This Evidence-to-Decision (EtD) framework addresses **cemiplimab + chemotherapy, tremelimumab + durvalumab + chemotherapy, ipilimumab + nivolumab + chemotherapy and pembrolizumab + chemotherapy** for **oncogenic driver wild-type non-small cell lung cancer (NSCLC), irrespective of PD-L1 expression**.

QUESTION

Should immune checkpoint inhibitors vs. alternative regimens be used for adult non-small cell lung cancer?	
POPULATION:	adult non-small cell lung cancer (NSCLC) • oncogenic-driver wild-type NSCLC irrespective of PD-L1 expression
INTERVENTION:	immune checkpoint inhibitors (ICIs)
COMPARISON:	alternative regimens
MAIN OUTCOMES:	overall survival; progression-free survival; health-related quality of life; adverse events (CTCAE ≥ 3)
SETTING:	treatment in the palliative 1st line setting
BACKGROUND:	application includes four ICI-containing treatment regimens for oncogenic-driver wild-type NSCLC irrespective of PD-L1 expression: • cemiplimab-containing treatment regimen (ESMO-MCBS non-curative score = 4) • tremelimumab+durvalumab-containing treatment regimen (ESMO-MCBS non-curative score = 4) • ipilimumab+nivolumab-containing treatment regimen (ESMO-MCBS non-curative score = 4) • pembrolizumab-containing treatment regimen (ESMO-MCBS non-curative score = 4)

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate** (durvalumab, ipilimumb+nivolumab, pembrolizumab)	**Large** (cemiplimab)		Varies	Don't know
REDUCTION IN UNDESIRABLE EFFECTS	**Increased harms and toxicity** (ipilimumb+nivolumab, cemiplimab)	**Trivial/No** (durvalumab, pembrolizumab)	Small	Moderate	Large	Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low** (durvalumab, ipilimumb+nivolumab)	**Moderate** (cemiplimab, pembrolizumab)	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability** (durvalumab, ipilimumb+nivolumab, pembrolizumab)	**No important uncertainty or variability** (cemiplimab)			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention** (durvalumab, ipilimumb+nivolumab, pembrolizumab)	**Favors the intervention** (cemiplimab)	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
AVAILABILITY	Not available in most settings	**Probably not available in most settings**	Probably available in most settings	Available in most settings		Varies	Don't know

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	An application addressing ICIs for the treatment of 12 adult cancer entities in the palliative 1st line setting has been submitted for consideration by the Expert Committee. This Evidence-to-Decision framework focuses on NSCLC (irrespective of PD-L1 expression), for which four ICI-containing treatment regimens are proposed: cemiplimab, durvalumab, nivolumab and pembrolizumab. NSCLC makes up over 80% of all lung cancer cases (1). The global age-standardized incidence rate of lung cancer was estimated at 23.6 per 100,000 in 2022 and represents the leading cause of cancer-related deaths worldwide (2). The standard of care includes platinum-based chemotherapy, which has limited benefit for overall survival and is associated with a reduced quality of life in treated patients because of its cytotoxic effects (1).

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial or no ○ Small ○ **Moderate** (tremelimumab+durvalumab, ipilimumb+nivolumab, pembrolizumab) ○ **Large** (cemiplimab) ○ Varies ○ Don't know	The application presents multiple randomized trials as evidence for the desirable effects of ICIs for oncogenic-driver wild-type NSCLC irrespective of PD-L1 expression: one for cemiplimab-containing treatment regimens (3-5), one for tremelimumab+durvalumab-containing treatment regimens (6, 7), one for ipilimumab+nivolumab-containing treatment regimens (8-10) and three for pembrolizumab-containing treatment regimens (11-18).

Cemiplimab-containing treatment regimens 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[a]	**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) [death]	466 (1 RCT)	⊕⊕⊕◯ Moderate[b,c]	Cemiplimab-containing treatment regimens probably increase overall survival.
	27 per 100	**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)				
Progression-free survival (PFS) At follow-up: 12 months	16 per 100	**37 per 100** (29 to 45)	**HR 0.55** (0.44 to 0.68) [disease progression or death]	466 (1 RCT)	⊕⊕⊕⊕ High	Cemiplimab-containing treatment regimens increase progression-free survival.
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)[d]	-	466 (1 RCTs)	⊕⊕⊕⊕ High[e]	Cemiplimab-containing treatment regimens result in little to no difference in global Health Score/Quality of Life (GHS/QoL).

