consistent with our defined comparison criteria) could be identified. These included avelumab (MITO END-3; phase 2 study) and atezolizumab (AtTEnd; phase 3 study), both in combination with carboplatin and paclitaxel [154, 155]. In both studies, a statistically significant difference in their primary outcome of PFS was noted in favour of the intervention. In either case, this difference was more pronounced in the dMMR/MSI-H cohort of patients. For the outcome of OS in both instances, median overall survival was not reached yet in the dMMR/MSI-H cohorts.

Cervical carcinoma

Prioritisation and search results

Our search identified two EMA approvals for two ICIs concerning the indication of cervical carcinoma: pembrolizumab and cemiplimab. Only one, pembrolizumab, was approved in the palliative first-line treatment setting and thus considered for systematic review.

Cemiplimab was restricted to patients who had progressed only after receiving platinum-containing chemotherapy in the first-line setting.

PRIORITISATION

ICI/-combination	Setting	Diagnostic requirement	Treatment details	MCBS-Score	RCT	LTS
Cemiplimab	P2	NR	Monotherapy	5	Yes	–
Pembrolizumab	P1	CPS ≥1	Pembrolizumab + CTx	4	Yes	✓

Reason for exclusion (red colour); LTS – long-term survival benefit as reported by ESMO-MCBS Scorecard based on PFS and/or OS outcomes (not defined as a prioritisation criterion)

Based on this selection, a search strategy including search terms for pembrolizumab and cervical carcinoma was devised, identifying 158 records in the CENTRAL and MEDLINE databases. Deduplication and using the Cochrane RCT classifier, narrowed down the number of records to be screened to 72. Of these, 48 were excluded during title and abstract, and further five reports during full-text screening. All 15 reports remaining pertained to Keynote-826 (NCT03635567) [156-158]. No studies were identified for exclusion during full-text screening.

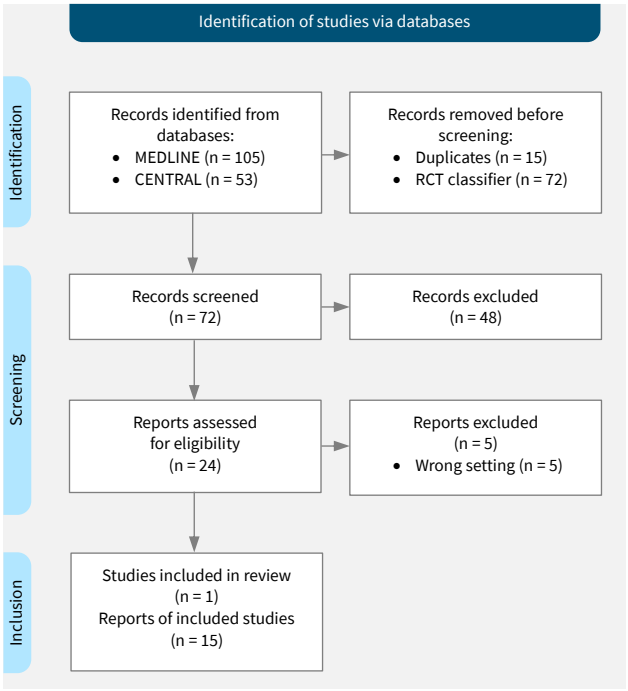


Figure 14. *PRISMA flow diagram: CC*

Included studies and participants

For a detailed description of the study, see the Characteristics of included studies. Here, we provide a brief overview.

Keynote-826 was a phase 3, double-blind, active and placebo-controlled, multicentre, RCT that investigated the combination of pembrolizumab with carboplatin and paclitaxel to carboplatin and paclitaxel. In both treatment arms the addition of bevacizumab was optional by investigators choice. Cervical cancer patients were eligible for participation if the had persistent, recurrent or metastatis cervical cancer with either squamous, adenosquamous or mixed adenosquamous histology in the palliative first-line setting, i.e. not amenable to curative therapy. Chemotherapy was allowed if received in a curative setting with radiosensitising intend. Further criteria were a good performance status (ECOG 0-1), adequate organ function (e.g. creatinine ≤ 1.5x the upper limit of normal and GFR ≥ 60 mL/min). Patients with CNS metastases were permitted, provided they have been treated and were radiologically stable. Patients with an active autoimmune disease or recent history of systemic treatment requiring autoimmune disease (within 2 years) were excluded. PD-L1 expression was not an eligibility criterion.

Overall, 617 patients were randomised of which 548 had a PD-L1 expression of CPS ≥ 1. Stratification was based on three factors, namely whether the disease was primarily metastatic, the investigators' decision of using bevacizumab or not and the PD-L1 status (CPS < 1, CPS 1-10, CPS ≥ 10). The median age of patients, irrespective of the PD-L1 status was 51 years. Most included patients had a squamous cell tumour histology, which was however slightly higher in the verum-treatment arm (76.3 vs 68.3%). The proportion of patients with PD-L1 CPS < 1 was around 11% in both arms. Among included patients only around 20% did not receive any previous cancer therapy. Bevacizumab was used in 63% of patients across treatment arms. Demographic and disease characteristics were similarly distributed in the PD-L1 CPS ≥ 1 subset of participants.

The longest median follow-up reported was 39.1 months from randomisation.

Merck Sharp & Dohme LLC funded the study.

Interventions and comparisons

Pembrolizumab was administered intravenously at a dose of 200 mg on day one of every three-week cycle for up to 35 cycles.

Chemotherapy in both treatment arms consisted of either cisplatin 50 mg/m^2 or carboplatin AUC 5, given together with paclitaxel 175 mg/m^2 on day 1 of each 3-week cycle for six cycles. In addition, patients could receive bevacizumab in either treatment arm at a

dose of 15 mg/kg every three weeks, per the investigators' discretion.

Cross-over to the pembrolizumab-based regimen upon progression in the comparator group of placebo plus chemotherapy was not allowed according to the trial protocol.

Outcomes of interventions

The primary outcomes of Keynote-826 were PFS as assessed by blinded independent review and OS. Relevant secondary or exploratory outcomes included quality of life measured by the EORTC QLQ-C30 and QLQ-CX24 extension, adverse events and overall response rate.

Risk of bias

The risk of bias in included studies is summarised in the corresponding section.

Allocation (selection bias)

The randomisation in Keynote-826 was based on an interactive voice response or integrated web response system, stratified based on PD-L1 status, investigator's decision to use bevacizumab and metastasis at presentation. No significant baseline differences were noted in the PD-L1 CPS ≥ 1 subgroup. The risk of bias due to selection bias was rated as low.

Blinding (performance bias and detection bias)

Participants, personell and outcome assessors were unaware of the treatment allocation, so we judged risk of bias as low for all outcomes.

Incomplete outcome reporting (attrition bias)

The participant flow in Keynote-826 was reported adequately, including all patients in the ITT analysis for survival outcomes and nearly all for the as treated analysis of adverse events. Compliance of quality of life assessment was more than 90% in both groups up until week 30. Therefore we did not downgrade for attrition bias.

Selective reporting (reporting bias)

The trial protocol was accessible, and the predefined outcomes of interest were adequately reported. Although adverse events were reported irrespective of treatment attribution, only adverse events experienced by a certain percentage of participants were reported, leaving potential for underreporting of important rare toxicities. Therefore, we judged risk of bias as low for efficacy and quality of life outcomes and unclear for adverse events.

Effects of interventions

See the summary of findings table: Pembrolizumab-based treatment compared to SoC in cervical cancer with PD-L1 ≥ 1% expression

Overall survival

Pembrolizumab-based treatment, compared to SoC of platinum-based doublet chemotherapy with paclitaxel, in cervical cancer with PD-L1 CPS ≥ 1, likely results in a large increase in overall survival (HR 0.60 [95% CI, 0.49 to 0.74]; 1 study, 548 participants; high-certainty evidence; Analysis 12.1.). In absolute terms, this translates to 17.8% more patients alive at 2 years (10.8 to 24% more) and 18.6% more patients alive at 3 years (11 to 25.6% more). The median overall survival difference was 11 months (5.8 to 17.2 months) longer with pembrolizumab-based treatment based on a median OS with control treatment of 16.5 months. Adequate randomisation methods with stratification of participants by PD-L1 expression, as well as double-blinding, were used. Consequently, we did not downgrade the certainty in the evidence.

Progression-free survival

Pembrolizumab-based treatment likely results in a large increase in progression-free survival (HR 0.60 [95% CI, 0.48 to 0.75]; 1 study, 548 participants; high-certainty evidence; Analysis 12.2.), leading to an 18.4% improvement (10.5 to 25.6% more) in progression-free survival at one year.

Health-related quality of life

Pembrolizumab-based treatment likely results in little to no difference in global health score/quality of life (GHS/QoL) at 30 weeks compared to SoC (MD 1.3 [3.02 lower to 5.62 higher]; 1 study, 519 participants; high-certainty evidence; Analysis 12.3.).

Adverse events

Pembrolizumab-based treatment in cervical cancer with CPS ≥ 1 may slightly increase the number of adverse events graded as CTCAE ≥ 3 (RR 1.09 [95% CI, 1.01 to 1.19]; 1 study, 616 participants; moderate-certainty evidence; Analysis 12.4.). The evidence is downgraded for indirectness due to the reporting threshold of adverse events only, including those occurring in more than 10% or 20% of participants.

Evidence discussion

Summary of main results

The combination of pembrolizumab with a platinum and paclitaxel leads likely improves overall survival in cervical cancer patients with PD-L1 CPS ≥ 1, when compared to chemotherapy without ICI partner. However, while not significantly affecting patients' quality of life, their risk of higher-grade adverse events is likely increased slightly.

Adding pembrolizumab to SoC in cervical cancer in the palliative first-line treatment, considering a balanced effect of harms and benefits, not assuming differential outcome importance leads, is 2.6 times as likely to improve survival at two years, than cause additional toxicity from higher-grade AEs (best-case scenario: 24.0 times as likely; worst-case scenario: 0.7 times as likely), based on a single study of 548 participants.

Quality of evidence

The overall certainty of the evidence was moderate to high across outcomes. Reasons for downgrading were mainly linked to incomplete reporting of adverse events. Considering that the subgroup analysis of participants with and without PD-L1 expression was prespecified and patient stratification by PD-L1 expression was part of the randomisation process, we did not downgrade the evidence in the evidence. The proportion of patients who have received ICIs upon progression in the comparator treatment arm was not reported.

Overall completeness and applicability of evidence

PD-L1 expression and mutational dependence

Results of subgroup analyses in Keynote-826 indicate that the beneficial effect of adding pembrolizumab to the regimen depends on the PD-L1 expression, with statistically significant differences regarding the OS outcome not having been shown for patients with PD-L1 CPS < 1. This consequently also led to only approving the regimen for cervical cancer patients with PD-L1 positivity.

Generalizability of data for other patient populations or settings

Aside from Keynote-826, no RCTs investigating a pembrolizumab-based treatment regimen in the palliative first-line could be identified by our search. Regulatory approvals of pembrolizumab,

including regimens, exist in both the curative and palliative second-line setting after platinum-based chemotherapy, with the latter being based on a single-arm study [159, 160].
Considering the inclusion criteria of trials, limitations regarding PD-L1 expression, and our review's restriction to RCTs, the presented data applies only to cervical cancer patients who meet the specifications of good performance status, eligibility for platinum-based chemotherapy, and absence of significant comorbidities, particularly autoimmune diseases that require or have recently required systemic treatment.

AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES

Other ICIs and contradictory findings

The update of the EMA register search revealed further approvals for pembrolizumab, namely its use in the curative setting, together with radiochemotherapy. Aside from pembrolizumab, approval exists for cemiplimab, following progression after platinum-based chemotherapy, based on a phase 3 study [161].

Our pragmatic search of MEDLINE via PubMed to identify RCTs of currently not EMA-approved treatments involving ICIs in the palliative first-line setting in comparison to the established treatment standard identified a study investigating the addition of atezolizumab to platinum, paclitaxel and bevacizumab (BEATcc; phase III study) [162], with patient inclusion irrespective of PD-L1 expression and randomisation not stratified PD-L1 status. A statistically significant benefit was reported for both OS and PFS in favour of the ICI-including regimen.

Summary of findings

Pembrolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression

Patient or population: Oncogenic driver wild-type NSCLC with high PD-L1 expression (TPS ≥ 50%)
Intervention: Pembrolizumab monotherapy
Comparison: SoC (platinum-based doublet chemotherapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with pembrolizumab monotherapy**				
Overall survival (OS) follow-up: median 60.7 months[a]	**At 2 years**		**HR 0.66** (0.57 to 0.76) [death]	904 (2 RCTs)[c]	⊕⊕⊕◯ Moderate[d]	Pembrolizumab monotherapy likely results in a large increase in overall survival at 2 and 5 years. However, considering the open-label study design and the opportunity for treatment switching in control arms, the treatment effect might be underestimated.
	30 per 100	**45 per 100** (40 to 50)				
	At 5 years					
	10 per 100	**22 per 100** (17 to 27)				
	The median OS was **12.2** months[b]	The median OS was **6.3 months more** (3.9 more to 9.2 more)[e]				
Progression-free survival (PFS) follow-up: median 60.7 months	**At 1 year**		**HR 0.66** (0.39 to 1.12) [disease progression or death]	904 (2 RCTs)	⊕⊕◯◯ Low[g,h]	Pembrolizumab monotherapy may result in an increase in progression-free survival.
	21 per 100[f]	**35 per 100** (17 to 54)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 15 weeks from baseline	The mean GHS/QoL was **-0.9** change score from baseline	MD **7.85 change score from baseline higher** (2.51 higher to 13.19 higher)	-	297 (1 RCT)	⊕⊕◯◯ Low[i,j]	Pembrolizumab monotherapy may increase global Health Score/Quality of Life slightly.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	43 per 100	**21 per 100** (16 to 29)	**RR 0.49** (0.37 to 0.66)	1555 (2 RCTs)	⊕⊕⊕◯ Moderate[i,k]	Pembrolizumab monotherapy probably results in a large reduction in adverse events (CTCAE ≥ 3).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Weight-adjusted median length of follow-up across trials
b. The risk estimate comes from Keynote-042's control group, which, due to its design, did not permit cross-over to receive ICIs and, therefore, more closely represents the baseline risk
c. Keynote-024 (NCT02142738) [59-61]; Keynote-042 (NCT02220894) [62, 63]
d. Participants in the comparator arms received ICI treatment, on- or off-trial, in 66% (Keynote-024) and 23% (Keynote-042) of cases, respectively, which potentially underestimates the effect, (downgrade by 1 for indirectness)
e. The difference in median survival time was calculated using the directly reported median survival estimate from the relevant trial's control arm(s) and pooled HR and CIs, assuming proportional hazards throughout the trial's follow-up
f. The baseline risk comes from the pooled control group estimate of studies
g. Downgraded for unexplained inconsistency; Data from Keynote-042 are based on a predetermined subgroup analysis; Trial participant randomisation was stratified based on their PD-L1 expression
h. The pooled effect estimate's CI overlaps both with the line of no effect and appreciable benefit at 0.75
i. Downgrade for risk of bias due to open-label study design and risk of detection and performance bias
j. CI crosses the line of minimal important difference of 10, we downgraded by 1 for imprecision
k. Adverse events in Keynote-042 were only reported for the entire ITT population, not for the subgroup of patients with PD-L1 expression ≥ 50%; We did not judge the tumour's PD-L1 expression to lead to sufficient indirectness with respect to adverse event outcomes, justifying a downgrade for indirectness

Atezolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression

Patient or population: Oncogenic driver wild-type NSCLC with high PD-L1 expression (TC3 or IC3)
Intervention: Atezolizumab monotherapy
Comparison: SoC (chemotherapeutic drug regimen with or without platinum depending on patient suitability)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC[b]	**Risk with atezolizumab monotherapy**				
Overall survival (OS) follow-up: median 35.6 months[a]	**At 2 years**		**HR 0.79** (0.54 to 1.09) [death]	280 (2 RCTs)	⨁⨁◯◯ Low[d,e]	Atezolizumab monotherapy may increase overall survival slightly. Considering that a proportion of trial participants received ICIs in the subsequent treatment line, the effect might be underestimated.
	30 per 100	**39 per 100** (27 to 52)				
	The median overall survival was **13.9** months	The median survival was **3.7 months more** (1.1 fewer to 11.8 more)[f]				
Progression-free survival (PFS) follow-up: median 35.6 months	**At 1 year**		**HR 0.63** (0.48 to 0.84) [disease progression or death]	280 (2 RCTs)[b]	⨁⨁◯◯ Low[g,h]	Atezolizumab monotherapy may increase progression-free survival.
	18 per 100	**34 per 100** (24 to 44)				
Health-related quality of life - not reported	*see comments*		-	-	-	Both studies measured and reported aspects of quality of life; however, reporting of total or global QoL scores was insufficient
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	57 per 100	**46 per 100** (31 to 70)	**RR 0.81** (0.54 to 1.22)	996 (2 RCTs)	⨁⨁◯◯ Low[e,g]	Atezolizumab monotherapy may reduce adverse events (CTCAE ≥ 3) slightly irrespective of treatment attribution. Studies varied with respect to the age and performance status of included participants, suggesting that while the intervention leads to fewer higher-grade adverse events in young, fit patients, this advantage is potentially lost in elderly/unfit patients.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Weight-adjusted pooled median follow-up across studies
b. The baseline risk is derived from the pooled control group estimate of studies
c. IMpower 110 (NCT02409342) [56,57]; IPSOS (NCT03191786) [58]
d. According to protocol, crossover to receive ICIs was not permitted in the comparator arms. However, patients in IMpower 110 received ICIs as subsequent therapy in 34.7% of cases; the proportion in IPSOS was not reported. Consequently, the effect of Atezolizumab might be underestimated. Therefore, we downgraded by 1 for indirectness
e. The pooled effect estimate's CI overlaps both the line of no effect as well as the line of appreciable benefit at 0.75 (downgraded for serious imprecision)
f. The difference in median survival time was calculated using the directly reported median survival estimate from the relevant trial's control arm(s) and pooled HR and CIs, assuming proportional hazards throughout the trial's follow-up
g. Both studies were at high risk of bias due to the open-label trial design and investigator-assessed outcome reporting
h. Downgraded by 1 for imprecision. Even though the OIS criterion was met, imprecision resulted from the CI crossing the line of appreciable benefit at 0.75

Cemiplimab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression

Patient or population: Oncogenic driver wild-type NSCLC with high PD-L1 expression (TPS ≥ 50%)
Intervention: Cemiplimab monotherapy
Comparison: SoC (platinum-based doublet chemotherapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC[a]	**Risk with cemiplimab monotherapy**				
Overall survival (OS) follow-up: median 35 months	**At 2 years**		**HR 0.63** (0.52 to 0.77) [death]	712 (1 RCT)[b]	⊕⊕⊕◯ Moderate[c]	Cemiplimab monotherapy probably results in a large increase in overall survival. Considering the open-label study design and opportunity for treatment switching in the control-arm, the treatment effect might be underestimated.
	34 per 100[a]	**50 per 100** (43 to 57)				
	At 3 years					
	23 per 100	**40 per 100** (32 to 47)				
	The median OS was **13.7** months	The median OS was **8 months more** (4.1 more to 12.6 more)				
Progression-free survival (PFS) follow-up: median 35 months	**At 1 year**		**HR 0.56** (0.47 to 0.67) [disease progression or death]	712 (1 RCT)	⊕⊕⊕◯ Moderate[d]	Cemiplimab monotherapy likely results in a large increase in progression-free survival.
	8 per 100[a]	**24 per 100** (18 to 30)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 1 year from baseline	The mean global Health Score/Quality of Life was **2.2** change score from baseline	MD **5.03 change score from baseline higher** (2.11 higher to 7.96 higher)[e]	-	563 (1 RCT)	⊕⊕⊕◯ Moderate[f,g]	Cemiplimab monotherapy likely results in little to no difference in global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	52 per 100	**46 per 100** (39 to 53)	**RR 0.89** (0.76 to 1.03)	699 (1 RCT)	⊕⊕◯◯ Low[f,h]	Cemiplimab monotherapy may reduce adverse events (CTCAE ≥ 3) irrespective of treatment attribution slightly.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Baseline risks derived from the control arm of the EMPOWER-Lung 1 trial; datapoints extracted from KM-curve graphs
b. EMPOWER-Lung 1 (NCT03088540) [64-66]
c. Downgraded by 1 due to indirectness from switching treatments in the comparator arm, with 56% of participants receiving the experimental treatment upon progression. Thus, potentially leading to an underestimated effect size.
d. Downgraded by 1 due to open-label trial design and potential deviation due to contextual bias
e. Estimates as directly reported in publication
f. Downgraded by 1 due to open-label trial design and potential for performance and detection bias
g. The effect estimate and CI do not cross the line of minimal important difference of 10
h. Downgraded due to imprecision; the CI includes the null effect line

Pembrolizumab-based treatment compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression

Patient or population: oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression
Intervention: Pembrolizumab-containing treatment regimens
Comparison: SoC (platinum-based doublet chemotherapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with pembrolizumab-containing regimens**				
Overall survival (OS) follow-up: median 59.8 months[a]	**At 2 years**		**HR 0.66** (0.58 to 0.74) [death]	1298 (3 RCTs)[c]	⊕⊕⊕◯ Moderate[d,e]	Pembrolizumab-containing treatment regimens probably increase overall survival. Considering the high proportion of cross-over, with 56% of controls receiving ICIs, the effect is potentially underestimated.
	33 per 100[b]	**48 per 100** (44 to 52)				
	At 5 years					
	10 per 100[b]	**22 per 100** (19 to 27)				
	The median OS was **12.3** months	The median OS was **6.3 months more** (4.3 more to 8.9 more)[f]				
Progression-free survival (PFS) follow-up: median 59.8 months	**At 1 year**		**HR 0.55** (0.48 to 0.64) [disease progression or death]	1298 (3 RCTs)[b]	⊕⊕⊕⊕ High[g]	Pembrolizumab-containing treatment regimens results in large increase in progression-free survival.
	21 per 100	**43 per 100** (37 to 47)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC QLQ-C30 Scale from: 0 to 100 follow-up: 19.3 weeks from baseline	The mean global Health Score/Quality of Life (GHS/QoL) was **-1.99** change score from baseline	MD **5 change score from baseline higher** (2.13 higher to 7.87 higher)	-	1156 (2 RCTs)	⊕⊕⊕◯ Moderate[h,i]	Pembrolizumab-containing treatment regimens may result in little to no difference in global Health Score/Quality of Life (GHS/QoL).
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	65 per 100	**70 per 100** (65 to 75)	**RR 1.08** (1.00 to 1.16)	1286 (3 RCTs)	⊕⊕⊕◯ Moderate[j]	Pembrolizumab-containing treatment regimens may result in little to no difference in adverse events (CTCAE ≥ 3) irrespective of treatment attribution.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. The median follow-up time was derived from a weight-adjusted pooling across studies
b. The 2-year baseline risk was derived from the pooled estimate of all three trials comparator arms; the 5-year risk is derived from a pooled estimate of Keynote-407 and Keynote-189 since the follow-up of Keynote-021 did not include this timepoint
c. Keynote-021 (NCT02039674) [79, 80]; Keynote-407 (NCT02775435) [84-86]; Keynote-189 (NCT02578680) [81-83]
d. Downgraded for indirectness due to subsequently received ICIs in control arms of included trials (50.9% in Keynote-407, 57.3% in Keynote-189; 70% in Keynote-021)
e. Although study participants differed in that Keynote-407 only included participants with squamous cell NSCLC and the other two trials included only non-squamous cell NSCLC subtypes, we did not identify relevant subgroup differences (I-Squared 30.4%)
f. The difference in median survival time was calculated using the directly reported median survival estimate from control arms and the pooled HR and CIs, assuming proportional hazards throughout the trial's follow-up
g. The test for subgroup differences (SqC vs NSqC histology) resulted in a p-value of 0.10 and an I-squared of 62.4%. The CIs indicated significant overlap and consistently showed appreciable benefit for both subgroups. Therefore, we did not downgrade the rating for indirectness.
h. Downgraded for risk of attrition bias
i. The difference in change scores from baseline did not cross the MID line at 10; therefore, we did not downgrade for imprecision
j. Regarding concerns around non-inferiority, and confidence interval close to the null effect and appreciable harm, we downgraded by 1 for imprecision

Cemiplimab-based treatment compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression

Patient or population: oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression
Intervention: Cemiplimab-containing treatment regimens
Comparison: SoC (platinum-based doublet chemotherapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Cemiplimab-containing treatment regimens**				
Overall survival (OS) follow-up: median 28.4 months	**At 2 years**		**HR 0.65** (0.51 to 0.82) [survival]	466 (1 RCT)[b]	⊕⊕⊕◯ Moderate[c,d]	Cemiplimab-containing treatment regimens likely increases overall survival.
	27 per 100[a]	**43 per 100** (34 to 51)				
	The median OS was **12.9** months	The median OS was **6.9 months more** (2.8 more to 12.4 more)[e]				
Progression-free survival (PFS) follow-up: median 28.4 months	**At 1 year**		**HR 0.55** (0.44 to 0.68) [survival, remission or stable disease]	466 (1 RCT)[a]	⊕⊕⊕⊕ High	Cemiplimab-containing treatment regimens results in large increase in progression-free survival.
	16 per 100	**37 per 100** (29 to 45)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC QLQ-C30 Scale from: 0 to 100 follow-up: 24 months from baseline	The mean global Health Score/Quality of Life (GHS/QoL) was **1.08** change score from baseline	MD **0.61 change score from baseline higher** (2.23 lower to 3.45 higher)[f]	-	466 (1 RCT)	⊕⊕⊕⊕ High	Cemiplimab-containing treatment regimens does not increase global Health Score/Quality of Life (GHS/QoL).
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	31 per 100	**44 per 100** (33 to 57)	**RR 1.39** (1.06 to 1.81)	465 (1 RCT)	⊕⊕⊕◯ Moderate[g]	Cemiplimab-containing treatment regimens likely increases adverse events (CTCAE ≥ 3) irrespective of treatment attribution.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. The baseline risk stems from the 2-year survival estimate of the control group of the EMPOWER-Lung 3 trial
b. EMPOWER-Lung 3 (NCT03409614) [87-89]
c. Only around 15% of patients in the control group received subsequent immunotherapy upon disease progression and unblinding, therefore, we did not downgrade for indirectness. However, the trial was stopped early by IDMC due to shown superiority in OS
d. Downgraded for imprecision; although the OIS criterion was met, the CI crosses the line of appreciable benefit at 0.75
e. The difference in median survival time was calculated using the directly reported median survival estimate from the relevant trial's control arm(s) and pooled HR and CIs, assuming proportional hazards throughout the trial's follow-up
f. The mean difference between the intervention and comparator arm was directly taken as reported by trial authors for the length of follow-up
g. CI crosses the line of appreciable harm at 1.25, so we downgraded for imprecision

Ipilimumab/nivolumab-based treatment vs SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression

Patient or population: oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression
Intervention: Ipilimumab/nivolumab-containing treatment regimens
Comparison: SoC (platinum-based doublet chemotherapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Ipilimumab/nivolumab-containing regimens**				
Overall survival (OS) follow-up: median 54.5 months	**At 2 years**		**HR 0.74** (0.63 to 0.87) [death]	719 (1 RCT)[b]	⨁⨁◯◯ Low[c,d,e]	Ipilimumab/nivolumab-containing treatment regimens likely increase overall survival. However, considering that 36% of patients in the control arm subsequently received immunotherapy, the effect might be underestimated.
	26 per 100[a]	**37 per 100** (31 to 43)				
	At 5 years					
	11 per 100	**20 per 100** (15 to 25)				
	The median OS was **11.0** months	The median OS was **3.9 months more** (1.6 more to 6.5 more)				
Progression-free survival (PFS) follow-up: median 54.5 months	**At 1 year**		**HR 0.70** (0.59 to 0.83) [disease progression or death]	719 (1 RCT)	⨁⨁⨁◯ Moderate[d]	Ipilimumab/nivolumab-containing treatment regimens likely increase progression-free survival.
	19 per 100	**31 per 100** (25 to 38)				
Health-related Quality of life assessed with: LCSS 3-IGI Scale Scale from: 0 to 300 follow-up: 24 months from baseline	The mean health-related Quality of life was **4.7** change score from baseline[a]	MD **4.7 change score from baseline higher** (3.26 lower to 12.66 higher)	-	646 (1 RCT)	⨁⨁⨁◯ Moderate[f,g]	Ipilimumab/nivolumab-containing treatment regimens likely results in little to no difference in global Health Score/Quality of Life (GHS/QoL).
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	47 per 100	**57 per 100** (49 to 65)	**RR 1.21** (1.05 to 1.40)	707 (1 RCT)	⨁⨁◯◯ Low[f,h]	Ipilimumab/nivolumab-containing treatment regimens may increase adverse events (CTCAE ≥ 3) irrespective of treatment attribution slightly.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Baseline risk taken from comparator arm of CheckMate 9LA
b. CheckMate 9LA (NCT03215706) [90-92]
c. Downgraded due to indirectness; 36% participants in the control arm received subsequent immunotherapy, potentially underestimating the effect (Carbone et al. 2024)
d. Downgraded due to imprecision; the CI crosses the line of appreciable benefit at 0.75
e. Not applicable due to preceding prioritisation process
f. Downgraded due to risk of detection and performance bias because of the open-label trial design
g. Not downgraded for imprecision; the effect estimate and confidence interval lie close to the null-effect line and do not include either appreciable harm or benefit, with a minimally important difference defined as 30 points for the LCSS 3-IGI
h. Downgraded for imprecision; the CI crosses the line for appreciable harm at 1.25

Durvalumab/tremelimumab-based treatment vs SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression

Patient or population: Oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression
Intervention: Durvalumab/tremelimumab-containing treatment regimens
Comparison: SoC (platinum-based doublet chemotherapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Durvalumab/tremelimumab-containing treatment regimens**				
Overall survival (OS) follow-up: median 63.4 months	**At 2 years**		**HR 0.77** (0.65 to 0.92) [death]	675 (1 RCT)[a,b,c]	⊕⊕◯◯ Low[d,e]	Durvalumab/tremelimumab-containing treatment regimens may increase overall survival slightly. Considering that more than 30% of trial participants in the control arm subsequently received immunotherapy, the beneficial effect is potentially underestimated.
	22 per 100	**31 per 100** (25 to 37)				
	At 5 years					
	7 per 100	**13 per 100** (8 to 17)				
	The median OS was **11.7** months	The median OS was **3.5 months more** (1 more to 6.3 more)[f]				
Progression-free survival (PFS) follow-up: median 10.3 months	**At 1 year**		**HR 0.72** (0.60 to 0.86) [disease progression or death]	675 (1 RCT)[b]	⊕⊕⊕◯ Moderate[e]	Durvalumab/tremelimumab-containing treatment regimens likely increases progression-free survival slightly.
	13 per 100	**23 per 100** (17 to 30)				
Global Health Score/Quality of Life (GHS/QoL) - not reported	See comment	-	-	-	-	EORTC QLQ-C30 changes, although assessed were not reported as change scores from baseline
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	54 per 100	**57 per 100** (50 to 65)	**RR 1.05** (0.92 to 1.21)	664 (RCTs)	⊕⊕⊕◯ Moderate[g]	Durvalumab/tremelimumab-containing treatment regimens may result in little to no difference in adverse events (CTCAE ≥ 3) irrespective of treatment attribution.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. The point estimate of the median absolute survival rate with durvalumab/tremelimumab-containing regimens at 5 years, using the relative effect is slightly lower, than reported in the trial, but lies within the calculated CI
b. The baseline risk stems from the 2-year survival estimate of the control group of POSEIDON
c. POSEIDON (NCT03164616) [93, 94]
d. Downgraded for indirectness; 33.2% of patients in the control arm of POSEIDON received immunotherapy in the second line of therapy
e. Downgraded for imprecision; the CI crosses the line of appreciable benefit at 0.75
f. The difference in median survival time was calculated using the directly reported median survival estimate from the trial, HR and CI, assuming proportional hazards throughout the trial's follow-up
g. Downgraded for risk of detection and performance bias due to the open-label trial design and partly subjective component of adverse events and patient-reported outcome data

Pembrolizumab-based treatment compared to SoC in HNSCC with PD-L1 expression

Patient or population: HNSCC with PD-L1 expression (CPS ≥ 1)
Intervention: Pembrolizumab-containing treatment regimens
Comparison: SoC (cetuximab + cisplatin/carboplatin + 5-fluorouracil)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC[c]	**Risk with Pembrolizumab-containing treatment regimens**				
Overall survival (OS) follow-up: median 45 months	**At 2 years**		**HR 0.64** (0.53 to 0.78) [death]	477 (1 RCT)[a]	⊕⊕⊕◯ Moderate[b]	Pembrolizumab-containing treatment regimens results in large increase in overall survival.
	17 per 100	**32 per 100** (25 to 39)				
	At 3 years					
	9 per 100	**21 per 100** (15 to 27)				
	The median OS was **10.6** months	The median OS was **6 months more** (3 more to 9.4 more)[d]				
Progression-free survival (PFS) follow-up: median 11.9 months	**At 1 year**		**HR 0.82** (0.67 to 1.00) [disease progression or death]	477 (1 RCT)[f]	⊕⊕◯◯ Low[f]	Pembrolizumab-containing treatment regimens may result in little to no difference in progression-free survival.
	11 per 100	**16 per 100** (11 to 23)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC QLQ-C30 Scale from: 0 to 100 follow-up: 15 weeks from baseline	The mean GHS/QoL was **0.77** change score from baseline	MD **0.4 change score from baseline higher** (3.8 lower to 4.6 higher)	-	527 (1 RCT)	⊕⊕⊕◯ Moderate[g]	Pembrolizumab-containing treatment regimens likely results in little to no difference in global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	83 per 100	**85 per 100** (79 to 92)	**RR 1.02** (0.95 to 1.10)	563 (1 RCT)	⊕⊕⊕◯ Moderate[g]	Pembrolizumab-containing treatment regimens likely results in little to no difference in adverse events (CTCAE ≥ 3) irrespective of treatment attribution.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Keynote-048 (NCT02358031) [109-112]
b. Downgraded for indirectness; 25.2% of participants, receiving the control treatment subsequently received ICIs upon progression which might have led to an underestimation of the effect
c. Baseline risk derived from control arm of Keynote-048
d. The difference in median survival time was calculated using median OS point estimate of control group as directly reported and the HR and corresponding CIs (assuming proportional hazards throughout the trial's follow-up)
e. Weight-adjusted median follow-up across relevant treatment arms (outcome irrespective of subgroup only reported in primary publication)
f. Downgraded by 2 levels for imprecision. The 95% CI crosses both the line of appreciable benefit and null effect
g. Downgraded due to open-label trial design and risk of performance and detection bias

Ipilimumab/nivolumab compared to ICI monotherapy for malignant melanoma

Patient or population: malignant melanoma
Intervention: ipilimumab/nivolumab
Comparison: ICI monotherapy (ipilimumab or nivolumab, respectively)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ICI monotherapy	Risk with Ipilimumab/nivolumab				
Overall survival (OS) follow-up: median 34.6 months[a]	**At 2 years**		**HR 0.68** (0.50 to 0.93) [death]	1133 (3 RCTs)[c]	⊕⊕⊕◯ Moderate[d,e]	Ipilimumab/nivolumab likely increases overall survival. The median overall survival in the intervention group calculated using the pooled hazard ratio underestimates the actual median overall survival reported in the relevant study publication.
	52 per 100[b]	**64 per 100** (55 to 72)				
	At 5 years					
	35 per 100[b]	**49 per 100** (38 to 59)				
	The median overall survival was **28.4** months[a]	The median overall survival was **12.8 months more** (3.9 more to 24.2 more)[f]				
Progression-free survival (PFS) follow-up: median 35.7 months[a]	**At 2 years**		**HR 0.50** (0.31 to 0.82) [disease progression or death][g]	1087 (2 RCTs)	⊕⊕◯◯ Low[h]	Ipilimumab/nivolumab may increase progression-free survival.
	24 per 100[b]	**49 per 100** (31 to 64)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC QLQ-C30 Scale from: 0 to 100 follow-up: 55 weeks from baseline	The mean GHS/QoL was **-4.72** change score from baseline[b]	MD **1.08 change score from baseline lower** (3.44 lower to 1.28 higher)	-	758 (1 RCT)[i]	⊕⊕⊕◯ Moderate[j,k]	Ipilimumab/nivolumab likely results in little to no difference in Global Health Score/Quality of Life compared to ICI monotherapy.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	25 per 100	**59 per 100** (51 to 69)	**RR 2.37** (2.03 to 2.77)	1137 (3 RCTs)	⊕⊕⊕⊕ High	Ipilimumab/nivolumab results in a large increase in adverse events (CTCAE ≥ 3) compared to ICI monotherapy.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Weight-adjusted median follow-up and overall survival across studies and treatment arms
b. The baseline risks were pooled or adopted from the control group estimates of different studies and treatment arms (overall survival at 2 years: all three trials; overall survival at 5 years: all but the CheckMate 069 trial (insufficient follow-up); progression-free survival at 2 years: all but the ABC trial (lack of reporting); quality of life: CheckMate 067)
c. ABC (NCT02374242, comparison: ipilimumab/nivolumab vs. nivolumab) [163-165], CheckMate 067 (NCT01844505, comparisons: ipilimumab/nivolumab vs. nivolumab vs. ipilimumab) [166, 167], CheckMate 069 (NCT01927419, comparison: ipilimumab/nivolumab vs. ipilimumab) [168]
d. Not downgraded for risk of bias because the one study at high risk of bias (ABC) due to inadequate random treatment allocation has a weight of only 8.0% in the meta-analysis, and sensitivity analysis showed that the study does not change the point estimate. Publication bias not applicable due to prespecified selection process
e. Downgraded for imprecision because of a wide confidence interval that crosses the defined appreciable effect at 0.75
f. The corresponding difference in median survival time was calculated by means of the pooled median overall survival point estimates of the control groups as directly reported in the relevant trial publication with sufficiently long follow-up, the pooled HR and corresponding CIs (assuming proportional hazards throughout the trial follow-up period). The calculated difference in median survival time deviates from the pooled difference in observed median survival time of 43.7 months reported in the relevant trial publication
g. A subgroup effect was identified for different ICI monotherapies used as control treatment. The comparison with ipilimumab monotherapy yielded a lower hazard ratio and contributes approximately two-thirds to the effect estimate, while the comparison with nivolumab monotherapy yielded a higher hazard ratio and contributes about one-third to the effect estimate
h. The heterogeneity (I^2 = 88%) identified in the meta-analysis can likely be explained by the inclusion of different standard of care treatments (ipilimumab vs. nivolumab monotherapy). A downgrade by 2 in total for inconsistency and imprecision is justified, considering the wide confidence interval crossing the defined appreciable effect at 0.75
i. CheckMate 067 (NCT01844505)
j. Downgraded for risk of attrition bias due to completion rates of the EORTC QLQ-C30 questionnaire slightly above 50% after 55 weeks from baseline
k. No inconsistency was observed, as two studies with smaller sample sizes and shorter follow-up (ABC, CheckMate 069), also utilizing the EORTC QLQ-C30 but not suitable for pooling, support the findings

Ipilimumab/nivolumab compared to BRAF/MEK inhibitors for BRAF V600-mutant malignant melanoma

Patient or population: BRAF V600-mutant malignant melanoma
Intervention: ipilimumab/nivolumab
Comparison: BRAF/MEK inhibitors (encorafenib/binimetinib or dabrafenib/trametinib)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with BRAF/MEK inhibitors	**Risk with Ipilimumab/nivolumab**				
Overall survival (OS) follow-up: median 32.2 months	**At 2 years**		**HR 0.73** (0.42 to 1.27) [death][b]	138 (1 RCT)[c]	⨁◯◯◯ Very low[d,e,f]	The evidence is very uncertain about the effect of ipilimumab/nivolumab on overall survival.
	65 per 100[a]	**73 per 100** (58 to 83)				
	At 3 years					
	54 per 100[a]	**64 per 100** (46 to 77)				
	Median overall survival was reached neither in the control nor intervention group.					
Progression-free survival (PFS)	No comparative results were reported for PFS. The pooled 2-year PFS rates were 40.1% with ipilimumab/nivolumab and 23.9% with BRAF/MEK inhibitors.			403 (2 RCTs)	⨁◯◯◯ Very low[g,h,i]	The evidence is very uncertain about the effect of ipilimumab/nivolumab on progression-free survival.
Global Health Score/Quality of Life - not reported[j]	see explanation		-	-	-	There is no evidence about the effect of ipilimumab/nivolumab on Global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatement attribution	48 per 100	**61 per 100** (45 to 82)	**RR 1.26** (0.94 to 1.69)	394 (2 RCTs)	⨁⨁◯◯ Low[g,k]	Ipilimumab/nivolumab may increase adverse events (CTCAE ≥ 3) slightly.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Baseline risk for overall survival at 2 and 3 years as directly reported for the control group in SECOMBIT
b. The hazard ratio for overall survival stems from an exploratory analysis of a non-comparative trial
c. SECOMBIT (NCT02631447, comparison: ipilimumab/nivolumab vs. encorafenib/binimetinib) [169]. The second relevant RCT, DREAMseq (NCT02224781, comparison: ipilimumab/nivolumab vs. dabrafenib/trametinib) [170, 171], provided usable data on progression-free survival and adverse events, only
d. Downgraded for indirectness because 36/69 (52.2%) of patients crossed over to ipilimumab/nivolumab per protocol in case of progressive disease as planned
e. Downgraded by 2 levels for imprecision because the confidence interval crosses both the line of appreciable benefit and of appreciable harm
f. Publication bias not applicable due to prespecified selection process
g. Downgraded for risk of performance and detection bias due to open-label design and absence of blinded independent central review in both relevant studies
h. Downgraded for inconsistency because the reported 2-year progression-free survival rates and the magnitude of survival benefit with ipilimumab/nivolumab differ between studies
i. Narrative synthesis was conducted, point estimates are not precise and no confidence intervals were provided in one of two studies
j. Global Health Score/Quality of Life was planned to be assessed using EORTC QLQ-C30, EQ-5D, and WPAI:GH in SECOMBIT, but no results were reported. Although in DREAMseq PROMIS-29 was used, no total score was reported
k. Downgraded for imprecision because the confidence interval crosses both the line of appreciable harm and null effect