*__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. The baseline risk stems from the 2-year survival estimate of the control group of the EMPOWER-Lung 3 trial
b. Only around 15% of patients in the control group received subsequent immunotherapy upon disease progression and unblinding, therefore we did not downgrade for indirectness
c. Downgraded for imprecision; although the OIS criterion was met, the CI crosses the line of appreciable benefit at 0.75
d. The mean difference between the intervention and comparator arm was directly taken as reported by trial authors for the length of follow-up
e. Did not rate down for imprecision because confidence interval does not contain the minimally important difference defined as a 10-point change in score for the EORTC QLQ-C30.

Durvalumab/tremelimumab-containing treatment regimens 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: Durvalumab/tremelimumab-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[b]	**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)	⊕⊕◯◯ Low[c,d]	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 may be underestimated.
	22 per 100	**31 per 100** (25 to 37)				
	At 5 years					
	7 per 100	**13 per 100**[a] (8 to 17)				
	The median OS was **11.7** months	The median OS was **3.5 months more** (1 more to 6.3 more)				
Progression-free survival (PFS) follow-up: 12 months	13 per 100	**23 per 100** (17 to 30)	**HR 0.72** (0.60 to 0.86) [disease progression or death]	675 (1 RCT)	⊕⊕⊕◯ Moderate[d]	Durvalumab/tremelimumab-containing treatment regimens likely increase progression-free survival slightly.
Global Health Score/Quality of Life (GHS/QoL) - not reported	*see comments*		-	-	-	QoL was measured, but not reported as a continuous outcome.

*__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. 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 risks stem from the estimates of the control group in the POSEIDON trial
c. Downgraded for indirectness; 33.2% of patients in the control arm of POSEIDON received immunotherapy in the second-line of therapy
d. Downgraded for imprecision; the CI crosses the line of appreciable benefit at 0.75

Ipilimumab/nivolumab-containing treatment regimens 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: 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[a]	**Risk with Ipilimumab/nivolumab-containing treatment regimens**				
Overall survival (OS) follow-up: median 64.5 months	**At 2 years**		**HR 0.74** (0.63 to 0.87) [death]	719 (1 RCT)	⨁⨁◯◯ Low[b,c,d]	Ipilimumab/nivolumab-containing treatment regimens may increase overall survival. However, considering that 36% of patients in the control arm subsequently received immunotherapy, the effect might be underestimated.
	26 per 100	**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) At follow-up: 12 months	19 per 100	**31 per 100** (25 to 38)	**HR 0.70** (0.59 to 0.83) [disease progression or death]	719 (1 RCT)	⨁⨁⨁◯ Moderate[c]	Ipilimumab/nivolumab-containing treatment regimens likely increase progression-free survival.
Global Health Score/Quality of Life (GHS/QoL) assessed with: LCSS 3-IGI Scale Scale from: 0 to 300 follow-up: 24 months from baseline	The mean global Health Score/Quality of Life (GHS/QoL) was **4.7** change score from baseline[e]	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 result in little to no difference in global Health Score/Quality of Life (GHS/QoL).

*__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. Baseline estimate taken from the control-group estimates of CheckMate 9LA
b. Downgraded due to indirectness; 36% participants in the control arm received subsequent immunotherapy, potentially underestimating the effect (Carbone et al. 2024)
c. Downgraded due to imprecision; the CI crosses the line of appreciable benefit at 0.75
d. Publication bias not applicable due to preceding prioritisation process
e. Baseline risk taken from comparator arm of CheckMate-9LA

f. Downgraded due to risk of detection and performance bias as a consequence 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

Pembrolizumab-containing treatment regimens 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[b]	**Risk with pembrolizumab-containing treatment 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)	⊕⊕⊕◯ Moderate[c,d]	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	**48 per 100** (44 to 52)				
	At 5 years					
	10 per 100	**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)				
Progression-free survival (PFS) At follow-up: 12 months	21 per 100	**43 per 100** (37 to 47)	**HR 0.55** (0.48 to 0.64) [disease progression or death]	1298 (3 RCTs)	⊕⊕⊕⊕ High[e]	Pembrolizumab-containing treatment regimens result in an increase in progression-free survival.
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[f]	Pembrolizumab-containing treatment regimens probably have trivial to no effect on global Health Score/Quality of Life (GHS/QoL).

*__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. The median follow-up time was derived from a weight-adjusted pooling across studies
b. The baseline risk over two years comes from the combined data of all three trial comparator arms. The five-year risk is based on the pooled estimates of Keynote-407 and Keynote-189, as the follow-up for Keynote-021 did not include this data timepoint
c. 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)
d. 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%)
e. 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 benefits for both subgroups. Therefore, we did not downgrade the rating for indirectness
f. Even though the OIS criterion was met, the difference in change scores from baseline did not cross the MID line at 10. Therefore, we downgraded by 1 for imprecision

Magnitude of effect judgements:

Domain	Judgement per critical outcome		Judgement across desirable critical outcomes
ICIs	**Overall survival**	**Health-related quality of life**	**Overall**
Cemiplimab-containing treatment regimen	Large	Trivial or no	Large
Tremelimumab+durvalumab-containing treatment regimen	Moderate	NR	Moderate
Ipilimumab+nivolumab-containing treatment regimen	Moderate	Trivial or no	Moderate
Pembrolizumab-containing treatment regimen	Moderate	Trivial or no	Moderate

Additional considerations:

In 2019, the Expert Committee recommended adoption of a threshold for benefit of at least 4-6 months overall survival gain and without detriment to quality of life for cancer medicines or regimens to be considered as candidates for inclusion on the WHO EML (19). Based on this recommendation, the following decision rules were considered in judging the magnitude of effects:

- The outcomes overall survival and health-related quality of life were considered of critical importance to patients with NSCLC – more weight was placed on them in the decision-making process when compared to progression-free survival and adverse events.
- ICIs demonstrating a median overall survival benefit greater than the recommended WHO threshold (i.e. > 4-6 months) would be considered to have a large benefit.
- ICIs demonstrating a median overall survival benefit within the range of the recommended WHO threshold (i.e. between 4 and 6 months) would be considered to have a moderate benefit.
- ICIs demonstrating a median overall survival benefit smaller than the recommended WHO threshold (i.e. < 4-6 months) would be considered to have a small benefit.

The median overall survival was rounded to 4 months more in people treated with tremelimumab+durvalumab-containing treatment regimens, rounded to 4 months more in people treated with ipilimumab+nivolumab-containing treatment regimens, was 6.3 months more in people treated with pembrolizumab-containing treatment regimens and was 6.9 months more in people treated with cemiplimab-containing treatment regimens. The ESMO-MCBS Scorecards reported a score of 4 for tremelimumab+durvalumab-, ipilimumab+nivolumab-, pembrolizumab- and cemiplimab-containing treatment regimens. The magnitude of desirable effect for the outcome overall survival, based on the point estimates, WHO benefit thresholds and ESMO-MCBS Scorecards, was judged as moderate, moderate, moderate, and large, respectively.

In terms of health-related quality of life, ipilimumab+nivolumab- and pembrolizumab-containing treatment regimens likely result in no to little difference (moderate certainty evidence) and cemiplimab-containing treatment regimens result in no to little difference (high certainty evidence). Reporting was insufficient in tremelimumab+durvalumab-containing treatment regimens to quantify changes in health-related quality of life.

The overall judgement related to the magnitude of desirable effects cannot be lower than the highest rating across critical outcomes. Therefore, the overall magnitude of desirable effects was judged as moderate for tremelimumab+durvalumab-, ipilimumab+nivolumab- and pembrolizumab-containing treatment regimens, and large for cemiplimab-containing treatment regimens.

Undesirable Effects
How substantial is the **reduction** in undesirable anticipated effects?

JUDGEMENT

RESEARCH EVIDENCE

○ **Increased harms and toxicity** **(cemiplimab, ipilimumb+nivolumab)**

Magnitude of reduction in harms and toxicity:

○ **Trivial or no** (**tremelimumab+durvalumab, pembrolizumab)**
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

The application presents multiple randomized trials as evidence for the undesirable effects of ICIs for oncogenic-driver wild-type non-small cell lung cancer irrespective of PD-L1 expression: one for cemiplimab-containing treatment regimens (3-5), one for tremelimumab+durvalumab-containing treatment regimens (6, 7), one for ipilimumab+nivolumab-containing treatment regimens (8-10) and three for pembrolizumab-containing treatment regimens (11-18).