Ipilimumab/nivolumab compared to SoC in renal cell carcinoma

Patient or population: Renal cell carcinoma, irrespective of PD-L1 expression or IMDC (International Metastatic Renal Cell Carcinoma Database Consortium) risk classification
Intervention: Ipilimumab/nivolumab
Comparison: SoC (sunitinib)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with ipilimumab/nivolumab**				
Overall survival (OS) follow-up: median 92.6 months[a]	**At 2 years**		**HR 0.72** (0.62 to 0.84) [death]	1178 (2 RCTs)[c]	⨁⨁◯◯ Low[d,e,f]	The evidence suggests ipilimumab/nivolumab increases overall survival.
	60 per 100[b]	**69 per 100** (65 to 73)				
	At 5 years					
	36 per 100	**48 per 100** (42 to 53)				
	The median OS was **36.9** months	median **13 months more** (6.5 more to 20.8 more)				
Progression-free survival follow-up: median 92.6 months[a]	**At 1 year**		**HR 0.96** (0.66 to 1.40) [disease progression or death]	1169 (2 RCTs)[g]	⨁⨁◯◯ Low[e,f,h]	Ipilimumab/nivolumab may result in little to no difference in progression-free survival at 1 year.
	43 per 100	**45 per 100** (31 to 58)				
Health-related quality of life assessed with: FACT-G Scale from: 0 to 108 follow-up: 103 weeks from baseline	The mean health-related quality of life was **-3.10** change score from baseline[i]	MD **6.28 change score from baseline higher** (2.6 higher to 9.96 higher)	-	923 (1 RCT)	⨁⨁◯◯ Low[j,k]	Ipilimumab/nivolumab may increase health-related quality of life slightly.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	78 per 100	**64 per 100** (50 to 81)	**RR 0.82** (0.64 to 1.04)	1223 (2 RCTs)	⨁⨁◯◯ Low[f,j,l]	Ipilimumab/nivolumab may reduce adverse events (CTCAE ≥ 3) irrespective of treatment attribution slightly.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Weight-adjusted median follow-up across studies
b. Control group estimate from CheckMate 214
c. BIONIKK (NCT02960906) [172-174]; CheckMate 214 (NCT02231749) [175-177]
d. Downgraded for indirectness due to 44% of patients in the control arm of CheckMate 214 subsequently received at least part of the investigational treatment (nivolumab), potentially resulting in an underestimation of the effect
e. Downgraded for imprecision; the CI crosses the line of appreciable benefit at 0.75
f. Publication bias not applicable due to prespecified selection process
g. PFS in BIONIKK was only reported for the ccrcc2 subgroup
h. Although the distinct biomolecular tumour subtypes in the BIONIKK trial might have affected the relative effect estimate, considering the trial's weight in the meta-analysis, we did not downgrade for either indirectness or inconsistency
i. Datapoints extracted from the corresponding plot in CheckMate 214; not reported directly in trial publications
j. Downgraded for performance and detection bias due to the subjectivity of outcomes, at least in part, and open-label trial design
k. Downgraded for imprecision; the CI crosses the line of minimal important difference at 7
l. Downgraded for imprecision; the CI crosses the benefit and null effect lines

Pembrolizumab-containing combination regimens compared to SoC in renal cell carcinoma

Patient or population: Renal cell carcinoma, irrespective of PD-L1 expression or IMDC risk classification
Intervention: Pembrolizumab-containing combination regimens (pembrolizumab + axitinib or pembrolizumab + lenvatinib)
Comparison: SoC (sunitinib)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with pembrolizumab-containing combination regimens**				
Overall survival (OS) follow-up: median 59.2 months[a]	**At 2 years**		**HR 0.83** (0.72 to 0.94) [death]	1573 (2 RCTs)[c]	⊕⊕◯◯ Low[d,e,f]	Pembrolizumab-containing combination regimens may increase overall survival slightly. Considering the high proportion of patients in the control arms subsequently receiving ICIs, the effect might be underestimated.
	67 per 100	**72 per 100** (69 to 75)				
	At 5 years					
	37 per 100	**44 per 100** (39 to 49)				
	The median OS was **46.9** months[b]	median **9.6 months more** (3 more to 18.3 more)				
Progression-free survival follow-up: median 37.1 months	**At 1 year**		**HR 0.54** (0.33 to 0.86) [disease progression or death]	1573 (2 RCTs)	⊕⊕⊕◯ Moderate[e,f,g]	Pembrolizumab-containing combination regimens likely reduces progression-free survival.
	43 per 100	**64 per 100** (49 to 76)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC QLQ-C30 Scale from: 0 to 100 follow-up: mean 41.6 weeks from baseline[h]	The mean global Health Score/Quality of Life was **-4.33** change score from baseline[i]	MD **0.34 change score from baseline lower** (2.78 lower to 2.1 higher)	-	1543 (2 RCTs)	⊕⊕⊕◯ Moderate[j]	Pembrolizumab-containing combination regimens likely results in little to no difference in global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	69 per 100	**76 per 100** (71 to 81)	**RR 1.11** (1.04 to 1.18)	1546 (2 RCTs)	⊕⊕⊕◯ Moderate[f,j]	Pembrolizumab-containing combination regimens likely increase adverse events (CTCAE ≥ 3) irrespective of treatment attribution slightly.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Longest reported weight-adjusted median follow-up across studies
b. 2- and 5-year baseline risk and median OS are pooled estimates of included trials' control groups
c. CLEAR (NCT02811861) [178-181]; Keynote-426 (NCT02853331) [182-186]
d. In both studies, control group patients subsequently received ICIs (60.5% in CLEAR and 48.7% in Keynote-426), justifying a downgrade for indirectness
e. Downgraded for imprecision; the CI crosses the line of appreciable benefit at 0.75
f. Publication bias not applicable due to the prespecified selection process
g. Even though a high I^2 of 92% suggests significant heterogeneity, both effect estimates are on the left side of the line of appreciable benefit and exclude the null effect; we did not downgrade for inconsistency
h. Timepoints reported differed in that CLEAR reported the endpoint at 46 weeks and Keynote-426 at 30 weeks after the start of treatment
i. Weight-adjusted mean change score from baseline across trials' control arms
j. Downgraded for performance and detection bias owing to the outcome's partially subjective nature and open-label trial design

Atezolizumab-based treatment regimens compared to SoC for hepatocellular carcinoma

Patient or population: Hepatocellular carcinoma, irrespective of PD-L1 expression
Intervention: Atezolizumab-based treatment regimens (atezolizumab + bevacizumab)
Comparison: SoC (sorafenib)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with atezolizumab-based treatment regimens**				
Overall survival (OS) follow-up: median 15.6 months	**At 1.5 years**		**HR 0.66** (0.52 to 0.85) [death]	501 (1 RCT)[b]	⊕⊕⊕◯ Moderate[c,d,e]	Atezolizumab-based treatment regimens likely increases overall survival.
	40 per 100[a]	**55 per 100** (46 to 62)				
	The median OS was **13.4** months	The median OS was **6.9 months more** (2.4 more to 12.4 more)[f]				
Progression-free survival (PFS) follow-up: median 15.6 months	**At 1 year**		**HR 0.65** (0.53 to 0.81) [disease progression or death]	501 (1 RCT)	⊕⊕⊕◯ Moderate[c,e]	Atezolizumab-based treatment regimens may increase progression-free survival.
	21 per 100[g]	**36 per 100** (28 to 44)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 15 weeks from baseline	The mean GHS/QoL was **-5.83** change score from baseline	MD **2.54 change score from baseline higher** (1.31 lower to 6.39 higher)	-	481 (1 RCT)	⊕⊕⊕◯ Moderate[h]	Atezolizumab-based treatment regimens likely results in little to no difference in global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	63 per 100	**70 per 100** (61 to 80)	**RR 1.11** (0.97 to 1.28)	485 (1 RCT)	⊕◯◯◯ Very low[c,h,i]	Atezolizumab-based treatment regimens may result in little to no difference in adverse events (CTCAE ≥ 3) irrespective of treatment attribution. Patients in the investigational arm had a substantially longer exposure to the treatment and, therefore, a higher likelihood of experiencing adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 18-month overall survival rate (40%) in control arm as directly reported in publication
b. IMbrave 150 (NCT03434379) [187-189]
c. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process
d. In the control arm 26% subsequently received immunotherapy upon progression, and another TKI in 33%; similarly 32% of patients in the investigational arm received TKIs at disease progression, which is why we did not downgrade for indirectness
e. Downgraded for imprecision (confidence interval crosses defined appreciable effect at 0.75; single study only)
f. The corresponding difference in median survival time was calculated using the directly reported median survival estimate from the relevant trial's control arm and the pooled HR and CIs, assuming proportional hazards throught the trial's follow-up period
g. 12-month PFS rate in control arm extracted from survival plot reported in publication
h. Downgraded for risk of performance and detection bias due to open-label design
i. Downgraded by two levels for imprecision (CI crosses line of appreciable harm at 1.25 as well as the null effect line)

Durvalumab monotherapy compared to SoC for hepatocellular carcinoma

Patient or population: Hepatocellular carcinoma, irrespective of PD-L1 expression
Intervention: Durvalumab monotherapy
Comparison: SoC (sorafenib)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with durvalumab monotherapy**				
Overall survival (OS) follow-up: median 47.9 months[a]	**At 2 years**		**HR 0.86** (0.74 to 1.01) [death]	778 (1 RCT)[c]	⊕⊕◯◯ Low[d,e,f]	Durvalumab monotherapy may increase overall survival slightly.
	33 per 100[b]	**38 per 100** (32 to 44)				
	At 4 years					
	15 per 100	**20 per 100** (15 to 25)				
	The median OS was **13.8** months	The median OS was **2.25 months more** (0.14 fewer to 4.85 more)[g]				
Progression-free survival (PFS) follow-up: median 32.4 months[h]	**At 1 year**		**HR 1.02** (0.88 to 1.19) [disease progression or death]	778 (1 RCT)	⊕⊕⊕◯ Moderate[d,j]	Durvalumab monotherapy may result in little to no difference in progression-free survival. Cross-over in study not reported.
	33 per 100[h]	**32 per 100** (27 to 38)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 24 weeks from baseline	The mean GHS/QoL was **-6.08** change score from baseline[j]	MD **4.3 change score from baseline higher** (0.41 higher to 8.19 higher)[k]	-	778 (1 RCT)	⊕⊕⊕◯ Moderate[i,j]	Durvalumab monotherapy may result in little to no difference in global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution[l]	60 per 100	**44 per 100** (38 to 51)	**RR 0.73** (0.64 to 0.85)	762 (1 RCT)	⊕⊕◯◯ Low[d,i,m]	Durvalumab monotherapy may reduce adverse events (CTCAE ≥ 3).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. Weight-adjusted mean follow-up across treatment arms
b. 24- and 48-months overall survival rates in control arm directly reported in the publication
c. HIMALAYA (NCT03298451) [190-192]
d. Inconsistency not applicable (single trial only); publication bias not applicable due to the prespecified selection process
e. Downgraded for imprecision by two levels (confidence interval crosses line of null effect and line of appreciable benefit at 0.75; single study only)
f. Participants received subsequent anticancer therapy in 44.0% and 45.8% in the durvalumab monotherapy and sorafenib arms, respectively. Switching upon progression, to receive ICIs in the control arm occurred at 23.4% of cases. Considering switching in the intervention arm to receive targeted therapies, we did not downgrade for indirectness
g. The corresponding difference in median survival time was calculated using the directly reported median survival estimate from the relevant trial's control arm and the pooled HR and CIs, assuming proportional hazards throughout the trial's follow-up period
h. PFS-rate in control arm extracted from survival plot reported in publication with shorter follow-up (32.4 months, weighted median) because longer follow-up publication did not report PFS data
i. Downgraded for risk of performance and detection bias due to open-label design
j. Values estimates were extracted from the graph representing the point estimates and confidence intervals, since the outcome was only reported narratively
k. Though showing statistical significance, the CI did not cross the line for minimal important difference at 10, therefore we did not downgrade for imprecision
l. Safety data from primary publication; no adverse events stratified by CTCAE class reported in longer-term follow-up publication
m. Downgraded for imprecision (confidence interval crosses defined appreciable effect; single study only)

Durvalumab/tremelimumab compared to SoC for hepatocellular carcinoma

Patient or population: Hepatocellular carcinoma, irrespective of PD-L1 expression
Intervention: Durvalumab/tremelimumab (STRIDE regimen of single tremelimumab regular interval durvalumab)
Comparison: SoC (sorafenib)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with durvalumab/ tremelimumab**				
Overall survival (OS) follow-up: median 48.2 months[a]	**At 2 years**		**HR 0.78** (0.67 to 0.92) [death]	782 (1 RCT)[c]	⊕⊕⊕◯ Moderate[d,e,f]	Durvalumab/tremelimumab likely increases overall survival slightly.
	33 per 100[b]	**42 per 100** (36 to 47)				
	At 4 years					
	15 per 100	**23 per 100** (18 to 28)				
	The median OS was **13.8** months	The median OS was **3.9 months more** (1.2 more to 6.8 more)[g]				
Progression-free survival (PFS) follow-up: median 32.7 months[h]	**At 1 year**		**HR 0.90** (0.77 to 1.05) [disease progression or death]	782 (1 RCT)	⊕⊕◯◯ Low[d,i,j]	Durvalumab/tremelimumab may increase progression-free survival slightly.
	33 per 100[h]	**37 per 100** (31 to 43)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 24 weeks from baseline	The mean GHS/QoL was **-6.08** change from baseline[k]	MD **0.35 change score from baseline lower** (4.21 lower to 3.51 higher)	-	782 (1 RCT)	⊕⊕⊕◯ Moderate[j,k]	Durvalumab/tremelimumab may result in little to no difference in global Health Score/Quality of Life compared to SoC.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution[l]	60 per 100	**58 per 100** (52 to 66)	**RR 0.98** (0.87 to 1.10)	762 (1 RCT)	⊕⊕⊕◯ Moderate[d,i,j]	Durvalumab/tremelimumab likely results in little to no difference in adverse events (CTCAE ≥ 3) irrespective of treatment attribution.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Weight-adjusted mean follow-up across respective treatment arms
b. 24- and 48-months overall survival rates in control arm directly reported in publication
c. HIMALAYA (NCT03298451) [190-192]
d. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process
e. Participants received subsequent anticancer therapy in 42.2% and 45.8% in the durvalumab/tremelimumab and sorafenib arms, respectively. Switching upon progression, to receive ICIs in the control arm occurred at 23.4% of cases. Considering, switching in the intervention arm to receive targeted therapies, we did not downgrade for indirectness
f. Downgraded for imprecision (CI crosses defined appreciable effect at 0.75; single study only)
g. The corresponding difference in median survival time was calculated using the directly reported median survival estimate from the relevant trial's control arm and the pooled HR and CIs, assuming proportional hazards throughout the trial's follow-up period
h. PFS-rate in control arm extracted from survival plot reported in publication with shorter follow-up (32.4 months, weighted median) because longer follow-up publication did not report PFS data
i. Downgraded for imprecision (confidence interval crosses line of null effect; single study only)
j. Downgraded for risk of performance and detection bias due to open-label design
k. Values estimates were extracted from the graph representing the point estimates and confidence intervals, since the outcome was only reported narratively
l. Safety data from main publication; no adverse events stratified by CTCAE class reported in longer-term follow-up publication

Durvalumab-based treatment regimen compared to SoC for biliary tract cancer

Patient or population: Biliary tract cancer, irrespective of PD-L1 expression
Intervention: Durvalumab-based treatment regimen (durvalumab + cisplatin/gemcitabine)
Comparison: SoC (cisplatin + gemcitabine)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with durvalumab-based treatment regimen**				
Overall survival (OS) follow-up: median 22.9 months[a]	**At 1 year**		**HR 0.76** (0.64 to 0.91) [death]	685 (1 RCT) [c]	⊕⊕⊕◯ Moderate[d,e,f]	Durvalumab-based treatment regimens likely increases overall survival slightly.
	47 per 100[b]	**56 per 100** (50 to 61)				
	At 1.5 years					
	24 per 100	**34 per 100** (27 to 40)				
	The median OS was **11.3** months	The median OS was **3.6 months more** (1.1 more to 6.4 more)[g]				
Progression-free survival (PFS) follow-up: median 16.4 months	**At 1 year**		**HR 0.75** (0.63 to 0.89) [disease progression or death]	685 (1 RCT)	⊕⊕⊕◯ Moderate[d,e]	Durvalumab-based treatment regimens likely increases progression-free survival.
	6 per 100[h]	**12 per 100** (8 to 17)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 9.9 months from baseline	The mean GHS/QoL was **0.35** change score from baseline	MD **0.88 change score from baseline higher** (1.8 fewer to 3.65 more)	-	646 (1 RCT)	⊕⊕⊕◯ Moderate[d,i]	Durvalumab-based treatment regimens may result in little to no difference in global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution[j]	79 per 100	**78 per 100** (72 to 84)	**RR 0.98** (0.91 to 1.06)	680 (1 RCT)	⊕⊕⊕⊕ High	Durvalumab-based treatment regimens likely results in little to no difference in adverse events (CTCAE ≥ 3) irrespective of treatment attribution.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Weight-adjusted median follow-up across treatment arms
b. 12-month survival rate in control arm extracted from KM-curve; 18-month overall survival rate directly reported in publication
c. TOPAZ-1 (NCT03875235) [132, 133, 193]
d. Inconsistency not applicable (single trial only); publication bias not applicable due to prespecified selection process
e. Downgraded for imprecision (confidence interval crosses defined appreciable effect at 0.75; single study only)
f. Only 7% of trial participants in the control arm subsequently received immunotherapy therefore we did not downgrade for imprecision
g. The corresponding difference in median survival time was calculated using the directly reported median survival point estimate from the relevant trial publication and the pooled HR and CIs (assuming proportional hazards throughout the trial follow-up period)
h. 12-months progression-free survival rate (6%) in control arm extracted from survival plot reported in publication with shorter follow-up, because long term follow-up publication did not report progression-free survival data
i. Downgraded for risk of attrition bias (considerable proportion of participants without QoL assessments)
j. Safety data from safety analysis set; number of any adverse events of maximum grade 3 and 4 added to number of adverse events leading to death

Pembrolizumab-based treatment regimens compared to SoC for OESCC with PD-L1 CPS ≥ 10

Patient or population: Oesophageal squamous cell carcinoma with PD-L1 CPS ≥ 10
Intervention: Pembrolizumab-based treatment regimens
Comparison: SoC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with pembrolizumab-based treatment regimens**				
Overall survival follow-up: median 22.6 months	**At 2 years**		**HR 0.57** (0.43 to 0.75) [death from any cause]	286 (1 RCT) [b,c]	⨁⨁◯◯ Low[d,e,f,g]	Pembrolizumab-based treatment regimens may increase overall survival.
	15 per 100[a]	**34 per 100** (24 to 44)				
	The median OS was **8.8** months[h]	The median OS was **6.64 months more** (2.93 more to 11.67 more)				
Progression-free survival (PFS) follow-up: median 22.6 months	**At 2 years**		**HR 0.53** (0.40 to 0.60) [disease progression or death]	286 (1 RCT)[b,i]	⨁⨁◯◯ Low[d,f,g,j]	Pembrolizumab-based treatment regimens may increase progression-free survival.[d,e,f]
	4 per 100	**17 per 100** (13 to 26)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC QLQ-C30 Scale from: 0 to 100 follow-up: 18 weeks from baseline	The mean GHS/QoL was **0.5** change score from baseline	MD **1.95 change score from baseline lower** (7.72 lower to 3.82 higher)[k]	-	274 (1 RCT)[b]	⨁⨁◯◯ Low[d,f,g,l]	Pembrolizumab-based treatment regimens may result in little to no difference in health-related quality of life, but the evidence is very uncertain.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution[m]	83 per 100	**86 per 100** (81 to 92)	**RR 1.03** (0.97 to 1.10)	740 (1 RCT)	⨁⨁◯◯ Low[d,f,g,m]	Pembrolizumab-based treatment regimens may result in little to no difference in adverse events (CTCAE ≥ 3), but the evidence is very uncertain.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. 24-months overall survival rate (15%) in control arm directly reported in publication for prespecified subgroup population of individuals with oesophageal squamous cell carcinoma and PD-L1 CPS ≥ 10
b. Outcome data stems from prespecified subgroup analysis of individuals with oesophageal squamous cell carcinoma and a PD-L1 CPS ≥ 10
c. Keynote-590 (NCT03189719) [194-196]
d. Downgraded for serious risk of attrition bias (approximately 10% of patients left study because of patient or physicians decision in each arm)
e. Downgraded for imprecision (defined appreciable effect of 0.25 crossed by confidence interval; single trial only)
f. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process
g. No cross-over between treatment groups was allowed
h. The corresponding difference in median survival time was calculated by means of the directly reported median survival point estimate from the relevant trial publication and the pooled HR and CIs (assuming proportional hazards throughout the trial follow-up period)
i. 24-months progression-free survival rate (approx. 3.5%) in control arm estimated from survival curve reported for progression-free survival of complete population with PD-L1 CPS ≥10 irrespective of oesophageal carcinoma type, because not data or plot for subgroup with squamous cell carcinoma and PD-L1 CPS ≥ 10 were reported
j. Downgraded for imprecision due to the small sample size and risk of type II error
k. The difference in the least squares mean change from baseline as directly reported in the trial publication for the prespecified subgroup of individuals with oesophageal squamous cell carcinoma and a PD-L1 CPS ≥10
l. Downgraded for imprecision (line of null effect crossed by confidence interval; single trial only)
m. Adverse event data were not reported separately in Keynote-590 for the PD-L1 CPS ≥ 10 subpopulation. We did not judge the PD-L1 expression to lead to sufficient indirectness for adverse event outcomes that would justify downgrade for indirectness

Nivolumab-based treatment regimens compared to SoC for OESCC with PD-L1 ≥ 1% expression

Patient or population: Oesophageal squamous cell carcinoma with PD-L1 ≥ 1% expression (TC/TPS ≥ 1%)
Intervention: Nivolumab-based treatment regimens
Comparison: SoC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with nivolumab-based treatment regimens**				
Overall survival (OS) follow-up: median 39.5 months	**At 2 years**		**HR 0.59** (0.46 to 0.76) [death]	315 (1 RCT)[c]	⨁⨁◯◯ Low[d,e,f]	Nivolumab-based treatment regimens may increase overall survival.
	12 per 100[a]	**29 per 100** (20 to 38)				
	At 3 years					
	10 per 100[b]	**26 per 100** (17 to 35)				
	The median OS was **9.1** months	The median OS was **6.3 months more** (2.9 more to 10.7 more)[g]				
Progression-free survival (PFS) follow-up: 39.5 months	**At 1 year**		**HR 0.67** (0.51 to 0.89) [disease progression or death]	315 (1 RCT)	⨁⨁⨁◯ Moderate[f]	Nivolumab-based treatment regimens likely increases progression-free survival.
	10 per 100[b]	**21 per 100** (13 to 31)				
Health-related quality of life (HR-QoL) assessed with: FACT-Esophageal Scale from: 0 to 176 follow-up: 49 weeks from baseline	The mean HR-QoL was **1.54** change score from baseline	MD **3.44 change score from baseline higher** (0.03 lower to 6.91 higher)	-	522 (1 RCT)	⨁⨁⨁◯ Moderate[h,i,j]	Nivolumab-based treatment regimens likely result in little to no difference in health-related quality of life.
Adverse events (CTCAE ≥ 3)	37 per 100	**49 per 100** (41 to 59)	**RR 1.33** (1.11 to 1.61)	614 (1 RCT)	⨁⨁◯◯ Low[f,h,k,l]	Nivolumab-based treatment regimens may increase adverse events (CTCAE ≥ 3).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 24-month overall survival rate (12%) and 12-months progression-free survival rate (10%) in control arm as directly reported in publication
b. 36-months overall survival rate (10%) in control arm extracted from survival plot reported in publication
c. CheckMate 648 (NCT03143153) [197, 198]
d. Inconsistency not applicable (single trial only); publication bias not applicable due to prespecified selection process
e. Participants in the comparator arm received subsequent ICI treatment in 15.9% of cases (irrespective of PD-L1 expression) in CheckMate 648, which potentially leads to underestimation of the effect. In conjunction with the suggested imbalance in trial withdrawals due to deviations from the intended treatment in the open-label design, a downgrade by 1 is justified
f. Downgraded for imprecision because confidence interval crosses defined appreciable effect at 0.75 or 1.25, and risk of type II error due to the low sample size
g. The corresponding difference in median survival time was calculated by means of the directly reported median survival point estimate from the relevant trial publication and the pooled HR and CIs (assuming proportional hazards throughout the trial follow-up period)
h. Downgraded for risk of performance and detection bias due to open-label design
i. Quality of life data were not reported separately for the PD-L1 ≥ 1% subpopulation, but authors state that findings were similar to all randomized patients, not justifying a downgrade
j. The effect estimate and CI do not cross the line of MID of 9.5
k. Adverse event data were not reported separately in CheckMate 648 for the TC PD-L1 ≥ 1% subpopulation. We did not judge the tumour's PD-L1 expression to lead to sufficient indirectness for adverse event outcomes that would justify downgrade for indirectness
l. Only treatment-related adverse events were reported in CheckMate 648, no any-cause adverse events could be extracted

Ipilimumab/nivolumab compared to SoC for OESCC with PD-L1 ≥ 1% expression

Patient or population: OESCC with PD-L1 ≥ 1% expression (TC/TPS ≥ 1%)
Intervention: Ipilimumab/nivolumab-based treatment regimens
Comparison: SoC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Ipilimumab/nivolumab-based treatment regimens**				
Overall survival (OS) follow-up: median 39.7 months	**At 2 years**		**HR 0.62** (0.48 to 0.80) [death]	315 (1 RCT)[c]	⨁⨁◯◯ Low[d,e,f]	Ipilimumab/nivolumab-based treatment regimens may increase overall survival.
	12 per 100[a]	**27 per 100** (18 to 36)				
	At 3 years					
	10 per 100[b]	**24 per 100** (16 to 33)				
	The median OS was **9.1** months	The median OS was **5.6 months more** (3.7 more to 9 more)[g]				
Progression-free survival (PFS) follow-up: 39.7 months	**At 1 year**		**HR 1.04** (0.79 to 1.36) [disease progression or death]	315 (1 RCT)	⨁⨁◯◯ Low[h]	Ipilimumab/nivolumab-based treatment regimens may result in little to no difference in progression-free survival. However, the evidence is very uncertain.
	10 per 100[b]	**9 per 100** (4 to 16)				
Health-related quality of Life (HR-QoL) assessed with: FACT-Esophageal Scale from: 0 to 176 follow-up: 49 weeks from baseline	The mean HR-QoL was **1.54** change score from baseline	MD **1.91 change score from baseline more** (1.7 fewer to 5.51 more)	-	529 (1 RCT)	⨁⨁⨁◯ Moderate[i,j,k]	Ipilimumab/nivolumab-based treatment regimens likely result in little to no difference in health-related quality of life.
Adverse events (CTCAE ≥ 3)	37 per 100	**33 per 100** (27 to 41)	**RR 0.91** (0.73 to 1.13)	626 (1 RCT)	⨁⨁◯◯ Low[i,l,m,n]	Ipilimumab/nivolumab-based treatment regimens may reduce adverse events (CTCAE ≥ 3) slightly.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 24-month overall survival rate (12%) and 12-months progression-free survival rate (10%) in control arm as directly reported in publication
b. 36-months overall survival rate (10%) in control arm extracted from survival plot reported in publication
c. CheckMate 648 (NCT03143153) [197, 198]
d. Inconsistency not applicable (single trial only); publication bias not applicable due to prespecified selection process
e. Participants in the comparator arm received subsequent ICIs in 16% of cases (irrespective of PD-L1 expression) in CheckMate 648, which potentially leads to underestimation of the effect. In conjunction with the suggested imbalance in trial withdrawals due to deviations from the intended treatment in the open-label design, a downgrade by 1 is justified
f. Downgraded for imprecision; the CI crosses the line of appreciable benefit at 0.75 and risk of type II error due to low sample size
g. The corresponding difference in median survival time was calculated by means of the directly reported median survival point estimate from the relevant trial publication, the HR and corresponding CIs (assuming proportional hazards throughout the trial follow-up period)
h. Downgraded by 2 for imprecision; the CI crosses both the null-effect line as well as the line of appreciable harm at 1.25
i. Downgraded for risk of performance and detection bias due to open-label design
j. Quality of life data were not reported separately for the PD-L1 ≥ 1% subpopulation, but the authors state that findings were similar to all randomized patients
k. The effect estimate and CI do not cross the line of MID at 9.5
l. Adverse event data were not reported separately in CheckMate 648 for the TC PD-L1 ≥ 1% subpopulation. We did not judge the tumour's PD-L1 expression to lead to sufficient indirectness for adverse event outcomes that would justify downgrading for indirectness
m. Downgraded for imprecision because of a wide CI that includes appreciable benefit, the null effect line and harm
n. Only treatment-related adverse events were reported in CheckMate 648, no any-cause adverse events could be extracted

Pembrolizumab-based treatment vs SoC for ERBB2-negative gastric and gastro-oesophageal adenocarcinoma with PD-L1 ≥ 1% expression

Patient or population: ERBB2-negative gastric and gastro-oesophageal adenocarcinoma with PD-L1 ≥ 1% expression (CPS ≥ 1)
Intervention: Pembrolizumab-based treatment regimens
Comparison: SoC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with pembrolizumab-based treatment regimens**				
Overall survival (OS) follow-up: median 30.2 months[a]	**At 2 years** 18 per 100[b]	**26 per 100** (22 to 31)	**HR 0.78** (0.68 to 0.89) [death]	1742 (2 RCTs)[c]	⊕⊕◯◯ Low[d,e,f]	Pembrolizumab-based treatment regimens may increase overall survival.
	The median OS was **11.25** months[g]	The median OS was **3.17 months more** (1.39 more to 5.29 more)[h]				
Progression-free survival (PFS) follow-up: median 30.2 months	**At 2 years** 8 per 100[i]	**14 per 100** (11 to 19)	**HR 0.77** (0.66 to 0.89) [disease progression or death]	1742 (2 RCTs)	⊕⊕◯◯ Low[d,e,f]	Pembrolizumab-based treatment regimens may increase progression-free survival.
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC QLQ-C30 Scale from: 0 to 100 follow-up: 18 weeks from baseline	The mean GHS/QoL was **–0.85** change score from baseline	MD **1.25 change score from baseline more** (1.07 fewer to 3.58 more)	-	1542 (1 RCT)[j]	⊕⊕◯◯ Low[k,l,m]	Pembrolizumab-based treatment regimens likely results in little to no difference in global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution[n]	55 per 100	**61 per 100** (56 to 68)	**RR 1.11** (1.01 to 1.23)	2066 (2 RCTs)	⊕◯◯◯ Very low[f,k,o,p]	Pembrolizumab-based treatment regimens may increase adverse events (CTCAE ≥ 3). However, the evidence is very uncertain.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Median follow-up of both trials was calculated by means of a weighted median of the median follow-up in both trials. For the Keynote-859 trial, because no median follow-up duration for the eligible subgroup was reported, we used the median follow-up of the entire enrolled trial population.
b. 24-months OS (18%) in control arm directly reported in publication of Keynote 859 trial for prespecified subgroup population of individuals with PD-L1 CPS ≥1. Data from Keynote 062 trial was not used because it was judged at high risk of bias.
c. Keynote-859 (NCT03675737) [199, 200];Keynote-062 (NCT02494583) [201-203]
d. Downgraded for imprecision (line of appreciable effect crossed by confidence interval)
e. Publication bias not applicable due to prespecified selection process
f. Downgraded for risk of attrition bias (larger number of patient withdrawal in both arms (24/257 and 21/250) in addition to protocol violations)
g. Median survival in the control arm was calculated as a weighted mean of the median survival times of both included trials
h. The corresponding difference in median survival time was calculated by means of a weighted mean of the directly reported median survival point estimates from the relevant trial publications and the pooled HR and CIs (assuming proportional hazards throughout the trial follow-up periods)
i. 24-months PFS (8%) in control arm directly reported in publication of Keynote 859 trial for prespecified subgroup population of individuals with PD-L1 CPS ≥1. Data from Keynote 062 trial was not used because it was judged at high risk of bias
j. GHS/QoL data was used from the Keynote 859 only, because the Keynote 062 trial did not report such data. Data from the Keynote 859 was available for the entire randomized population only and not for the prespecified subgroup with PD-L1 CPS ≥1. Thus we rated down for indirectness.
k. Inconsistency is not applicable (single trial only), and publication bias is not applicable due to the prespecified selection process
l. Downgraded for imprecision (line of null effect crossed by confidence interval; single study only)
m. GHS/QoL data from the Keynote 859 trial was only available for the entire randomized population and not, as corresponding with the question addressed here, for the prespecified subgroup of individuals with PD-L1 CPS ≥1
n. Safety data from safety population; treatment-related adverse events
o. Downgraded for indirectness; Keynote-859 did not report adverse events for the PD-L1 ≥ 1% subpopulation but only for the entire trial population, irrespective of PD-L1 expression status and only if they occurred in at least 10% of participants in either treatment arm, potentially omitting important rare adverse events
p. Downgraded for imprecision (line of appreciable effect crossed by confidence interval)

Nivolumab-based treatment vs SoC for ERBB2-negative gastric and gastro-oesophageal adenocarcinoma with PD-L1 ≥ 5% expression

Patient or population: ERBB2-negative gastric and gastro-oesophageal adenocarcinoma with PD-L1 ≥ 5% expression (CPS ≥ 5)
Intervention: Nivolumab-based treatment regimens
Comparison: SoC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with nivolumab-based treatment regimens**				
Overall survival (OS) follow-up: median 47.35 months	**At 2 years**		**HR 0.70** (0.61 to 0.81) [death]	955 (1 RCT)[b,c]	⊕⊕⊕◯ Moderate[d,e]	Nivolumab-based treatment regimens likely increases overall survival slightly.
	19 per 100[a]	**31 per 100** (26 to 36)				
	The median OS was **11.1** months	The median OS was **4.76 months more** (2.6 more to 7.1 more)[f]				
Progression-free survival (PFS) follow-up: median 47.35 months	**At 2 years**		**HR 0.70** (0.60 to 0.81) [disease progression or death]	955 (1 RCT)[c,g]	⊕⊕◯◯ Low[d,e]	Nivolumab-based treatment regimens may increase progression-free survival slightly.
	11 per 100	**21 per 100** (17 to 27)				
Health-related quality of life (HR-QoL) assessed with: Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) Scale from: 0 to 100 follow-up: 55 weeks from baseline	The mean HR-QoL was **0.97** change score from baseline[i]	MD **6.42 change score from baseline higher** (0.67 higher to 12.17 higher)	-	797 (1 RCT)	⊕⊕⊕◯ Moderate[e,h,j]	Nivolumab-based treatment regimens likely results in little to no difference in health-related quality of life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	45 per 100	**61 per 100** (55 to 67)	**RR 1.35** (1.23 to 1.49)	1549 (1 RCT)[k]	⊕⊕◯◯ Low[d,e,h,l]	Nivolumab-based treatment regimens may increase adverse events (CTCAE ≥ 3) irrespective of treatment attribution.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 24-months overall survival rate (19%) in control arm directly reported in publication for prespecified subgroup population of individuals with PD-L1 CPS ≥5.
b. CheckMate 649 (NCT02872116) [204-206]
c. Outcome data stems from prespecified subgroup analysis of individuals with PD-L1 CPS ≥ 5
d. Downgraded for imprecision (line of defined appreciable effect at 0.75 or 1.25 crossed by confidence interval; single study only)
e. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process
f. The corresponding difference in median survival time was calculated by means of the directly reported median survival point estimate from the relevant trial publication and the pooled HR and CIs (assuming proportional hazards throughout the trial follow-up period)
g. 24-months progression-free survival rate (11%) in control arm directly reported in publication for prespecified subgroup population of individuals with PD-L1 CPS ≥5.
h. Downgraded for risk of performance and detection bias due to open-label design
i. Relevant datapoints for the LS-mean change were extracted from the provided graph; not directly reported in publication
j. Although showing a statistically significant difference, the CI did not cross the line of MIC at 15.1 for FACT-Ga; therefore we did not downgrade for imprecision
k. Data on adverse events not reported for relevant trial subgroup and data from the entire enrolled trial population was used instead
l. We did not judge the tumour's PD-L1 expression to lead to sufficient indirectness with respect to adverse event outcomes, justifying a downgrading for indirectness

Pembrolizumab monotherapy compared to SoC for dMMR/MSI-H colorectal carcinoma

Patient or population: dMMR/MSI-H colorectal carcinoma
Intervention: Pembrolizumab monotherapy
Comparison: SoC (fluoropyrimidine-based chemotherapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with pembrolizumab monotherapy**				
Overall survival (OS) follow-up: median 44.5 months	**At 3 years** 50 per 100[a]	**60 per 100** (49 to 69)	**HR 0.74** (0.53 to 1.03) [death]	307 (1 RCT)[b]	⨁⨁◯◯ Low[c,d,e]	Pembrolizumab monotherapy may increase overall survival.
	The median OS was **36.7** months	The median OS was **12.89 months more** (1.07 fewer to 32.55 more)[f]				
Progression-free survival (PFS) follow-up: median 44.5 months	**At 3 years** 39 per 100[g]	**57 per 100** (48 to 65)	**HR 0.59** (0.45 to 0.79) [disease progression or death]	307 (1 RCT)	⨁⨁◯◯ Low[c,e,h,i]	Pembrolizumab monotherapy may increase progression-free survival.
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 18 weeks from baseline	The mean GHS/QoL was **-5.63** change score from baseline	MD **8.96 change score from baseline higher** (4.24 higher to 13.69 higher)[j]	-	292 (1 RCT)	⨁⨁◯◯ Low[c,e,h,i]	Pembrolizumab monotherapy may increase global Health Score/Quality of Life slightly.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	78 per 100	**56 per 100** (47 to 66)	**RR 0.72** (0.61 to 0.85)	296 (1 RCT)	⨁⨁◯◯ Low[c,e,h,i]	Pembrolizumab monotherapy may reduce adverse events (CTCAE ≥ 3).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 36-months overall survival rate (50.3%) in control arm directly reported in publication
b. Keynote 177 (NCT02563002) [207-209]
c. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process
d. Downgraded for very serious imprecision (Confidence interval crosses line of defined appreciable effect and line of null effect; single study only)
e. Cross-over protocol specified. "At time of data cutoff, 56 of 154 patients (36%) randomly assigned to the chemotherapy group had crossed over to the pembrolizumab group after disease progression was confirmed. An additional 35 patients in the chemotherapy group received anti–PD-1 or anti–programmed death ligand 1 (anti–PD-L1) therapies outside the trial, for an effective crossover rate to anti–PD-1 or anti–PD-L1 therapy of 59%."
f. The corresponding difference in median survival time was calculated by means of the directly reported median survival point estimate from the relevant trial publication and the pooled HR and CIs (assuming proportional hazards throughout the trial follow-up period)
g. 36-months progression-free survival rate (30.9%) in control arm directly reported in publication
h. Downgraded for risk of performance and detection bias due to open-label design
i. Downgraded for imprecision (confidence interval crosses defined appreciable effect)
j. Uncertainty of absolute effect (MD) taken into account because confidence interval for MD directly reported in publication

Pembrolizumab-based treatment compared to SoC for triple-negative breast cancer with PD-L1 ≥ 10% expression

Patient or population: TNBC with PD-L1 ≥ 10% expression (CPS ≥ 10)
Intervention: Pembrolizumab-based treatment regimens
Comparison: SoC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Pembrolizumab-based treatment regimens**				
Overall survival (OS) follow-up: median 44.1 months	**At 2 years**		**HR 0.73** (0.55 to 0.95) [death]	323 (1 RCT)[b,c]	⨁⨁◯◯ Low[d,e]	Pembrolizumab-based treatment regimens may increase overall survival slightly.
	34 per 100[a]	**45 per 100** (36 to 55)				
	At 3 years					
	23 per 100	**34 per 100** (24 to 44)				
	The median OS was **16.1** months	The median OS was **6 months more** (0.8 more to 13.2 more)[f]				
Progression-free survival (PFS) follow-up: median 44.1 months	**At 1 year**		**HR 0.66** (0.50 to 0.88) [disease progression or death]	323 (1 RCT)	⨁⨁◯◯ Low[d,e,g]	Pembrolizumab-based treatment regimens may increase progression-free survival.
	23 per 100	**38 per 100** (27 to 48)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 15 weeks from baseline	The mean global Health Score/Quality of Life was **-0.88** change score from baseline	MD **1.8 change score from baseline lower** (7.33 lower to 3.73 higher)	-	317 (1 RCT)	⨁⨁⨁◯ Moderate[d,g]	Pembrolizumab-based treatment regimens likely results in little to no difference in global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	74 per 100	**78 per 100** (71 to 85)	**RR 1.06** (0.97 to 1.15)	843 (1 RCT)[h]	⨁⨁⨁◯ Moderate[h,i]	Pembrolizumab-based treatment regimens results in little to no difference in adverse events (CTCAE ≥ 3).

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Overall survival estimates in the control arm, at specific timepoints were extracted from the respective KM-curves
b. Baseline risk estimates taken from the comparator treatment arm
c. Keynote-355 (NCT02819518) [210-212]
d. Downgraded due to risk of reporting bias; analysis based on the 10% CPS cut-off was only introduced after the interim analysis and full acrual of participants
e. Downgraded by 1 due to imprecision; the CI crosses the line of appreciable benefit at 0.75
f. The corresponding difference in median survival time was calculated using the directly reported median survival point estimate from the relevant trial publication and the pooled HR and CIs (assuming proportional hazards throughout the trial follow-up period)
g. Inconsistency not applicable (single trial only); publication bias not applicable due to prespecified selection process
h. ITT population; irrespective of PD-L1 expression status
i. Downgraded by 1 for indirectness; While a link between PD-L1 expression and incidence of irAE is not clearly established, considering its correlation with tumor response patients with CPS < 10 might have experienced the competing event of tumor progression, thus having less treatment exposure and not being considered for safety follow-up

Pembrolizumab-based treatment compared to SoC in cervical cancer with PD-L1 ≥ 1% expression

Patient or population: cervical cancer with PD-L1 ≥ 1% expression (CPS ≥ 1)
Intervention: Pembrolizumab-based treatment regimens
Comparison: SoC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Pembrolizumab-based treatment regimens**				
Overall survival (OS) follow-up: median 39.1 months	**At 2 years**		**HR 0.60** (0.49 to 0.74) [death]	548 (1 RCT)[a]	⊕⊕⊕⊕ High[b,c]	Pembrolizumab-based treatment regimens result in a large increase in overall survival. Subsequent ICI exposure upon disease progression in the control arm was not reported.
	39 per 100	**57 per 100** (50 to 63)				
	At 3 years					
	27 per 100	**46 per 100** (38 to 53)				
	The median OS was **16.5** months	The median OS was **11 months more** (5.8 more to 17.2 more)				
Progression-free survival (PFS) follow-up: median 39.1 months	**At 1 year**		**HR 0.60** (0.48 to 0.75) [disease progression or death]	548 (1 RCT)	⊕⊕⊕⊕ High[b,c]	Pembrolizumab-based treatment regimens results in large increase in progression-free survival.
	34 per 100	**52 per 100** (44 to 59)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 30 weeks from baseline	The mean global Health Score/Quality of Life was **-0.8** change score from baseline	MD **1.3 change score from baseline higher** (3.02 lower to 5.62 higher)	-	519 (1 RCT)	⊕⊕⊕⊕ High[c]	Pembrolizumab-based treatment regimens results in little to no difference in global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	75 per 100	**82 per 100** (76 to 90)	**RR 1.09** (1.01 to 1.19)	616 (1 RCT)	⊕⊕⊕◯ Moderate[d]	Pembrolizumab-based treatment regimens likely increases adverse events (CTCAE ≥ 3) irrespective of treatment attribution slightly.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Keynote-826 (NCT03635567) [156-158]
b. Patient stratification and subgroup analyses according to PD-L1 expression were preplanned therefore, we did not downgrade for risk of selective outcome reporting bias
c. Inconsistency not applicable (single trial only); publication bias not applicable due to prespecified selection process
d. Adverse events were only reported if occurring in > 10% or > 20% of trial participants, potentially not accounting for rare but serious adverse events; thus, we downgraded for indirectness

Dostarlimab-based treatment compared to SoC for dMMR/MSI-H endometrial carcinoma

Patient or population: dMMR/MSI-H endometrial carcinoma
Intervention: Dostarlimab-based treatment regimens (dostarlimab + carboplatin + paclitaxel)
Comparison: SoC (carboplatin + paclitaxel)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with dostarlimab-based treatment regimens**				
Overall survival (OS) follow-up: median 36.6 months	**At 2 years**		**HR 0.32** (0.17 to 0.63) [death]	118 (1 RCT)[b]	⨁⨁◯◯ Low[c,d,e]	Dostarlimab-based treatment regimens may results in a large increase in overall survival.
	57 per 100[a]	**84 per 100** (71 to 91)				
	At 3 years					
	46 per 100	**78 per 100** (61 to 88)				
	The median overall survival was **31.4** months	The median OS was **66.7 months more** (18.4 more to 153.3 more)[f]				
Progression-free survival (PFS) follow-up: median 36.6 months	**At 1 year**		**HR 0.28** (0.16 to 0.50) [disease progression or death]	118 (1 RCT)	⨁⨁⨁◯ Moderate[d,e]	Dostarlimab-based treatment regimens likely results in a large increase in progression-free survival.
	24 per 100	**67 per 100** (49 to 80)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 19 weeks from baseline	The mean GHS/QoL was **-5.41** change score from baseline[g]	MD **9.38 change score from baseline higher** (5.45 higher to 13.31 higher)	-	115 (1 RCT)	⨁⨁◯◯ Low[d,e,h]	Dostarlimab-based treatment regimens may results in an increase in global Health Score/Quality of Life.
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	60 per 100	**72 per 100** (64 to 82)	**RR 1.20** (1.06 to 1.36)	487 (1 RCT)	⨁⨁◯◯ Low[i,j]	Dostarlimab-based treatment regimens may increase adverse events (CTCAE ≥ 3) irrespective of treatment attribution slightly.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Baseline risk at 2-year and 3-year timepoints as directly reported in OS update publication
b. RUBY (NCT03981796)
c. Downgraded for indirectness; 38.5% of patients who received the control therapy were subsequently treated with ICIs, which might lead to an underestimation of the effect
d. Downgraded for imprecision due to small sample size and risk of beta-error (OIS criterion)
e. Inconsistency not applicable (single trial only); publication bias not applicable due to prespecified selection process
f. The corresponding difference in median survival time was calculated using the directly reported median survival point estimate from the relevant trial publication and the pooled HR and CIs (assuming proportional hazards throughout the trial follow-up period). In RUBY the median OS was not reached yet in the intervention group
g. Datapoints extracted from the graph in the relevant publication
h. Downgraded for imprecision; CI crosses the line of minimal important change at 10
i. Adverse events were not reported based on the MMR/MSI-status but only for the ITT population; the potentially worse disease response in the control group may have shortened safety follow-up, biasing the outcome
j. Downgraded for imprecision; the CI crosses the line of appreciable harm at 1.25

Data summary

Characteristics of included studies

Non-small cell lung cancer

Keynote-024	
Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre, 2-arm, active controlled **Locations:** 16 countries (142 sites)
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: SqC/NSqC - Pathomolecular determinants: EGFR-, ALK- - PD-L1 status: strong as determined by IHC at central laboratory - ECOG: 0-1 - Adequate organ function (incl. GFR ≥ 60 mL/min or creatinine < 1.5x ULN) • **Key exclusion criteria** - Treatment in neoadjuvant/adjuvant setting completed at least 6 months prior to enrollement - Treatment wit systemic steroid therapy < 3 days prior to first trial dose or any other form of immunosuppressive medication - RT to lung > 30 Gy within 6 mts. prior to first dose of trial treatment - Untreated CNS metastases; if treated, radiologically stable, neurologic symptoms must have returned to baseline, if having received corticosteroids, administration must be completed at least 3 days prior to study medication - Active autoimmune disease that required systemic treatment in past 2 years, apart from hormone replacement (e.g. insulin, thyroxine, corticosteroids) or inhalatory corticosteroids (e.g. in asthma) - Active infection requiring therapy - Known history of HIV, active Hepatitis B or C, TBC - History of interstitial lung disease or pneumonitis requiring systemic glucocorticoids - Participant has received a live-virus vaccine within 30 days before first dose of study treatment - Psychiatric or substance abuse disorder that would interfere with cooperation with requirements of trial **Number of participants:** • **Randomised** - Intervention group (I): 154 - Comparator group (C): 151 • **Evaluated (efficacy analysis)** - I: 154 - C: 151 • **Evaluated (safety analysis)** - I: 154 - C: 150 **Median age:** I: 64.5 (range, 33-90), C: 66 (range, 38–85) **Female:** I: 40.3%, C: 37.1% **Never-smoker:** I: 3.2%, C: 12.6% **Brain metastases (at baseline):** I: 11.7%, C: 6.6%
Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** Pembrolizumab monotherapy **Intervention details:** • Route of administration: - Pembrolizumab: IV • Dosage: - Pembrolizumab: 200 mg (q3w) • Length of treatment cycles and day(s) of application: d1 q3w - Pembrolizumab: d1 q3w for up to 35 cycles (i.e., 2 years) **Comparator treatment(s):** Carboplatin or cisplatin/paclitaxel or pemetrexed or gemcitabine • Route of administration: - Carboplatin or cisplatin/paclitaxel or pemetrexed or gemcitabine: IV • Dosage: - Carboplatin: carboplatin AUC of 5 or 6 mg/mL/min - Cisplatin: 75 mg/m² - Paclitaxel: 200 mg/m² - Pemetrexed: 500 mg/m² - Gemcitabine: 1250 mg/m², d1/8 q3w • Length of treatment cycles and day(s) of application: d1 q3w for 4-6 cycles **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** allowed, effective crossover-rate of 66%
Outcomes according to the trial protocol	**Primary outcome(s):** • PFS – by BICR **Relevant secondary or exploratory outcome(s):**

	• OS • ORR – by BICR • Safety and tolerability • PFS2 • PROs: QLQ-C30 and LC13, EQ-5D **Longest median follow-up for survival outcomes:** 59.9 months (range, 55.1 to 68.4)
Notes	**ClinicalTrials.gov ID:** NCT02142738 **Trial status:** completed **Sponsors and collaborators:** Merck Sharp & Dohme LLC

Keynote-042

Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre, 2-arm, active-controlled **Locations:** 32 countries (213 medical centres)
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: NSqC/SqC - Pathomolecular determinants: EGFR-, ALK- - PD-L1 status: ≥ 1% (TPS) - ECOG: 0-1 - Adequate organ function (incl. GFR ≥ 50 mL/min or creatinine < 1.5x ULN) • **Key exclusion criteria** - RT to lung > 60 Gy within 6 mts. Prior to first dose of trial treatment - Known CNS metastases; if treated, no evidence of new or enlarging lesions by imaging at least 4 weeks after treatment and off steroids for at least 3 days prior to the first dose of study medication - Active, autoimmune disease that required systemic treatment in past 2 years, apart from hormone replacement (e.g. insulin, thyroxine, corticosteroids) or inhalatory corticosteroids (e.g. in asthma) - Active infection requiring therapy - Known history of HIV, active Hepatitis B or C - History of interstitial lung disease or pneumonitis requiring systemic glucocorticoids - Participant has received a live-virus vaccine within 30 days before first dose of study treatment - Psychiatric disorder and substance (drug/alcohol) abuse **Number of participants:** 1274 • **Randomised** - Intervention group (I): 299 (with PD-L1 ≥ 50%) - Comparator group (C): 300 (with PD-L1 ≥ 50%) • **Evaluated (efficacy analysis)** - I: 299 (with PD-L1 ≥ 50%) - C: 300 (with PD-L1 ≥ 50%) • **Evaluated (safety analysis)** - I: 636 (ITT) - C: 615 (ITT) **Median age:** 63 years (IQR 57-69) **Female:** I: 31%, C: 30% **Never-smoker:** I: 21%, C: 22% **Brain metastases (at baseline):** I: 6%, C: 5% **Squamous cell histology:** I: 36%, C: 38%
Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** Pembrolizumab monotherapy **Intervention details:** • Route of administration: - Pembrolizumab: IV • Dosage: - Pembrolizumab: 200 mg (q3w) • Length of treatment cycles and day(s) of application: d1 q3w - Pembrolizumab: d1 q3w for up to 35 cycles (i.e., 2 years) **Comparator treatment(s):** Carboplatin/paclitaxel or pemetrexed • Route of administration: - Carboplatin/paclitaxel or pemetrexed: IV • Dosage: - Carboplatin: carboplatin AUC of 5 or 6 mg/mL/min - Paclitaxel: 200 mg/m² - Pemetrexed: 500 mg/m² (provided non-squamous histology) • Length of treatment cycles and day(s) of application: d1 q3w for 4-6 cycles with optional pemetrexed maintenance **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** not permitted, 23% received ICIs upon progression

Outcomes according to the trial protocol	**Primary outcome(s):** • OS (by PD-L1 expression levels) **Relevant secondary or exploratory outcome(s):** • PFS – by BICR • ORR – by BICR • DOR • Safety assessment **Longest median follow-up for survival outcomes:** 56.9 months (range, 49.9 to 66.2)
Notes	**ClinicalTrials.gov ID:** NCT02220894 **Trial status:** completed **Sponsors and collaborators:** Merck Sharp & Dohme LLC

Keynote-407

Methods	**Phase:** 3 **Study design:** RCT, double-blind, multicentre, 2-arm, active and placebo-controlled **Locations:** global (17 countries)
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: SqC - Pathomolecular determinants: testing not mandated (since EGFR and ALK aberrations are uncommon in SqC NSCLC) - PD-L1 status: not required - ECOG: 0-1 - Adequate organ function (incl. GFR ≥ 60 mL/min or creatinine < 1.5x ULN) • **Key exclusion criteria** - RT to lung > 60 Gy within 6 mts. Prior to first dose of trial treatment - Active or untreated symptomatic CNS metastases; if treated, clinically stable for at least 2 weeks and off steroids 3 days before first dose of trial treatment - Preexisting peripheral neuropathy (CTCAE Grade ≥ 2) - Active, autoimmune disease that required systemic treatment in past 2 years, apart from hormone replacement (e.g. insulin, thyroxine, corticosteroids) or inhalatory corticosteroids (e.g. in asthma) - Active infection requiring therapy - Known history of HIV, active Hepatitis B or C - History of interstitial lung disease or pneumonitis requiring systemic glucocorticoids - Participant has received a live-virus vaccine within 30 days before first dose of study treatment **Number of participants:** 559 • **Randomised** - Intervention group (I): 278 - Comparator group (C): 281 • **Evaluated (efficacy analysis)** - I: 278 - C: 281 • **Evaluated (safety analysis)** - I: 278 - C: 280 **Median age:** 65 years, I: 65 (range, 29-87), C: 65 (range, 36–88) **Female:** 18.6% **Never-smoker:** 7.3% **Brain metastases (at baseline):** 7.8%
Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** Pembrolizumab + carboplatin/paclitaxel or nab-paclitaxel **Intervention details:** • Route of administration: - Pembrolizumab: IV - Carboplatin/paclitaxel or nab-paclitaxel: IV • Dosage: - Pembrolizumab: 200 mg (q3w) - Carboplatin: carboplatin AUC of 6 mg/mL/min - Paclitaxel: 200 mg/m^2 body-surface area - Nab-Paclitaxel: 100 mg/m^2 body-surface area • Length of treatment cycles and day(s) of application: d1 q3w - Pembrolizumab: d1 q3w for up to 35 cycles (i.e., 2 years) - Carboplatin/paclitaxel: d1 q3w for 4 cycles **Comparator treatment(s)** • Placebo plus carboplatin/paclitaxel or nab-paclitaxel **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** allowed, effective crossover-rate of 50.9%

Outcomes according to the trial protocol	**Primary outcome(s):** • PFS – by BICR • OS **Relevant secondary or exploratory outcome(s):** • ORR – by BICR • DOR – by BICR • Safety and tolerability • PFS2 – assessed by investigator review • PFS by irRECIST – assessed by site investigator • PFS, ORR, OS by PD-L1 status and taxane choice • PRO assessment by EORTC QLQ-C30 and QLQ-LC13, EQ-5D **Longest median follow-up for survival outcomes:** 56.9 months (range, 49.9 to 66.2)
Notes	**ClinicalTrials.gov ID:** NCT02775435 **Trial status:** completed **Sponsors and collaborators:** Merck Sharp & Dohme LLC

Keynote-021

Methods	**Phase:** 1/2 **Study design:** RCT, open-label, multicentre, multicohort **Locations:** 26 medical centres (2 countries – USA, Taiwan)
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: NSqC - Pathomolecular determinants: EGFR-, ALK- - PD-L1 status: not required - ECOG: 0-1 - Adequate organ function (incl. GFR ≥ 60 mL/min or creatinine < 1.5x ULN) • **Key exclusion criteria** - RT to lung > 60 Gy within 6 mts. Prior to first dose of trial treatment - Active or untreated symptomatic CNS metastases; if treated, clinically stable for at least 2 weeks and off steroids 3 days before first dose of trial treatment - Active, autoimmune disease that required systemic treatment in past 2 years, apart from hormone replacement (e.g. insulin, thyroxine, corticosteroids) or inhalatory corticosteroids (e.g. in asthma) - Active infection requiring therapy - Known history of HIV, active Hepatitis B or C - Symptomatic ascites or pleural effusion - History of interstitial lung disease or pneumonitis requiring systemic glucocorticoids - Participant has received a live-virus vaccine within 30 days before first dose of study treatment - Clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction or abdominal carcinomatosis - Psychiatric disorder and substance (drug/alcohol) abuse **Number of participants:** 123 • **Randomised** - Intervention group (I): 60 - Comparator group (C): 63 • **Evaluated (efficacy analysis)** - I: 60 - C: 63 • **Evaluated (safety analysis)** - I: 59 - C: 62 **Median age:** 63 years, I: 62.5 (IQR, 54-70), C: 63.2 (IQR, 58–70) **Female:** 60.9% **Never-smoker:** I: 25%, C: 14% **Brain metastases (at baseline):** I: 15%, C: 10%
Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** Pembrolizumab + carboplatin/pemetrexed **Intervention details:** • Route of administration: - Pembrolizumab: IV - Carboplatin/pemetrexed: IV • Dosage: - Pembrolizumab: 200 mg (q3w) - Carboplatin: carboplatin AUC of 5 mg/mL/min - Pemetrexed: 500 mg/m^2 body-surface area • Length of treatment cycles and day(s) of application: d1 q3w - Pembrolizumab: d1 q3w for up to 35 cycles (i.e., 2 years) - Carboplatin/pemetrexed: d1 q3w for 4 cycles, with optional pemetrexed maintenance **Comparator treatment(s)**

	• Carboplatin/pemetrexed + optional maintenance with pemetrexed **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** allowed, effective crossover-rate of 70%
Outcomes according to the trial protocol	**Primary outcome(s):** • ORR – by BICR **Relevant secondary or exploratory outcome(s):** • PFS – by BICR • OS • DOR • Safety assessment **Longest median follow-up for survival outcomes:** 56.9 months (range, 49.9 to 66.2)
Notes	**ClinicalTrials.gov ID:** NCT02039674 **Trial status:** completed **Sponsors and collaborators:** Merck Sharp & Dohme LLC Only characteristics relevant to cohort G, which investigates regimens aligned with the reviews inclusion criteria, were extracted

Keynote-189

Methods	**Phase:** 3 **Study design:** RCT, double-blind, multicentre, 2-arm, active and placebo-controlled **Locations:**
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: NSqC - Pathomolecular determinants: EGFR-, ALK- - PD-L1 status: not required - ECOG: 0-1 - Adequate organ function (incl. GFR ≥ 50 mL/min) • **Key exclusion criteria** - RT to lung > 60 Gy within 6 mts. Prior to first dose of trial treatment - Active or untreated symptomatic CNS metastases; if treated, clinically stable for at least 2 weeks and off steroids 3 days before first dose of trial treatment - Active, autoimmune disease that required systemic treatment in past 2 years, apart from hormone replacement (e.g. insulin, thyroxine, corticosteroids) or inhalatory corticosteroids (e.g. in asthma) - Chronic systemic corticosteroids - Active infection requiring therapy - Known history of HIV, active Hepatitis B or C - Symptomatic ascites or pleural effusion - History of non-infectious pneumonitis requiring systemic glucocorticoids - Clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction or abdominal carcinomatosis - Psychiatric disorder and substance (drug/alcohol) abuse **Number of participants:** 616 • **Randomised:** 2 to 1 - Intervention group (I): 410 - Comparator group (C): 206 • **Evaluated (efficacy analysis)** - I: 410 - C: 206 • **Evaluated (safety analysis)** - I: 405 - C: 202 **Median age:** 64.5 years, I: 65.0 (range, 34.0–84.0), C: 63.5 (range, 34.0–84.0) **Female:** 41% **Never-smoker:** 11.8% **Brain metastases (at baseline):** 17.5%
Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** Pembrolizumab + carboplatin/pemetrexed **Intervention details:** • Route of administration: - Pembrolizumab: IV - Carboplatin or cisplatin/pemetrexed: IV • Dosage: - Pembrolizumab: 200 mg (q3w) - Carboplatin: carboplatin AUC of 5 mg/mL/min - Cisplatin: 75 mg/m^2 body-surface area

	- Pemetrexed: 500 mg/m² body-surface area • Length of treatment cycles and day(s) of application: d1 q3w - Pembrolizumab: d1 q3w for up to 35 cycles (i.e., 2 years) - Carboplatin or cisplatin/pemetrexed: d1 q3w for 4 cycles, continued maintenance with pemetrexed d1 q3w **Comparator treatment(s)** • Placebo + carboplatin or cisplatin/pemetrexed + maintenance with placebo/pemetrexed **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** allowed, effective crossover rate of 57.3%
Outcomes according to the trial protocol	**Primary outcome(s):** • PFS – by BICR • OS (promoted to primary outcome after protocol amendment) **Relevant secondary or exploratory outcome(s):** • ORR – by BICR • DOR – by BICR • Safety and tolerability • Effect of PD-L1 expression levels on efficacy endpoints (PFS, OS, ORR) • PFS, ORR, DOR by investigator assessment • PFS, ORR, DOR by investigator assessment and irRECIST • PFS2 and OS after crossover • PRO assessment using EORTC QLQ-C30, QLQ-LC13, EQ-5D **Longest median follow-up for survival outcomes:** 64.6 months (range, 60.1 to 72.4)
Notes	**ClinicalTrials.gov ID:** NCT02578680 **Trial status:** completed **Sponsors and collaborators:** Merck Sharp & Dohme LLC

EMPOWER Lung 1

Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre, 2-arm **Locations:** global
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: SqC/NSqC - Pathomolecular determinants: NSCLC with stage IIIB/IIIC/IV disease - PD-L1 status: 50% - ECOG: 0-1 • **Key exclusion criteria** - Non-smoker - Active/known or suspected autoimmune disease requiring systemic therapy in past 2 years - PDN > 10 mg/day for immunosuppression - Hep/HIV - Active/latent TBC **Number of participants:** • **Randomised** - Intervention group (I): 356 - Comparator group (C): 354 • **Evaluated (efficacy analysis)** - I: 355 - C: 342 • **Evaluated (safety analysis)** - I: 355 - C: 342 **Median age:** 64 **Sex (female %):** 14,6%
Interventions	**Immune checkpoint inhibitor(s):** Cemiplimab **Treatment regimen:** Cemiplimab monotherapy **Intervention details:** • Route of administration: - Cemiplimab: IV • Dosage: - Cemiplimab: 350 mg • Length of treatment cycles and day(s) of application: q21d - Cemiplimab: d1 • Number of cycles: up to 36 **Comparator treatment(s)**

	• 4-6 cycles of cisplatin/carboplatin + paclitaxel/pemetrexed/gemcitabine, q21 days **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** yes
Outcomes according to the trial protocol	**Primary outcome(s):** OS, PFS **Relevant secondary or exploratory outcome(s):** ORR, AE, QoL **Longest median follow-up for survival outcomes:** 35 months
Notes	**ClinicalTrials.gov ID and status:** NCT03088540 active, not recruiting **Sponsors and collaborators:** Regeneron Pharmaceuticals and Sanofi

EMPOWER-Lung 3

Methods	**Phase:** 3 **Study design:** RCT, double-blind, multicentre, 2-part (only part 1 open-label), 2-arm, active and placebo-controlled **Locations:** global, 10 countries, 74 sites
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: SqC/NSqC - Pathomolecular determinants: EGFR-, ALK-, ROS1- - PD-L1 status: not required - ECOG: 0-1 - Adequate organ function (incl. GFR ≥ 30 mL/min) • **Key exclusion criteria** - RT to lung > 60 Gy within 6 mts. Prior to first dose of trial treatment - Active or untreated symptomatic CNS metastases; if treated, clinically stable for at least 2 weeks and off immunosuppressive dose of corticosteroid therapy - Active, autoimmune disease that required systemic treatment in past 2 years, apart from hormone replacement (e.g. insulin, thyroxine, corticosteroids) or inhalatory corticosteroids (e.g. in asthma) - Conditions requiring systemic corticosteroid therapy (> 10mg prednisone/day or equivalent) within 14 days of randomisation - Active infection requiring therapy within 14 days of randomisation - Known history of HIV, active hepatitis B or known hepatitis C - Active or latent TBC - Live vaccine within 30 days of planned start of study medication - History of interstitial lung disease or pneumonitis requiring systemic glucocorticoids - Encephalitis, meningities or uncontrolled seizures in the year prior to enrollment - Participant has received a live-virus vaccine within 30 days before first dose of study treatment - Psychiatric disorder and substance (drug/alcohol) abuse **Number of participants:** 466 • **Randomised:** 2 to 1 - Intervention group (I): 312 - Comparator group (C): 154 • **Evaluated (efficacy analysis)** - I: 312 - C: 154 • **Evaluated (safety analysis)** - I: 312 - C: 153 **Median age:** 63 years, I: 63.0 (IQR, 57-68), C: 63.0 (IQR, 57-68) **Female:** 16.1%, I: 14.1%, C: 20.1% **Never-smoker:** 14.4% **Brain metastases (at baseline):** 6.7%, I: 7.7%, C: 4.5% **Squamous cell histology:** 42.9%
Interventions	**Immune checkpoint inhibitor(s):** Cemiplimab **Treatment regimen:** Cemiplimab + carboplatin or cisplatin/pemetrexed or paclitaxel **Intervention details:** • Route of administration: - Cemiplimab: IV - Carboplatin or cisplatin/pemetrexed or paclitaxel: IV • Dosage: - Cemiplimab: 350 mg (q3w) - Carboplatin: carboplatin AUC of 5 or 6 mg/mL/min - Cisplatin: 75 mg/m^2 body-surface area - Pemetrexed: 500 mg/m^2 body-surface area - Paclitaxel: 200mg/m^2 body-surface area • Length of treatment cycles and day(s) of application: d1 q3w - Cemiplimab: d1 q3w for up to 108 weeks - Carboplatin or cisplatin/pemetrexed or paclitaxel: d1 q3w for 4 cycles + mandatory pemetrexed maintenance (if NSqC histology)

	Comparator treatment(s) • Placebo + carboplatin or cisplatin/pemetrexed or paclitaxel + mandatory pemetrexed maintenance (if NSqC histology) **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** yes
Outcomes according to the trial protocol	**Primary outcome(s):** • OS **Relevant secondary or exploratory outcome(s):** • ORR –by IRC • PFS – by IRC • Safety and tolerability • BOR – by IRC • PRO assessment using EORTC QLQ-C30, QLQ-LC13 **Longest median follow-up for survival outcomes:** 28.4 months
Notes	**ClinicalTrials.gov ID:** NCT03409614 **Trial status:** active, not recruiting **Sponsors and collaborators:** Regeneron Pharmaceuticals and Sanofi Only part 2 of the study was extracted and relevant for this review

Impower 110

Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre, 2-arm **Locations:** global
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: SqC/NSqC - Pathomolecular determinants: NSCLC with stage IV disease - PD-L1 status: 50% - ECOG: 0-1 • **Key exclusion criteria** - Known sensitizing mutation in the EGFR gene or ALK fusion oncogene - Active or untreated central nervous system (CNS) metastases - Pregnant or lactating women - History of autoimmune disease - History of idiopathic pulmonary fibrosis, organizing pneumonia, drug induced pneumonitis, idiopathic pneumonitis - HIV, hepatitis B or hepatitis C - Significant history of cardiovascular disease **Number of participants:** • **Randomised** - Intervention group (I): 285 - Comparator group (C): 287 • **Evaluated (efficacy analysis)** - I: 277 - C: 277 • **Evaluated (safety analysis)** - I: 286 - C: 263 **Median age:** 65 **Sex (female %):** 29.8%
Interventions	**Immune checkpoint inhibitor(s):** Atezolizumab **Treatment regimen:** Atezolizumab monotherapy **Intervention details:** • Route of administration: - Atezolizumab: IV • Dosage: - Atezolizumab: 1200 mg • Length of treatment cycles and day(s) of application: q21d - Atezolizumab: d1 • Number of cycles: up to 36 **Comparator treatment(s)** • 4-6 cycles of cisplatin/carboplatin + paclitaxel/pemetrexed/gemcitabine, Q3W **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** 34.7%

Outcomes according to the trial protocol	**Primary outcome(s):** OS **Relevant secondary or exploratory outcome(s):** AE, PFS, QoL **Longest median follow-up for survival outcomes:** 31.3 months
Notes	**ClinicalTrials.gov ID and status:** NCT02409342, completed **Sponsors and collaborators:** Hoffmann–La Roche/Genentech

IPSOS

Methods

Phase: 3
Study design: RCT, open-label, multicentre, 2-arm, active controlled
Locations: 23 countries (91 sites)

Participants

Eligibility criteria

- **Key inclusion criteria**
  - Histologic subtype: SqC/NSqC
  - Pathomolecular determinants: EGFR-, ALK-
  - PD-L1 status: not required
  - ECOG: 2-3 or older than 70 years with ECOG 0-1 but substantial comorbidities or contraindications for platinum-doublet chemotherapy
  - Adequate hematologic and end-organ function (e.g. creatinine < 1.5 x ULN)
- **Key exclusion criteria**
  - Untreated CNS metastases; if treated, radiologically stable, without ongoing requirement for corticosteroids as therapy for CNS disease
  - Uncontrolled tumor-related pain, pleural effusion, pericardial effusion or ascites requiring recurrent drainage
  - Patients with prior neo-adjuvant or adjuvant chemo-/radiotherapy only if treatment-free interval of at least 6 months
  - Uncontrolled symptomatic hypercalcemia
  - History of autoimmune disease (aside from well controlled DM I or autoimmune hypothyroidism)
  - Severe infection within 4 weeks prior to randomisation
  - Known history of HIV, active Hepatitis B or C, active TBC
  - History of interstitial lung disease or pneumonitis
  - Participant has received a live-virus vaccine within 30 days before first dose of study treatment
  - Psychiatric or substance abuse disorder that would interfere with cooperation with requirements of trial
  - Treatment with systemic corticosteroids or other immunosuppressive medications

Number of participants:

- **Randomised**
  - Intervention group (I): 302 (ITT)
  - Comparator group (C): 151 (ITT)
- **Evaluated (efficacy analysis)**
  - I: 50 (TC ≥ 50%)
  - C: 50 (TC ≥ 50%)
- **Evaluated (safety analysis)**
  - I: 300 (as treated)
  - C: 147 (as treated)

Median age: 75 years (IQR, 69.0 to 80.0)
Female: I: 27%, C: 28%
Never-smoker: I: 12%, C: 13%
Brain metastases (at baseline): 9%

Interventions

Immune checkpoint inhibitor(s): Atezolizumab
Treatment regimen: Atezolizumab monotherapy
Intervention details:

- Route of administration:
  - Atezolizumab: IV
- Dosage:
  - Atezolizumab: 1200 mg (q3w)
- Length of treatment cycles and day(s) of application: d1 q3w
  - Atezolizumab d1 q3w until disease progression, intolerable toxicity or death

Comparator treatment(s): vinorelbine or gemcitabine single-agent chemotherapy

- Route of administration:
  - Vinorelbine: IV or PO
  - Gemcitabine: IV
- Dosage:
  - Vinorelbine IV: 25-30 mg/m^2 d1/8, q3w or d1/8/15, q4w
  - Vinorelbine PO: 60-80 mg/m^2 d1/8, q3w or d1/8/15 q4w
  - Gemcitabine: 1000-1250 mg/m^2 d1/8 q3w or d1/8/15 q4w
- Length of treatment cycles and day(s) of application: until disease progression, intolerable toxicity or death

Treatment switching in comparator arm (crossover to receive ICIs upon progression): not allowed, 19% received subsequent immunotherapy in the comparator arm

Outcomes according to the trial protocol	**Primary outcome(s):** • OS **Relevant secondary or exploratory outcome(s):** • ORR – by investigator • PFS – by investigator • DOR – by investigator • Safety and tolerability • PROs: QLQ-C30 and LC13, EQ-5D **Longest median follow-up for survival outcomes:** 41·0 months (IQR, 36.7 to 47.8)
Notes	**ClinicalTrials.gov ID:** NCT03191786 **Trial status:** completed **Sponsors and collaborators:** Hoffmann-La Roche and Genentech Inc

CheckMate 9LA

Methods	**Phase:** 3 **Study design:** open-label, multicentre, 2-arm RCT **Locations:** 103 sites globally
Participants	**Eligibility criteria** • **Key inclusion criteria** - Advanced (not amenable to curative surgery or radiation therapy) or metastatic stage IV NSCLC of squamous or non-squamous histology - No prior primary systemic anti-cancer therapy (including EGFR and ALK inhibitors) for advanced or metastatic disease - Prior definitive chemoradiation for locally advanced disease is permitted if the last administration of chemotherapy or radiotherapy occurred at least 6 months prior to enrollment - Prior adjuvant or neoadjuvant chemotherapy for early-stage lung cancer is permitted if completed at least 6 months prior to initiating study treatment - ECOG Performance Status of ≤ 1 - Life expectancy of at least 3 months - Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site after the completion of radiation therapy • **Key exclusion criteria** - Known EGFR mutations or ALK translocations - Untreated CNS metastases - Carcinomatous meningitis - ≥ grade 2 peripheral neuropathy - Active, known or suspected autoimmune disease - Interstitial lung disease that is symptomatic or may interfere with the detection or management of drug-related pulmonary toxicity **Number of participants:** 719 • **Randomised** - Intervention group (I): 361 - Comparator group (C): 358 • **Evaluated (efficacy analysis)** - I: 361 - C: 358 • **Evaluated (safety analysis)** - I: 358 - C: 349 **Median age:** I: 65 (IQR 59–70); C: 65 (IQR 58–70) **Female:** 30% **Never-smoker:** 13.6% **Brain metastases (at baseline):** 16.9% **Squamous cell histology:** 31%
Interventions	**Immune checkpoint inhibitor(s):** ipilimumab, nivolumab **Treatment regimen:** ipilimumab plus nivolumab plus histology-based chemotherapy **Intervention details:** • Route of administration: - Ipilimumab: IV - Nivolumab: IV - Carboplatin: IV - Paclitaxel: IV - Pemetrexed: IV • Dosage: - Ipilimumab: 1 mg/kg - Nivolumab: 360 mg - Histology-based chemotherapy: see below for comparator treatment

	• Length of treatment cycles and day(s) of application: q42d
	  - Ipilimumab: d1
	  - Nivolumab: d1, d22
	  - Histology-based chemotherapy: d1, d22
	• Number of cycles: 4 cycles induction, optional discontinuation of nivolumab maintenance after two years
	Comparator treatment(s)
	• Histology-based chemotherapy for 4 cycles:
	  - Squamous histology: carboplatin AUC 6 plus paclitaxel 200 mg/m^2
	  - Non-squamous histology: carboplatin AUC 5 or 6, or cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2
	Treatment switching in comparator arm (crossover to receive ICIs upon progression): yes, 106/358 (29.6%) of patients in the control group received ICIs upon disease progression

Outcomes according to the trial protocol	**Primary outcome(s):** OS **Relevant secondary or exploratory outcome(s):** PFS, AEs, HRQoL (EQ-5D, LCSS-ASBI) **Longest median follow-up for survival outcomes:** median follow-up of 54.5 months
Notes	**ClinicalTrials.gov ID:** NCT03215706 **Trial status:** completed **Sponsors and collaborators:** Bristol Myers Squibb

POSEIDON

Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre, 3-arm, active controlled (only findings from ICI-doublet and control arms extracted) **Locations:** global, 18 countries, 142 sites

Participants	**Eligibility criteria**
	• **Key inclusion criteria**
	  - Histologic subtype: SqC/NSqC
	  - Pathomolecular determinants: EGFR-, ALK-
	  - PD-L1 status: not required
	  - ECOG: 0-1
	  - Adequate organ function (incl. GFR ≥ 40 mL/min)
	• **Key exclusion criteria**
	  - RT to lung > 60 Gy within 6 mts. Prior to first dose of trial treatment
	  - CNS metastases require being stable for 4 weeks after intervention (by imaging), return to neurological baseline, off corticosteroids for at least 5 days prior to randomisation
	  - Active or prior documented autoimmune or inflammatory disorders, incl. diverticulitis with exception of (hypothyroidism with stable hormone replacement, vitiligo, chronic skin condition not requiring systemic therapy, patients without active disease in last 5 years, celiac disease controlled by diet alon)
	  - Contraindication to platinum-based doublet chemotherapy
	  - History of active primary immunodeficiency
	  - Active infection including TBC, hepatitis B, hepatitis C or HIV
	  - Current or prior immunosuppressive medication within 14 days of first dose of durvalumab or tremelimumab, apart from inhalatory or topic corticosteroids, systemic corticosteroids at physiologic doses not exceeding 10 mg/day of prednisone equivalent, steroid premedication e.g. in case of hypersensitivity reactions
	  - Live virus vaccine within 30 days of planned start of study medication
	  - Uncontrolled intercurrent illness, including active or ongoing infection, cardiovascular, serious gastrointestinal condition or psychiatric illness/social situations that would limit compliance
	Number of participants: 675
	• **Randomised:** 1 to 1 (to 1)
	  - Intervention group (I): 338
	  - Comparator group (C): 337
	• **Evaluated (efficacy analysis)**
	  - I: 338
	  - C: 337
	• **Evaluated (safety analysis)**
	  - I: 330
	  - C: 333
	Median age: I: 63.0 (range, 27-87), C: 64.0 (range, 32-84)
	Female: I: 20.4%, C: 26.4%
	Never-smoker: I: 17.5%, C: 23.4%
	Brain metastases (at baseline): I: 9.8%, C: 13.4%
	Squamous cell histology: 36.4%

Interventions	**Immune checkpoint inhibitor(s):** Durvalumab + tremelimumab
	Treatment regimen: Durvalumab/tremelimumab + carboplatin or cisplatin/pemetrexed or nab-paclitaxel or gemcitabine (depending on SqC or NSqC histology
	Intervention details:
	• Route of administration:
	  - Durvalumab: IV
	  - Tremelimumab: IV

	- Carboplatin or cisplatin/pemetrexed or nab-paclitaxel or gemcitabine: IV • Dosage: - Durvalumab: 1500 mg (q3w for 4 cycles, thereafter q4w) - Tremelimumab: 75 mg (q3w for 4 cycles then single dose at week 16) - Carboplatin: carboplatin AUC of 5 or 6 mg/mL/min - Cisplatin: 75 mg/m^2 body-surface area - Pemetrexed: 500 mg/m^2 body-surface area - Nab-paclitaxel: 100 mg/m^2 body-surface area (d1/8/15 q3w) - Gemcitabine: 1000 or 1250 mg/m^2 body-surface area (d1/8 q3w) • Length of treatment cycles and day(s) of application: d1 q3w - Durvalumab: d1 q3w for 4 cycles and q4w thereafter - Tremelimumab: d1 q3w for 4 cycles, single dose at week 16, then stopped - Carboplatin or cisplatin/pemetrexed: d1 q3w for 4-6 cycles, pemetrexed maintenance q3w or q4w (if NSqC) - Carboplatin or cisplatin/nab-paclitaxel: d1/8/15 q3w for 4-6 cycles, pemetrexed maintenance q3w or q4w (if NSqC) - Carboplatin or cisplatin/gemcitabine: d1/8 q3w for 4-6 cycles, pemetrexed maintenance q3w or q4w (if NSqC) **Comparator treatment(s)** • Carboplatin or cisplatin/pemetrexed or nab-paclitaxel or gemcitabine followed by pemetrexed maintenance (if NSqC) **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** switching to ICI at progression, 33.2%
Outcomes according to the trial protocol	**Primary outcome(s):** PFS and OS for comparison of durvalumab + CTx vs CTx **Relevant secondary or exploratory outcome(s):** • OS • PFS – by BICR • Safety and tolerability • PFS, OS, ORR, BoR, DoR, PFS2 – by BICR and different TC expressions • PRO assessment using EORTC QLQ-C30, QLQ-LC13 and WHO/ECOG performance status assessments **Longest median follow-up for survival outcomes:** 28.4 months
Notes	**ClinicalTrials.gov ID:** NCT03164616 **Trial status:** active, not recruiting **Sponsors and collaborators:** AstraZeneca

Head and neck squamous cell carcinoma

Keynote-048	
Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre, 3-arm **Locations:** global
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: SqC - Pathomolecular determinants: head and neck squamous cell carcinoma - PD-L1 status: not required - ECOG: 0-1 • **Key exclusion criteria** - Immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy - Additional malignancy within 5 years prior to randomization - Allogeneic tissue/solid organ transplant - Active central nervous system metastases and/or carcinomatous meningitis - Autoimmune disease that has required systemic treatment in past 2 years - History of (non-infectious) pneumonitis - HIV, active Hepatitis B or C **Number of participants:** • **Randomised** - Intervention group 1 (I1): 301; Intervention group 2 (2): 281 - Comparator group (C): 300 • **Evaluated (efficacy analysis)** - I1: 301; I2: 281 - C: 300 • **Evaluated (safety analysis)** - I1: 300; I2: 276 - C: 287 **Median age:** 61,3 **Sex (female %):** 16,7%

Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** • Pembrolizumab (I1) • Pembrolizumab + cisplatin or carboplatin + 5-fluorouracil (I2) **Intervention details:** • Route of administration: - Pembrolizumab: IV • Dosage: - Pembrolizumab: 200mg • Length of treatment cycles and day(s) of application: - Pembrolizumab: q21d • Number of cycles: up to 35 **Comparator treatment(s)** • 6 cycles of cetuximab + cisplatin + carboplatin + 5-fluorouracil, Q3W **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** no
Outcomes according to the trial protocol	**Primary outcome(s):** OS, PFS **Relevant secondary or exploratory outcome(s):** AE, QoL **Longest median follow-up for survival outcomes:** 45 months
Notes	**ClinicalTrials.gov ID and status:** NCT02358031, completed **Sponsors and collaborators:** Merck Sharp & Dohme LLC

Malignant melanoma

ABC (Anti-PD1 Brain Collaboration)

Methods	**Phase:** 2 **Study design:** RCT, open-label, multicentre, 2-arm and additional non-randomized arm **Locations:** 4 sites in Australia
Participants	**Eligibility criteria** • **Key inclusion criteria** - Stage IV histologically confirmed or unknown primary melanoma - At least 1 radiological definitive brain metastasis ≥ 5 mm and ≤ 40 mm - Neurologically asymptomatic from brain metastases - ECOG: 0-2 and life expectancy > 30 days • **Key exclusion criteria** - Brain metastasis > 40 mm - Active, known or suspected autoimmune disease - PDN > 10 mg/day for immunosuppression - Prior ICI treatment **Number of participants:** • **Randomised** - Intervention group (I): 26 (full intervention cohort: 35) - Comparator group (C): 19 (full comparator cohort: 25) • **Evaluated (efficacy analysis, treatment-naïve patients in the respective full cohort)** - I: 27 - C: 19 • **Evaluated (safety analysis)** - I: 35 - C: 25 **Median age:** 61 **Sex (female %):** 20.0%
Interventions	**Immune checkpoint inhibitor(s):** Ipilimumab, nivolumab **Treatment regimen:** Ipilimumab plus nivolumab induction, nivolumab monotherapy maintenance **Intervention details:** • Route of administration: - Ipilimumab: IV - Nivolumab: IV • Dosage: - Ipilimumab: 3 mg/kg - Nivolumab: 1 mg/kg induction, 3 mg/kg maintenance • Length of treatment cycles and day(s) of application: q21d induction, q14d maintenance

	- Ipilimumab (induction): d1 - Nivolumab (induction, maintenance): d1 • Number of cycles: 4 cycles induction, up to 46 cycles maintenance **Comparator treatment(s)** • Nivolumab 3 mg/kg, q14d for up to 52 cycles **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** yes, 5 patients received ipilimumab (± PD-1 inhibitor) after intracranial progression
Outcomes according to the trial protocol	**Primary outcome(s):** intracranial response **Relevant secondary or exploratory outcome(s):** OS, PFS, AE, QoL **Longest median follow-up for survival outcomes:** 15.3 months
Notes	**ClinicalTrials.gov ID:** NCT02374242 **Trial status:** active, not recruiting **Sponsors and collaborators:** Melanoma Institute Australia, Bristol Myers Squibb

CheckMate 067

Methods	**Phase:** 3 **Study design:** RCT, double-blind, placebo-controlled, 3-arm **Locations:** 137 sites globally
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologically confirmed unresectable stage III or stage IV melanoma - Treatment naïve for unresectable or metastatic melanoma, but prior (neo-) adjuvant melanoma therapy is permitted if completed 6 weeks prior to randomization - Known PD-L1 and BRAF V600 mutational status - ECOG: 0-1 • **Key exclusion criteria** - Active brain metastases or leptomeningeal metastases - Ocular melanoma - PDN > 10 mg/day for immunosuppression - Active, known or suspected autoimmune disease - Prior ICI treatment **Number of participants:** • **Randomised** - Intervention group (I): 314 - Comparator group 1 (C1): 316 - Comparator group 2 (C2): 315 • **Evaluated (efficacy analysis)** - I: 314 - C1: 316 - C2: 315 • **Evaluated (safety analysis)** - I: 313 - C1: 313 - C2: 311 **Median age:** 61 **Sex (female %):** 35.4%
Interventions	**Immune checkpoint inhibitor(s):** Ipilimumab, nivolumab **Treatment regimen:** Ipilimumab plus nivolumab induction, nivolumab monotherapy maintenance **Intervention details:** • Route of administration: - Ipilimumab: IV - Nivolumab: IV • Dosage: - Ipilimumab: 3 mg/kg - Nivolumab: 1 mg/kg induction, 3 mg/kg maintenance • Length of treatment cycles and day(s) of application: q21d induction, q14d maintenance - Ipilimumab (induction): d1 - Nivolumab (induction, maintenance): d1 • Number of cycles: 4 cycles induction, up to 46 cycles maintenance **Comparator treatment(s)** • C1: Nivolumab 3 mg/kg, q14d for up to 52 cycles • C2: Ipilimumab 3 mg/kg, q21d for 4 cycles