Cemiplimab-containing treatment regimens 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[a]	**Risk with cemiplimab-containing treatment regimens**				
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[b]	Cemiplimab-containing treatment regimens probably 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

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. The baseline risk stems from the 2-year survival estimate of the control group of the EMPOWER-Lung 3 trial
b. Although the CI touches the null-effect line and lies within the boundaries of appreciable harm, considering the relatively small event rate, we downgraded for imprecision

Durvalumab/tremelimumab-containing treatment regimens 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: Durvalumab/tremelimumab-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[a]	**Risk with Durvalumab/tremelimumab-containing treatment regimens**				
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 (1 RCTs)	⊕⊕⊕◯ Moderate[b]	Durvalumab/tremelimumab-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

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. The baseline risks stem from the estimates of the control group in the POSEIDON trial
b. 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

Ipilimumab/nivolumab-containing treatment regimens 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: 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[a]	**Risk with Ipilimumab/nivolumab-containing treatment regimens**				
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[b,c]	Ipilimumab/nivolumab-containing 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

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. Baseline estimate taken from the control-group estimates of CheckMate 9LA
b. Downgraded due to risk of detection and performance bias as a consequence of the open-label trial design
c. Downgraded for imprecision; the CI crosses the line for appreciable harm at 1.25

Pembrolizumab-containing treatment regimens 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	№ of participants	Certainty of	Comments

	Risk with SoC[a]	Risk with pembrolizumab-containing treatment regimens	(95% CI)	(studies)	the evidence (GRADE)	
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[b]	Pembrolizumab-containing treatment regimens likely 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

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. The baseline risk over two years comes from the combined data of all three trial comparator arms. The five-year risk is based on the pooled estimates of Keynote-407 and Keynote-189, as the follow-up for Keynote-021 did not include this data timepoint
b. Although the CI touches the null-effect line and lies within the boundaries of appreciable harm, considering the relatively small event rate, we downgraded for imprecision

Additional considerations:

Moderate certainty evidence showed that tremelimumab+durvalumab- and pembrolizumab-containing treatment regimens probably have trivial to no effect on adverse events when compared to standard of care. Based on moderate certainty evidence, cemiplimab-containing treatment regimens probably results in a moderate increase in adverse events. Based on low certainty evidence, ipilimumab+nivolumab-containing treatment regimens may result in a moderate increase in adverse events.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

○ Very low
○ **Low** **(tremelimumab+durvalumab, ipilimumab+nivolumab)**
○ **Moderate** **(cemiplimab, pembrolizumab)**
○ High

RESEARCH EVIDENCE

Domain	Judgement per critical outcome			Judgement across critical outcomes
ICIs	**Overall survival**	**Health-related quality of life**	**Adverse events**	**Overall**
Cemiplimab-containing treatment regimens	Moderate	High	Moderate	Moderate
Durvalumab/tremelimumab-containing treatment regimens	Low	NA	Moderate	Low
Ipilimumab/nivolumab-containing treatment regimens	Low	Moderate	Low	Low
Pembrolizumab-containing treatment	Moderate	Moderate	Moderate	Moderate

○ No included studies	regimens **Additional considerations:** Across the critical outcomes, the lowest certainty of evidence rating was moderate for both cemiplimab- and pembrolizumab-containing treatment regimens, and low for tremelimumab+durvalumab- and ipilimumab+nivolumab-containing treatment regimens.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ **Probably no important uncertainty or variability** (tremelimumab+durvalumab, ipilimumab+nivolumab, pembrolizumab) ○ **No important uncertainty or variability** (cemiplimab)	A systematic review of qualitative research identified 17 studies published between 2017 and 2022 that addressed the experience of patients considering or using checkpoint inhibitors in cancer. Five (29%) addressed lung cancer specifically (20). Overall, patients viewed immune checkpoint inhibitors positively when compared to other anti-cancer treatments, noting newfound hope, fewer or more manageable treatment-related side effects, and among those experiencing treatment success, improved quality of life when compared to chemotherapy and radiation therapy. In some cases, patients were uncertain about response durability long-term and checkpoint inhibitor-specific adverse events. Patient concerns around checkpoint inhibitors may be mitigated, at least in part, by positive patient-practitioner relationships and support from other patients with lived checkpoint inhibitor experience by way of community groups. Further, fatigue is a common checkpoint inhibitor-specific adverse event. Implementing supportive care programs can help patients undergoing checkpoint inhibitor treatment cope with fatigue and maximize their quality of life. It was noted that most studies included in this systematic review omitted patients that discontinued checkpoint inhibitor treatment due to serious adverse events or failed to respond to checkpoint inhibitor treatment limiting our understanding of patient experiences with checkpoint inhibitors in this regard.