	Treatment switching in comparator arm (crossover to receive ICIs upon progression): yes, 34% and 48% of patients in the control groups received subsequent immunotherapy (predominantly anti-PD-1 and anti-CTLA-4 agents)
Outcomes according to the trial protocol	**Primary outcome(s):** OS, PFS **Relevant secondary or exploratory outcome(s):** AE, QoL **Longest median follow-up for survival outcomes:** 37.4 months
Notes	**ClinicalTrials.gov ID:** NCT01844505 **Trial status:** completed **Sponsors and collaborators:** Bristol Myers Squibb

CheckMate 069

Methods	**Phase:** 2 **Study design:** RCT, open-label, multicentre, 2-arm **Locations:** 19 sites in France and the US
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologically confirmed unresectable stage III or stage IV melanoma - Treatment naïve for unresectable or metastatic melanoma, but prior (neo-) adjuvant melanoma therapy is permitted if completed 6 weeks prior to randomization - Known PD-L1 and BRAF V600 mutational status - ECOG: 0-1 • **Key exclusion criteria** - Active brain metastases or leptomeningeal metastases - Ocular melanoma - PDN > 10 mg/day for immunosuppression - Active, known or suspected autoimmune disease - Prior ICI treatment **Number of participants:** • **Randomised** - Intervention group (I): 95 - Comparator group (C): 47 • **Evaluated (efficacy analysis)** - I: 95 - C: 47 • **Evaluated (safety analysis)** - I: 94 - C: 46 **Median age:** 65 **Sex (female %):** 33%
Interventions	**Immune checkpoint inhibitor(s):** Ipilimumab, nivolumab **Treatment regimen:** Ipilimumab plus nivolumab induction, nivolumab monotherapy maintenance **Intervention details:** • Route of administration: - Ipilimumab: IV - Nivolumab: IV • Dosage: - Ipilimumab: 3 mg/kg - Nivolumab: 1 mg/kg induction, 3 mg/kg maintenance • Length of treatment cycles and day(s) of application: q21d induction, q14d maintenance - Ipilimumab (induction): d1 - Nivolumab (induction, maintenance): d1 • Number of cycles: 4 cycles induction, up to 46 cycles maintenance **Comparator treatment(s)** • Ipilimumab 3 mg/kg, q21d for 4 cycles **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** no
Outcomes according to the trial protocol	**Primary outcome(s):** ORR **Relevant secondary or exploratory outcome(s):** OS, PFS, QoL, AE **Longest median follow-up for survival outcomes:** 24.5 months
Notes	**ClinicalTrials.gov ID:** NCT01927419 **Trial status:** completed **Sponsors and collaborators:** Bristol Myers Squibb

DREAMseq/EA6134	
Methods	**Phase:** 3 **Study design:** RCT, open-label, 2-step, 2-arm **Locations:** global
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologically confirmed unresectable stage III or stage IV melanoma - BRAF V600 mutation-positive - Prior systemic treatment in the adjuvant setting allowed, except for PD-1, CTLA-1, or BRAF/MEK inhibitors - ECOG: 0-1 • **Key exclusion criteria** - Known active and definitive CNS metastases - Serious or unstable preexisting medical conditions - Active autoimmune disease or history of autoimmune disease that might recur - History of cardiovascular risks **Number of participants:** • **Randomised** - Intervention group (I): 133 - Comparator group (C): 132 • **Evaluated (efficacy analysis)** - I: 133 - C: 132 • **Evaluated (safety analysis)** - I: 126 - C: 130 **Median age:** 61 **Sex (female %):** 49%
Interventions	**Immune checkpoint inhibitor(s):** Ipilimumab, nivolumab **Treatment regimen (referring to step 1 of the RCT):** Ipilimumab plus nivolumab induction, nivolumab monotherapy maintenance **Intervention details:** • Route of administration: - Ipilimumab: IV - Nivolumab: IV • Dosage: - Ipilimumab: 3 mg/kg (or ipilimumab 1 mg/kg if nivolumab 3 mg/kg) - Nivolumab: 1 mg/kg induction (or nivolumab 3 mg/kg if ipilimumab 1 mg/kg), 3 mg/kg maintenance • Length of treatment cycles and day(s) of application: q21d induction, q14d maintenance - Ipilimumab (induction): d1 - Nivolumab (induction, maintenance): d1 • Number of cycles: 4 cycles induction, up to 46 cycles maintenance **Comparator treatment(s)** • dabrafenib 150 mg bid days 1–42 + trametinib 2 mg qd days 1–42 q6w **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** yes, patients in the control group were planned to cross over to ipilimumab/nivolumab in case of progression per protocol, and 29.5% of patients crossed over
Outcomes according to the trial protocol	**Primary outcome(s):** OS **Relevant secondary or exploratory outcome(s):** PFS, QoL, AE **Longest median follow-up for survival outcomes:** 27.7 months
Notes	**ClinicalTrials.gov ID:** NCT02224781 **Trial status:** active, not recruiting **Sponsors and collaborators:** Bristol Myers Squibb, Novartis, ECOG-ACRIN Cancer Research Group

SECOMBIT	
Methods	**Phase:** 2 **Study design:** RCT, open-label, 2-step, 2-arm **Locations:** 37 sites in Europe
Participants	**Eligibility criteria** • **Key inclusion criteria**

	- Histologic subtype: other - Pathomolecular determinants: mismatch repair–deficient (dMMR), microsatellite instability–high (MSI-H) EC - PD-L1 status: not required - ECOG: 0-1 • **Key exclusion criteria** - Uncontrolled central nervous system metastases, carcinomatosis meningitis - Serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection requiring systemic therapy - Clinically significant cardiovascular disease - Myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) **Number of participants:** • **Randomised** - Intervention group (I): 71 - Comparator group (C): 69 • **Evaluated (efficacy analysis)** - I: 69 - C: 69 • **Evaluated (safety analysis)** - I: 69 - C: 69 **Median age:** 55 **Sex (female %):** 45.7%
Interventions	**Immune checkpoint inhibitor(s):** Ipilimumab, nivolumab **Treatment regimen (referring to step 1 of the RCT):** Ipilimumab plus nivolumab induction, nivolumab monotherapy maintenance **Intervention details:** • Route of administration: - Ipilimumab: IV - Nivolumab: IV • Dosage: - Ipilimumab: 3 mg/kg - Nivolumab: 1 mg/kg induction, 3 mg/kg maintenance • Length of treatment cycles and day(s) of application: q21d induction, q14d maintenance - Ipilimumab (induction): d1 - Nivolumab (induction, maintenance): d1 • Number of cycles: 4 cycles induction, maintenance until PD **Comparator treatment(s)** • encorafenib 450 mg qd + binimetinib 45 mg bid until PD **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** yes, patients in the control group were planned to cross over to ipilimumab/nivolumab in case of progression per protocol, and 52.2% of patients crossed over
Outcomes according to the trial protocol	**Primary outcome(s):** OS **Relevant secondary or exploratory outcome(s):** AE, QoL **Longest median follow-up for survival outcomes:** 32.2 months
Notes	**ClinicalTrials.gov ID:** NCT02631447 **Trial status:** completed **Sponsors and collaborators:** Bristol Myers Squibb, Array Biopharma Inc/Pfizer, Fondazione Melanoma (ONLUS)

Renal cell carcinoma

BIONIKK	
Methods	**Phase:** 2 **Study design:** open-label, multicentre, biomarker-driven, 3-arm RCT **Locations:** 15 sites in France
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histological confirmation of RCC with a clear-cell component. Patients with TFE3 or TFEB translocation proven by cytogenetic analysis or fluorescence in situ hybridization (FISH) are eligible - Metastatic (AJCC Stage IV) RCC - No prior systemic therapy for mRCC (patients with relapse > 1 year after adjuvant treatment discontinuation are eligible) - ECOG performance status of ≤ 2 - Measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

	- Frozen or fresh tumor samples must be available and received by the central laboratory to determine molecular groups prior to randomization - Formalin-fixed, paraffin-embedded tumor tissue available for biomarker (gene expression and immunohistochemistry) analysis • **Key exclusion criteria** - Any untreated symptomatic CNS metastases - Prior systemic treatment with vascular endothelial growth factor (VEGF) or VEGF receptor targeted therapy (including, but not limited to, sunitinib, pazopanib, axitinib, and bevacizumab) except in an adjuvant setting with a free interval of more than 1 year - Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other drug specifically targeting T-cell co-stimulation or checkpoint pathways - Known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications - Any condition requiring systemic treatment with corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug - Uncontrolled adrenal insufficiency **Number of participants:** • **Randomised** - Intervention group (I): 101 (thereof included in this review: 42) - Comparator group 1 (C1): 40 (thereof included in this review: 40) - Comparator group 2 (C2): 61 (thereof included in this review: 0; arm omitted) • **Evaluated (efficacy analysis)** - I: 101 (thereof included in this review: 42) - C1: 40 (thereof included in this review: 40) - C2: 58 (thereof included in this review: 0; arm omitted) • **Evaluated (safety analysis)** - I: 101 (thereof included in this review: 42) - C1: 40 (thereof included in this review: 40) - C2: 58 (thereof included in this review: 0; arm omitted) **Median age:** ccRCC2 (I: 65 (IQR 57–69); C1: 66 (IQR 56–71)), ccRCC3 (I: 59 (IQR 49–63); C1: 64 (IQR 55–68)) **Sex (female %):** ccRCC2 (I: 10.8%; C1: 30.6%), ccRCC3 (I: 60%; C1: 75%)
Interventions	**Immune checkpoint inhibitor(s):** ipilimumab, nivolumab **Treatment regimen:** ipilimumab plus nivolumab induction, nivolumab monotherapy maintenance **Intervention details:** • Route of administration: - Ipilimumab: IV - Nivolumab: IV • Dosage: - Ipilimumab: 1 mg/kg - Nivolumab: 3 mg/kg induction, 240 mg maintenance • Length of treatment cycles and day(s) of application: q21d induction, q14d maintenance - Ipilimumab: d1 - Nivolumab: d1 • Number of cycles: 4 cycles induction, nivolumab maintenance for up to two years **Comparator treatment(s)** • Investigator's choice of sunitinib 50 mg daily for 4 weeks, and 2 weeks off continuously, or pazopanib 800 mg daily until end of study at 18 months • Patients in the second comparator group (C2), which was omitted from this review, received nivolumab 240 mg q14d for up to two years **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** yes, 20/40 (50%) of patients in the control group received nivolumab upon disease progression after TKI
Outcomes according to the trial protocol	**Primary outcome(s):** ORR per RECIST 1.1 **Relevant secondary or exploratory outcome(s):** PFS, OS, AEs **Longest median follow-up for survival outcomes:** median follow-up of 46.5 months
Notes	**ClinicalTrials.gov ID:** NCT02960906 **Trial status:** completed **Sponsors and collaborators:** Bristol Myers Squibb, Association pour la Recherche de Thérapeutiques Innovantes en Cancérologie (ARTIC) **Tumour groups:** Four biologically distinct clear cell renal cell carcinoma tumor groups were differentiated (ccRCC1: immune-low tumor micro-environment, ccRCC2: angiogenic- and immune-high, ccRCC3: molecular and pathological closest to normal kidney tissue, ccRCC4: immune-high tumor microenvironment). Patients from groups ccRCC2 and ccRCC3 were randomized between ipilimumab/nivolumab and TKI therapy, patients from groups ccRCC1 and ccRCC4 were randomized between ipilimumab/nivolumab and nivolumab. Therefore, only the groups ccRCC2 and ccRCC3 were considered for this review considering the prioritisation framework. Hence, the second comparator arm (nivolumab monotherapy) was omitted from analysis.

CheckMate 214

Methods

Phase: 3

Study design: open-label, multicentre, 2-arm RCT

Locations: 175 sites globally

Participants

Eligibility criteria

- **Key inclusion criteria**
  - Histological confirmation of RCC with a clear-cell component
  - Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC
  - No prior systemic therapy for RCC except for one prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent targeting VEGF or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy
  - Karnofsky Performance Status of at least 70%
  - Measurable disease as per RECIST 1.1
  - Favorable or intermediate and poor risk category. Categorization at registration. The favorable-risk cohort may close to enrollment earlier than the intermediate- or poor-risk cohort
- **Key exclusion criteria**
  - Any history of or current CNS metastases. Baseline imaging of the brain is required within 28 days prior to randomization
  - Prior systemic treatment with VEGF or VEGF receptor targeted therapy (including, but not limited to, sunitinib, pazopanib, axitinib, tivozanib, and bevacizumab)
  - Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
  - Known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications
  - Uncontrolled adrenal insufficiency
  - Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of sunitinib (e.g., malabsorptive disorder, ulcerative disease, or small bowel resection)

Number of participants:

- **Randomised**
  - Intervention group (I): 550
  - Comparator group (C): 546
- **Evaluated (efficacy analysis)**
  - I: 550
  - C: 546
- **Evaluated (safety analysis)**
  - I: 547
  - C: 535

Median age: 63, I: 62 (range 26–85); C: 61 (21–85)

Sex (female %): I: 24.9%; C: 27.7%

Interventions

Immune checkpoint inhibitor(s): ipilimumab, nivolumab

Treatment regimen: ipilimumab plus nivolumab induction, nivolumab monotherapy maintenance

Intervention details:

- Route of administration:
  - Ipilimumab: IV
  - Nivolumab: IV
- Dosage:
  - Ipilimumab: 1 mg/kg
  - Nivolumab: 3 mg/kg (switch to 240 mg flat dose for maintenance possible)
  - SOC as seen below
- Length of treatment cycles and day(s) of application: q21d induction, q14d maintenance
  - Ipilimumab: d1
  - Nivolumab: d1
- Number of cycles: 4 cycles induction, optional discontinuation of nivolumab maintenance after two years

Comparator treatment(s)

- Sunitinib 50 mg daily for 4 weeks on, and 2 weeks off continuously

Treatment switching in comparator arm (crossover to receive ICIs upon progression): yes, 268/546 (49.1%) of patients in the control group received an PD-(L)1 inhibitor, and 24/546 (4.4%) received ipilimumab upon disease progression

Outcomes according to the trial protocol

Primary outcome(s): OS and PFS in intermediate/poor-risk patients

Relevant secondary or exploratory outcome(s): OS, PFS in the ITT-population, AEs, HRQoL (FACT-G, FACT KSI-19, EQ-5D)

Longest median follow-up for survival outcomes: median follow-up of 67.7 months

Notes

ClinicalTrials.gov ID: NCT02231749

Trial status: active, not recruiting

Sponsors and collaborators: Bristol Myers Squibb, Ono Pharmaceutical

CLEAR

Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre **Locations:** international, 183 locations
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: clear-cell renal cell carcinoma - Pathomolecular determinants: none - PD-L1 status: positive and negative possible - ECOG: 0-1 (Karnofsky ≥70) - Adequate organ function: kidney (CrCl ≥ 30), liver (TBIL ≤ 1.5 x ULN, ALP/ALT/AST ≤ 3-5 ULN), heart (NYHA < II), bone marrow (PLT ≥ 100 G/L, ANC ≥ 1.5 G/L, Hgb ≥ 9 g/dL), coagulation (INR ≤ 1.5) • **Key exclusion criteria** - central nervous system (CNS) metastases, unless completed local therapy (example, whole brain radiation therapy (WBRT), surgery or radiosurgery) and discontinued the use of corticosteroids for this indication for at least 4 weeks - received a live vaccine in the last 30 days - major gastrointestinal absorption deficiency - HIV, interstitial lung disease, HepB, HepC, active infection, diagnosis of immunodeficiency or who are receiving chronic systemic steroid therapy - Active autoimmune disease that required systemic treatment in past 2 years (apart from replacement therapy, e.g. thyroxine, insulin) **Number of participants: 1417** • **Randomised: 1069** - Intervention group (I): 355 - Comparator group 1 (C1): 357 - Comparator group 2 (C2): 357 • **Evaluated (efficacy analysis)** - I: 355 - C1: 357 - C2: 357 • **Evaluated (safety analysis)** - I: 352 - C1: 355 - C2: 350 **Median age: 62**, I: 64, C1: 62, C2: 61 **Sex (female %): 26%,** I: 28%, C1: 25%, C2: 23%
Interventions	**Immune checkpoint inhibitor(s):** pembrolizumab **Treatment regimen:** pembrolizumab + lenvatinib **Intervention details:** • Route of administration: - Pembrolizumab: IV - Lenvatinib: PO • Dosage: - Pembrolizumab: 200mg abs. - Lenvatinib: 20mg • Length of treatment cycles and day(s) of application: q3w - Pembrolizumab: d1 - Lenvatinib: d1-21 • Number of cycles: until progression, unacceptable toxicity, completion of 35 treatments with pembrolizumab (approx. 2 years) **Comparator treatment(s)** • C1: Lenvatinib + Everolimus • C2. Sunitinib **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** No
Outcomes according to the trial protocol	**Primary outcome(s):** PFS (BICR) **Relevant secondary or exploratory outcome(s):** OS, AE, QoL (EORTC QLQ-C30, EQ-5D **Longest median follow-up for survival outcomes:** 33.7 months
Notes	**ClinicalTrials.gov ID and status:** NCT02811861; active, not recruiting **Other IDs:** KEYNOTE-581 **Sponsors and collaborators:** Eisai Inc., Merck Sharp & Dohme LLC

KEYNOTE-426	
Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre **Locations:** international, 129 locations
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: RCC with clear cell component with or without sarcomatoid features - Pathomolecular determinants: none mentioned - PD-L1 status: positive and negative possible - ECOG: 0-1, - Radiologically measurable target lesion according to RECIST 1.1 - locally advanced/metastatic disease (i.e., newly diagnosed Stage IV RCC per American Joint Committee on Cancer) or recurrent disease - no prior systemic therapy for advanced RCC. - adequate organ function - written informed consent + willingness and ability to comply with the protocol • **Key exclusion criteria** - prior treatment with any anti-programmed cell death (anti-PD-1), or programmed cell death ligand 1 (PD-L1), or PD-L2 agent or an antibody targeting any other immune-regulatory receptors or mechanisms - diagnosis of immunodeficiency OR is receiving a systemic steroid therapy exceeding physiologic corticosteroid - active malignancy except for RCC within past 36 months - cns metastases or carcinomatous meningitis - major gastrointestinal absorption deficiency - HIV, interstitial lung disease, HepB, HepC, active infection, diagnosis of immunodeficiency or who are receiving chronic systemic steroid therapy - NYHA III or IV, thrombosis or pulmonary embolism within last 6 months - llogenic tissue/solid organ transplant **Number of participants:** 861 • **Randomised** - Intervention group (I): 432 - Comparator group (C): 429 • **Evaluated (efficacy analysis)** - I: 432 - C: 429 • **Evaluated (safety analysis) → not explicitly mentioned** - I: 429 - C: 425 **Median age: 62**, I: 62, C: 61 **Sex (female %): 27%,** I: 28,7%, C: 25.4%
Interventions	**Immune checkpoint inhibitor(s):** pembrolizumab **Treatment regimen:** pembrolizumab + axitinib **Intervention details:** • Route of administration: - Pembrolizumab: IV - Axitinib: PO • Dosage: - Pembrolizumab: 200mg abs. - Axitinib: 5mg • Length of treatment cycles and day(s) of application: q3w - Pembrolizumab: d1 - Axitinib: d1-21, twice daily • Number of cycles: until progression **Comparator treatment(s)** • C: Sunitinib **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** No
Outcomes according to the trial protocol	**Primary outcome(s):** PFS, OS **Relevant secondary or exploratory outcome(s):** AE, QOL (EORTC QLQ-C30) **Longest median follow-up for survival outcomes:** median follow-up of 12.8 months, median survival was not reached in either group.
Notes	**ClinicalTrials.gov ID and status: NCT02853331, active, not recruiting**

	Other IDs: 3475-426, 163460 (Registry Identifier) (REGISTRY: JAPIC-CTI), MK-3475-426 (Other Identifier) (OTHER: Merck), 2016-000588-17 (EudraCT Number) **Sponsors and collaborators:** Merck Sharp & Dohme LLC

Hepatocellular carcinoma

HIMALAYA	
Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre, initially 4-arm, 3-arm after protocol amendment, active controlled **Locations:** 16 countries (181 sites)
Participants	**Eligibility criteria** • **Key inclusion criteria** - HCC based on histopathological confirmation - No prior systemic therapy for HCC - Barcelona Clinic Liver Cancer (BCLC) stage B (that is not eligible for locoregional therapy) or stage C - Child-Pugh Score class A - ECOG performance status of 0 or 1 at enrollment - Adequate hematologic and end-organ function • **Key exclusion criteria** - Hepatic encephalopathy within past 12 months or requirement for medication to prevent or control encephalopathy - Clinically meaningful ascites - Main portal vein tumor thrombosis - Active or prior documented GI bleeding (eg, esophageal varices or ulcer bleeding) within 12 months - HBV and HVC co-infection, or HBV and Hep D co-infection - Brain metastases or spinal cord compression **Number of participants:** • **Randomised** - Intervention group 1 (I1): 393 (ITT) - Intervention group 2 (I2): 389 (ITT) - Comparator group (C): 389 (ITT) • **Evaluated (efficacy analysis)** - I1: 393 - I2: 389 - C: 389 • **Evaluated (safety analysis)** - I1: 388 (as treated) - I2: 388 (as treated) - C: 374 (as treated) **Median age:** 64 years (range, 18 to 88) **Female:** I1: 16.8%, I2: 17%, C: 13.4%
Interventions	**Immune checkpoint inhibitor(s):** Durvalumab, tremelimumab **Treatment regimen(s):** • STRIDE regimen: tremelimumab plus Durvalumab • Durvalumab monotherapy **Intervention details:** • Route of administration: - Tremelimumab: IV - Durvalumab: IV • Dosage: - STRIDE: tremelimumab 300 mg once, durvalumab 1500 mg q28d - Durvalumab 1500 mg q28d • Length of treatment cycles and day(s) of application: d1 q28d - Treatment continued until progression, unacceptable toxicity, consent withdrawal, or other discontinuation criteria were met **Comparator treatment(s):** sorafenib • Route of administration: - Sorafenib: PO • Dosage: - Sorafenib 400 mg BID • Length of treatment cycles and day(s) of application: Treatment continued until progression, unacceptable toxicity, consent withdrawal, or other discontinuation criteria were met **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** not allowed, 17.2% received subsequent immunotherapy in the comparator arm
Outcomes according to the trial protocol	**Primary outcome(s):** • OS for STRIDE vs. sorafenib **Relevant secondary or exploratory outcome(s):**

	• OS for durvalumab vs. sorafenib • PFS • Safety and tolerability • HR-QoL: EORTC QLQ-C30, EORTC QLQ-HCC18 **Longest median follow-up for survival outcomes:** 48.2 months
Notes	**ClinicalTrials.gov ID:** NCT03298451 **Trial status:** active, not recruiting **Sponsors and collaborators:** AstraZeneca

IMbrave 150

Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre, 2-arm, active controlled **Locations:** 17 countries (111 sites)
Participants	**Eligibility criteria** • **Key inclusion criteria** - Locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma (HCC) - No prior systemic therapy for HCC. Previous use of herbal therapies/traditional Chinese medicines with anti-cancer activity included in the label is allowed, provided that these medications are discontinued prior to randomization. - At least one measurable untreated lesion - ECOG Performance Status of 0 or 1 - Adequate hematologic and end-organ function - Child-Pugh class A • **Key exclusion criteria** - Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC - History of leptomeningeal disease - Active or history of autoimmune disease or immune deficiency - Moderate or severe ascites - Co-infection of HBV and HCV - Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases - History of hepatic encephalopathy **Number of participants:** • **Randomised** - Intervention group (I): 336 (ITT) - Comparator group (C): 165 (ITT) • **Evaluated (efficacy analysis)** - I: 336 - C: 165 • **Evaluated (safety analysis)** - I: 329 (as treated) - C: 156 (as treated) **Median age:** I: 64 years (IQR, 56 to 71), C: 66 years (IQR, 59 to 71) **Female:** I: 18%, C: 17%
Interventions	**Immune checkpoint inhibitor(s):** Atezolizumab **Treatment regimen(s):** • Atezolizumab combined with bevacizumab **Intervention details:** • Route of administration: - Atezolizumab: IV - Bevacizumab: IV • Dosage: - Atezolizumab 1200 mg - Bevacizumab 15 mg/kg • Length of treatment cycles and day(s) of application: d1 q21d - Treatment continued until unacceptable toxic effects occurred or there was loss of clinical benefit **Comparator treatment(s):** sorafenib • Route of administration: - Sorafenib: PO • Dosage: - Sorafenib 400 mg BID • Length of treatment cycles and day(s) of application: Treatment continued until unacceptable toxic effects occurred or there was loss of clinical benefit **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** not allowed, 18.8% received subsequent immunotherapy in the comparator arm
Outcomes according to the trial protocol	**Primary outcome(s):** • OS • PFS (BICR) **Relevant secondary or exploratory outcome(s):**

	• ORR • DOR • Safety and tolerability • HR-QoL: EORTC QLQ-C30 **Longest median follow-up for survival outcomes:** 15.6 months (range, 0 to 28.6)
Notes	**ClinicalTrials.gov ID:** NCT03434379 **Trial status:** completed **Sponsors and collaborators:** F. Hoffmann–La Roche/Genentech

Biliary tract cancer

TOPAZ-1	
Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre **Locations:** 129 locations, international
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: Histologically confirmed, unresectable advanced or metastatic biliary tract, including cholangiocarcinoma (intrahepatic or extrahepatic) and gallbladder carcinoma - Pathomolecular determinants: none - PD-L1 status: none mentioned - ECOG: 0-1 - untreated disease if unresectable or metastatic at initial diagnosis eligible. - recurrent disease >6 months after curative surgery or >6 months after the completion of adjuvant therapy (chemotherapy and/or radiation) eligible • **Key exclusion criteria** - History of another primary malignancy - Brain metastases or spinal cord compression - Uncontrolled intercurrent illness - Major surgical procedure within 28 days prior to the first dose of IP. - Prior locoregional therapy such as radioembolization **Number of participants: 914** • **Randomised: 685** - Intervention group (I): 341 - Comparator group (C): 344 • **Evaluated (efficacy analysis)** - I: 341 - C: 344 • **Evaluated (safety analysis)** - I: 338 - C: 342 **Median age: 64** **Sex (female %): 49.6%**
Interventions	**Immune checkpoint inhibitor(s):** Durvalumab + Gemcitabine + Cisplatin **Treatment regimen:** Durvalumab + Gemcitabine + Cisplatin **Intervention details:** • Route of administration: - Durvalumab: IV - Gemcitabine + Cisplatin: IV • Dosage: - Durvalumab: 1500mg - Gemcitabine + Cisplatin: gemcitabine (1000 mg/m2) and cisplatin (25 mg/m2) • Length of treatment cycles and day(s) of application: 21-day cycle for up to eight cycles - Durvalumab: d1 - Gemcitabine + Cisplatin: d1 and d8 • Number of cycles: 8 **Comparator treatment(s)** • C: Placebo + Gemcitabine + Cisplatin **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** No

	After completion of gemcitabine and cisplatin, 1500 mg of durvalumab or placebo monotherapy was administered once every 4 weeks
Outcomes according to the trial protocol	**Primary outcome(s):** OS **Relevant secondary or exploratory outcome(s):** PFS, AE **Longest median follow-up for survival outcomes:** median duration of follow-up 16.8 months (95% CI, 14.8 to 17.7) in the durvalumab group and 15.9 months (95% CI, 14.9 to 16.9) in the placebo group
Notes	**ClinicalTrials.gov ID and status:** NCT03875235; active, not recruiting **Other IDs:** TOPAZ-1 **Sponsors and collaborators:** AstraZeneca, Investigators: Gordon Cohen

Oesophageal squamous cell carcinoma

KEYNOTE-590

Methods	**Phase:** 3 **Study design:** RCT, double-blind, placebo-controlled **Locations:** 168 sites globally
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologically- or cytologically-confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction (EGJ) - ECOG: 0-1 (Karnofsky ≥70) - Measurable disease per RECIST 1.1 as determined by the local site investigator/radiology assessment - Provided either a newly obtained or archival tissue sample for PD-L1 testing by immunohistochemistry analysis - Adequate organ function **Key exclusion criteria** - Locally advanced esophageal carcinoma that is resectable or potentially curable with radiation therapy - Previous therapy for advanced/metastatic adenocarcinoma or squamous cell cancer of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ - Major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study treatment - Known active central nervous system metastases and/or carcinomatous meningitis - Active autoimmune disease that has required systemic treatment in past 2 years - Prior therapy with an anti-programmed cell death protein-1 (anti-PD-1), anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor or has previously participated in a pembrolizumab (MK-3475) clinical trial **Number of participants:** • **Randomised** - Intervention group (I): 373 (thereof squamous cell histology, PD-L1 CPS ≥ 10: 143) - Comparator group (C): 376 (thereof squamous cell histology, PD-L1 CPS ≥ 10: 143) • **Evaluated (efficacy analysis)** - I: 373 (thereof squamous cell histology, PD-L1 CPS ≥ 10: 143) - C: 376 (thereof squamous cell histology, PD-L1 CPS ≥ 10: 143) • **Evaluated (safety analysis)** - I: 370 - C: 370 **Median age:** I: 64 (28–94), C: 62 (27–89) **Sex (female %):** I: 18.0%, C: 15.2%
Interventions	**Immune checkpoint inhibitors:** Pembrolizumab **Treatment regimen:** Pembrolizumab combined with chemotherapy (cisplatin plus 5-fluorouracil) **Intervention details:** • Route of administration: - Pembrolizumab: IV - Cisplatin: IV - 5-fluorouracil: IV • Dosage: - Pembrolizumab 200 mg - Cisplatin 80 mg/m^2 - 5-fluorouracil 800 mg/m^2 • Length of treatment cycles and day(s) of application: q21d - Cisplatin: d1

	- 5-fluorouracil: d1-d5 - Pembrolizumab: d1 • Number of cycles: up to 35 (cisplatin for a maximum of six cycles) **Comparator treatment:** • Cisplatin 80 mg/m² on day 1 + 5-fluorouracil 800 mg/m² on days 1–5 q21d for up to 35 cycles **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** no
Outcomes according to the trial protocol	**Primary outcome(s):** OS, PFS **Relevant secondary or exploratory outcome(s):** AE, QoL **Longest median follow-up for survival outcomes:** 22.6 months
Notes	**ClinicalTrials.gov ID:** NCT03189719 **Trial status:** completed **Sponsors and collaborators:** Merck Sharp & Dohme LLC

CheckMate 648

Methods	**Phase:** 3 **Study design:** RCT, open-label, 3-arm **Locations:** 182 sites globally
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologically confirmed squamous cell carcinoma or adenosquamous cell carcinoma (predominant squamous differentiation) of the oesophagus - Unresectable advanced, recurrent or metastatic OESCC - Subjects must not be amenable to curative approaches such as definitive chemoradiation and/or surgery - No prior systemic anticancer therapy given as primary therapy for advanced or metastatic disease. Prior adjuvant, neoadjuvant, or definitive, chemotherapy/radiotherapy/chemoradiotherapy for OESCC is permitted if given as part of curative intent regimen and completed before enrolment - ECOG performance status of 0 or 1 - At least one measurable lesion by CT or MRI per RECIST 1.1 - Tumor tissue must be provided for biomarker analyses - Evaluable PD-L1 expression classification ≥ 1% or < 1%, or indeterminate) as determined by central lab **Key exclusion criteria** - Subjects with adenocarcinoma - Any metastasis in the brain or meninx that is symptomatic or requires treatment - Recovered from the effects of major surgery or significant traumatic injury at least 14 days before randomization - Prior malignancy requiring active treatment within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, or breast - Active, known, or suspected autoimmune disease - Condition requiring systemic treatment with corticosteroids (> 10 mg daily PDN equivalent) or other immunosuppressive medications within 14 days of starting study treatment - Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways **Number of participants:** • **Randomised** - Intervention group 1 (I1, ipilimumab/nivolumab): 325 (thereof PD-L1 ≥ 1%: 158) - Intervention group 2 (I2, nivolumab-based regimen): 321 (thereof PD-L1 ≥ 1%: 158) - Comparator group (C): 324 (thereof PD-L1 ≥ 1%: 157) • **Evaluated (efficacy analysis)** - I1: 325 (thereof PD-L1 ≥ 1%: 158) - I2: 321 (thereof PD-L1 ≥ 1%: 158) - C: 315 (thereof PD-L1 ≥ 1%: 157) • **Evaluated (safety analysis)** - I1: 322 - I2: 310 - C: 304 **Median age:** I1: 62 (57–69), I2: 64 (57–69), C: 64 (58–70) **Sex (female %):** I1: 17.2%, I2: 21.2%, C: 15.1%
Interventions	**Immune checkpoint inhibitors:** Ipilimumab, nivolumab **Treatment regimen:** • I1 (ipilimumab/nivolumab): ipilimumab plus nivolumab induction, nivolumab monotherapy maintenance • I2 (nivolumab/chemotherapy): nivolumab plus platinum-based doublet chemotherapy **Intervention details:**

	• Route of administration: - Ipilimumab: IV - Nivolumab: IV • Dosage: - I1: ipilimumab: 1 mg/kg, nivolumab: 3 mg/kg (same dosage for induction and maintenance) - I2: nivolumab 240 mg, fluorouracil 800 mg/m², cisplatin 80 mg/m² • Length of treatment cycles and day(s) of application: q42d ipilimumab induction, q14d nivolumab induction and maintenance - Ipilimumab (induction): d1 - Nivolumab (induction, maintenance): d1 • Number of cycles: treatment with nivolumab or ipilimumab/nivolumab was limited to a maximum of 2 years **Comparator treatment:** • Fluorouracil 800 mg/m² on days 1–5 + cisplatin 80 mg/m² on day 1 Q4W **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** yes, 15.9% of patients in the control group subsequently received ICIs upon disease progression
Outcomes according to the trial protocol	**Primary outcome(s):** OS, PFS (BICR) **Relevant secondary or exploratory outcome(s):** AE, QoL **Longest median follow-up for survival outcomes:** 39.6 months
Notes	**ClinicalTrials.gov ID:** NCT03143153 **Trial status:** active, not recruiting **Sponsors and collaborators:** Bristol Myers Squibb, ONO Pharmaceutical

Gastric, oesophageal and gastro-oesophageal adenocarcinoma

CheckMate 649	
Methods	**Phase:** 3 **Study design:** Randomized, Multicenter, Open-Label, Phase 3 Study **Locations:** international, 179 locations
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: gastric cancer or gastroesophageal junction cancer adenocarcinoma NSqC - PD-L1 status: not required - ECOG: 0-1 (Karnofsky ≥70) - Has adequate organ function - Must have gastric cancer or gastroesophageal junction cancer that cannot be operated on and that is advanced or has spread out - Did not receive neoadjuvant or adjuvant treatment (chemotherapy, radiotherapy, or both) for their disease within the last 6 months - EGFR2+ excluded; previous adjuvant chemo/radiotherapy allowed - Must have full activity or, if limited, must be able to walk and carry out light activities such as light housework or office work • **Key exclusion criteria** - Presence of tumor cells in the brain or spinal cord that have not been treated - Active known or suspected autoimmune disease - Any serious or uncontrolled medical disorder or active infection - Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) - Any positive test result for hepatitis B or C indicating acute or chronic infection **Number of participants: 2687** • **Randomised: 1581** - Intervention group (I): 789 - Comparator group (C): 792 • **Evaluated (efficacy analysis)** - I: 782 - C: 776 • **Evaluated (safety analysis)** - I: 738 - C: 679 **Median age: 62**, I: 62 (range 18-88); C: 61 (21-90) **Sex (female %): 30%, I: 32%; C: 28%**
Interventions	**Immune checkpoint inhibitor(s):** Nivolumab

	Treatment regimen: Nivolumab + Chemotherapy (XELOX or FOLFOX) **Intervention details:** • Route of administration: - Nivolumab: IV - XELOX: IV, except capecitabine - orally - FOLFOX: IV • Dosage: - Nivolumab: 360 / 240 mg abs. - XELOX or FOLFOX as below indicated • Length of treatment cycles and day(s) of application: q3w - Nivolumab and chemotherapy regimen: nivolumab was administered either at a dose of 360 mg once every 3 weeks or 240 mg once every 2 weeks with investigator's choice of chemotherapy (XELOX [capecitabine 1,000 mg/m2 twice daily, days 1-14, and oxaliplatin 130 mg/m2, day 1, once every 3 weeks], or FOLFOX [leucovorin 400 mg/m2, once on day 1, fluorouracil 400 mg/m2, once on day 1 and 1,200 mg/m2, once on days 1-2, and oxaliplatin 85 mg/m2, day 1, once every 2 weeks]); Capecitabine was administered orally; all other treatments were administered intravenously - Number of cycles: Treatment continued until documented disease progression, unacceptable toxicity, withdrawal of consent, or study end. Nivolumab was given for a maximum of 2 years. **Comparator treatment(s)** • C: Chemotherapy • XELOX [capecitabine 1,000 mg/m2 twice daily, days 1-14, and oxaliplatin 130 mg/m2, day 1, once every 3 weeks], or FOLFOX [leucovorin 400 mg/m2, once on day 1, fluorouracil 400 mg/m2, once on day 1 and 1,200 mg/m2, once on days 1-2, and oxaliplatin 85 mg/m2, day 1, once every 2 weeks]); Capecitabine was administered orally; all other treatments were administered intravenously • **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** No
Outcomes according to the trial protocol	**Primary outcome(s):** OS and PFS in participants with PD-L1 CPS ≥ 5 **Relevant secondary or exploratory outcome(s):** OS in ITT population, AE, **Longest median follow-up for survival outcomes:** median follow-up 47.4 months (range, 36.2-61.5) in the nivolumab plus chemotherapy arm and 47.3 months (range, 36.6-61.3) in the chemotherapy arm
Notes	**ClinicalTrials.gov ID and status:** NCT02872116; completed **Other IDs:** CheckMate 649 **Sponsors and collaborators:** Bristol Myers Squibb

KEYNOTE-062	
Methods	**Phase:** 3 **Study design:** randomized, controlled, partially blinded phase 3 study **Locations:** international, 200 locations, 29 countires
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma, NSqC - PD-L1 status: positive (not further specified) - ECOG: 0-1 (Karnofsky ≥70) - Has adequate organ function - Human epidermal growth factor receptor 2- (HER2/neu-) negative and programmed cell death ligand 1 (PD-L1) -positive - Has measurable disease • **Key exclusion criteria** - Squamous cell or undifferentiated gastric cancer - Previous therapy for locally advanced, unresectable or metastatic gastric/GEJ cancer. Participant may have received prior neoadjuvant or adjuvant therapy as long as it was completed at least 6 months prior to randomization - Major surgery, open biopsy or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study treatment. - Known additional malignancy that is progressing or requires active treatment with the exception of basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer - Known active central nervous system (CNS) metastases and/or carcinomatous meningitis - Active autoimmune disease that has required systemic treatment in past 2 years - Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior the first dose of study medication, History of non-infectious pneumonitis that required steroids or current pneumonitis - Active infection requiring systemic therapy - Prior therapy with an anti-programmed cell death (PD)-1, anti-PD-L1, or anti-PD-L2 agent - Known history of human immunodeficiency virus (HIV), Known active Hepatitis B or C

	- Received a live vaccine within 30 days prior to the first dose of study medication **Number of participants: 1787** • **Randomised: 763** - Intervention group (I1): 257 - Intervention group (I2): 256 - Comparator group (C): 250 • **Evaluated (efficacy analysis)** - Intervention group (I1): 257 - Intervention group (I2): 256 - Comparator group (C): 250 • **Evaluated (safety analysis)** - Intervention group (I1): 250 - Intervention group (I2): 254 - Comparator group (C): 244 **Median age:** 62 (20-87) **Sex (female %):** 72.6%
Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** I1: Pembrolizumab + chemotherapy (Cisplatin + 5-FU + Capecitabine), I2: Pembrolizumab monotherapy **Intervention details:** • Route of administration: - Pembrolizumab: IV - Capecitabine: orally - 5-FU: IV - Cisplatin: IV • Dosage: - Pembrolizumab 200 mg IV - Cisplatin 80 mg/m^2 IV - 5-FU 800 mg/m^2/day IV - Capecitabine 1000 mg/m^2 twice daily • Length of treatment cycles and day(s) of application: q3w - Pembrolizumab 200 mg IV on Day 1 of each week in 3-week cycles for up to 35 cycles (approximately 2 years). - Cisplatin 80 mg/m^2 IV on Day 1 of each week in 3-week cycles (6 cycle maximum per local country guidelines). - 5-FU 800 mg/m^2/day IV continuous from Day 1-5 of each 3-week cycle. - Capecitabine 1000 mg/m^2 twice daily by oral tablet on Day 1-14 of each 3-week cycle. - Number of cycles: 35 cycles, Eligible participants who stop pembrolizumab with Stable Disease (SD) or better but progress after discontinuation may be able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion. **Comparator treatment(s)** • C: Placebo + Chemotherapy • Participants receive placebo IV Q3W plus cisplatin 80 mg/m^2 Q3W plus 5-FU 800 mg/m^2/day IV infusion on Days 1-5 Q3W. Capecitabine 1000 mg/m^2 BID on Days 1-14 Q3W may be substituted for 5-FU per local guidelines. • **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** No
Outcomes according to the trial protocol	**Primary outcome(s):** OS, PFS **Relevant secondary or exploratory outcome(s):** AE, QoL (EORTC QLQ-C30 Global Health Status/Quality of Life (Items 29 and 30) Combined Score and EORTC QLQ-Module for Gastric Cancer (STO22) Pain Symptom Subscale **Longest median follow-up for survival outcomes:** 29.4 (22.0-41.3) months
Notes	**ClinicalTrials.gov ID and status:** NCT02494583; completed **Other IDs:** KEYNOTE-062, MK-3475-062 **Sponsors and collaborators:** Merck Sharp & Dohme LLC

KEYNOTE-811	
Methods	**Phase:** 3 **Study design:** randomised, double-blind, placebo-controlled, phase 3 **Locations:** international, 192 locations
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: diagnosis of previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or GOJ adenocarcinoma - PD-L1 status: not required - ECOG: 0-1 (Karnofsky ≥70)

	- HER2-positive defined as either immunohistochemistry (IHC) 3+ or IHC 2+ in combination with in-situ hybridization positive (ISH+) or fluorescent in-situ hybridization (FISH), as assessed by central review on primary or metastatic tumor - Has measurable disease as defined by RECIST 1.1 as determined by the site investigator - Has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale within 3 days prior to the first dose of trial treatment - Has a life expectancy of greater than 6 months - Has adequate organ function • **Key exclusion criteria** - Has had previous therapy for locally advanced unresectable or metastatic gastric/GEJ cancer - Has had radiotherapy within 14 days of randomization - Has a known additional malignancy that is progressing or has required active treatment within the past 5 years - known active central nervous system (CNS) metastases and/or carcinomatous meningitis - active autoimmune disease that has required systemic treatment in past 2 years - Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy, history of (non-infectious) pneumonitis that required steroids or current pneumonitis - Has a known history of active tuberculosis (TB; Mycobacterium tuberculosis) - Has an active infection requiring systemic therapy - Has poorly controlled diarrhea - Accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to enrollment. If the participant is receiving diuretic drugs for other reasons, it is acceptable - Has peripheral neuropathy > Grade 1 - Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial - A WOCBP who has a positive urine pregnancy test within 24 hours prior to randomization or treatment allocation - Has active or clinically significant cardiac disease - Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies) - Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection - Has severe hypersensitivity (≥Grade 3) to pembrolizumab, trastuzumab, study chemotherapy agents and/or to any excipients, murine proteins, or platinum-containing products - Has had an allogeneic tissue/solid organ transplant - Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], OX 40, Cluster of Differentiation 137 [CD137]) **Number of participants: 1327** • **Randomised:** 698 - Intervention group (I): 350 - Comparator group (C): 348 • **Evaluated (efficacy analysis)** - I: 350 - C: 348 • **Evaluated (safety analysis)** - I: 350 - C: 346 **Median age: 63 (IQR 54-70)** **Sex (female %): 19%**
Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** Pembrolizumab + Trastuzumab + Chemotherapy (FP or CAPOX) **Intervention details:** • Route of administration: - Pembrolizumab: IV - CAPOX: IV, except capecitabine and S1 - orally - FP: IV • Dosage: - Pembrolizumab: 200 mg - FP or CAPOX as below indicated • Length of treatment cycles and day(s) of application: q3w - 200 mg pembrolizumab IV every 3 weeks (Q3W) plus trastuzumab (8 mg/kg loading dose, 6 mg/kg maintenance thereafter) IV Q3W in combination with FP or CAPOX chemotherapy (Global Cohort) or SOX chemotherapy (Japan cohort) - Trastuzumab: 8 mg/kg loading dose and then 6 mg/kg maintenance dose administered IV on day 1 of each 3-week cycle.