Importance of uncertainty and variability of how people value outcomes

ICIs	Net balance	Judgement
Cemiplimab-containing treatment regimens	Large net desirable	No important uncertainty or variability
Durvalumab/tremelimumab-containing treatment regimens	Moderate net desirable	Probably no important uncertainty or variability
Ipilimumab/nivolumab-containing treatment regimens	Moderate net desirable	Probably no important uncertainty or variability
Pembrolizumab-containing treatment regimens	Moderate net desirable	Probably no important uncertainty or variability

Additional considerations:

A judgement was made that how much people value the main outcomes, including overall survival, lies on a spectrum, and depends on the magnitude of

benefit and harm from treatment. In a situation with trivial benefit and large harm, it was inferred that most people would not choose to pursue treatment if available. In a situation with large benefit and trivial harm, it was inferred that all or almost all people would choose to pursue treatment if available.

Cemiplimab-containing treatment regimens probably result in a large increase in OS (6.9 months), have trivial to no effect on health-related quality of life and probably have trivial to no effect in reducing adverse events when compared to standard of care. Based on this and the ESMO-MCBS Scorecard, it was judged that cemiplimab-containing treatment regimens offer a large net desirable effect and people would have no important uncertainty or variability in how much they value the main outcomes, particularly preferring avoiding premature death.

Pembrolizumab-containing treatment regimens probably result in a moderate increase in OS (6.3 months), and probably have trivial to no effect on health-related quality of life and in reducing adverse events when compared to standard of care. Based on this and the ESMO-MCBS Scorecard, it was judged that pembrolizumab-containing treatment regimens offer a moderate net desirable effect and people would probably have no important uncertainty or variability in how much they value the main outcomes, particularly preferring avoiding premature death.

Ipilimumab/nivolumab-containing treatment regimens may result in a moderate increase in OS (3.9 months), probably have trivial to no effect on health-related quality of life and may increase adverse events slightly when compared to standard of care. Based on this and the ESMO-MCBS Scorecard, it was judged that ipilimumab/nivolumab-containing treatment regimens offer a moderate net desirable effect and people would probably have no important uncertainty or variability in how much they value the main outcomes, particularly preferring avoiding premature death.

Durvalumab/tremelimumab-containing treatment regimens may result in a moderate increase in OS (3.5 months) and probably have trivial to no effect in reducing adverse events when compared to standard of care. Eligible data on their effect on health-related quality of life was not available. Based on this and the ESMO-MCBS Scorecard, it was judged that durvalumab/tremelimumab-containing treatment regimens offer moderate net desirable effect and people would probably have no important uncertainty or variability in how much they value the main outcomes, particularly preferring avoiding premature death.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

○ Favors the comparison
○ Probably favors the comparison
○ Does not favor either the intervention or the comparison
○ **Probably favors the intervention** **(tremelimumab+durvalumab, ipilimumab+nivolumab,**

RESEARCH EVIDENCE

ICIs	Net balance	Values	Certainty of evidence	Balance of effects
Cemiplimab-containing treatment regimens	Large net desirable	No important uncertainty or variability	Moderate	Favors the intervention
Durvalumab/tremelimumab-containing treatment regimens	Moderate net desirable	Probably no important uncertainty or variability	Low	Probably favors the intervention
Ipilimumab/nivolumab-containing treatment regimens	Moderate net desirable	Probably no important uncertainty or variability	Low	Probably favors the intervention
Pembrolizumab-containing treatment regimens	Moderate net desirable	Probably no important uncertainty or variability	Moderate	Probably favors the intervention