	- FP: Cisplatin: 80 mg/m^2 on Day 1 of each 3-week cycle as an IV infusion, administered as part of FP chemotherapy regimen, 800 mg/m^2/day continuous on Days 1-5 of each 3-week cycle (120 hours or per local standard), administered as part of FP chemotherapy regimen. - CAPOX: Oxaliplatin: 130 mg/m^2 on Day 1 of each 3-week cycle over 2 hours as an IV infusion, administered as part of CAPOX chemotherapy regimen and as part of SOX chemotherapy regimen. Capecitabine: 1000 mg/m^2 as oral capsules BID on Days 1-14 of each 3-week cycle, administered as part of CAPOX chemotherapy regimen. S1: Combination product of tegafur, CDHP, and Oxo. Oral capsules BID on Days 1-14 of each 3-week cycle based on body surface area (BSA) : <1.25 m^2 BSA =40 mg, 1.25 to <1.5 m^2 BSA=50 mg, ≥1.5 m^2 BSA=60 mg. Administered as part of SOX chemotherapy regimen. - Number of cycles: Treatment continued until documented disease progression, unacceptable toxicity, withdrawal of consent, or study end. **Comparator treatment(s)** • C: Chemotherapy + Trastuzumab + Placebo • Participants receive matched placebo to pembrolizumab IV Q3W plus trastuzumab (8mg/kg loading dose, 6mg/kg maintenance thereafter) IV Q3W in combination with FP or CAPOX chemotherapy (Global Cohort) or SOX chemotherapy (Japan cohort). **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** No
Outcomes according to the trial protocol	**Primary outcome(s):** Progression Free Survival (PFS) per RECIST 1.1 assessed by BICR, Overall Survival (OS) **Relevant secondary or exploratory outcome(s):** Objective Response Rate (ORR) per RECIST 1.1 assessed by BICR, Duration of Response (DOR) per RECIST 1.1 assessed by BICR, Adverse Events (AE), Treatment Discontinuations Due to AEs **Longest median follow-up for survival outcomes:** median follow-up 38.4 months (IQR 29.5–44.4) in the pembrolizumab group and 38.6 months (30.2–44.4) in the placebo group
Notes	**ClinicalTrials.gov ID and status:** NCT03615326; active, not recruting **Other IDs:** Keynote-811 **Sponsors and collaborators:** Merck Sharp & Dohme Corp

KEYNOTE-859	
Methods	**Phase:** 3 **Study design:** double-blind, randomised, phase 3 study **Locations:** international, 215 locations
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: adenocarcinoma of the stomach or gastroesophageal junction - Pathomolecular determinants: Her2/neu negative - PD-L1 status: not required - ECOG: 0-1 (Karnofsky ≥70) - measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by investigator assessment - provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated - provided tumor tissue sample deemed adequate for PD-L1 biomarker analysis - provided tumor tissue sample for microsatellite instability (MSI) biomarker analysis - adequate organ function as demonstrated by laboratory testing within 10 days prior to the start of study treatmen • **Key exclusion criteria** - squamous cell or undifferentiated gastric cancer - preexisting peripheral neuropathy >Grade 1 - previous therapy for locally advanced, unresectable or metastatic gastric/GEJ cancer. Participants may have received prior neoadjuvant and/or adjuvant therapy as long as it was completed ≥6 months prior to randomization - Has received prior therapy with an anti-programmed cell death (PD)-1, anti-PD-L1 or anti-programmed cell death ligand 2 (PD-L2) agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), OX- 40, CD137) - diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment - Has a known additional malignancy that is progressing or has required active treatment within the past 5 years with the exception of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy - known active CNS metastases and/or carcinomatous meningitis - severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients - active autoimmune disease that has required systemic treatment in past 2 years - history of (non-infectious) pneumonitis that required steroids or has current pneumonitis, active infection requiring systemic therapy - history of human immunodeficiency virus (HIV) infection

	- history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as Hepatitis C virus [HCV] ribonucleic acid [RNA] detected qualitatively) infection - known history of active tuberculosis - hypokalemia, hypomagnesemia, hypocalcemia - Has had an allogenic tissue/solid organ transplant - Has a known severe hypersensitivity (≥ Grade 3) to any of the study chemotherapy agents (including, but not limited to, infusional 5-fluorouracil or oral capecitabine) and/or to any of their excipients - For participants taking cisplatin: has Grade ≥2 audiometric hearing loss **Number of participants:** • **Randomised: 1579** - Intervention group (I): 790 - Comparator group (C): 789 • **Evaluated (efficacy analysis)** - I: 790 - C: 789 • **Evaluated (safety analysis)** - I: 785 - C: 787 **Median age: 62**, I: 61 (NR 52–67); C: 62 (52–69) **Sex (female %): 32%, I:33%; C: 31%**
Interventions	**Immune checkpoint inhibitor(s):** pembrolizumab **Treatment regimen:** Pembrolizumab + Chemotherapy (FP or CAPOX regimen) **Intervention details:** • Route of administration: - Pembrolizumab: IV - Cisplatin: IV - 5-FU: IV - Oxaliplatin: IV - Capecitabine: Oral • Dosage: - Pembrolizumab: 200mg abs. - FP and CAPOX regimen see below • Length of treatment cycles and day(s) of application: q3w - Pembrolizumab: d1 - FP regimen: cisplatin 80 mg/m^2 IV on Day 1 Q3W and 5-fluorouracil (5FU) 800 mg/m^2/day via continuous IV infusion on Days 1 to 5 Q3W - CAPOX regimen: oxaliplatin 130 mg/m^2 IV on Day 1 Q3W + capecitabine 1000 mg/m^2 orally twice a day (BID) on Days 1 to 14 Q3W • Number of cycles: 35 cycles, Participants who complete up to 35 administrations of pembrolizumab (approximately 2 years) or achieve a complete response (CR) but experience progression of disease (PD), can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 additional year). **Comparator treatment(s)** • C: Placebo + Chemotherapy (FP or CAPOX regimen) • Participants receive placebo on Day 1 Q3W for up to 35 cycles (approximately 2 years) + physicians' choice of either cisplatin 80 mg/m^2 IV on Day 1 Q3W and 5FU 800 mg/m^2/day via continuous IV infusion on Days 1 to 5 Q3W (FP regimen) OR oxaliplatin 130 mg/m^2 IV on Day 1 Q3W + capecitabine 1000 mg/m^2 orally BID on Days 1 to 14 Q3W (CAPOX regimen). **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** No
Outcomes according to the trial protocol	**Primary outcome(s):** OS up to approximately 54 months, PFS - Responses are according to RECIST 1.1 as assessed by BICR up to approximately 54 months **Relevant secondary or exploratory outcome(s):** Objective Response Rate (ORR) RECIST 1.1 as assessed by BICR, DOR up to approximately 54 months, Percentage of AEs up to approximately 54 months, Percentage of Participants Discontinuing Study Drug Due to AEs, Percentage of participants discontinuing study treatment due to an AE Up to approximately 54 months **Longest median follow-up for survival outcomes:** Median follow-up at the data cutoff was 31.0 months (IQR 23.0–38.3)
Notes	**ClinicalTrials.gov ID and status:** NCT03675737; active, not recruiting **Other IDs:** KEYNOTE-859 **Sponsors and collaborators:** Merck Sharp & Dohme LLC

Colorectal cancer

KEYNOTE-177	
Methods	**Phase:** 3 **Study design:** international, randomised, open-label, phase 3 study

	Locations: international, 193 locations
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: Locally confirmed dMMR or MSI-H stage IV colorectal carcinoma - PD-L1 status: not required - ECOG: 0-1 (Karnofsky ≥70) - untreated microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer - Life expectancy of at least 3 months - Measurable disease - Adequate organ function • **Key exclusion criteria** - Active autoimmune disease that has required systemic treatment in past 2 years - Diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization on this study - Radiation therapy within 4 weeks prior to randomization on this study and not recovered to baseline from adverse events due to radiation therapy - Known active central nervous system (CNS) metastases and/or carcinomatous meningitis - Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to randomization on this study - Has received prior therapy with an immune checkpoint inhibitor (e.g., anti-programmed cell death [PD]-1, anti-PD ligand 1 [L1], anti-PD-L2 agent, or anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] agent, etc.) - Another malignancy that is progressing or requires active treatment with the exception of non-melanomatous skin cancer that has undergone potentially curative therapy and in situ cervical carcinoma - Received a live or a live attenuated vaccine within 30 days of planned start of study medication - Known history of Human Immunodeficiency Virus (HIV), Hepatitis B or C - Known history of, or any evidence of interstitial lung disease or active, non-infectious pneumonitis - Known history of active tuberculosis (Bacillus tuberculosis [TB]) - Active infection requiring systemic therapy - Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study **Number of participants:** • **Randomised:** 307 - Intervention group (I): 153 - Comparator group (C): 154 • **Evaluated (efficacy analysis)** - I: 153 - C: 143 • **Evaluated (safety analysis)** - I: 153 - C: 143 **Median age:** 63 (IQR 50–73) **Sex (female %): 51%,** pembrolizumab 54%; chemotherapy 47%
Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** Pembrolizumab mono **Intervention details:** • Route of administration: - Pembrolizumab: IV • Dosage: - Pembrolizumab: 200 mg • Length of treatment cycles and day(s) of application: q3w - Participants receive pembrolizumab 200 mg intravenously (IV) on Day 1 of each 21-day cycle (Q3W) • Cycles : for up to 35 treatments (approximately 2 years). Participants that have stopped the initial course of pembrolizumab and have stable disease but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 year additional). **Comparator treatment(s)** • C: chemotherapy: mFOLFOX6 or mFOLFOX6+bevacizumab or mFOLFOX6+cetuximab 400 mg/m^2 IV or FOLFIRI, or FOLFIRI+bevacizumab or FOLFIRI+cetuximab • Participants receive 1 of 6 possible standard chemotherapy regimens: mFOLFOX6, or mFOLFOX6+bevacizumab 5 mg/kg IV on Day 1 of each 2-week cycle, or mFOLFOX6+cetuximab 400 mg/m^2 IV over 2 hours then 250 mg/m^2 over 1 hour weekly in each 2-week cycle, or FOLFIRI, or FOLFIRI+bevacizumab 5 mg/kg IV on Day 1 of each 2-week cycle, or FOLFIRI+cetuximab 400 mg/m^2 IV over 2 hours then 250 mg/m^2 over 1 hour weekly in each 2-week cycle. • mFOLFOX6: oxaliplatin 85 mg/m^2 IV on Day 1, leucovorin 400 mg/m^2 or levoleucovorin 200 mg/m^2 IV on Day 1, 5-fluorouracil (5-FU) 400 mg/m^2 IV bolus on Day 1 and then 1200 mg/m^2/day IV over 2 days for total dose of 2400 mg/m^2 in each 2-week cycle

	• FOLFIRI: Regimen consists of irinotecan 180 mg/m^2 IV on Day 1, leucovorin 400 mg/m^2 or levoleucovorin 200 mg/m^2 IV on Day 1, 5-FU 400 mg/m^2 IV bolus on Day 1 and then 1200 mg/m^2/day IV over 2 days for total dose of 2400 mg/m^2 in each 2-week cycle **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** yes. Participants with documented disease progression following chemotherapy can crossover to receive pembrolizumab for up to 35 cycles (approximately 2 years). Participants that have stopped pembrolizumab and have stable disease but progress after discontinuation can initiate a second course of pembrolizumab for up to 17 cycles (approximately 1 year additional).
Outcomes according to the trial protocol	**Primary outcome(s):** Progression-Free Survival (PFS) Per RECIST1.1 As Assessed by Central Imaging Vendor, Overall Survival (OS) **Relevant secondary or exploratory outcome(s):** Overall Response Rate (ORR) Per RECIST1.1 as Assessed by Central Imaging Vendor, Number of Participants Who Experienced an Adverse Event (AE), Number of Participants Who Discontinued Study Treatment Due to an AE **Longest median follow-up for survival outcomes:** median follow-up of 44·5 months [IQR 39·7–49·8]
Notes	**ClinicalTrials.gov ID and status:** NCT02563002; completed **Other IDs:** Keynote-590 **Sponsors and collaborators:** Merck Sharp & Dohme Corp

Endometrial carcinoma

RUBY	
Methods	**Phase:** 3 **Study design:** RCT, double-blind, 2-part, placebo-controlled, multicentre (herein only characteristics relevant to part 1 are presented) **Locations:** 163 locations, international
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: mixed, except uterine sarcoma - Pathomolecular determinants: irrespective of MMR/MSI-status - PD-L1 status: not required - ECOG: 0-1 - adequate organ function - primary Stage III or Stage IV disease or first recurrent endometrial cancer with a low potential for cure by radiation therapy or surgery alone or in combination - primary stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per (RECIST1.1) **or** primary stage IIIC1 disease with carcinosarcoma, clear cell, serous, or mixed histology (containing ≥ 10% carcinosarcoma, clear cell, or serous histology) regardless of presence of evaluable or measurable disease on imaging; **or** primary stage IIIC2 or Stage IV disease regardless of the presence of evaluable or measurable disease **or** first recurrent disease naïve to systemic anticancer therapy **or** prior neo-adjuvant/adjuvant systemic anticancer therapy and recurrence or progression of disease ≥ 6 months after completing treatment (first recurrence only) • **Key exclusion criteria** - Prior therapy with ICIs - Prior anticancer therapy within 21 days or less than 5x the half-life of the most recent therapy - Concomitant malignancy, or disease-free for more than 3 years (apart from NMSC) - Known uncontrolled CNS metastases, carcinomatosis meningitis, or both - Participant has not recovered (that is to grade ≤ 1 or baseline) from cytotoxic therapy induced AEs or has received transfusion of blood products (including platelets or red blood cells) or G-CSF within 21 days prior to the first dose of study drug - Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection requiring systemic therapy - Participant has received, or is scheduled to receive, a live vaccine within 30 days before first dose of study treatment **Number of participants: 494** • **Randomised** - Intervention group (I): 245 - Comparator group (C): 249 • **Evaluated (efficacy analysis)** - I: 245 - C: 249 • **Evaluated (safety analysis)** - I: 241 - C: 246 **Median age: 65**, I: 64 (41–81), C: 65 (28–85)
Interventions	**Immune checkpoint inhibitor(s):** Dostarlimab **Treatment regimen:** Dostarlimab + carboplatin/paclitaxel **Intervention details:** • Route of administration: - Dostarlimab: IV

	- Carboplatin/paclitaxel: IV • Dosage: - Dostarlimab: 500 mg (q3w), 1000 mg (q6w) - Carboplatin: carboplatin AUC of 5 mg/mL/min - Paclitaxel: 175 mg/m² body-surface area • Length of treatment cycles and day(s) of application: d1 q3w, then: d1 q6w - Dostarlimab: d1 q3w for 6 cycles, then d1 q6w max. up to 3 years - Carboplatin/paclitaxel: d1 q3w for 6 cycles **Comparator treatment(s)** • Placebo plus carboplatin/paclitaxel **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** yes
Outcomes according to the trial protocol	**Primary outcome(s):** PFS - investigator assessement, up to 6 years **Relevant secondary or exploratory outcome(s):** • PFS - blinded independent central review (BICR) • ORR - BICR and Investigator assessment • DOR - BICR and Investigator assessment • DCR - BICR and Investigator assessment • PROs in the European Quality of Life scale, 5-Dimensions, 5-Levels (EQ-5D-5L), PROs in the EORTC, QLQ-C30 [Core], PROs in the EORTC Quality of Life Questionnaire (Endometrial Cancer Module [QLQ-EN24]) • Progression-free survival 2 (PFS2) • AEs, SAEs and treatment-emergent adverse events (TEAEs) **Longest median follow-up for survival outcomes: 25.4 months (range, 19.2 to 37.8)**
Notes	**ClinicalTrials.gov ID:** NCT03981796, **Trial status:** active, not recruiting **Sponsors and collaborators:** Tesaro Inc., GlaxoSmithKline, European Network of Gynaecological Oncological Trial Groups (ENGOT), GOG Foundation

Cervical cancer

Keynote-826	
Methods	**Phase:** 3 **Study design:** RCT, double-blind, multicentre, 2-arm **Locations:** global
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: SqC/NSqC - Pathomolecular determinants: cervival cancer - PD-L1 status: not required - ECOG: 0-1 • **Key exclusion criteria** - Active autoimmune disease - Immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy - Central nervous system metastases and/or carcinomatous meningitis - Pneumonitis that required steroids or current pneumonitis - Interstitial lung disease, tuberculosis, active infection requiring systemic therapy, HIV, hepatitis B or hepatitis C, TB **Number of participants:** • **Randomised** - Intervention group (I): 308 - Comparator group (C): 309 • **Evaluated (efficacy analysis)** - I: 307 - C: 309 • **Evaluated (safety analysis)** - I: 307 - C: 309 **Median age:** 51 **Sex (female %):** 100%
Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** • Pembrolizumab + cisplatin/carboplatin + paclitaxel ± bevacizumab

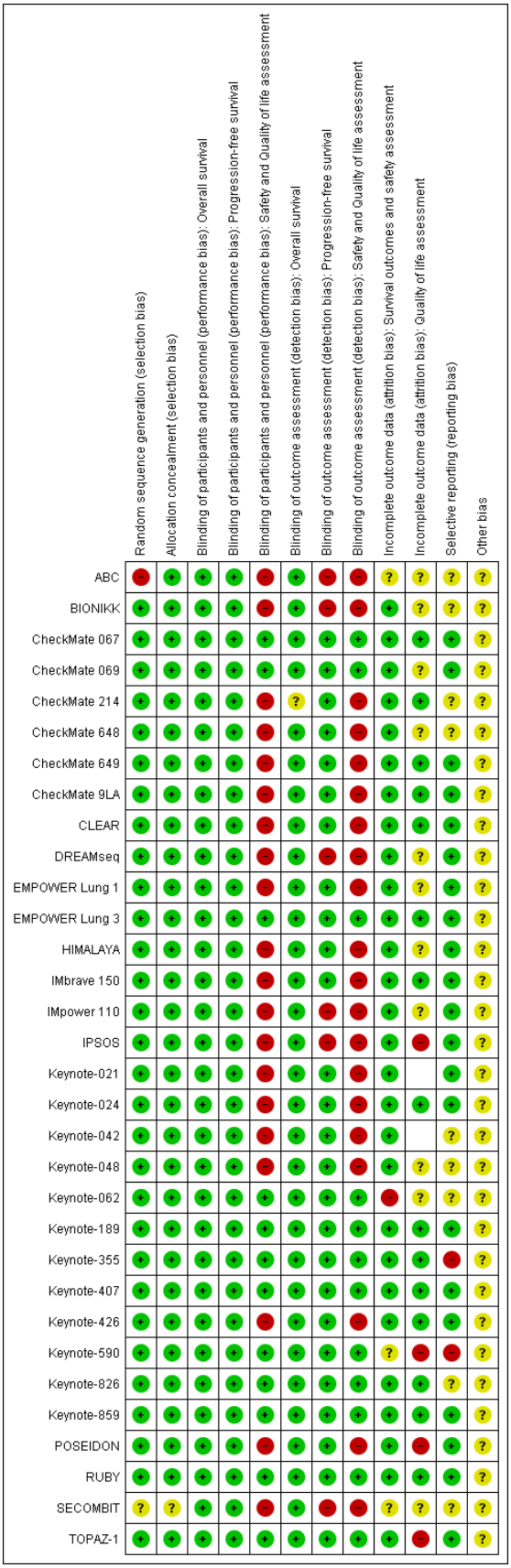
	Intervention details: • Route of administration: - Pembrolizumab: IV • Dosage: - Pembrolizumab: 200mg • Length of treatment cycles and day(s) of application: - Pembrolizumab: q21d • Number of cycles: up to 35 **Comparator treatment(s)** • Placebo + 6 cycles of cisplatin/carboplatin + paclitaxel ± bevacizumab **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** no
Outcomes according to the trial protocol	**Primary outcome(s):** OS, PFS **Relevant secondary or exploratory outcome(s):** AE, ORR, QoL **Longest median follow-up for survival outcomes:** 39.1 months
Notes	**ClinicalTrials.gov ID and status:** NCT03635567, completed **Sponsors and collaborators:** Merck Sharp & Dohme LLC

Triple-negative breast cancer

Keynote-355	
Methods	**Phase:** 3 **Study design:** RCT, double-blind, multicentre, 2-arm **Locations:** global
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: - - Pathomolecular determinants: triple-negative breast cancer - PD-L1 status: not required - ECOG: 0-1 • **Key exclusion criteria** - Neuropathy ≥ Grade 2 - Active autoimmune disease - Immunodeficiency or systemic steroid therapy or other form of immunosuppressive therapy - Central nervous system metastases and/or carcinomatous meningitis - Pneumonitis that required steroids or current pneumonitis - Interstitial lung disease, tuberculosis, active infection requiring systemic therapy, HIV, hepatitis B or hepatitis C **Number of participants:** • **Randomised** - Intervention group (I): 566 - Comparator group (C): 281 • **Evaluated (efficacy analysis)** - I: 562 - C: 281 • **Evaluated (safety analysis)** - I: 562 - C: 281 **Median age:** 53 **Sex (female %):** 100%
Interventions	**Immune checkpoint inhibitor(s):** Pembrolizumab **Treatment regimen:** • Pembrolizumab + carboplatin + paclitaxel/gemcitabine/nab-paclitaxel **Intervention details:** • Route of administration: - Pembrolizumab: IV • Dosage: - Pembrolizumab: 200mg • Length of treatment cycles and day(s) of application: up to 35 cycles - Pembrolizumab: q21d **Comparator treatment(s)**

	• Placebo + carboplatin + paclitaxel/gemcitabine/nab-paclitaxel (continued at the investigator's discretion) **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** no
Outcomes according to the trial protocol	**Primary outcome(s):** OS, PFS, AE **Relevant secondary or exploratory outcome(s):** ORR, DOR, DCR, QoL **Longest median follow-up for survival outcomes:** 26.3 months
Notes	**ClinicalTrials.gov ID and status:** NCT02819518, completed **Sponsors and collaborators:** Merck Sharp & Dohme LLC

Risk of bias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Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias): Overall survival
Blinding of participants and personnel (performance bias): Progression-free survival
Blinding of participants and personnel (performance bias): Safety and Quality of life assessment
Blinding of outcome assessment (detection bias): Overall survival
Blinding of outcome assessment (detection bias): Progression-free survival
Blinding of outcome assessment (detection bias): Safety and Quality of life assessment
Incomplete outcome data (attrition bias): Survival outcomes and safety assessment
Incomplete outcome data (attrition bias): Quality of life assessment
Selective reporting (reporting bias)
Other bias
ABC
BIONIKK
CheckMate 067
CheckMate 069
CheckMate 214
CheckMate 648
CheckMate 649
CheckMate 9LA
CLEAR
DREAMseq
EMPOWER Lung 1
EMPOWER Lung 3
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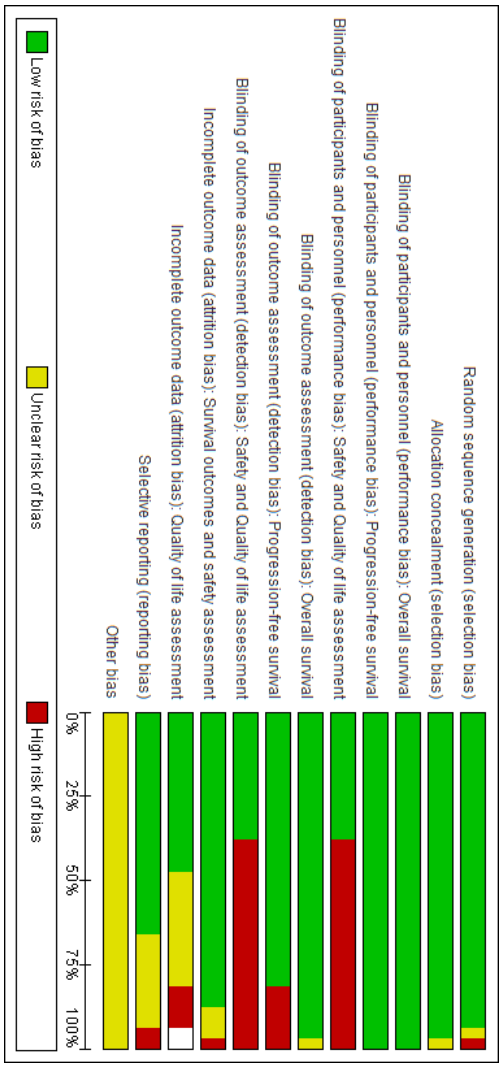
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Unclear risk of bias
High risk of bias
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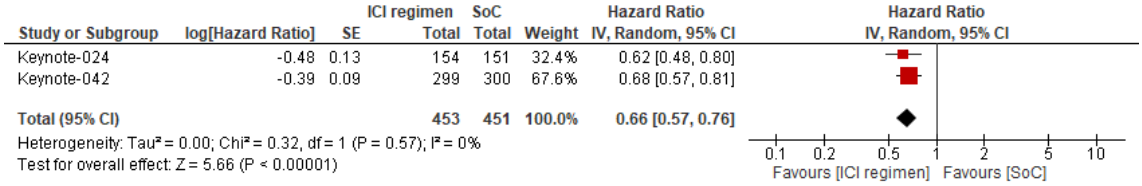
100%
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias): Overall survival
Blinding of participants and personnel (performance bias): Progression-free survival
Blinding of participants and personnel (performance bias): Safety and Quality of life assessment
Blinding of outcome assessment (detection bias): Overall survival
Blinding of outcome assessment (detection bias): Progression-free survival
Blinding of outcome assessment (detection bias): Safety and Quality of life assessment
Incomplete outcome data (attrition bias): Survival outcomes and safety assessment
Incomplete outcome data (attrition bias): Quality of life assessment
Selective reporting (reporting bias)
Other bias

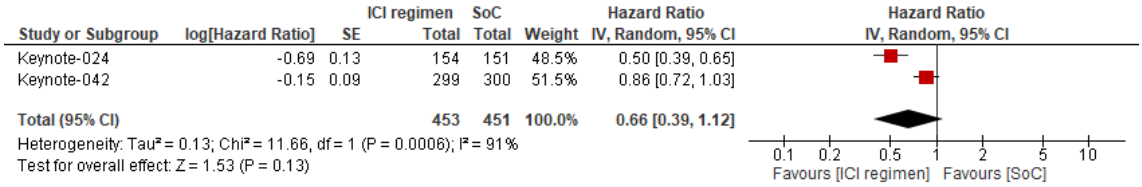
Analyses

Analyses 1: Non-small cell lung cancer (monotherapy)

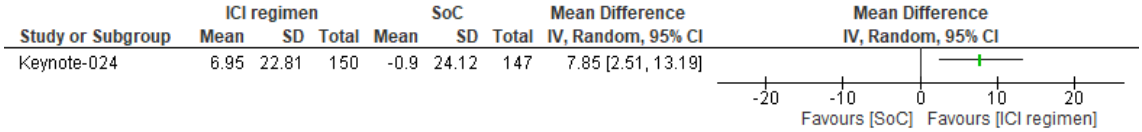
ANALYSIS 1.1.
Pembrolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: OS



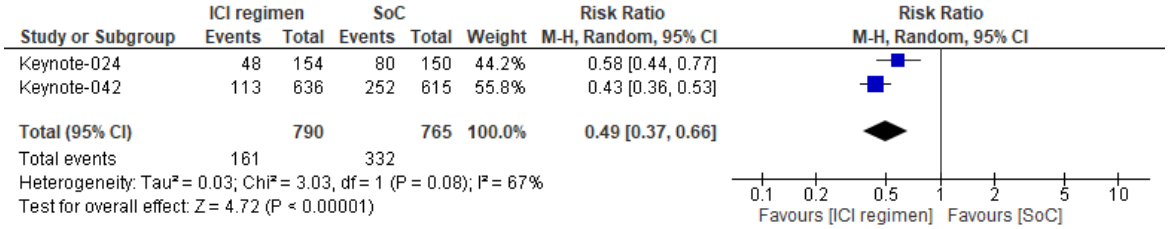
ANALYSIS 1.2.
Pembrolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: PFS



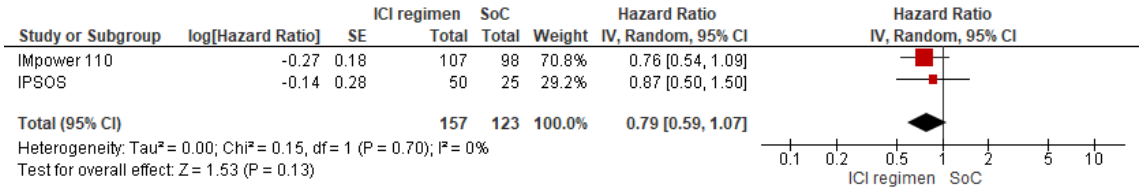
ANALYSIS 1.3.
Pembrolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)



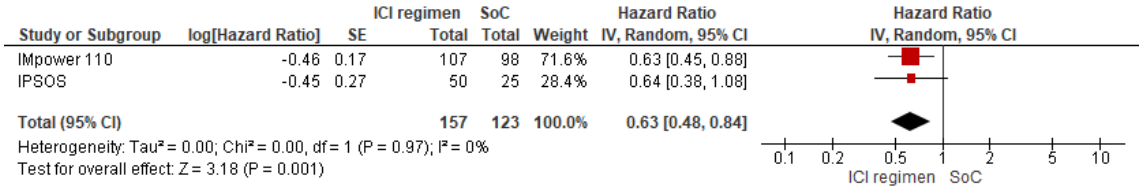
ANALYSIS 1.4.
Pembrolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution



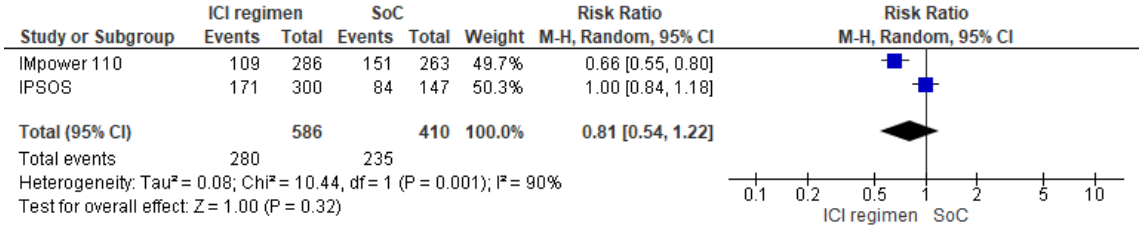
ANALYSIS 1.5.
Atezolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: OS



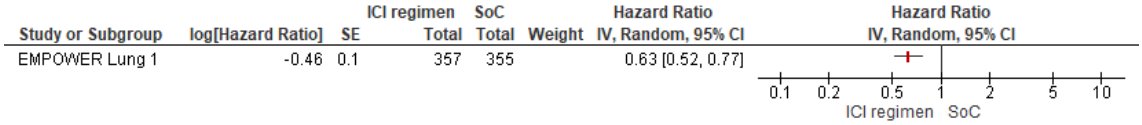
ANALYSIS 1.6.
Atezolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: PFS



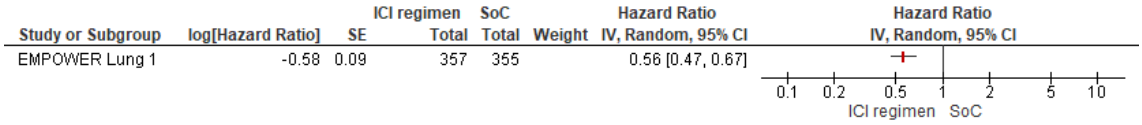
ANALYSIS 1.7.
Atezolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution



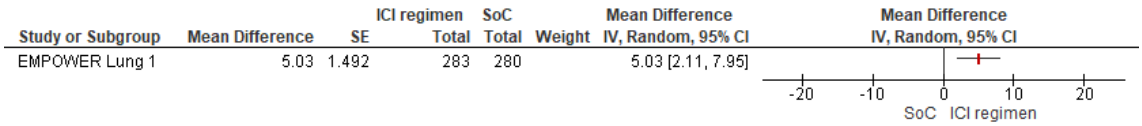
ANALYSIS 1.8.
Cemiplimab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: OS



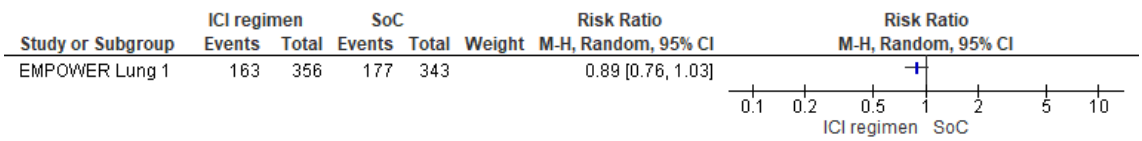
ANALYSIS 1.9.
Cemiplimab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: PFS



ANALYSIS 1.10.
Cemiplimab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)



ANALYSIS 1.11.
Cemiplimab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

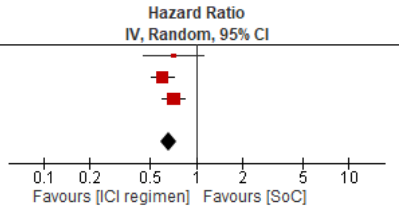


Analyses 2: Non-small cell lung cancer (immunochemotherapy)

ANALYSIS 2.1.
Pembrolizumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: OS

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Weight	Hazard Ratio IV, Random, 95% CI
Keynote-021	-0.34	0.23	60	63	7.1%	0.71 [0.45, 1.12]
Keynote-189	-0.51	0.09	410	206	46.4%	0.60 [0.50, 0.72]
Keynote-407	-0.34	0.09	278	281	46.4%	0.71 [0.60, 0.85]
Total (95% CI)			**748**	**550**	**100.0%**	**0.66 [0.58, 0.74]**

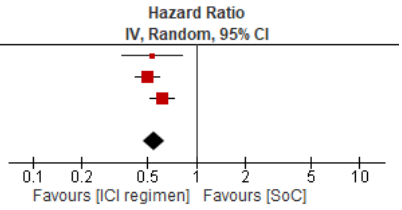
Heterogeneity: Tau² = 0.00; Chi² = 1.91, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 6.83 (P < 0.00001)



ANALYSIS 2.2.
Pembrolizumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: PFS

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Weight	Hazard Ratio IV, Random, 95% CI
Keynote-021	-0.62	0.22	60	63	10.9%	0.54 [0.35, 0.83]
Keynote-189	-0.69	0.09	410	206	44.6%	0.50 [0.42, 0.60]
Keynote-407	-0.48	0.09	278	281	44.6%	0.62 [0.52, 0.74]
Total (95% CI)			**748**	**550**	**100.0%**	**0.55 [0.48, 0.64]**

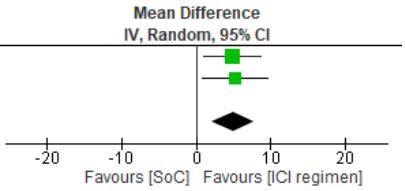
Heterogeneity: Tau² = 0.00; Chi² = 2.75, df = 2 (P = 0.25); I² = 27%
Test for overall effect: Z = 7.73 (P < 0.00001)



ANALYSIS 2.3.
Pembrolizumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)

Study or Subgroup	ICI regimen Mean	SD	Total	SoC Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Keynote-407	4.3	22.04	276	-0.55	23.39	278	57.6%	4.85 [1.07, 8.63]
Keynote-189	1.2	24.55	402	-4	26.7	200	42.4%	5.20 [0.79, 9.61]
Total (95% CI)			**678**			**478**	**100.0%**	**5.00 [2.13, 7.87]**

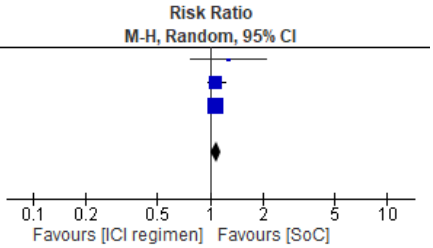
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 3.41 (P = 0.0006)



ANALYSIS 2.4.
Pembrolizumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

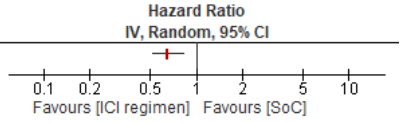
Study or Subgroup	ICI regimen Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Keynote-021	23	59	19	62	2.3%	1.27 [0.78, 2.08]
Keynote-189	295	405	136	202	44.1%	1.08 [0.97, 1.21]
Keynote-407	208	278	196	280	53.5%	1.07 [0.96, 1.18]
Total (95% CI)		**742**		**544**	**100.0%**	**1.08 [1.00, 1.16]**
Total events	526		351			

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)



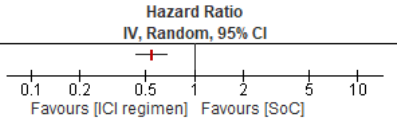
ANALYSIS 2.5.
Cemiplimab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: OS

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Weight	Hazard Ratio IV, Random, 95% CI
EMPOWER Lung 3	-0.43	0.12	312	154		0.65 [0.51, 0.82]



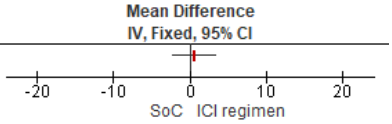
ANALYSIS 2.6.
Cemiplimab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: PFS

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Weight	Hazard Ratio IV, Random, 95% CI
EMPOWER Lung 3	-0.6	0.11	312	154		0.55 [0.44, 0.68]



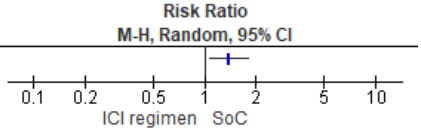
ANALYSIS 2.7.
Cemiplimab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)

Study or Subgroup	Mean Difference	SE	ICI regimen Total	SoC Total	Weight	Mean Difference IV, Fixed, 95% CI
EMPOWER Lung 3	0.61	1.449	312	154		0.61 [-2.23, 3.45]



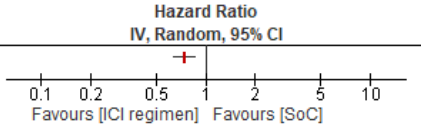
ANALYSIS 2.8.
Cemiplimab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

Study or Subgroup	ICI regimen Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
EMPOWER Lung 3	136	312	48	153		1.39 [1.06, 1.81]



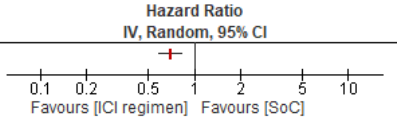
ANALYSIS 2.9.
Ipilimumab/Nivolumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: OS

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Hazard Ratio IV, Random, 95% CI
CheckMate 9LA	-0.3	0.08	361	358	0.74 [0.63, 0.87]



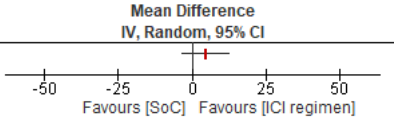
ANALYSIS 2.10.
Ipilimumab/Nivolumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: PFS

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Weight	Hazard Ratio IV, Random, 95% CI
CheckMate 9LA	-0.36	0.09	361	358		0.70 [0.58, 0.83]



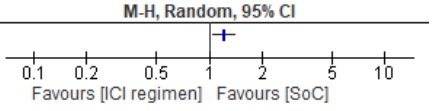
ANALYSIS 2.11.
Ipilimumab/Nivolumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: Health-related quality of life (LCSS 3-IGI; measured by Lung Cancer Symptom Scale (LCSS) – 3 item global index)

Study or Subgroup	Mean Difference	SE	ICI regimen Total	SoC Total	Weight	Mean Difference IV, Random, 95% CI
CheckMate 9LA	4.7	4.061	333	313		4.70 [-3.26, 12.66]



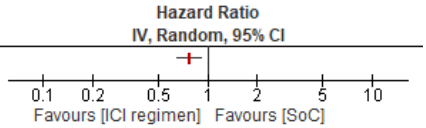
ANALYSIS 2.12.
Ipilimumab/Nivolumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

Study or Subgroup	ICI regimen Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CheckMate 9LA	202	358	163	349		1.21 [1.05, 1.40]



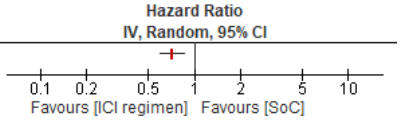
ANALYSIS 2.13.
Durvalumab/tremelimumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: OS

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Hazard Ratio IV, Random, 95% CI
POSEIDON	-0.26	0.09	338	337	0.77 [0.65, 0.92]



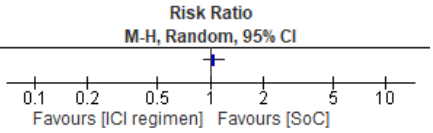
ANALYSIS 2.14.
Durvalumab/tremelimumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: PFS

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Weight	Hazard Ratio IV, Random, 95% CI
POSEIDON	-0.33	0.09	338	337		0.72 [0.60, 0.86]



ANALYSIS 2.15.
Durvalumab/tremelimumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

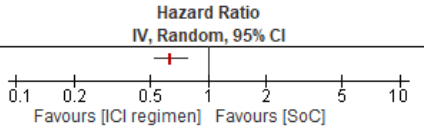
Study or Subgroup	ICI regimen Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
POSEIDON	187	330	180	334		1.05 [0.92, 1.21]



Analyses 3: Head and neck squamous cell carcinoma

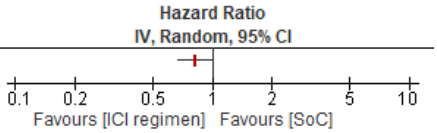
ANALYSIS 3.1.
Pembrolizumab-based treatment regimen compared to SoC in HNSCC with ≥ 1% PD-L1 expression, Outcome: OS

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Hazard Ratio IV, Random, 95% CI
Keynote-048	-0.45	0.1	242	235	0.64 [0.52, 0.78]



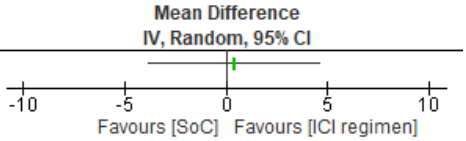
ANALYSIS 3.2.
Pembrolizumab-based treatment regimen compared to SoC in HNSCC with ≥ 1% PD-L1 expression, Outcome: PFS

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Hazard Ratio IV, Random, 95% CI
Keynote-048	-0.2	0.1	242	235	0.82 [0.67, 1.00]



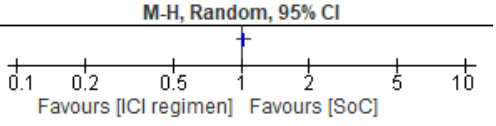
ANALYSIS 3.3.
Pembrolizumab-based treatment regimen compared to SoC in HNSCC with ≥ 1% PD-L1 expression, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Random, 95% CI
Keynote-048	1.17	24.68	268	0.77	24.55	259	0.40 [-3.80, 4.60]



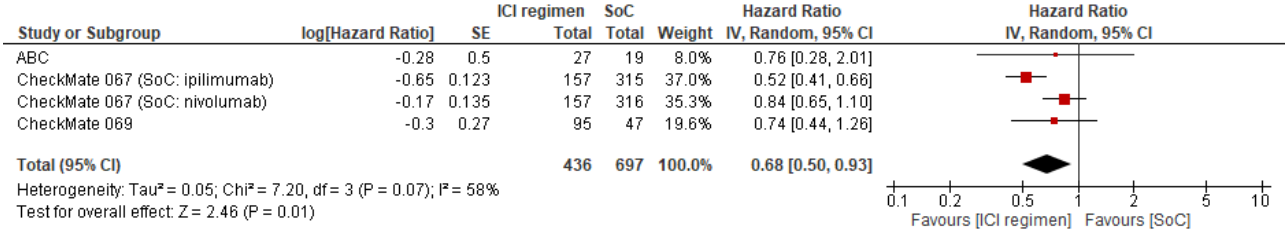
ANALYSIS 3.4.
Pembrolizumab-based treatment regimen compared to SoC in HNSCC with ≥ 1% PD-L1 expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

Study or Subgroup	Experimental Events	Total	Control Events	Total	Risk Ratio M-H, Random, 95% CI
Keynote-048	235	276	239	287	1.02 [0.95, 1.10]

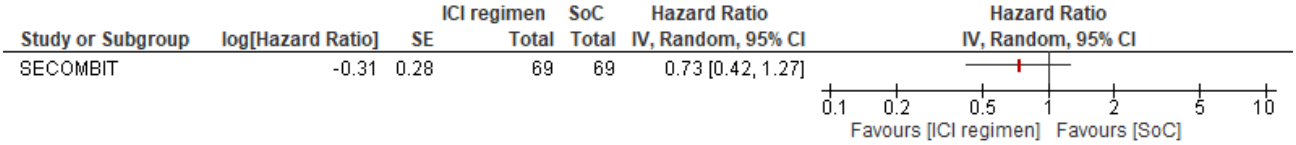


Analyses 4: Malignant melanoma

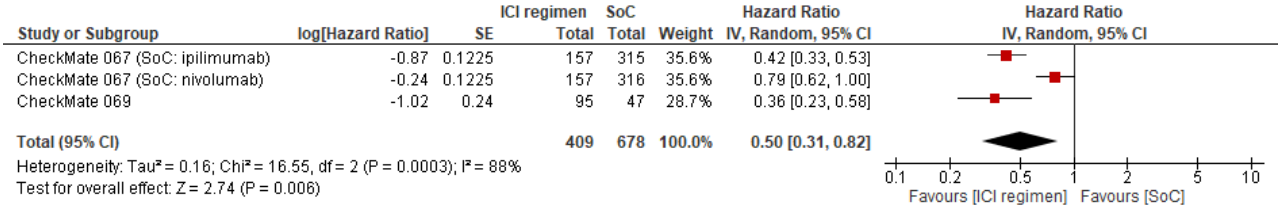
ANALYSIS 4.1.
Ipilimumab/nivolumab compared to ICI monotherapy in malignant melanoma, Outcome: Overall survival



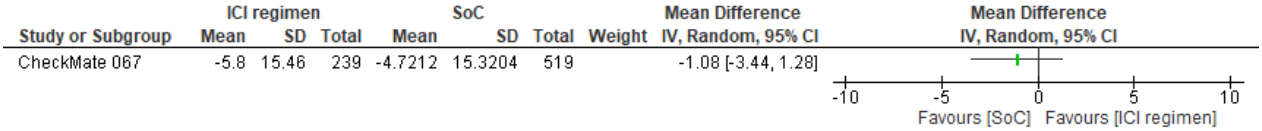
ANALYSIS 4.2.
Ipilimumab/nivolumab compared to BRAF/MEK inhibitors in malignant melanoma, Outcome: Overall survival



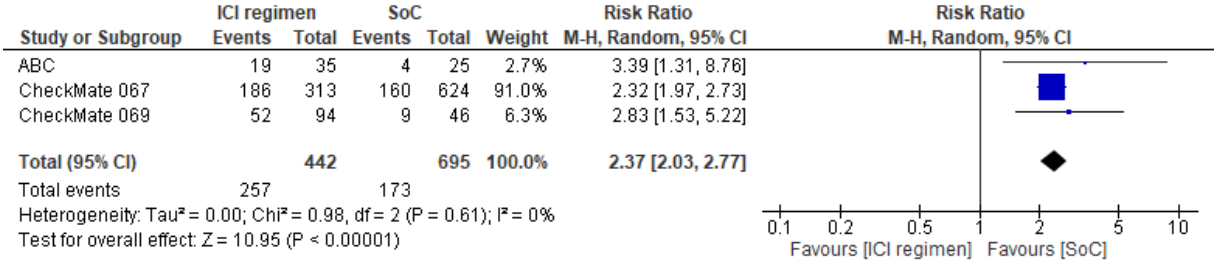
ANALYSIS 4.3.
Ipilimumab/nivolumab compared to ICI monotherapy in malignant melanoma, Outcome: Progression-free survival



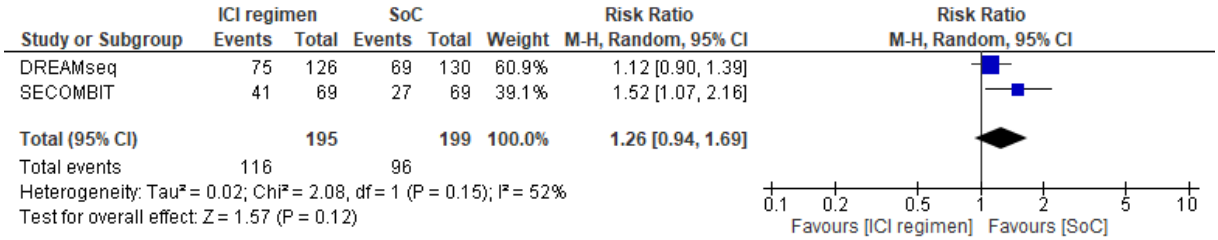
ANALYSIS 4.4.
Ipilimumab/nivolumab compared to ICI monotherapy in malignant melanoma, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)



ANALYSIS 4.5.
Ipilimumab/nivolumab compared to ICI monotherapy in malignant melanoma, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

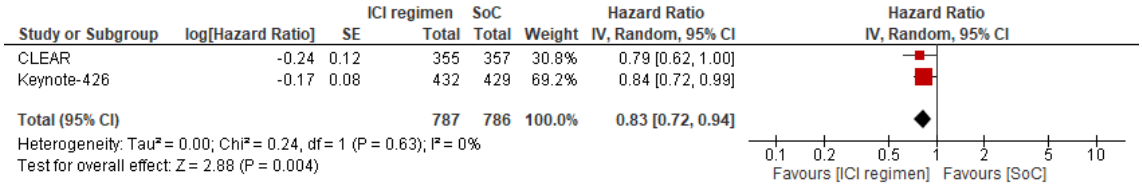


ANALYSIS 4.6.
Ipilimumab/nivolumab compared to BRAF/MEK inhibitors in malignant melanoma, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

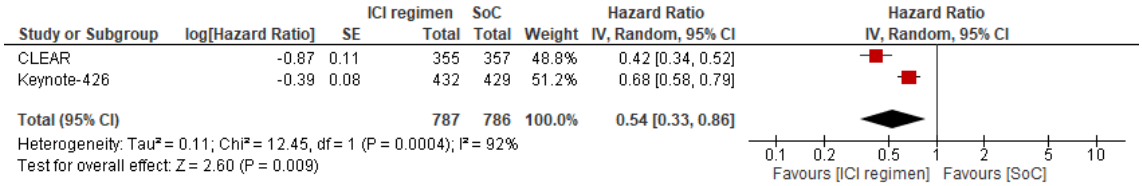


Analyses 5: Renal cell carcinoma

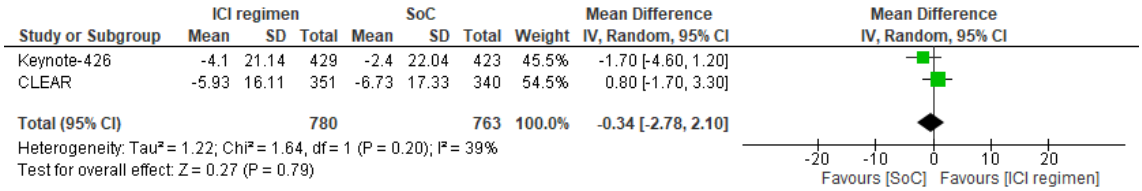
ANALYSIS 5.1.
Pembrolizumab-based treatment regimen compared to SoC in renal cell carcinoma, Outcome: Overall survival



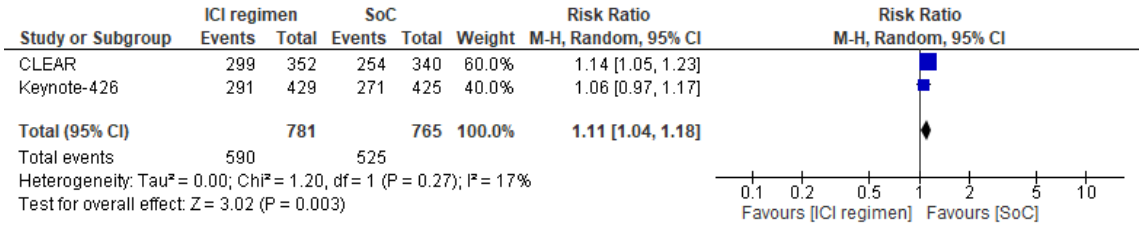
ANALYSIS 5.2.
Pembrolizumab-based treatment regimen compared to SoC in renal cell carcinoma, Outcome: Progression-free survival



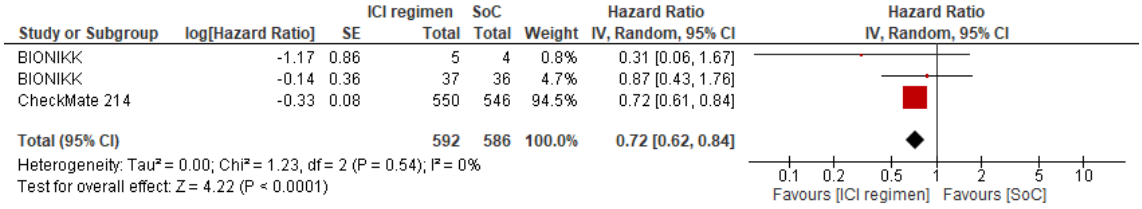
ANALYSIS 5.3.
Pembrolizumab-based treatment regimen compared to SoC in renal cell carcinoma, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)



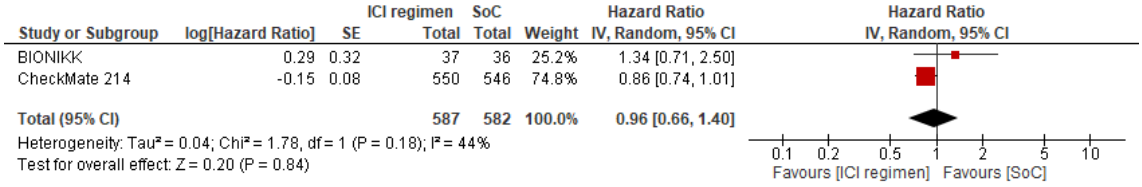
ANALYSIS 5.4.
Pembrolizumab-based treatment regimen compared to SoC in renal cell carcinoma, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution



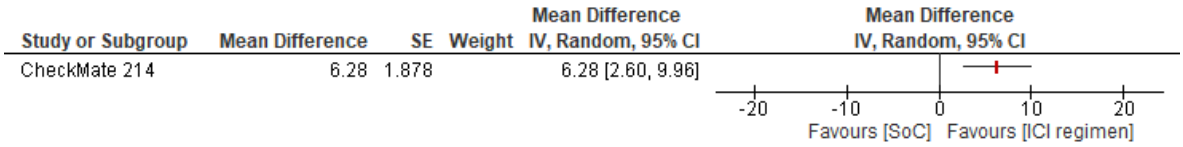
ANALYSIS 5.5.
Ipilimumab/nivolumab compared to SoC in renal cell carcinoma, Outcome: Overall survival



ANALYSIS 5.6.
Ipilimumab/nivolumab compared to SoC in renal cell carcinoma, Outcome: Progression-free survival



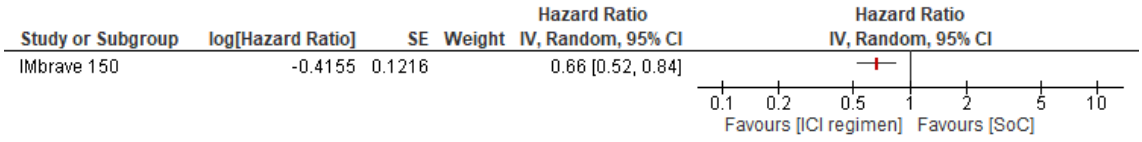
ANALYSIS 5.7.
Ipilimumab/nivolumab compared to SoC in renal cell carcinoma, Outcome: Healt-related quality of life (HR-QoL; measured by FACT-G)



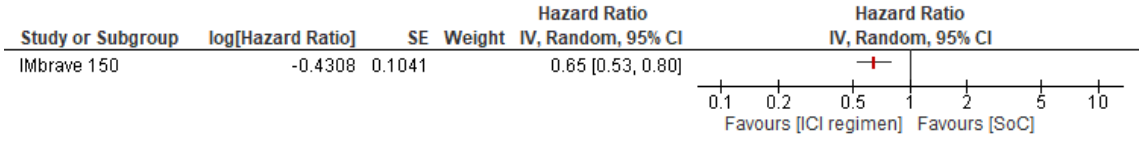
ANALYSIS 5.8.
Ipilimumab/nivolumab compared to SoC in renal cell carcinoma, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

Analyses 6: Hepatocellular carcinoma

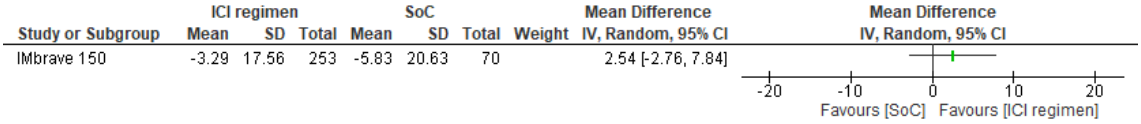
ANALYSIS 6.1.
Atezolizumab-based treatment regimen compared to SoC in hepatocellular carcinoma, Outcome: Overall survival



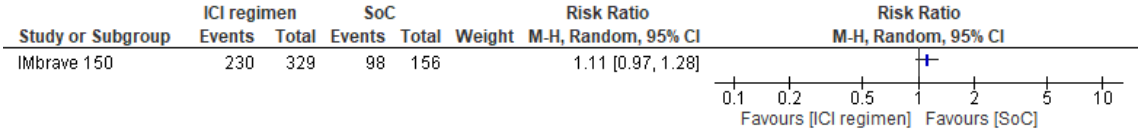
ANALYSIS 6.2.
Atezolizumab-based treatment regimen compared to SoC in hepatocellular carcinoma, Outcome: Progression-free survival



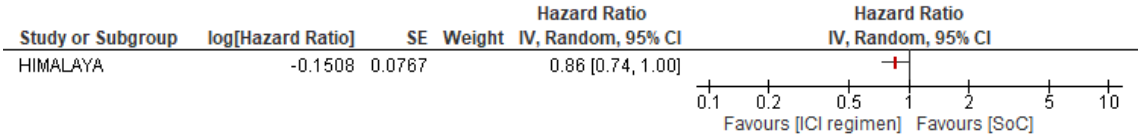
ANALYSIS 6.3.
Atezolizumab-based treatment regimen compared to SoC in hepatocellular carcinoma, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)



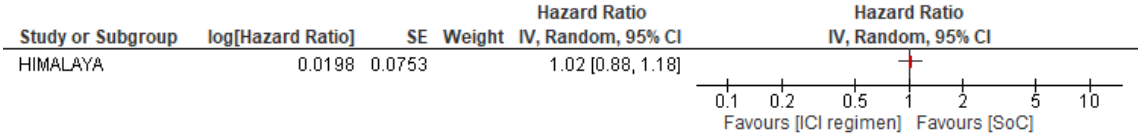
ANALYSIS 6.4.
Atezolizumab-based treatment regimen compared to SoC in hepatocellular carcinoma, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution



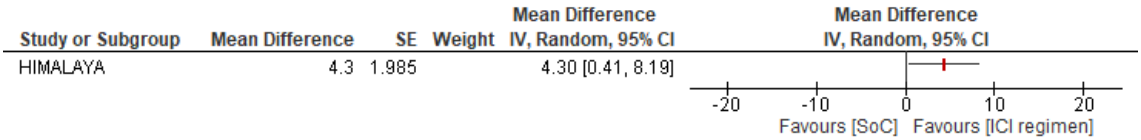
ANALYSIS 6.5.
Durvalumab monotherapy compared to SoC in hepatocellular carcinoma, Outcome: Overall survival



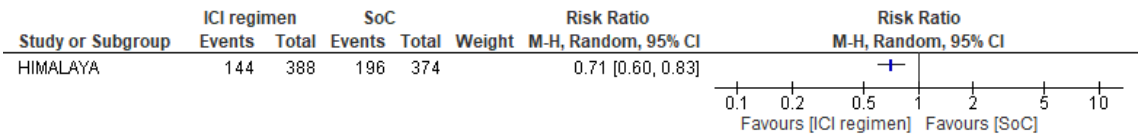
ANALYSIS 6.6.
Durvalumab monotherapy compared to SoC in hepatocellular carcinoma, Outcome: Progression-free survival



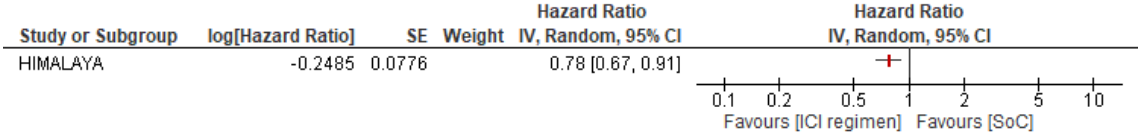
ANALYSIS 6.7.
Durvalumab monotherapy compared to SoC in hepatocellular carcinoma, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)



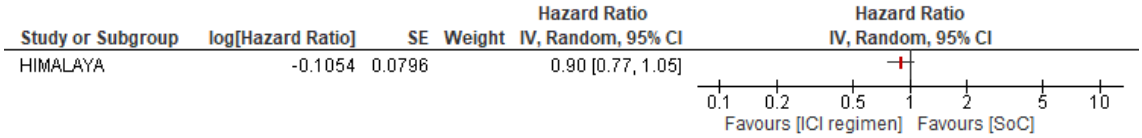
ANALYSIS 6.8.
Durvalumab monotherapy compared to SoC in hepatocellular carcinoma, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution



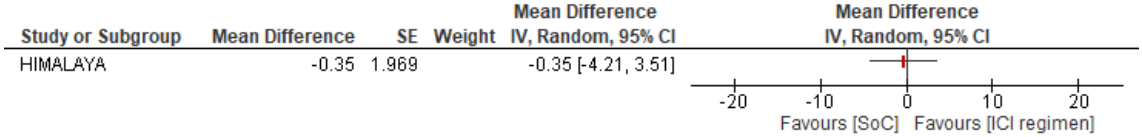
ANALYSIS 6.9.
Durvalumab/tremelimumab compared to SoC in hepatocellular carcinoma, Outcome: Overall survival



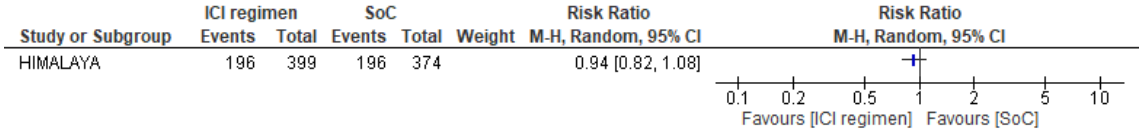
ANALYSIS 6.10.
Durvalumab/tremelimumab compared to SoC in hepatocellular carcinoma, Outcome: Progression-free survival



ANALYSIS 6.11.
Durvalumab/tremelimumab compared to SoC in hepatocellular carcinoma, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)

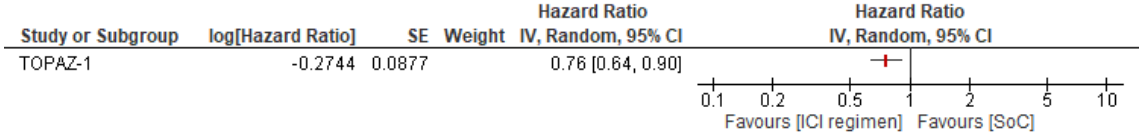


ANALYSIS 6.12.
Durvalumab/tremelimumab compared to SoC in hepatocellular carcinoma, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

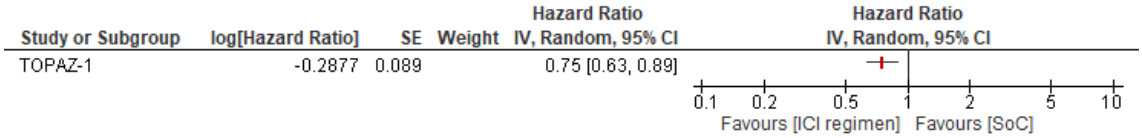


Analyses 7: Biliary tract cancer

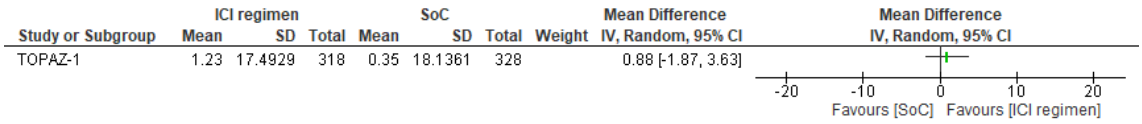
ANALYSIS 7.1.
Durvalumab-based treatment regimen compared to SoC in biliary tract cancer, Outcome: Overall survival



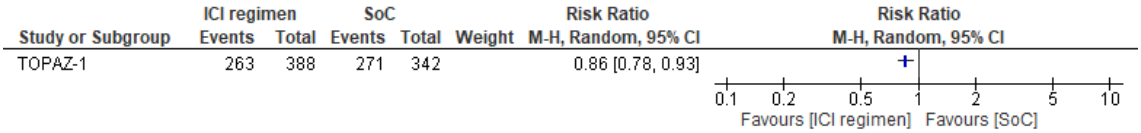
ANALYSIS 7.2.
Durvalumab-based treatment regimen compared to SoC in biliary tract cancer, Outcome: Progression-free survival



ANALYSIS 7.3.
Durvalumab-based treatment regimen compared to SoC in biliary tract cancer, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)

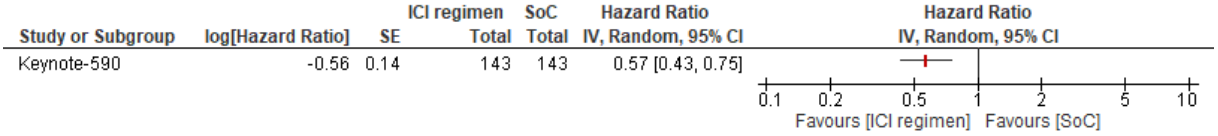


ANALYSIS 7.4.
Durvalumab-based treatment regimen compared to SoC in biliary tract cancer, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

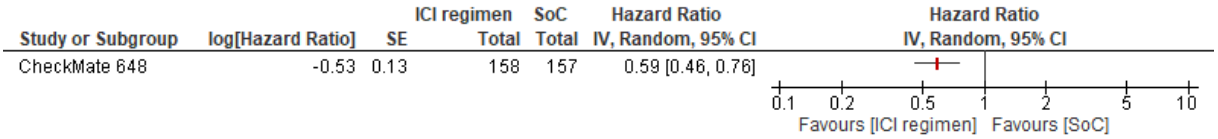


Analyses 8: Oesophageal squamous cell carcinoma

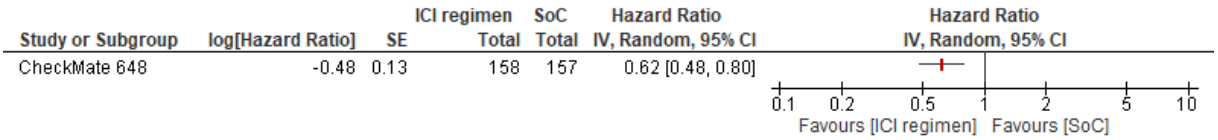
ANALYSIS 8.1.
Pembrolizumab-based regimen compared to SoC in PD-L1 positive OESCC, Outcome: Overall survival



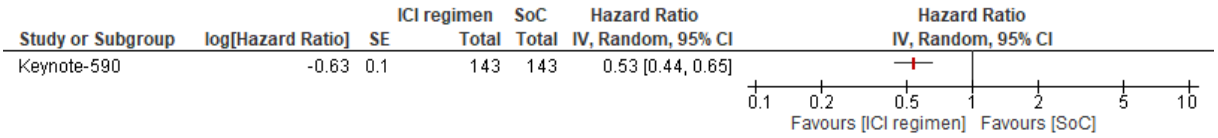
ANALYSIS 8.2.
Nivolumab-based regimen compared to SoC in PD-L1 positive OESCC, Outcome: Overall survival



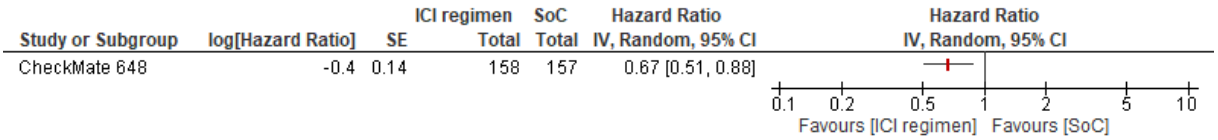
ANALYSIS 8.3.
Ipilimumab/nivolumab compared to SoC in PD-L1 positive OESCC, Outcome: Overall survival



ANALYSIS 8.4.
Pembrolizumab-based regimen compared to SoC in PD-L1 positive OESCC, Outcome: Progression-free survival

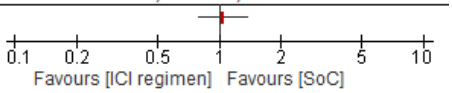


ANALYSIS 8.5.
Nivolumab-based regimen compared to SoC in PD-L1 positive OESCC, Outcome: Progression-free survival



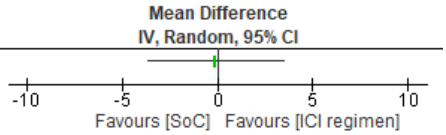
ANALYSIS 8.6.
Ipilimumab/nivolumab compared to SoC in PD-L1 positive OESCC, Outcome: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Hazard Ratio IV, Random, 95% CI
CheckMate 648	0.04	0.14	158	157	1.04 [0.79, 1.37]



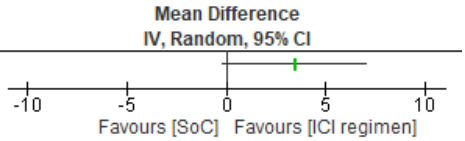
ANALYSIS 8.7.
Pembrolizumab-based regimen compared to SoC in OESCC, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)

Study or Subgroup	ICI regimen Mean	SD	Total	SoC Mean	SD	Total	Mean Difference IV, Random, 95% CI
Keynote-590	-1.74	24.2242	366	-1.64	24.8022	363	-0.10 [-3.66, 3.46]



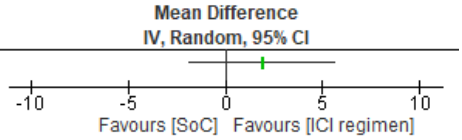
ANALYSIS 8.8.
Nivolumab-based regimen compared to SoC in OESCC, Outcome: Health-related Quality of Life (HRQoL; measured by FACT-Esophageal)

Study or Subgroup	ICI regimen Mean	SD	Total	SoC Mean	SD	Total	Mean Difference IV, Random, 95% CI
CheckMate 648	4.98	19.2	269	1.54	22.68	253	3.44 [-0.18, 7.06]



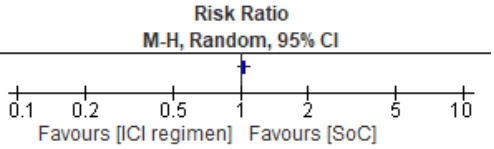
ANALYSIS 8.9.
Ipilimumab/nivolumab compared to SoC in OESCC, Outcome: Health-related Quality of Life (HRQoL; measured by FACT-Esophageal)

Study or Subgroup	ICI regimen Mean	SD	Total	SoC Mean	SD	Total	Mean Difference IV, Random, 95% CI
CheckMate 648	3.45	21.11	276	1.54	22.68	253	1.91 [-1.83, 5.65]



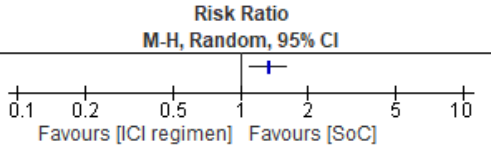
ANALYSIS 8.10.
Pembrolizumab-based regimen compared to SoC in PD-L1 positive OESCC, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

Study or Subgroup	ICI regimen Events	Total	SoC Events	Total	Risk Ratio M-H, Random, 95% CI
Keynote-590	318	370	308	370	1.03 [0.97, 1.10]



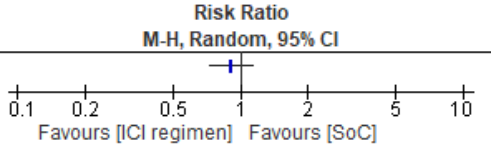
ANALYSIS 8.11.
Nivolumab-based regimen compared to SoC in PD-L1 positive OESCC, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

Study or Subgroup	ICI regimen Events	Total	SoC Events	Total	Risk Ratio M-H, Random, 95% CI
CheckMate 648	151	310	111	304	1.33 [1.11, 1.61]



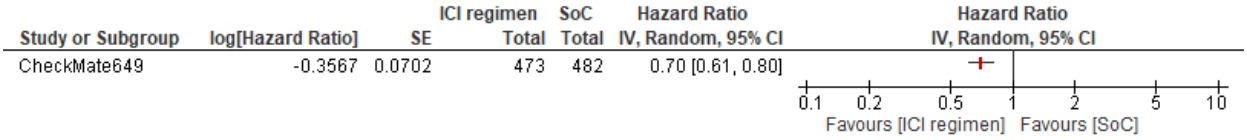
ANALYSIS 8.12.
Ipilimumab/nivolumab compared to SoC in PD-L1 positive OESCC, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

Study or Subgroup	ICI regimen Events	Total	SoC Events	Total	Risk Ratio M-H, Random, 95% CI
CheckMate 648	107	322	111	304	0.91 [0.73, 1.13]

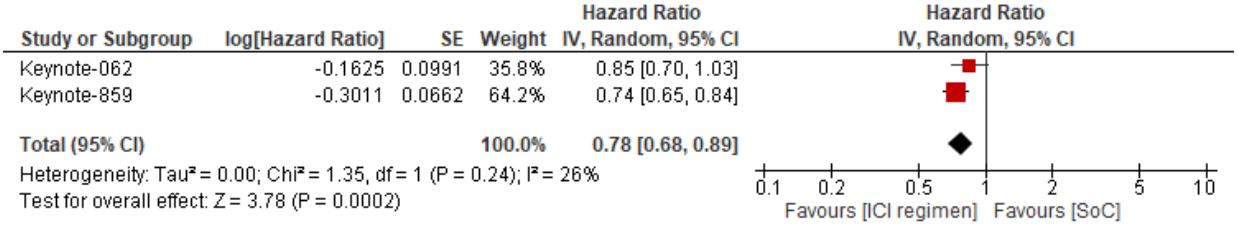


Analyses 9: Gastric, oesophageal and gastro-oesophageal junction adenocarcinoma

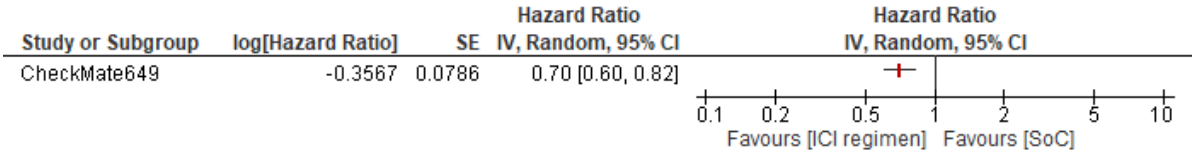
ANALYSIS 9.1.
Nivolumab-based regimen compared to SoC in ERBB2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 ≥ 5% expression, Outcome: Overall survival



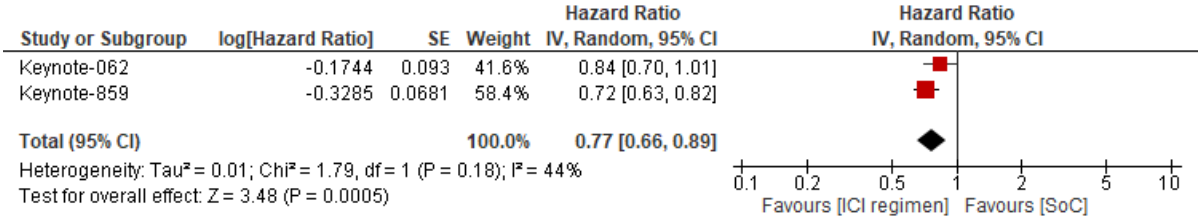
ANALYSIS 9.2.
Pembrolizumab-based regimen compared to SoC in ERBB2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 ≥ 1% expression, Outcome: Overall survival



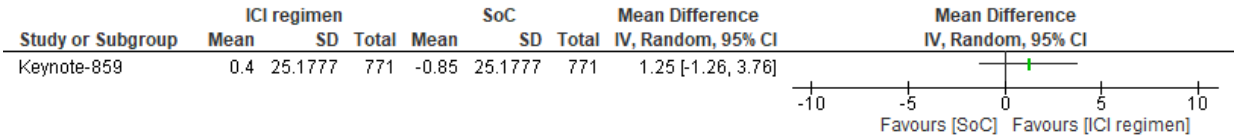
ANALYSIS 9.3.
Nivolumab-based regimen compared to SoC in ERBB2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 ≥ 5% expression, Outcome: Progression-free survival



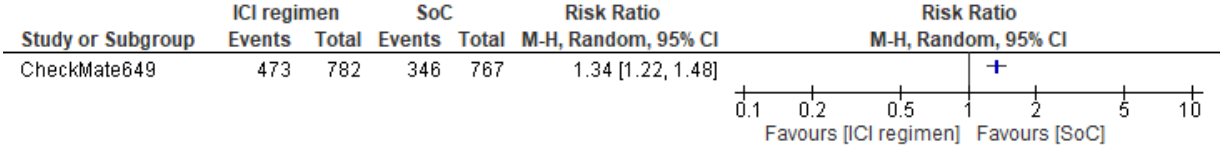
ANALYSIS 9.4.
Pembrolizumab-based regimen compared to SoC in ERBB2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD- L1 ≥ 1% expression, Outcome: Progression-free survival



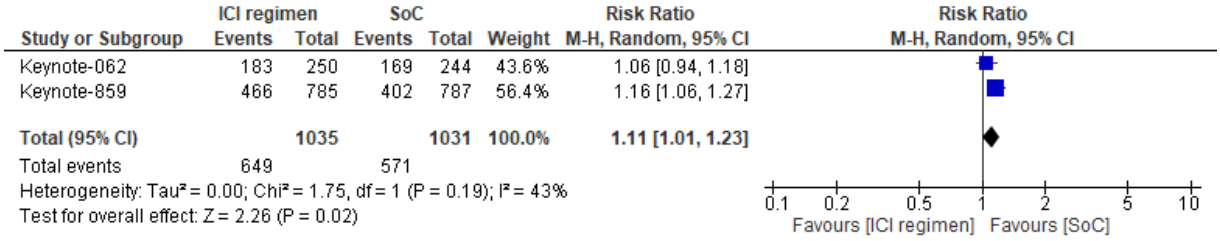
ANALYSIS 9.5.
Pembrolizumab-based regimen compared to SoC in ERBB2-negative gastric and gastro-oesophageal junction adenocarcinoma irrespective of PD-L1 expression, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)



ANALYSIS 9.6.
Nivolumab-based regimen compared to SoC in ERBB2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 ≥ 5% expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

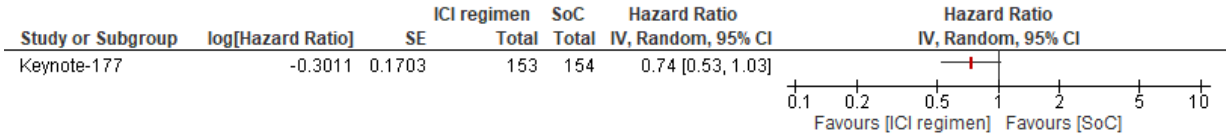


ANALYSIS 9.7.
Pembrolizumab-based regimen compared to SoC in ERBB2-negative gastric and gastro-oesophageal junction adenocarcinoma with PD-L1 ≥ 1% expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

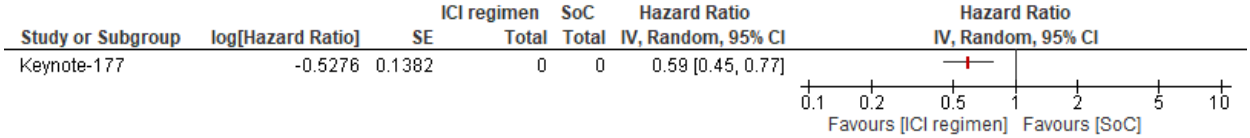


Analyses 10: Colorectal carcinoma

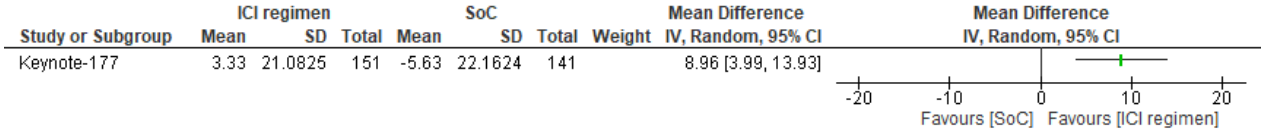
ANALYSIS 10.1.
Pembrolizumab monotherapy compared to SoC in colorectal carcinoma with dMMR/MSI-H, Outcome: Overall survival



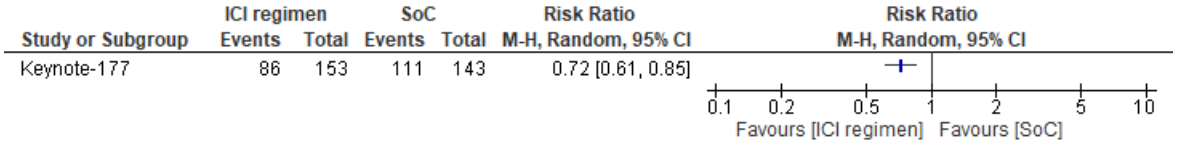
ANALYSIS 10.2.
Pembrolizumab monotherapy compared to SoC in colorectal carcinoma with dMMR/MSI-H, Outcome: Progression-free survival



ANALYSIS 10.3.
Pembrolizumab monotherapy compared to SoC in colorectal carcinoma with dMMR/MSI-H, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)

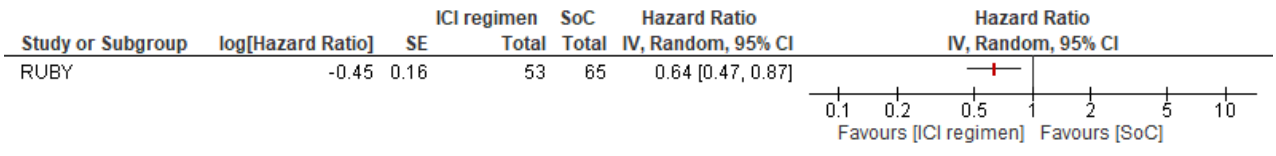


ANALYSIS 10.4.
Pembrolizumab monotherapy compared to SoC in colorectal carcinoma with dMMR/MSI-H, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution



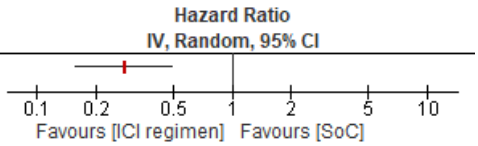
Analyses 11: Endometrial carcinoma

ANALYSIS 11.1.
Dostarlimab-based treatment regimen compared to SoC in EC with dMMR/MSI-H, Outcome: Overall survival



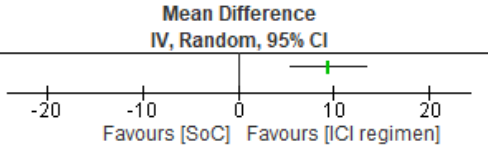
ANALYSIS 11.2.
Dostarlimab-based treatment regimen compared to SoC in EC with dMMR/MSI-H, Outcome: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Hazard Ratio IV, Random, 95% CI
RUBY	-1.27	0.29	53	65	0.28 [0.16, 0.50]



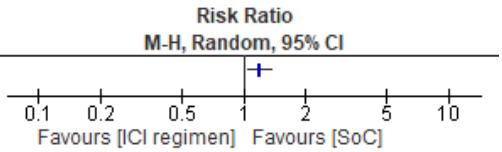
ANALYSIS 11.3.
Dostarlimab-based treatment regimen compared to SoC in EC with dMMR/MSI-H, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)

Study or Subgroup	ICI regimen Mean	SD	Total	SoC Mean	SD	Total	Mean Difference IV, Random, 95% CI
RUBY	1.54	11.27	51	-7.84	9.92	64	9.38 [5.45, 13.31]



ANALYSIS 11.4.
Dostarlimab-based treatment regimen compared to SoC in EC with dMMR/MSI-H, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

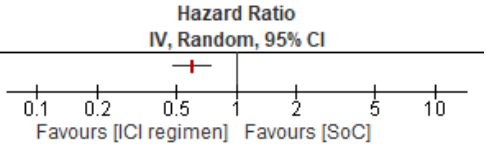
Study or Subgroup	ICI regimen Events	Total	SoC Events	Total	Risk Ratio M-H, Random, 95% CI
RUBY	174	241	148	246	1.20 [1.06, 1.36]



Analyses 12: Cervical cancer

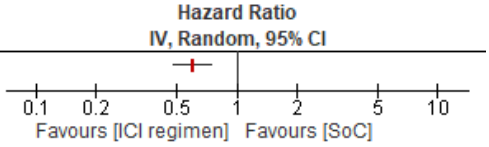
ANALYSIS 12.1.
Pembrolizumab-based treatment regimens compared to SoC in cervical cancer with PD-L1 ≥ 1% expression, Outcome: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Hazard Ratio IV, Random, 95% CI
Keynote-826	-0.51	0.11	273	275	0.60 [0.48, 0.74]



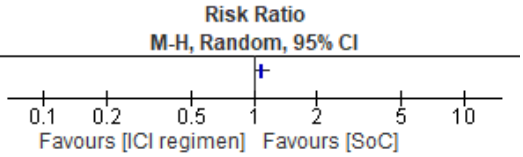
ANALYSIS 12.2.
Pembrolizumab-based treatment regimens compared to SoC in cervical cancer with PD-L1 ≥ 1% expression, Outcome: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Hazard Ratio IV, Random, 95% CI
Keynote-826	-0.51	0.11	273	275	0.60 [0.48, 0.74]

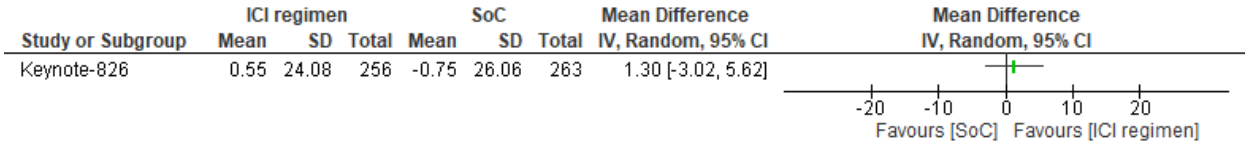


ANALYSIS 12.3.
Pembrolizumab-based treatment regimens compared to SoC in cervical cancer with PD-L1 ≥ 1% expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

Study or Subgroup	ICI regimen Events	Total	SoC Events	Total	Risk Ratio M-H, Random, 95% CI
Keynote-826	253	307	233	309	1.09 [1.01, 1.19]

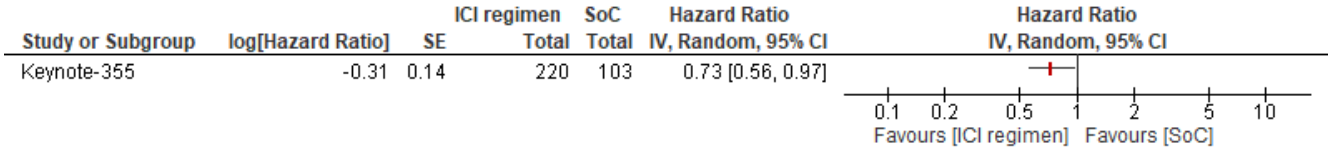


ANALYSIS 12.4.
Pembrolizumab-based treatment regimens compared to SoC in cervical cancer with PD-L1 ≥ 1% expression, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)

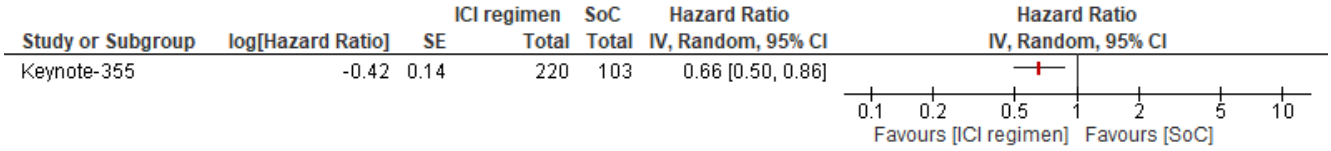


Analysis 13: Triple-negative breast cancer

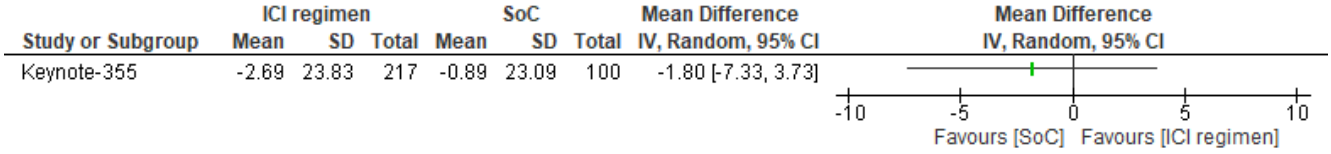
ANALYSIS 13.1.
Pembrolizumab-based treatment regimens compared to SoC in TNBC with PD-L1 ≥ 10% expression, Outcome: Overall survival



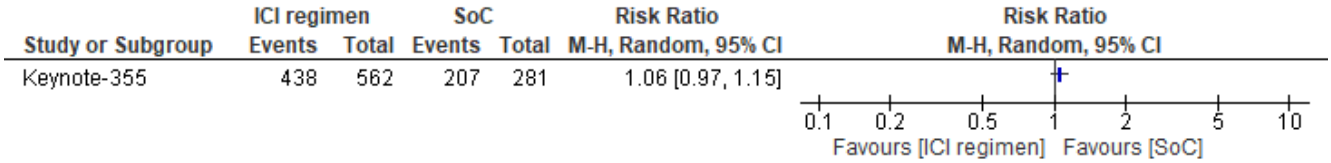
ANALYSIS 13.2.
Pembrolizumab-based treatment regimens compared to SoC in TNBC with PD-L1 ≥ 10% expression, Outcome: Progression-free survival



ANALYSIS 13.3.
Pembrolizumab-based treatment regimens compared to SoC in TNBC with PD-L1 ≥ 10% expression, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)



ANALYSIS 13.4.
Pembrolizumab-based treatment regimens compared to SoC in TNBC with PD-L1 ≥ 10% expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution



References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2024;74(3):229-63.
2. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. 2021;127(16):3029-30.
3. Anandasabapathy S, Asirwa C, Grover S, Mungo C. Cancer burden in low-income and middle-income countries. Nature Reviews Cancer. 2024;24(3):167-70.
4. Henke O, Qader AQ, Malle GL, Kuiate JR, Hennig L, Demeke T, et al. International cooperation to fight cancer's late-stage presentation in low- and middle-income countries. Clinical & experimental metastasis. 2023;40(1):1-3.
5. Pramesh CS, Badwe RA, Bhoo-Pathy N, Booth CM, Chinnaswamy G, Dare AJ, et al. Priorities for cancer research in low- and middle-income countries: a global perspective. Nature Medicine. 2022;28(4):649-57.
6. Brand NR, Qu LG, Chao A, Ilbawi AM. Delays and Barriers to Cancer Care in Low- and Middle-Income Countries: A Systematic Review. Oncologist. 2019;24(12):e1371-e80.
7. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute; 2024 Apr 17. [updated: 2024 Nov 5; cited 2025 Feb 19]. Available from: https://seer.cancer.gov/statistics-network/explorer/. Data source(s): SEER Incidence Data, November 2023 Submission (1975-2021), SEER 22 registries.
8. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63.
9. Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. Nature Reviews Clinical Oncology. 2022;19(4):254-67.
10. Marin-Acevedo JA, Kimbrough EO, Lou Y. Next generation of immune checkpoint inhibitors and beyond. Journal of Hematology & Oncology. 2021;14(1):45.
11. Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, et al. Immune Checkpoint Inhibitors in Cancer Therapy. Current Oncology. 2022;29(5):3044-60.
12. World Health Organisation. Online database of WHO essential medicines (eEML) [Available from: https://list.essentialmeds.org/.
13. Barroso A, Estevinho F, Hespanhol V, Teixeira E, Ramalho-Carvalho J, Araújo A. Management of infusion-related reactions in cancer therapy: strategies and challenges. ESMO Open. 2024;9(3):102922.
14. Matsumoto K, Ryushima Y, Sato J, Aizawa Y, Aoyama T, Akaishi Y, et al. Extravasation associated with cancer drug therapy: multidisciplinary guideline of the Japanese Society of Cancer Nursing, Japanese Society of Medical Oncology, and Japanese Society of Pharmaceutical Oncology. ESMO Open. 2024;9(10).
15. Pérez Fidalgo JA, García Fabregat L, Cervantes A, Margulies A, Vidall C, Roila F. Management of chemotherapy extravasation: ESMO–EONS Clinical Practice Guidelines[†]. Annals of Oncology. 2012;23:vii167-vii73.
16. European Medicines Agency (EMA). Keytruda: EPAR - Product information [accessed: May 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda.
17. European Medicines Agency (EMA). Opdivo: EPAR - Product information [accessed: June 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo.
18. Long GV, Tykodi SS, Schneider JG, Garbe C, Gravis G, Rashford M, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. Ann Oncol. 2018;29(11):2208-13.
19. European Medicines Agency (EMA). Yervoy: EPAR - Product information [accessed: June 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/yervoy.
20. European Medicines Agency (EMA). Tecentriq: EPAR - Product information [accessed: June 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tecentriq.
21. European Medicines Agency (EMA). Libtayo: EPAR - Product information [accessed: June 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/libtayo.
22. European Medicines Agency (EMA). Imfinzi: EPAR - Product information [accessed: June 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/imfinzi.
23. European Medicines Agency (EMA). Imjudo: EPAR - Product information [accessed: June 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/imjudo.
24. European Medicines Agency (EMA). Jemperli: EPAR - Product information [accessed: June 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/jemperli.
25. European Medicines Agency (EMA). Inlyta: EPAR - Product information [accessed: October 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/inlyta.
26. European Medicines Agency (EMA). Kisplyx: EPAR - Product information [accessed: October 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kisplyx.
27. European Medicines Agency (EMA). Avastin: EPAR - Product information [accessed: October 2024] [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/avastin.
28. Marletta S, Fusco N, Munari E, Luchini C, Cimadamore A, Brunelli M, et al. Atlas of PD-L1 for Pathologists: Indications, Scores, Diagnostic Platforms and Reporting Systems. J Pers Med. 2022;12(7).
29. De Marchi P, Leal LF, Duval da Silva V, da Silva ECA, Cordeiro de Lima VC, Reis RM. PD-L1 expression by Tumor Proportion Score (TPS) and Combined Positive Score (CPS) are similar in non-small cell lung cancer (NSCLC). J Clin Pathol. 2021;74(11):735-40.
30. Emancipator K, Huang L, Aurora-Garg D, Bal T, Cohen EEW, Harrington K, et al. Comparing programmed death ligand 1 scores for predicting pembrolizumab efficacy in head and neck cancer. Mod Pathol. 2021;34(3):532-41.
31. Cook S, Samuel V, Meyers DE, Stukalin I, Litt I, Sangha R, et al. Immune-Related Adverse Events and Survival Among Patients With Metastatic NSCLC Treated With Immune Checkpoint Inhibitors. JAMA Network Open. 2024;7(1):e2352302-e.
32. Jayathilaka B, Mian F, Franchini F, Au-Yeung G, Ijzerman M. Cancer and treatment specific incidence rates of immune-related adverse events induced by immune checkpoint inhibitors: a systematic review. British Journal of Cancer. 2025;132(1):51-7.
33. Schneider BJ, Lacchetti C, Bollin K. Management of the Top 10 Most Common Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy. JCO Oncology Practice. 2022;18(6):431-44.
34. Tang SQ, Tang LL, Mao YP, Li WF, Chen L, Zhang Y, et al. The Pattern of Time to Onset and Resolution of Immune-Related Adverse Events Caused by Immune Checkpoint Inhibitors in Cancer: A Pooled Analysis of 23 Clinical Trials and 8,436 Patients. Cancer Res Treat. 2021;53(2):339-54.

35. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. Journal of Clinical Oncology. 2021;39(36):4073-126.
36. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2022;33(12):1217-38.
37. Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer. 2021;9(6).
38. Özdemir BC, Espinosa da Silva C, Arangalage D, Monney P, Guler SA, Huynh-Do U, et al. Multidisciplinary recommendations for essential baseline functional and laboratory tests to facilitate early diagnosis and management of immune-related adverse events among cancer patients. Cancer Immunol Immunother. 2023;72(7):1991-2001.
39. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nature Reviews Clinical Oncology. 2019;16(9):563-80.
40. Cherny NI, Dafni U, Bogaerts J, Latino NJ, Pentheroudakis G, Douillard JY, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology. 2017;28(10):2340-66.
41. Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Annals of Oncology. 2015;26(8):1547-73.
42. Kiesewetter B, Cherny NI, Boissel N, Cerisoli F, Dafni U, de Vries EGE, et al. EHA evaluation of the ESMO—Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) for haematological malignancies. ESMO Open. 2020;5(1).
43. Kiesewetter B, Dafni U, de Vries EGE, Barriuso J, Curigliano G, González-Calle V, et al. ESMO-Magnitude of Clinical Benefit Scale for haematological malignancies (ESMO-MCBS:H) version 1.0. Annals of Oncology. 2023;34(9):734-71.
44. Garritty C, Hamel C, Trivella M, Gartlehner G, Nussbaumer-Streit B, Devane D, et al. Updated recommendations for the Cochrane rapid review methods guidance for rapid reviews of effectiveness. 2024;384:e076335.
45. Nussbaumer-Streit B, Sommer I, Hamel C, Devane D, Noel-Storr A, Puljak L, et al. Rapid reviews methods series: Guidance on team considerations, study selection, data extraction and risk of bias assessment. 2023;28(6):418-23.
46. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. 2011;343:d5928.
47. Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings tables'. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.
48. Jenei K, Aziz Z, Booth C, Cappello B, Ceppi F, de Vries EGE, et al. Cancer medicines on the WHO Model List of Essential Medicines: processes, challenges, and a way forward. Lancet Glob Health. 2022;10(12):e1860-e6.
49. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011;64(12):1283-93.
50. Musoro JZ, Coens C, Sprangers MAG, Brandberg Y, Groenvold M, Flechtner H-H, et al. Minimally important differences for interpreting EORTC QLQ-C30 change scores over time: A synthesis across 21 clinical trials involving nine different cancer types. European Journal of Cancer. 2023;188:171-82.
51. Bronte G. The likelihood of being helped or harmed obtained from clinical trial results for cancer therapy: Can it really help? Seminars in Oncology. 2025.
52. Mastrantoni L, Giordano G, Vita E, Horn G, Russo J, Orlandi A, et al. The likelihood of being helped or harmed as a patient-centred tool to assess ALK-Inhibitors clinical impact and safety in ALK-addicted non-small cell lung cancer: A systematic review and sensitivity-analysis. Cancer Treat Res Commun. 2024;41:100842.
53. Mastrantoni L, Orlandi A, Palazzo A, Garufi G, Fabi A, Daniele G, et al. The likelihood of being helped or harmed as a patient-centred tool to assess cyclin dependent kinase 4/6 inhibitors clinical impact and safety in metastatic breast cancer: a systematic review and sensitivity-analysis. EClinicalMedicine. 2023;56:101824.
54. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol. 2020;119:126-35.
55. European Society for Medical Oncology. ESMO-MCBS Scorecards [Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards.
56. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. New England journal of medicine. 2020;383(14):1328-39.
57. Jassem J, de Marinis F, Giaccone G, Vergnenegre A, Barrios CH, Morise M, et al. Updated Overall Survival Analysis From IMpower110: atezolizumab Versus Platinum-Based Chemotherapy in Treatment-Naive Programmed Death-Ligand 1-Selected NSCLC. Journal of thoracic oncology. 2021;16(11):1872-82.
58. Lee SM, Schulz C, Prabhash K, Kowalski D, Szczesna A, Han B, et al. First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label, randomised controlled study. Lancet (london, england). 2023;402(10400):451-63.
59. Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. The lancet Oncology. 2017;18(12):1600-9.
60. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. Journal of clinical oncology. 2021;39(21):2339-49.
61. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. New England journal of medicine. 2016;375(19):1823-33.
62. de Castro G, Kudaba I, Wu YL, Lopes G, Kowalski DM, Turna HZ, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy as First-Line Therapy in Patients With Non-Small-Cell Lung Cancer and Programmed Death Ligand-1 Tumor Proportion Score ≥ 1% in the KEYNOTE-042 Study. Journal of clinical oncology. 2023;41(11):1986-91.
63. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet (london, england). 2019;393(10183):1819-30.
64. Gumus M, Chen CI, Ivanescu C, Kilickap S, Bondarenko I, Ozguroglu M, et al. Patient-reported outcomes with cemiplimab monotherapy for first-line treatment of advanced non-small cell lung cancer with PD-L1 of ≥50%: the EMPOWER-Lung 1 study. Cancer. 2023;129(1):118-29.

65. Ozguroglu M, Kilickap S, Sezer A, Gumus M, Bondarenko I, Gogishvili M, et al. First-line cemiplimab monotherapy and continued cemiplimab beyond progression plus chemotherapy for advanced non-small-cell lung cancer with PD-L1 50% or more (EMPOWER-Lung 1): 35-month follow-up from a mutlicentre, open-label, randomised, phase 3 trial. The lancet Oncology. 2023;24(9):989-1001.
66. Sezer A, Kilickap S, Gumus M, Bondarenko I, Ozguroglu M, Gogishvili M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet (london, england). 2021;397(10274):592-604.
67. Marinis Fd, Giaccone G, Herbst RS, Oprean C-M, Szczesna A, Boukovinas I, et al. Patient-reported outcomes (PROs) in the randomized, phase III IMpower110 study of atezolizumab (atezo) vs chemotherapy in 1L metastatic NSCLC. Journal of Clinical Oncology. 2020;38(15_suppl):9594-.
68. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. The Lancet. 2021;398(10308):1344-57.
69. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. The Lancet. 2016;387(10027):1540-50.
70. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. The Lancet. 2017;389(10066):255-65.
71. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. The Lancet Oncology. 2022;23(10):1274-86.
72. Brahmer JR, Lee JS, Ciuleanu TE, Bernabe Caro R, Nishio M, Urban L, et al. Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer in CheckMate 227. J Clin Oncol. 2023;41(6):1200-12.
73. de Castro G, Jr., Rizvi NA, Schmid P, Syrigos K, Martin C, Yamamoto N, et al. NEPTUNE: Phase 3 Study of First-Line Durvalumab Plus Tremelimumab in Patients With Metastatic NSCLC. J Thorac Oncol. 2023;18(1):106-19.
74. Léna H, Greillier L, Cropet C, Bylicki O, Monnet I, Audigier-Valette C, et al. Nivolumab plus ipilimumab versus carboplatin-based doublet as first-line treatment for patients with advanced non-small-cell lung cancer aged ≥70 years or with an ECOG performance status of 2 (GFPC 08-2015 ENERGY): a randomised, open-label, phase 3 study. Lancet Respir Med. 2025;13(2):141-52.
75. Reck M, Barlesi F, Yang JC, Westeel V, Felip E, Özgüroğlu M, et al. Avelumab Versus Platinum-Based Doublet Chemotherapy as First-Line Treatment for Patients With High-Expression Programmed Death-Ligand 1-Positive Metastatic NSCLC: Primary Analysis From the Phase 3 JAVELIN Lung 100 Trial. J Thorac Oncol. 2024;19(2):297-313.
76. Rizvi NA, Cho BC, Reinmuth N, Lee KH, Luft A, Ahn MJ, et al. Durvalumab With or Without Tremelimumab vs Standard Chemotherapy in First-line Treatment of Metastatic Non-Small Cell Lung Cancer: The MYSTIC Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020;6(5):661-74.
77. Hellmann MD, Paz-Ares L, Caro RB, Zurawski B, Kim S-W, Costa EC, et al. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2019;381(21):2020-31.
78. Lu S, Wu L, Wang Q, Wang Z, Lv D, Ma R, et al. Durvalumab Versus Chemotherapy as First-line Treatment for Metastatic NSCLC With Tumor PD-L1 Expression of 25% or Higher: Results From the Randomized Phase 3 PEARL Study. Journal of Thoracic Oncology. 2024.
79. Awad MM, Gadgeel SM, Borghaei H, Patnaik A, Yang J-H, Powell SF, et al. Long-Term Overall Survival From KEYNOTE-021 Cohort G: pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC. Journal of thoracic oncology. 2020;16(1):162-8.
80. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. The lancet Oncology. 2016;17(11):1497-508.
81. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. New England journal of medicine. 2018;378:2078-92.
82. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. The lancet Oncology. 2020;21(3):387-97.
83. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Domine M, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. Journal of clinical oncology. 2023;41(11):1992-8.
84. Mazieres J, Kowalski D, Luft A, Vicente D, Tafreshi A, Gumus M, et al. Health-Related Quality of Life With Carboplatin-Paclitaxel or nab-Paclitaxel With or Without Pembrolizumab in Patients With Metastatic Squamous Non-Small-Cell Lung Cancer. Journal of clinical oncology. 2020;38(3):271-80.
85. Novello S, Kowalski DM, Luft A, Gumus M, Vicente D, Mazieres J, et al. Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer: 5-year update of the phase III KEYNOTE-407 study. Journal of clinical oncology. 2022;41(11):1999-2006.
86. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. New England journal of medicine. 2018;379(21):2040-51.
87. Gogishvili M, Melkadze T MT, Giorgadze D, Dvorkin M, Penkov K, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. Nature medicine. 2022;28:2374-80.
88. Makharadze T, Gogishvili M, Melkadze T, Baramidze A, Giorgadze D, Penkov K, et al. Cemiplimab Plus Chemotherapy Versus Chemotherapy Alone in Advanced NSCLC: 2-Year Follow-Up From the Phase 3 EMPOWER-Lung 3 Part 2 Trial. Journal of thoracic oncology. 2023;18(6):755-68.
89. Makharadze T, Quek RGW, Melkadze T, Gogishvili M, Ivanescu C, Giorgadze D, et al. Quality of life with cemiplimab plus chemotherapy for first-line treatment of advanced non-small cell lung cancer: patient-reported outcomes from phase 3 EMPOWER-Lung 3. Cancer. 2023;129(14):2256-65.
90. Paz-Ares L, Ciuleanu TE, Cobo M, Schenker M, Zurawski B, Menezes J, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. 2021;22(2):198-211.
91. Reck M, Ciuleanu T-E, Schenker M, Bordenave S, Cobo M, Juan-Vidal O, et al. Five-year outcomes with first-line nivolumab plus ipilimumab with 2 cycles of chemotherapy versus 4 cycles of chemotherapy alone in patients with metastatic non-small cell lung cancer in the randomized CheckMate 9LA trial. European Journal of Cancer. 2024;211.
92. Reck M, Ciuleanu TE, Cobo M, Schenker M, Zurawski B, Menezes J, et al. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in metastatic non-small cell lung cancer: checkMate 9LA 2-year patient-reported outcomes. 2023;183:174-87.
93. Johnson ML, Cho BC, Luft A, Alatorre-Alexander J, Geater SL, Laktionov K, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: the Phase III POSEIDON Study. Journal of clinical oncology. 2023;41(6):1213-27.

94. Peters S, Cho BC, Luft A, Alexander JAA, Geater SL, Laktionov K, et al. LBA3 Durvalumab (D) ± tremelimumab (T) + chemotherapy (CT) in first-line (1L) metastatic NSCLC (mNSCLC): 5-year (y) overall survival (OS) update from the POSEIDON study. Immuno-oncology and technology. 2023;20.
95. Cascone T, Awad MM, Spicer JD, He J, Lu S, Sepesi B, et al. Perioperative Nivolumab in Resectable Lung Cancer. New England Journal of Medicine. 2024;390(19):1756-69.
96. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. New England Journal of Medicine. 2022;386(21):1973-85.
97. Spicer JD, Garassino MC, Wakelee H, Liberman M, Kato T, Tsuboi M, et al. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2024;404(10459):1240-52.
98. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. The lancet Oncology. 2019;20(7):924-37.
99. Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodriguez-Abreu D, Hussein M, et al. Atezolizumab in Combination With Carboplatin and Nab-Paclitaxel in Advanced Squamous Non-Small-Cell Lung Cancer (IMpower131): results From a Randomized Phase III Trial. Journal of thoracic oncology. 2020;15(8):1351-60.
100. Nishio M, Barlesi F, West H, Ball S, Bordoni R, Cobo M, et al. Atezolizumab Plus Chemotherapy for First-Line Treatment of Non-Squamous Non-Small Cell Lung Cancer: results From the Randomized Phase III IMpower132 Trial. Journal of thoracic oncology. 2020;16(4):653-64.
101. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. New England journal of medicine. 2018;378(24):2288-301.
102. Zhou C, Dong X, Chen G, Wang Z, Wu X, Yao Y, et al. OA09.06 IMpower151: phase III Study of Atezolizumab + Bevacizumab + Chemotherapy in 1L Metastatic Nonsquamous NSCLC. Journal of thoracic oncology. 2023;18(11):S64-S5.
103. Kim HR, Sugawara S, Lee JS, Kang JH, Inui N, Hida T, et al. First-line nivolumab, paclitaxel, carboplatin, and bevacizumab for advanced non-squamous non-small cell lung cancer: Updated survival analysis of the ONO-4538-52/TASUKI-52 randomized controlled trial. Cancer Med. 2023;12(16):17061-7.
104. Borghaei H, O'Byrne KJ, Paz-Ares L, Ciuleanu TE, Yu X, Pluzanski A, et al. Nivolumab plus chemotherapy in first-line metastatic non-small-cell lung cancer: results of the phase III CheckMate 227 Part 2 trial. ESMO Open. 2023;8(6):102065.
105. Lim SM, Peters S, Ortega Granados AL, Pinto GDJ, Fuentes CS, Lo Russo G, et al. Dostarlimab or pembrolizumab plus chemotherapy in previously untreated metastatic non-squamous non-small cell lung cancer: the randomized PERLA phase II trial. Nat Commun. 2023;14(1):7301.
106. Shiraishi Y, Nomura S, Sugawara S, Horinouchi H, Yoneshima Y, Hayashi H, et al. Comparison of platinum combination chemotherapy plus pembrolizumab versus platinum combination chemotherapy plus nivolumab-ipilimumab for treatment-naive advanced non-small-cell lung cancer in Japan (JCOG2007): an open-label, multicentre, randomised, phase 3 trial. Lancet Respir Med. 2024;12(11):877-87.
107. Cho BC, Brana I, Cirauqui B, Aksoy S, Couture F, Hong RL, et al. Pembrolizumab plus epacadostat in patients with recurrent/metastatic head and neck squamous cell carcinoma (KEYNOTE-669/ECHO-304): a phase 3, randomized, open-label study. BMC cancer. 2024;23:1254.
108. Gruenwald V, Graeven U, Ivanyi P, Dietz A, Hahn D, Hackenberg S, et al. Results of a randomized phase II study comparing pembrolizumab with methotrexate in elderly, frail or cisplatin-ineligible patients with relapsed or metastatic squamous cell carcinoma of the head and neck (RM-SCCHN) (ELDORANDO-AIO-KHT-0115). Annals of oncology. 2021;32:S807-S8.
109. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet (london, england). 2019;394(10212):1915-28.
110. Harrington KJ, Burtness B, Greil R, Soulieres D, Tahara M, de Castro G, et al. Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: updated Results of the Phase III KEYNOTE-048 Study. Journal of clinical oncology. 2023;41(4):790-802.
111. Rischin D, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G, et al. Pembrolizumab alone or with chemotherapy for recurrent or metastatic head and neck squamous cell carcinoma: health-related quality-of-life results from KEYNOTE-048. Oral oncology. 2022;128:105815.
112. Burtness B, Rischin D, Greil R, Soulieres D, Tahara M, de Castro G, et al. Pembrolizumab alone or with chemotherapy for recurrent/metastatic head and neck squamous cell carcinoma in KEYNOTE-048: subgroup analysis by programmed death ligand-1 combined positive score. Journal of clinical oncology. 2022;40(21):2321-32.
113. Burtness B, Rischin D, Greil R, Soulières D, Tahara M, Jr GdC, et al. Pembrolizumab Alone or With Chemotherapy for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma in KEYNOTE-048: Subgroup Analysis by Programmed Death Ligand-1 Combined Positive Score. Journal of Clinical Oncology. 2022;40(21):2321-32.
114. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn M-J, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. The Lancet. 2019;393(10167):156-67.
115. Machiels JP, Tao Y, Licitra L, Burtness B, Tahara M, Rischin D, et al. Pembrolizumab plus concurrent chemoradiotherapy versus placebo plus concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (KEYNOTE-412): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2024;25(5):572-87.
116. Gruenwald V, Graeven U, Ivanyi P, Dietz A, Hahn D, Hackenberg S, et al. 912P Results of a randomized phase II study comparing pembrolizumab with methotrexate in elderly, frail or cisplatin-ineligible patients with relapsed or metastatic squamous cell carcinoma of the head and neck (RM-SCCHN) (ELDORANDO-AIO-KHT-0115). Annals of Oncology. 2021;32:S807-S8.
117. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016;375(19):1856-67.
118. Haddad RI, Harrington K, Tahara M, Ferris RL, Gillison M, Fayette J, et al. Nivolumab Plus Ipilimumab Versus EXTREME Regimen as First-Line Treatment for Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck: The Final Results of CheckMate 651. J Clin Oncol. 2023;41(12):2166-80.
119. Psyrri A, Fayette J, Harrington K, Gillison M, Ahn MJ, Takahashi S, et al. Durvalumab with or without tremelimumab versus the EXTREME regimen as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck: KESTREL, a randomized, open-label, phase III study. Ann Oncol. 2023;34(3):262-74.
120. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. The Lancet Oncology. 2018;19(5):672-81.
121. Thompson JR, Lai-Kwon J, Morton RL, Guminski AD, Gonzalez M, Atkinson V, et al. Health-related Quality of Life in Patients with Melanoma Brain Metastases Treated with Immunotherapy. Immunotherapy. 2023;15(8):593-610.

122. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rutkowski P, Lao CD, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. Journal of Clinical Oncology. 2022;40(2):127-37.
123. Schadendorf D, Larkin J, Wolchok J, Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Health-related quality of life results from the phase III CheckMate 067 study. European Journal of Cancer. 2017;82:80-91.
124. Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, McDermott DF, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. The Lancet Oncology. 2016;17(11):1558-68.
125. Abernethy AP, Postow MA, Chesney JA, Grossmann KF, Taylor F, Coon C, et al. Effect of nivolumab (NIVO) in combination with ipilimumab (IPI) versus IPI alone on quality of life (QoL) in patients (pts) with treatment-naïve advanced melanoma (MEL): Results of a phase II study (CheckMate 069). Journal of Clinical Oncology. 2015;33(15_suppl):9029-.
126. Atkins MB, Lee SJ, Chmielowski B, Tarhini AA, Cohen GI, Truong T-G, et al. Combination Dabrafenib and Trametinib Versus Combination Nivolumab and Ipilimumab for Patients With Advanced BRAF-Mutant Melanoma: The DREAMseq Trial—ECOG-ACRIN EA6134. Journal of Clinical Oncology. 2023;41(2):186-97.
127. Jensen RE, Zheng Y, Atkins MB, Chmielowski B, Tarhini AA, Truong T-G, et al. Early quality of life (QOL) and symptom analysis from the DREAMseq phase III randomized control trial of combination immunotherapy versus targeted therapy in patients (pts) with BRAF-mutant metastatic melanoma (MM) (ECOG-ACRIN EA6134). Journal of Clinical Oncology. 2022;40(16_suppl):9559-.
128. Ascierto PA, Mandalà M, Ferrucci PF, Guidoboni M, Rutkowski P, Ferraresi V, et al. Sequencing of Ipilimumab Plus Nivolumab and Encorafenib Plus Binimetinib for Untreated BRAF-Mutated Metastatic Melanoma (SECOMBIT): A Randomized, Three-Arm, Open-Label Phase II Trial. Journal of Clinical Oncology. 2023;41(2):212-21.
129. Cates C. Multiple-arm trial data: using a corrected standard error for GIV analyses | Cochrane Colloquium Abstracts. Cochrane Database of Systematic Reviews. 2015:Suppl: 1-327.
130. Rücker G, Cates CJ, Schwarzer G. Methods for including information from multi-arm trials in pairwise meta-analysis. Research Synthesis Methods. 2017;8(4):392-403.
131. Di Giacomo AM, Chiarion-Sileni V, Del Vecchio M, Ferrucci PF, Guida M, Quaglino P, et al. Nivolumab plus ipilimumab in melanoma patients with asymptomatic brain metastases: 7-year outcomes and quality of life from the multicenter phase III NIBIT-M2 trial. European Journal of Cancer. 2024;199:113531.
132. Burris HA, Okusaka T, Vogel A, Lee MA, Takahashi H, Breder V, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer (TOPAZ-1): patient-reported outcomes from a randomised, double-blind, placebo-controlled, phase 3 trial. 2024;25(5):626-35.
133. Oh DY, He AR, Bouattour M, Okusaka T, Qin S, Chen LT, et al. Durvalumab or placebo plus gemcitabine and cisplatin in participants with advanced biliary tract cancer (TOPAZ-1): updated overall survival from a randomised phase 3 study. 2024;9(8):694-704.
134. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2023;401(10391):1853-65.
135. Finn RS, Ueno M, Yoo C, Ren Z, Furuse J, Kelley RK, et al. Three-year follow-up data from KEYNOTE-966: Pembrolizumab (pembro) plus gemcitabine and cisplatin (gem/cis) compared with gem/cis alone for patients (pts) with advanced biliary tract cancer (BTC). Journal of Clinical Oncology. 2024;42(16_suppl):4093-.
136. Sun J-M, Shen L, Shah MA, Enzinger P, Adenis A, Doi T, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. The Lancet. 2021;398(10302):759-71.
137. Kato K, Doki Y, Chau I, Xu J, Wyrwicz L, Motoyama S, et al. Nivolumab plus chemotherapy or ipilimumab versus chemotherapy in patients with advanced esophageal squamous cell carcinoma (<scp>CheckMate</scp> 648): 29-month follow-up from a randomized, open-label, phase <scp>III</scp> trial. Cancer Medicine. 2024;13(9).
138. Mansoor W, Joo S, Norquist JM, Kato K, Sun J-M, Shah MA, et al. Health-related quality-of-life analysis from KEYNOTE-590: pembrolizumab plus chemotherapy versus chemotherapy for advanced esophageal cancer. The Oncologist. 2024;29(10):e1324-e35.
139. Kojima T, Shah MA, Muro K, Francois E, Adenis A, Hsu CH, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. J Clin Oncol. 2020;38(35):4138-48.
140. Kato K, Cho BC, Takahashi M, Okada M, Lin C-Y, Chin K, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. The Lancet Oncology. 2019;20(11):1506-17.
141. Wang Z-X, Cui C, Yao J, Zhang Y, Li M, Feng J, et al. Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): A multi-center phase 3 trial. Cancer Cell. 2022;40(3):277-88.e3.
142. Xu J, Kato K, Raymond E, Hubner RA, Shu Y, Pan Y, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study. The Lancet Oncology. 2023;24(5):483-95.
143. Diaz LA, Shiu K-K, Kim T-W, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. The Lancet Oncology. 2022;23(5):659-70.
144. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. New England Journal of Medicine. 2015;372(26):2509-20.
145. Gandini A, Puglisi S, Pirrone C, Martelli V, Catalano F, Nardin S, et al. The role of immunotherapy in microsatellites stable metastatic colorectal cancer: state of the art and future perspectives. Frontiers in Oncology. 2023;13.
146. André T, Elez E, Cutsem EV, Jensen LH, Bennouna J, Mendez G, et al. Nivolumab plus Ipilimumab in Microsatellite-Instability–High Metastatic Colorectal Cancer. New England Journal of Medicine. 2024;391(21):2014-26.
147. Auranen A, Black D, Sukhin V, Sharma S, Ronzino G, rum LM, et al. SAFETY of DOSTARLIMAB in COMBINATION with CHEMOTHERAPY in PATIENTS with PRIMARY ADVANCED or RECURRENT ENDOMETRIAL CANCER in A PHASE 3, RANDOMIZED, PLACEBO-CONTROLLED TRIAL (ENGOT-EN6-NSGO/GOG-3031/RUBY). International journal of gynecological cancer. 2023;33:A23.
148. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novak Z, Black D, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. New England journal of medicine. 2023;388(23):2145-58.
149. Powell MA, Bjorge L, Willmott L, Novak Z, Black D, Gilbert L, et al. Overall Survival in Patients with Endometrial Cancer Treated with Dostarlimab plus Carboplatin-Paclitaxel in the Randomized ENGOT-EN6/GOG-3031/RUBY Trial. Annals of oncology : official journal of the european society for medical oncology. 2024;35(8):728-38.

150. Valabrega G, Powell MA, Hietanen S, Miller EM, Novak Z, Holloway R, et al. Patient-reported outcomes (PROs) in patients (pts) with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (pA/rEC) in the ENGOT-EN6-NSGO/GOG3031/RUBY trial. Annals of oncology. 2023;34:S513-S4.
151. André T, Berton D, Curigliano G, Sabatier R, Tinker AV, Oaknin A, et al. Antitumor Activity and Safety of Dostarlimab Monotherapy in Patients With Mismatch Repair Deficient Solid Tumors: A Nonrandomized Controlled Trial. JAMA Netw Open. 2023;6(11):e2341165.
152. Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. N Engl J Med. 2023;388(23):2159-70.
153. Westin SN, Moore K, Chon HS, Lee JY, Thomes Pepin J, Sundborg M, et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. J Clin Oncol. 2024;42(3):283-99.
154. Colombo N, Biagioli E, Harano K, Galli F, Hudson E, Antill Y, et al. Atezolizumab and chemotherapy for advanced or recurrent endometrial cancer (AtTEnd): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2024;25(9):1135-46.
155. Pignata S, Scambia G, Schettino C, Arenare L, Pisano C, Lombardi D, et al. Carboplatin and paclitaxel plus avelumab compared with carboplatin and paclitaxel in advanced or recurrent endometrial cancer (MITO END-3): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Oncol. 2023;24(3):286-96.
156. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. 2021;385(20):1856-67.
157. Monk BJ, Colombo N, Tewari KS, Dubot C, Caceres MV, Hasegawa K, et al. First-Line Pembrolizumab + Chemotherapy Versus Placebo + Chemotherapy for Persistent, Recurrent, or Metastatic Cervical Cancer: final Overall Survival Results of KEYNOTE-826. 2023;41(36):5505-11.
158. Monk BJ, Tewari KS, Dubot C, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Health-related quality of life with pembrolizumab or placebo plus chemotherapy with or without bevacizumab for persistent, recurrent, or metastatic cervical cancer (KEYNOTE-826): a randomised, double-blind, placebo-controlled, phase 3 trial. 2023;24(4):392-402.
159. Chung HC, Ros W, Delord J-P, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Cervical Cancer: Results From the Phase II KEYNOTE-158 Study. Journal of Clinical Oncology. 2019;37(17):1470-8.
160. Lorusso D, Xiang Y, Hasegawa K, Scambia G, Leiva M, Ramos-Elias P, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. The Lancet. 2024;403(10434):1341-50.
161. Tewari KS, Monk BJ, Vergote I, Miller A, Melo ACd, Kim H-S, et al. Survival with Cemiplimab in Recurrent Cervical Cancer. New England Journal of Medicine. 2022;386(6):544-55.
162. Oaknin A, Gladieff L, Martínez-García J, Villacampa G, Takekuma M, De Giorgi U, et al. Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial. Lancet. 2024;403(10421):31-43.
163. Long GV, Atkinson V, Lo S, Guminski AD, Sandhu SK, Brown MP, et al. Five-year overall survival from the anti-PD1 brain collaboration (ABC Study): randomized phase 2 study of nivolumab (nivo) or nivo+ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets). 2021;39(15).
164. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. 2018;19(5):672-81.
165. Thompson JR, Lai-Kwon J, Morton RL, Guminski AD, Gonzalez M, Atkinson V, et al. Health-related quality of life in patients with melanoma brain metastases treated with immunotherapy. 2023;15(8):593-610.
166. Schadendorf D, Larkin J, Wolchok J, Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Health-related quality of life results from the phase III CheckMate 067 study. 2017;82:80-91.
167. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. 2022;40(2):127-37.
168. Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, McDermott DF, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. 2016;17(11):1558-68.
169. Ascierto PA, Mandala M, Ferrucci PF, Guidoboni M, Rutkowski P, Ferraresi V, et al. Sequencing of Ipilimumab Plus Nivolumab and Encorafenib Plus Binimetinib for Untreated BRAF-Mutated Metastatic Melanoma (SECOMBIT): a Randomized, Three-Arm, Open-Label Phase II Trial. 2023;41(2):212-21.
170. Atkins MB, Lee SJ, Chmielowski B, Tarhini AA, Cohen GI, Truong TG, et al. Combination Dabrafenib and Trametinib Versus Combination Nivolumab and Ipilimumab for Patients With Advanced BRAF-Mutant Melanoma: the DREAMseq Trial-ECOG-ACRIN EA6134. 2023;41(2):186-97.
171. Jensen RE, Zheng Y, Atkins MB, Chmielowski B, Tarhini AA, Truong TG, et al. Early quality of life (QOL) and symptom analysis from the DREAMseq phase III randomized control trial of combination immunotherapy versus targeted therapy in patients (pts) with BRAF-mutant metastatic melanoma (MM) (ECOG-ACRIN EA6134). 2022;40(16).
172. Epaillard N, Simonaggio A, Elaidi R, Azzouz F, Braychenko E, Thibault C, et al. BIONIKK: a phase 2 biomarker driven trial with nivolumab and ipilimumab or VEGFR tyrosine kinase inhibitor (TKI) in naive metastatic kidney cancer. 2020;107(5):eS22-eS7.
173. Vano Y, Elaidi RT, Bennamoun M, Chevreau CM, Borchiellini D, Pannier D, et al. Results from the phase II biomarker driven trial with nivolumab (N) and ipilimumab or VEGFR tyrosine kinase inhibitor (TKI) in naive metastatic kidney cancer (m-ccRCC) patients (pts): the BIONIKK trial. 2020;31:S1157.
174. Vano YA, Elaidi R, Bennamoun M, Chevreau C, Borchiellini D, Pannier D, et al. Nivolumab, nivolumab-ipilimumab, and VEGFR-tyrosine kinase inhibitors as first-line treatment for metastatic clear-cell renal cell carcinoma (BIONIKK): a biomarker-driven, open-label, non-comparative, randomised, phase 2 trial. 2022;23(5):612-24.
175. Cella D, Grunwald V, Escudier B, Hammers HJ, George S, Nathan P, et al. Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial. 2019;20(2):297-310.
176. Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. 2018;378(14):1277-90.
177. Tannir NM, Escudier B, McDermott DF, Burotto M, Choueiri TK, Hammers HJ, et al. Nivolumab plus ipilimumab (NIVO+IPI) vs sunitinib (SUN) for first-line treatment of advanced renal cell carcinoma (aRCC): long-term follow-up data from the phase 3 CheckMate 214 trial. 2024;42(4).
178. Choueiri TK, Eto M, Motzer R, De Giorgi U, Buchler T, Basappa NS, et al. Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the phase 3, randomised, open-label study. 2023;24(3):228-38.
179. Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. 2021;384(14):1289-300.

180. Motzer R, Porta C, Alekseev B, Rha SY, Choueiri TK, Mendez-Vidal MJ, et al. Health-related quality-of-life outcomes in patients with advanced renal cell carcinoma treated with lenvatinib plus pembrolizumab or everolimus versus sunitinib (CLEAR): a randomised, phase 3 study. 2022;18(2):39-57.
181. Motzer RJ, Porta C, Eto M, Powles T, Grunwald V, Hutson TE, et al. Lenvatinib Plus Pembrolizumab Versus Sunitinib in First-Line Treatment of Advanced Renal Cell Carcinoma: final Prespecified Overall Survival Analysis of CLEAR, a Phase III Study. 2024;42(11):1222-8.
182. Bedke J, Rini BI, Plimack ER, Stus V, Gafanov R, Waddell T, et al. Health-related Quality of Life Analysis from KEYNOTE-426: Pembrolizumab plus Axitinib Versus Sunitinib for Advanced Renal Cell Carcinoma. Eur Urol. 2022;82(4):427-39.
183. Plimack ER, Powles T, Stus V, Gafanov R, Nosov D, Waddell T, et al. Pembrolizumab Plus Axitinib Versus Sunitinib as First-line Treatment of Advanced Renal Cell Carcinoma: 43-month Follow-up of the Phase 3 KEYNOTE-426 Study. 2023;84(5):449-54.
184. Powles T, Plimack ER, Soulieres D, Waddell T, Stus V, Gafanov R, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. 2020;21(12):1563-73.
185. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. 2019;380(12):1116-27.
186. Rini BI, Plimack ER, Stus V, Gafanov R, Waddell T, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: 5-year analysis of KEYNOTE-426. 2023;41(17).
187. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. 2022;76(4):862-73.
188. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. 2020;382(20):1894-905.
189. Galle PR, Finn RS, Qin S, Ikeda M, Zhu AX, Kim TY, et al. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. 2021;22(7):991-1001.
190. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. 2022;1(8):EVIDoa2100070.
191. Sangro B, Chan SL, Kelley RK, Lau G, Kudo M, Sukeepaisarnjaroen W, et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. 2024;35(5):448-57.
192. Sangro B, Galle PR, Kelley RK, Charoentum C, De Toni EN, Ostapenko Y, et al. Patient-Reported Outcomes From the Phase III HIMALAYA Study of Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. 2024:JCO2301462.
193. Oh DY, Ruth He A, Qin S, Chen LT, Okusaka T, Vogel A, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. 2022;1(8):EVIDoa2200015.
194. Mansoor W, Joo S, Norquist JM, Kato K, Sun JM, Shah MA, et al. Health-related quality-of-life analysis from KEYNOTE-590: pembrolizumab plus chemotherapy versus chemotherapy for advanced esophageal cancer. Oncologist. 2024;30:30.
195. Shah MA, Sun JM, Shen L, Kato K, Enzinger PC, Adenis A, et al. First-line pembrolizumab (pembro) plus chemotherapy (chemo) for advanced esophageal cancer: 5-year outcomes from the phase 3 KEYNOTE-590 study. Journal of clinical oncology. 2024;42(3).
196. Sun JM, Shen L, Shah MA, Enzinger P, Adenis A, Doi T, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet (london, england). 2021;398(10302):759-71.
197. Doki Y, Ajani JA, Kato K, Xu J, Wyrwicz L, Motoyama S, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. New England journal of medicine. 2022;386(5):449-62.
198. Kato K, Doki Y, Chau I, Xu J, Wyrwicz L, Motoyama S, et al. Nivolumab plus chemotherapy or ipilimumab versus chemotherapy in patients with advanced esophageal squamous cell carcinoma (CheckMate 648): 29-month follow-up from a randomized, open-label, phase III trial. Cancer medicine. 2024;13(9):e7235.
199. Lowery M, Wyrwicz L, Oh DY, Shiu KK, Yanez Weber P, Bai Y, et al. 1516P Health-related quality of life (hrqol) analysis from KEYNOTE-859: first-line (1L) pembrolizumab (pembro) + chemotherapy (chemo) for advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. Annals of oncology. 2023;34:S854-S5.
200. Rha SY, Oh DY, Yanez P, Bai Y, Ryu MH, Lee J, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. The lancet Oncology. 2023;24(11):1181-95.
201. Shitara K, Van Cutsem E, Bang YJ, Fuchs C, Wyrwicz L, Lee KW, et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab plus Chemotherapy vs Chemotherapy Alone for Patients with First-line, Advanced Gastric Cancer: the KEYNOTE-062 Phase 3 Randomized Clinical Trial. JAMA oncology. 2020;6(10):1571-80.
202. Van Cutsem E, Valderrama A, Bang YJ, Fuchs CS, Shitara K, Janjigian YY, et al. Quality of life with first-line pembrolizumab for PD-L1-positive advanced gastric/gastroesophageal junction adenocarcinoma: results from the randomised phase III KEYNOTE-062 study. ESMO open. 2021;6(4):100189.
203. Wainberg ZA, Shitara K, Van Cutsem E, Wyrwicz L, Wook Lee K, Kudaba I, et al. Pembrolizumab with or without chemotherapy versus chemotherapy alone for patients with PD-L1-positive advanced gastric or gastroesophageal junction adenocarcinoma: update from the phase 3 KEYNOTE-062 trial. Journal of clinical oncology. 2022;40(4).
204. Janjigian YY, Ajani JA, Moehler M, Shen L, Garrido M, Gallardo C, et al. First-Line Nivolumab Plus Chemotherapy for Advanced Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinoma: 3-Year Follow-Up of the Phase III CheckMate 649 Trial. Journal of clinical oncology. 2024;42(17):2012-20.
205. Moehler M, Xiao H, Blum SI, Elimova E, Cella D, Shitara K, et al. Health-Related Quality of Life With Nivolumab Plus Chemotherapy Versus Chemotherapy in Patients With Advanced Gastric/Gastroesophageal Junction Cancer or Esophageal Adenocarcinoma From CheckMate 649. Journal of clinical oncology. 2023;41(35):5388-99.
206. Shitara K, Ajani JA, Moehler M, Garrido M, Gallardo C, Shen L, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. Nature. 2022;603(7903):942-8.
207. Andre T, Amonkar M, Norquist JM, Shiu KK, Kim TW, Jensen BV, et al. Health-related quality of life in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer treated with first-line pembrolizumab versus chemotherapy (KEYNOTE-177): an open-label, randomised, phase 3 trial. 2021;22(5):665-77.
208. Andre T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. 2020;383(23):2207-18.
209. Diaz LA, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. 2022;23(5):659-70.

210. Cescon DW, Schmid P, Rugo HS, Im SA, Md Yusof M, Gallardo C, et al. Health-related quality of life with pembrolizumab plus chemotherapy vs placebo plus chemotherapy for advanced triple-negative breast cancer: KEYNOTE-355. 2024;116(5):717-27.
211. Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. 2020;396(10265):1817-28.
212. Cortes J, Rugo HS, Cescon DW, Im S-A, Yusof MM, Gallardo C, et al. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. New England Journal of Medicine. 2022;387(3):217-26.

Appendices

Search strategies

Ipilimumab/nivolumab*	
Ovid MEDLINE(R) ALL 1946 to June 10, 2024	
#	Searches
1	Ipilimumab/
2	(Ipilimumab* or Yervoy* or "MDX 010" or MDX010 or MDX CTLA 4 or MDX CTLA4 or MDX 101 or MDX101 or bms 734016 or bms734016).ti,ab,kf,nm.
3	or/1-2
4	Nivolumab/
5	(Nivolumab* or Opdivo* or MDX 1106 or MDX1106 or bms936558 or bms 936558 or ono 4538 or ono4538).ti,ab,kf,nm.
6	or/4-5
7	3 and 6
8	exp randomized controlled trial/
9	controlled clinical trial.pt.
10	drug therapy.fs.
11	(randomi?ed or placebo or randomly or trial or groups).ab.
12	or/8-11
13	exp animals/ not humans.sh.
14	12 not 13*
15	clinical trial, phase III/ or ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.
16	exp animals/ not humans/
17	15 not 16**
18	14 or 17
19	7 and 18
20	remove duplicates from 19
Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)	
ID	Search
#1	MeSH descriptor: [Ipilimumab] this term only
#2	(Ipilimumab* or Yervoy* or "MDX 010" or MDX010 or MDX CTLA 4 or MDX CTLA4 or MDX 101 or MDX101 or bms 734016 or bms734016):TI,AB,KW
#3	#1 OR #2
#4	MeSH descriptor: [Nivolumab] this term only
#5	(Nivolumab* or Opdivo* or "MDX 1106" or MDX1106 or bms936558 or "bms 936558" or "ono 4538" or ono4538):TI,AB,KW
#6	#4 OR #5
#7	#3 AND #6
ClinicalTrials.gov (Expert search)	
(Ipilimumab OR Yervoy OR MDX 010 OR MDX-010 OR MDX010 OR MDX CTLA 4 OR MDX CTLA 4 OR MDX-CTLA 4 OR MDX CTLA4 OR MDX-CTLA4 OR MDX 101 OR MDX-101 OR MDX101 OR BMS 734016 OR BMS-734016 OR BMS734016) AND (Nivolumab OR Opdivo OR MDX 1106 OR MDX -1106 OR MDX1106 OR BMS936558 OR BMS 936558 OR BMS-936558 OR ONO 4538 OR ONO-4538 OR ONO4538)	
ICTRP (trialsearch.who.int/)	
(Ipilimumab OR Yervoy OR MDX 010 OR MDX-010 OR MDX010 OR MDX CTLA 4 OR MDX CTLA 4 OR MDX-CTLA 4 OR MDX CTLA4 OR MDX-CTLA4 OR MDX 101 OR MDX-101 OR MDX101 OR BMS 734016 OR BMS-734016 OR BMS734016) AND (Nivolumab OR Opdivo OR MDX 1106 OR MDX -1106 OR MDX1106 OR BMS936558 OR BMS 936558 OR BMS-936558 OR ONO 4538 OR ONO-4538 OR ONO4538)	

Non small cell lung cancer	
Ovid MEDLINE(R) ALL 1946 to July 18, 2024	
#	Searches
1	Carcinoma, Non-Small-Cell Lung/
2	(non small cell* or nonsmall cell* or NSCL*).ti,ab,kf.
3	or/1-2
4	(Atezolizumab* or MPDL3280A* or Tecentriq* or RG7446* or RG 7446* or antiPD1* or anti-PD1* or antiPDL1* or anti-PDL1*).ti,ab,kf,nm.
5	(Cemiplimab* or Imfinzi* or libtayo* or REGN-2810* or REGN2810*).ti,ab,kf,nm.
6	(Pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*).ti,ab,kf,nm.
7	(tremelimumab* or ticilimumab* or CP675* or CP 675* or imjudo*).ti,ab,kf,nm. and (Durvalumab* or MEDI4736* or MEDI-4736* or Imfinzi*).tw,kf,nm.
8	4 or 5 or 6 or 7
9	3 and 8
10	exp randomized controlled trial/
11	controlled clinical trial.pt.
12	drug therapy.fs.
13	(randomi?ed or placebo or randomly or trial or groups).ab.
14	or/10-13
15	exp animals/ not humans.sh.
16	14 not 15
17	9 and 16
18	limit 17 to yr="2010 -Current"

* Search conducted a spart of concurrently performed systematic review (PROSPERO: CRD42024548061)

19	remove duplicates from 18
Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)	
ID	Search
#1	[mh ^"Carcinoma, Non-Small-Cell Lung"]
#2	("non small cell" OR "nonsmall cell" OR NSCL*):TI,AB,KW
#3	#1 OR #2
#4	(Atezolizumab* or MPDL3280A* or Tecentriq* or RG7446* or RG 7446* or antiPD1* or anti-PD1* or antiPDL1* or anti-PDL1*):TI,AB,KW
#5	(Cemiplimab* or Imfinzi* or libtayo* or REGN-2810* or REGN2810*):TI,AB,KW
#6	(Pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*):TI,AB,KW
#7	(tremelimumab* or ticilimumab* or CP675* or CP 675* or imjudo*):TI,AB,KW
#8	(Durvalumab* or MEDI4736* or MEDI-4736* or Imfinzi*):TI,AB,KW
#9	#7 AND #8
#10	#4 OR #5 OR #6 OR #9
#11	#3 AND #10
#12	#11 with Publication Year from 2010 to 2024, in Trials

Head and neck squamous cell carcinoma

Ovid MEDLINE(R) ALL 1946 to August 26, 2024	
#	Searches
1	exp "head and neck neoplasms"/ and Carcinoma, Squamous Cell/
2	"squamous cell carcinoma of head and neck"/
3	exp head/ or exp neck/ or exp larynx/ or exp nose/ or exp pharynx/ or exp respiratory mucosa/ or exp palate/ or exp mouth/
4	exp Carcinoma, Squamous Cell/ or exp Neoplasms/
5	3 and 4
6	(HNSCC or SCCHN or OP-SCC or OPSCC or LASCCHN).ab,ti.
7	((upper aero-digestive tract* or upper aerodigestive tract* or uadt or head or neck or facial* or eyelid* or mout* or oral or gingival or epuli* or epilude* or lip* or palatal* or (salivary* adj1 gland*) or parotid* or ((sublingual* or submandibular*) adj1 gland*) or tongue* or otorhinolaryngolog* or ear* or auricular* or auricle* or laryng* or larynx* or nose* or nasal* or ((paranasal* or maxillary*) adj1 sinus*) or pharyng* or pharynx* or hypopharyng* or hypopharyx* or nasopharyng* or nasopharynx* or oropharyng* or oropharynx* or tonsil* or parathyroid* or thyroid* or tracheal* or epiglot* or glotti* or supraglot* or preepiglot*) adj8 (carcino* or cancer* or neoplas* or malign* or tumour* or tumor* or adenocarcinom* or epitheliom* or epidermoid* or planocellular* or squamo?s or plano-cellular*)).ti,ab,kf.
8	1 or 2 or 5 or 6 or 7
9	(Pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*).ti,ab,kf,nm.
10	exp randomized controlled trial/
11	controlled clinical trial.pt.
12	drug therapy.fs.
13	(randomi?ed or placebo or randomly or trial or groups).ab.
14	or/10-13
15	exp animals/ not humans.sh.
16	14 not 15
17	8 and 9 and 16
18	limit 17 to yr="2010 -Current"
19	remove duplicates from 18
Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)	
ID	Search
#1	[mh "head and neck neoplasms"] AND [mh "Carcinoma, Squamous Cell"]
#2	[mh "squamous cell carcinoma of head and neck"]
#3	[mh head] or [mh neck] or [mh larynx] or [mh nose] or [mh pharynx] or [mh "respiratory mucosa"] or [mh palate] or [mh mouth]
#4	[mh "Carcinoma, Squamous Cell"] or [mh Neoplasms]
#5	#3 AND #4
#6	(HNSCC or SCCHN or OP-SCC or OPSCC or LASCCHN):TI,AB,KW
#7	((upper aero-digestive tract* or upper aerodigestive tract* or uadt or head or neck or facial* or eyelid* or mout* or oral or gingival or epuli* or epilude* or lip* or palatal* or (salivary* adj1 gland*) or parotid* or ((sublingual* or submandibular*) adj1 gland*) or tongue* or otorhinolaryngolog* or ear* or auricular* or auricle* or laryng* or larynx* or nose* or nasal* or ((paranasal* or maxillary*) adj1 sinus*) or pharyng* or pharynx* or hypopharyng* or hypopharyx* or nasopharyng* or nasopharynx* or oropharyng* or oropharynx* or tonsil* or parathyroid* or thyroid* or tracheal* or epiglot* or glotti* or supraglot* or preepiglot*) NEAR/8 (carcino* or cancer* or neoplas* or malign* or tumour* or tumor* or adenocarcinom* or epitheliom* or epidermoid* or planocellular* or squamo?s or plano-cellular*)):TI,AB,KW
#8	#1 OR #2 OR #5 OR #6 OR #7
#9	(Pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*):TI,AB,KW
#10	#8 AND #9

Renal cell carcinoma

Ovid MEDLINE(R) ALL 1946 to July 23, 2024	
#	Searches
1	Carcinoma, Renal Cell/
2	((collecting duct* or hypernephroid* or nephroid*) adj2 carcinoma*).tw,kf.
3	((grawitz adj1 tumo?r*) or hypernephroma*).tw,kf.
4	((renal* or kidney*) adj6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor* or adenocarcinoma*)).tw,kf.
5	or/1-4

6	Nivolumab/
7	(Nivolumab* or Opdivo* or MDX 1106 or MDX1106 or bms936558 or bms 936558 or ono 4538 or ono4538).ti,ab,kf,nm.
8	(Pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*).ti,ab,kf,nm.
9	or/6-8
10	exp randomized controlled trial/
11	controlled clinical trial.pt.
12	drug therapy.fs.
13	(randomi?ed or placebo or randomly or trial or groups).ab.
14	or/10-13
15	exp animals/ not humans.sh.
16	14 not 15
17	5 and 9 and 16
18	limit 17 to yr="2010 -Current"
19	remove duplicates from 18

Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)

ID	Search
#1	[mh ^"Carcinoma, Renal Cell"]
#2	((collecting duct* or hypernephroid* or nephroid*) NEAR/2 carcinoma*):TI,AB,KW
#3	((grawitz NEAR/1 tumor*) or (grawitz NEAR/1 tumour*) or hypernephroma*):TI,AB,KW
#4	((renal* or kidney*) NEAR/6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor* or adenocarcinoma*)):TI,AB,KW
#5	#1 OR #2 OR #3 OR #4
#6	[mh Nivolumab]
#7	(Nivolumab* or Opdivo* or MDX 1106 or MDX1106 or bms936558 or bms 936558 or ono 4538 or ono4538):TI,AB,KW
#8	(Pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*):TI,AB,KW
#9	#6 OR #7 OR #8
#10	#5 AND #9

Biliary tract cancer and hepatocellular carcinoma

Ovid MEDLINE(R) ALL 1946 to July 26, 2024

#	Searches
1	exp Biliary Tract Neoplasms/
2	exp Cholangiocarcinoma/
3	((bil* or cholangio*) adj6 (carcinom* or cancer* or neoplasm* or malign* or tumo*)).ti,ab,kf.
4	cholangioc*.ti,ab,kf.
5	(klatskin adj2 tumo*).ti,ab,kf.
6	or/1-5
7	Carcinoma, Hepatocellular/
8	((liver or hepatic* or hepatocellular* or hepato-cellular*) adj2 (carcinom* or cancer* or neoplasm* or malign* or tumo*)).ti,ab,kf.
9	(hepatoma* or HCC).ti,ab,kf.
10	or/7-9
11	(durvalumab* or MEDI4736* or MEDI-4736* or imfinzi*).ti,ab,kf,nm.
12	(tremelimumab* or ticilimumab* or CP675* or CP 675* or imjudo*).ti,ab,kf,nm.
13	(Atezolizumab* or MPDL3280A* or Tecentriq* or RG7446* or RG 7446* or antiPD1* or anti-PD1* or antiPDL1* or anti-PDL1*).ti,ab,kf,nm.
14	or/11-13
15	exp randomized controlled trial/
16	controlled clinical trial.pt.
17	drug therapy.fs.
18	(randomi?ed or placebo or randomly or trial or groups).ab.
19	or/15-18
20	exp animals/ not humans.sh.
21	19 not 20
22	(6 or 10) and 14 and 21
23	limit 22 to yr="2010 -Current"
24	remove duplicates from 23

Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)

ID	Search
#1	[mh "Biliary Tract Neoplasms"]
#2	[mh Cholangiocarcinoma]
#3	((bil* or cholangio*) NEAR/6 (carcinom* or cancer* or neoplasm* or malign* or tumo*)):TI,AB,KW
#4	cholangioc*:TI,AB,KW
#5	(klatskin NEAR/2 tumo*):TI,AB,KW
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	[mh "Carcinoma, Hepatocellular"]
#8	((liver or hepatic* or hepatocellular* or hepato-cellular*) NEAR/2 (carcinom* or cancer* or neoplasm* or malign* or tumo*)):TI,AB,KW
#9	(hepatoma* or HCC):TI,AB,KW
#10	#7 OR #8 OR #9
#11	(durvalumab* or MEDI4736* or MEDI 4736* or imfinzi*):TI,AB,KW
#12	(tremelimumab* or ticilimumab* or CP675* or CP 675* or imjudo*):TI,AB,KW
#13	(Atezolizumab* or MPDL3280A* or Tecentriq* or RG7446* or RG 7446* or antiPD1* or anti-PD1* or antiPDL1* or anti-PDL1*):TI,AB,KW
#14	#11 OR #12 OR #13
#15	(#6 OR #10) AND #14

#16	#15 with Publication Year from 2010 to 2024, in Trials

Gastric and oesophageal cancers

Ovid MEDLINE(R) ALL 1946 to August 27, 2024

#	Searches
1	exp Gastrointestinal Neoplasms/
2	exp "Esophagogastric Junction"/ and exp "Digestive System Neoplasms"/
3	exp esophagus/ or exp stomach/
4	Adenocarcinoma/ or Carcinoma, Squamous Cell/
5	3 and 4
6	Esophageal Squamous Cell Carcinoma/
7	Esophageal Neoplasms/ and Carcinoma, Squamous Cell/
8	((oesophag* or esophag* or stomach* or gastr*) adj8 (epidermoid* or planocellular* or squamo?s or plano-cellular*)).ti,ab,kf.
9	((oesophag* or esophag* or stomach* or gastr*) adj8 (carcino* or cancer* or neoplas* or malign* or tumour* or tumor* or adenocarcinom* or epitheliom*)).ti,ab,kf.
10	1 or 2 or 5 or 6 or 7 or 8 or 9
11	Ipilimumab/
12	(Ipilimumab* or Yervoy* or "MDX 010" or MDX010 or MDX CTLA 4 or MDX CTLA4 or MDX 101 or MDX101 or bms 734016 or bms734016).ti,ab,kf,nm.
13	Nivolumab/
14	(Nivolumab* or Opdivo* or MDX 1106 or MDX1106 or bms936558 or bms 936558 or ono 4538 or ono4538).ti,ab,kf,nm.
15	(Pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*).ti,ab,kf,nm.
16	or/11-15
17	exp randomized controlled trial/
18	controlled clinical trial.pt.
19	drug therapy.fs.
20	(randomi?ed or placebo or randomly or trial or groups).ab.
21	or/17-20
22	exp animals/ not humans.sh.
23	21 not 22
24	10 and 16 and 23
25	limit 24 to yr="2010-Current"
26	remove duplicates from 25

Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)

ID	Search
#1	[mh esophagus] OR [mh stomach]
#2	[mh Adenocarcinoma] OR [mh "Carcinoma, Squamous Cell"]
#3	#1 AND #2
#4	[mh "Gastrointestinal Neoplasms"]
#5	[mh "Esophagogastric Junction"] AND [mh "Digestive System Neoplasms"]
#6	[mh "Esophageal Squamous Cell Carcinoma"]
#7	[mh "Esophageal Neoplasms"] AND [mh "Carcinoma, Squamous Cell"]
#8	((oesophag* or esophag* or stomach* or gastr*) NEAR/8 (epidermoid* or planocellular* or squamous or squamos or plano-cellular*)):TI,AB,KW
#9	((oesophag* or esophag* or stomach* or gastr*) NEAR/8 (carcino* or cancer* or neoplas* or malign* or tumour* or tumor* or adenocarcinom* or epitheliom*)):TI,AB,KW
#10	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	[mh Ipilimumab]
#12	(Ipilimumab* or Yervoy* or "MDX 010" or MDX010 or MDX CTLA 4 or MDX CTLA4 or MDX 101 or MDX101 or bms 734016 or bms734016):TI,AB,KW
#13	[mh Nivolumab]
#14	(Nivolumab* or Opdivo* or MDX 1106 or MDX1106 or bms936558 or bms 936558 or ono 4538 or ono4538):TI,AB,KW
#15	(Pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*):TI,AB,KW
#16	#11 OR #12 OR #13 OR #14 OR #15
#17	#10 AND #16

Colorectal carcinoma

Ovid MEDLINE(R) ALL 1946 to August 7, 2024

#	Searches
1	exp Colorectal Neoplasms/
2	exp Adenomatous Polyposis Coli/
3	exp colonic neoplasms/
4	Colorectal Neoplasms, Hereditary Nonpolyposis/
5	exp Rectal Neoplasms/
6	exp Anus Neoplasms/
7	(colon* adj3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)).tw,kf,ot.
8	(rect* adj3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)).tw,kf,ot.
9	(colorect* adj3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)).tw,kf,ot.
10	(anal* adj3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)).tw,kf,ot.
11	(anus* adj3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)).tw,kf,ot.
12	(intestin* adj3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)).tw,kf,ot.
13	(bowel* adj3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)).tw,kf,ot.
14	((colonrectal* or colon* adj4 nonpolyposis*).tw,kf,ot.
15	(lynch adj2 syndrom*).tw,kf,ot.

16	(adenomatous* adj polyposis* adj coli).tw,kf,ot.
17	(gardner* adj2 syndrom*).tw,kf,ot.
18	(sigmoid* adj3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or sarcom* or metastas* or polyp*)).tw,kf,ot.
19	or/1-18
20	(pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*).ti,ab,kf,nm.
21	exp randomized controlled trial/
22	controlled clinical trial.pt.
23	drug therapy.fs.
24	(randomi?ed or placebo or randomly or trial or groups).ab.
25	or/21-24
26	exp animals/ not humans.sh.
27	26 not 25.
28	19 and 20 and 27
29	limit 28 to yr="2010 -Current"
30	remove duplicates from 29

Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)

ID	Search
#1	[mh "Colorectal Neoplasms"]
#2	[mh "Adenomatous Polyposis Coli"]
#3	[mh "colonic neoplasms"]
#4	[mh "Colorectal Neoplasms, Hereditary Nonpolyposis"]
#5	[mh "Rectal Neoplasms"]
#6	[mh "Anus Neoplasms"]
#7	(colon* NEAR/3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)):TI,AB,KW
#8	(rect* NEAR/3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)):TI,AB,KW
#9	(colorect* NEAR/3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)):TI,AB,KW
#10	(anal* NEAR/3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)):TI,AB,KW
#11	(anus* NEAR/3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)):TI,AB,KW
#12	(intestin* NEAR/3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)):TI,AB,KW
#13	(bowel* NEAR/3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)):TI,AB,KW
#14	(colon* NEAR/4 nonpolyposis*):TI,AB,KW
#15	(colorectal* NEAR/4 nonpolyposis*):TI,AB,KW
#16	(lynch NEAR/2 syndrom*):TI,AB,KW
#17	(adenomatous* NEAR/1 polyposis* NEAR/1 coli):TI,AB,KW
#18	(gardner* NEAR/2 syndrom*):TI,AB,KW
#19	(sigmoid* NEAR/3 (cancer* or carcinom* or neoplas* or tumor* or tumour* or adenocarcinom* or adenom* or metastas* or polyp*)):TI,AB,KW
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21	(pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*):TI,AB,KW
#22	#20 AND #21
#23	#22 with Publication Year from 2010 to 2024, in Trials

Endometrial carcinoma

Ovid MEDLINE(R) ALL 1946 to August 7, 2024

#	Searches
1	exp Endometrial Neoplasms/
2	(endometr* adj6 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinom* or adenocarcinom*)).ti,ab,kf.
3	(uter* and lining and (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinom* or adenocarcinom*)).ti,kf.
4	exp Endometrial Neoplasms/
5	(endometr* adj6 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinom* or adenocarcinom*)).ti,ab,kf.
6	(uter* and lining and (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinom* or adenocarcinom*)).ti,ab,kf.
7	or/4-6
8	(dostarlimab* or Jemperli* or TSR-042* or TSR042*).ti,ab,kf,nm.
9	7 and 8
10	exp randomized controlled trial/
11	controlled clinical trial.pt.
12	drug therapy.fs.
13	(randomi?ed or placebo or randomly or trial or groups).ab.
14	or/10-13
15	exp animals/ not humans.sh.
16	14 not 15
17	7 and 8 and 16
18	limit 17 to yr="2010 -Current"
19	remove duplicates from 18

Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)

ID	Search
#1	[mh "Endometrial Neoplasms"]
#2	(endometr* NEAR/6 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinom* or adenocarcinom*)):Ti,AB,KW
#3	(uter* and lining and (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinom* or adenocarcinom*)):Ti,AB,KW
#4	#1 OR #2 OR #3
#5	(dostarlimab* or Jemperli* or TSR-042* or TSR042*):TI,AB,KW

#6	#4 AND #5
#7	#6 with Publication Year from 2010 to 2024, in Trials

Cervical cancer

Ovid MEDLINE(R) ALL 1946 to July 17, 2024

#	Searches
1	Uterine Cervical Neoplasms/
2	(cervi* adj6 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).ti,ab,kf.
3	Carcinoma, Squamous Cell/ and Cervix Uteri/
4	"glassy cell".ti,ab,kf.
5	(villoglandular* adj3 adenocarcinom*).ti,ab,kf.
6	or/1-5
7	(pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*).ti,ab,kf,nm.
8	6 and 7
9	exp randomized controlled trial/
10	controlled clinical trial.pt
11	drug therapy.fs
12	(randomi?ed or placebo or randomly or trial or groups).ab.
13	or/9-12
14	exp animals/ not humans.sh.
15	13 not 14
16	6 and 7 and 15
17	limit 16 to yr="2010 -Current"
18	remove duplicates from 17

Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)

ID	Search
#1	[mh "Uterine Cervical Neoplasms"]
#2	[mh "Carcinoma, Squamous Cell"] AND [mh "Cervix Uteri"]
#3	(cervi* NEAR/6 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)):TI,AB,KW
#4	"glassy cell":TI,AB
#5	(villoglandular* NEAR/3 adenocarcinom*):TI,AB,KW
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	(pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*):TI,AB,KW
#8	#6 AND #7
#9	#8 with Publication Year from 2010 to 2024, in Trials

Triple-negative breast cancer

Ovid MEDLINE(R) ALL 1946 to July 30, 2024

#	Searches
1	Triple Negative Breast Neoplasms/
2	(triple* adj2 negative* adj6 breast adj6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)).ti,ab,kf.
3	(triple* adj2 negative* adj6 mamma* adj6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)).ti,ab,kf.
4	(receptor* adj2 negative* adj6 breast adj6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)).ti,ab,kf.
5	(receptor* adj2 negative* adj6 mamma* adj6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)).ti,ab,kf.
6	(((hormone* adj2 negative*) or HER2*) adj6 breast adj6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)).ti,ab,kf.
7	(((hormone* adj2 negative*) or HER2*) adj6 mamma* adj6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)).ti,ab,kf.
8	(TNBC or triple* negative* BC).ti,ab,kf.
9	or/1-8
10	(pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*).ti,ab,kf,nm.
11	exp randomized controlled trial/
12	controlled clinical trial.pt.
13	drug therapy.fs.
14	(randomi?ed or placebo or randomly or trial or groups).ab.
15	or/11-14
16	exp animals/ not humans.sh.
17	15 not 16
18	9 and 10 and 17
19	limit 18 to yr="2010 -Current"
20	remove duplicates from 19

Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)

ID	Search
#1	[mh "Triple Negative Breast Neoplasms"]
#2	(triple* NEAR/2 negative* NEAR/6 breast NEAR/6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)):TI,AB,KW
#3	(triple* NEAR/2 negative* NEAR/6 mamma* NEAR/6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)):TI,AB,KW
#4	(receptor* NEAR/2 negative* NEAR/6 breast NEAR/6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)):TI,AB,KW
#5	(receptor* NEAR/2 negative* NEAR/6 mamma* NEAR/6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)):TI,AB,KW
#6	(((hormone* NEAR/2 negative*) or HER2*) NEAR/6 breast NEAR/6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)):TI,AB,KW
#7	(((hormone* NEAR/2 negative*) or HER2*) NEAR/6 mamma* NEAR/6 (cancer* or neoplasm* or carcinoma* or tumour* or tumor*)):TI,AB,KW
#8	(TNBC or triple* negative* BC):TI,AB,KW
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	(pembrolizumab* or MK-3475* or MK3475* or Keytruda* or lambrolizumab*):TI,AB,KW

#11	#9 AND #10
#12	#11 with Publication Year from 2010 to 2024, in Trials

Prioritisation details

IMMUNE CHECKPOINT INHIBITOR APPROVALS BASED ON THEIR EMA PRODUCT INFORMATION

Search date: May 2024

ICI/-combination	Indication	Setting	PD-L1 expression	Regimen	Treatment combination details	MCBS	LTB	RCT	Trial ID
Atezolizumab	HCC	P1	NR	IO-Ab	Atezolizumab + Bevazicumab	5	no	yes	IMbrave150
Atezolizumab	NSCLC (- driver)	A	50%	Monotherapy					
Atezolizumab	NSCLC (- driver)	P1	NR	IO-ICT	Atezolizumab + Carboplatin + Paclitaxel + Bevacizumab	3		yes	
Atezolizumab	NSCLC (- driver)	P1	NR	IO-CTx	Atezolizumab + Carboplatin + nab-Paclitaxel	3		yes	
Atezolizumab	NSCLC (- driver)	P1	50%	Monotherapy	-	5	no	yes	IMpower110
Atezolizumab	NSCLC (+ driver)	P2	NR	IO-ICT	Atezolizumab + Carboplatin + Paclitaxel + Bevacizumab				
Atezolizumab	SCLC	P1	NR	IO-CTx	Atezolizumab + Carboplatin + Etoposide	3		yes	
Atezolizumab	TNBC	P1	1%	IO-CTx	Atezolizumab + nab-Paclitaxel	3		yes	
Atezolizumab	UC	P2	NR	Monotherapy					
Atezolizumab	UC	P1c	5%	Monotherapy	-	NEB		yes	IMvigor22
Avelumab	MCC	P1	NR	Monotherapy	-	4		no	
Avelumab	RCC	P1	NR	IO-TKI	Avelumab + Axitinib	3		yes	
Avelumab	UC	M	NR	Monotherapy	-	4		yes	
Cemiplimab	BCC	P2	NR	Monotherapy	-				
Cemiplimab	CC	P2	NR	Monotherapy	-				
Cemiplimab	CSCC	P1	NR	Monotherapy	-	4		no	
Cemiplimab	NSCLC (- driver)	P1	50%	Monotherapy	-	4	no	yes	EMpower-Lung 1
Cemiplimab	NSCLC (- driver)	P1	1%	IO-CTx	Cemiplimab + platinum-based CTx	4	no	yes	EMpower-Lung 3
Dostarlimab	EC	P2	MSI-H/dMMR	Monotherapy	-				
Dostarlimab	EC	P1	MSI-H/dMMR	IO-CTx	Dostarlimab + carboplatin + paclitaxel	4	yes	yes	RUBY
Durvalumab	BTC	P1	NR	IO-CTx	Durvalumab + cisplatin + gemcitabine	4	no	yes	TOPAZ-1
Durvalumab	HCC	P1	NR	Monotherapy	-	4	no	yes	HIMALAYA
Durvalumab	NSCLC	A	1%	Monotherapy	-				
Durvalumab	SCLC	P1	NR	IO-CTx	Durvalumab + carboplatin/cisplatin + etoposide	3		yes	
Durvalumab + Tremelimumab	HCC	P1	NR	IO2	Durvalumab + Tremelimumab	4	no	yes	HIMALAYA
Durvalumab + Tremelimumab	NSCLC (- driver)	P1	NR	IO2-CTx	Durvalumab + Tremelimumab + platinum-based CTx	4	no	yes	POSEIDON
Ipilimumab	MEL	P1	NR	Monotherapy	-	4	yes	yes	CA184-024
Ipilimumab + Nivolumab	CRC	P2	MSI-H/dMMR	IO2	Ipilimumab + Nivolumab				
Ipilimumab + Nivolumab	MEL	P1	NR	IO2	Ipilimumab + Nivolumab	4	yes	yes	CheckMate 067
Ipilimumab + Nivolumab	MPM	P1	NR	IO2	Ipilimumab + Nivolumab	3		yes	
Ipilimumab + Nivolumab	NSCLC (- driver)	P1	NR	IO2-CTx	Ipilimumab + Nivolumab + platinum-based CTx	4	no	yes	CheckMate 9LA
Ipilimumab + Nivolumab	OSCC	P1	1%	IO2	Ipilimumab + Nivolumab	4	no	yes	CheckMate 648
Ipilimumab + Nivolumab	RCC	P1	NR	IO2	Ipilimumab + Nivolumab	4	no	yes	CheckMate 214
Nivolumab	AEG, GC, AOC	P1	5%	IO-CTx	Nivolumab + fluoropyrimidine/platinum-based CTx	4	no	yes	CheckMate 649
Nivolumab	AEG, GC, AOC	A	NR	Monotherapy	-				

Nivolumab	cHL	P1	NR		Monotherapy	-	4		no	
Nivolumab	HNSCC	P2	NR		Monotherapy	-				
Nivolumab	MEL	P1	NR		Monotherapy	-	4	yes	yes	CheckMate 067, CheckMate 066
Nivolumab	MEL	A	NR		Monotherapy	-				
Nivolumab	NSCLC	P2	NR		Monotherapy	-				
Nivolumab	NSCLC	N		1%	IO-CTx	Nivolumab + platinum-based CTx				
Nivolumab	OSCC	P2	NR		Monotherapy	-				
Nivolumab	OSCC	P1		1%	IO-CTx	Nivolumab + fluoropyrimidine/platinum-based CTx	4	no	yes	CheckMate 648
Nivolumab	RCC	P2	NR		Monotherapy	-				
Nivolumab	RCC	P1	NR		IO-TKI	Nivolumab + cabozantinib	1		yes	
Nivolumab	UC	P2	NR		Monotherapy	-				
Nivolumab	UC	A		1%	Monotherapy	-				
Pembrolizumab	AEG, GC, AOC	P1		1%	IO-CTx	Pembrolizumab + fluoropyrimidine/platinum-based CTx	4	no	yes	Keynote-590
Pembrolizumab	AEG, GC, AOC	P1		1%	IO-ICT	Pembrolizumab + fluoropyrimidine/platinum-based CTx + trastuzumab	2		yes	
Pembrolizumab	BTC	P1	NR		IO-CTx	Pembrolizumab + cisplatin + gemcitabine	1		yes	
Pembrolizumab	CC	P1		1%	IO-ICT	Pembrolizumab + CTx +/- Bevacizumab	4	no	yes	Keynote-826
Pembrolizumab	cHL	P1	NR		Monotherapy	-	4		no	
Pembrolizumab	CRC	P1	MSI-H/dMMR		Monotherapy	-	4	yes	yes	Keynote-177
Pembrolizumab	CRC	P2	MSI-H/dMMR		Monotherapy	-				
Pembrolizumab	EC	P2	MSI-H/dMMR		Monotherapy	-				
Pembrolizumab	EC	P2	NR		IO-TKI	Pembrolizumab + lenvatinib				
Pembrolizumab	HNSCC	P1		1%	IO-CTx	Pembrolizumab + fluoropyrimidine/platinum-based CTx	4	no	yes	Keynote-048
Pembrolizumab	HNSCC	P2		50%	Monotherapy	-				
Pembrolizumab	MEL	P1	NR		Monotherapy	-	4	yes	yes	Keynote-006
Pembrolizumab	MEL	A	NR		Monotherapy	-			yes	*Keynote-054*
Pembrolizumab	NSCLC	N	NR		IO-CTx	Pembrolizumab + platinum-based CTx				
Pembrolizumab	NSCLC	A	NR		Monotherapy	-				
Pembrolizumab	NSCLC	P2		1%	Monotherapy	-				
Pembrolizumab	NSCLC (- driver)	P1		50%	Monotherapy	-	5	yes	yes	Keynote-024
Pembrolizumab	NSCLC (- driver)	P1	NR		IO-CTx	Pembrolizumab + cisplatin/carboplatin + pemetrexed	4	yes	yes	Keynote-189
Pembrolizumab	OSCC	P1		10%	IO-CTx	Pembrolizumab + fluoropyrimidine-based CTx	4	no	yes	Keynote-590
Pembrolizumab	RCC	P1	NR		IO-TKI	Pembrolizumab + Axitinib	4	no	yes	Keynote-426
Pembrolizumab	RCC	A	NR		Monotherapy	-				
Pembrolizumab	RCC	P1	NR		IO-TKI	Pembrolizumab + Lenvatinib	4	no	yes	CLEAR
Pembrolizumab	SqC NSCLC	P1	NR		IO-CTx	Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel	4	yes	yes	Keynote-407
Pembrolizumab	TNBC	N	NR		IO-CTx	Pembrolizumab + CTx				
Pembrolizumab	TNBC	P1		10%	IO-CTx	Pembrolizumab + CTx	4	no	yes	Keynote-355
Pembrolizumab	UC	P2	NR		Monotherapy	-				
Pembrolizumab	UC	P1c		10%	Monotherapy	-	3		no	
Relatlimab + Nivolumab	MEL	P1	< 1%		IO2	Relatlimab + Nivolumab	3		yes	RELATIVITY-047
Tislelizumab	OSCC	P2	NR		Monotherapy	-				

Search update: January 2025

ICI/-combination	Indication	Setting	PD-L1 expression	Regimen	Treatment combination details	MCBS	LTB	RCT	Trial ID
Atezolizumab	NSCLC (- driver)	P1c (cis-unfit)	NR	Monotherapy	-	4	no	yes	IPSOS
Durvalumab	EC	P1	MSI-H/dMMR	IO-CTx	Durvalumab + carboplatin/paclitaxel	4	yes	yes	DUO-E
Durvalumab	EC	P1	NR	IO-CTx	Durvalumab + carboplatin/paclitaxel +/- olaparib	4	yes	yes	DUO-E
Ipilimumab + Nivolumab	CRC	P1	MSI-H/dMMR	IO2	Ipilimumab + Nivolumab	4	yes	yes	CheckMate 8HW
Nivolumab	UC	P1	NR	IO-CTx	Nivolumab + cisplatin + gemcitabine	2	-	yes	CheckMate 901
Pembrolizumab	UC	P1	NR	IO-ADC	Pembrolizumab + enfortumab vedotin	4	-	yes	EV-301
Pembrolizumab	CC	N	NR	IO-RCTx	Pembrolizumab + radiochemotherapy				
Pembrolizumab	EC	P1	NR	IO-CTx	Pembrolizumab + carboplatin + paclitaxel	4	yes	yes	Keynote-868
Tislelizumab	NSqC NSCLC (-driver)	P1	50%	IO-CTx	Tislelizumab + cisplatin/carboplatin + pemetrexed	4	no	yes	Rationale-304
Tislelizumab	SqC NSCLC	P1	NR	IO-CTx	Tislelizumab + carboplatin + paclitaxel/nab-paclitaxel	4	no	yes	Rationale-307
Tislelizumab	NSCLC (- driver)	P2	NR	Monotherapy	-				
Tislelizumab	AEG, GC, AOC	P1	5%	IO-CTx	Tislelizumab + fluoropyrimidine/platinum-based CTx	3			
Tislelizumab	OSCC	P1	5%	IO-CTx	Tislelizumab + platinum-based CTx	4	no	yes	Rationale-302
Sugemalimab	NSCLC (- driver)	P1	NR	IO-CTx	Sugemalimab + platinum-based CTx	4	no	yes	GEMSTONE-302
Serplulimab	SCLC	P1	NR	IO-CTx	Serplulimab + carboplatin + etoposide				
Toripalimab	HNSCC	P1	NR	IO-CTx	Toripalimab + cisplatin + gemcitabine	3	no	yes	JUPITER-02
Toripalimab	OSCC	P1	NR	IO-CTx	Toripalimab + cisplatin + paclitaxel	4	no	yes	JUPITER-06
Retifanimab	MCC	P1	NR	Monotherapy	-			no	