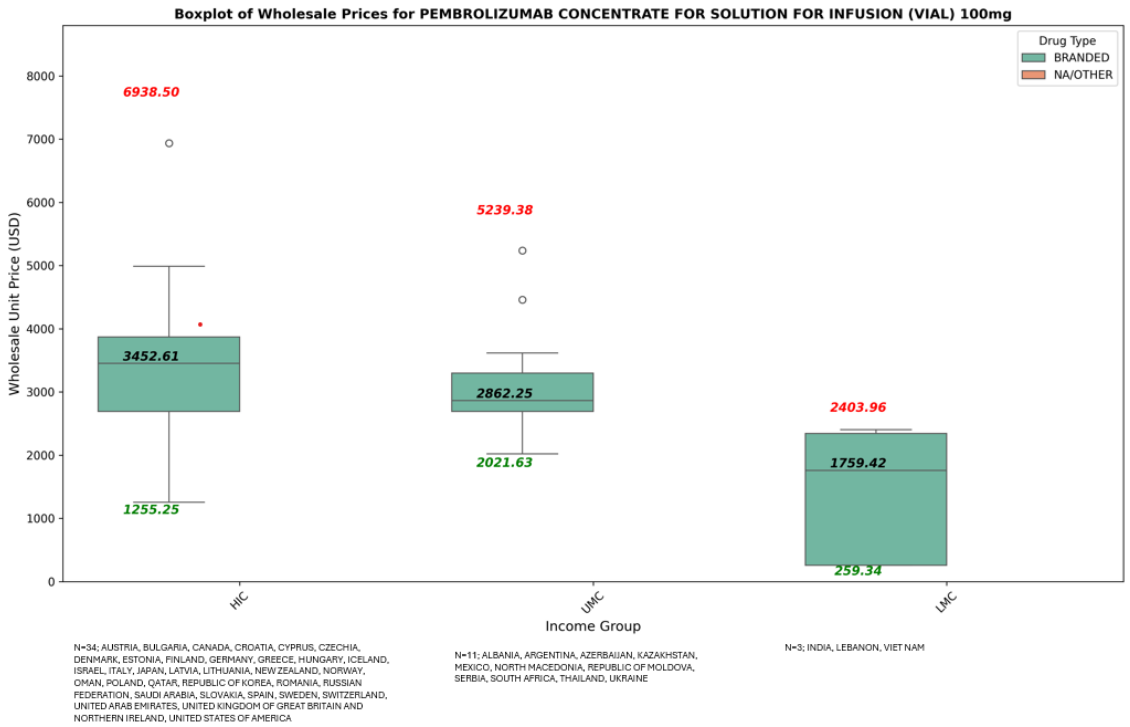
pembrolizumab) ○ **Favors the intervention** (cemiplimab) ○ Varies ○ Don't know	**Additional considerations:** A judgement based on the net balance between desirable and undesirable effects, patient values and the certainty of evidence was made that the balance of effects probably favors durvalumab/tremelimumab-, ipilimumab/nivolumab- and pembrolizumab-containing treatment regimens and favors cemiplimab-containing treatment regimens.

Resources required

How large are the resource requirements?

JUDGEMENT	RESEARCH EVIDENCE
○ **Large costs** ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Median wholesale unit price (USD) for pembrolizumab concentrate (100 mg vial) across World Bank income levels*:

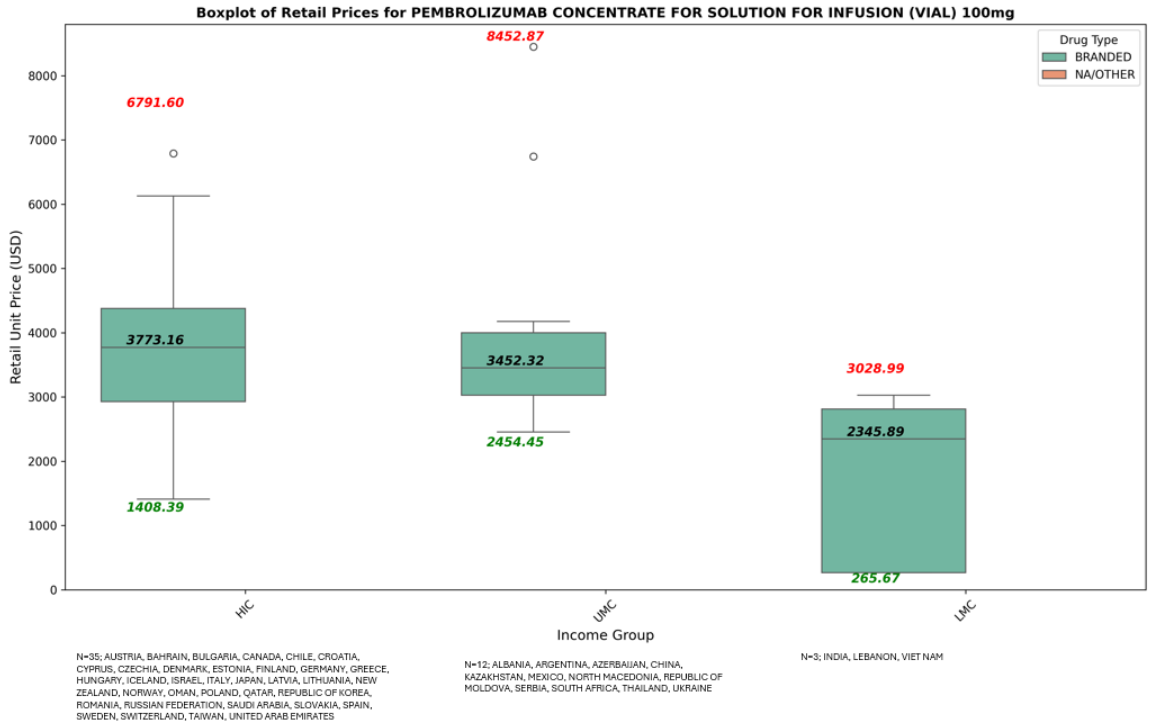
Income level	Median	IQR	Sample size based on number of countries
HIC	3452.61	2692.68 to 3871.57	34
UMIC	2862.25	2693.96 to 3299.45	11
LMIC	1759.42	259.34 to 2343.91	3



Source: author derived calculation based on most recent available wholesale prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: https://www.who.int/teams/health-product-and-policy-standards/medicines-selection-ip-and-affordability/affordability-pricing/med-price-info-source

Median retail unit price (USD) for pembrolizumab concentrate (100 mg vial) across World Bank income levels*:

Income level	Median	IQR	Sample size based on number of countries
HIC	3773.16	2928.38 to 4377.63	35
UMIC	3452.32	3027.62 to 4001.05	12
LMIC	2345.89	265.67 to 2812.69	3



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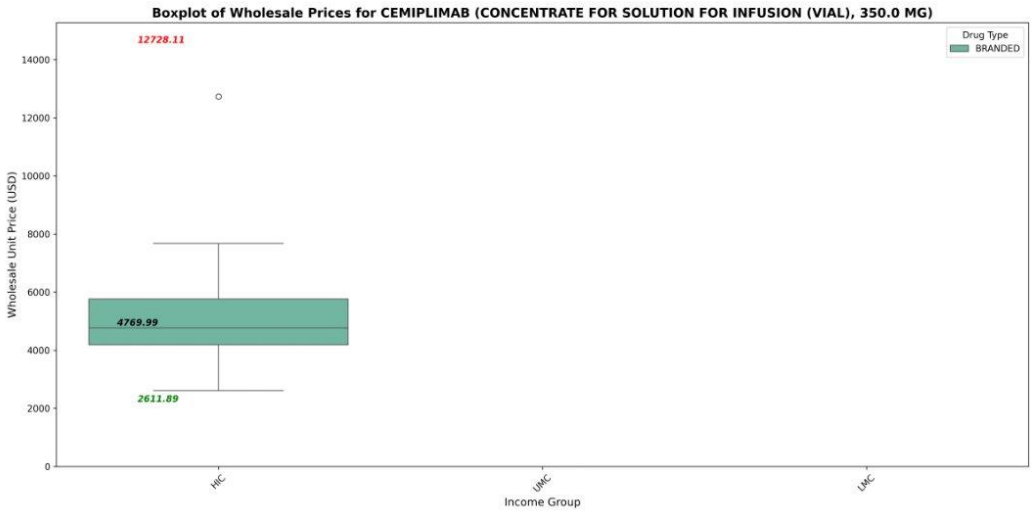
Median wholesale unit price (USD) for cemiplimab (concentrate for solution for infusion, 350.0 MG) across World Bank income levels*:

Income level	Median	IQR	Sample size based on number of countries
HIC	4769.99	4183.03 to 5760.73	25
UMIC	NR	NR	0
LMIC	NR	NR	0



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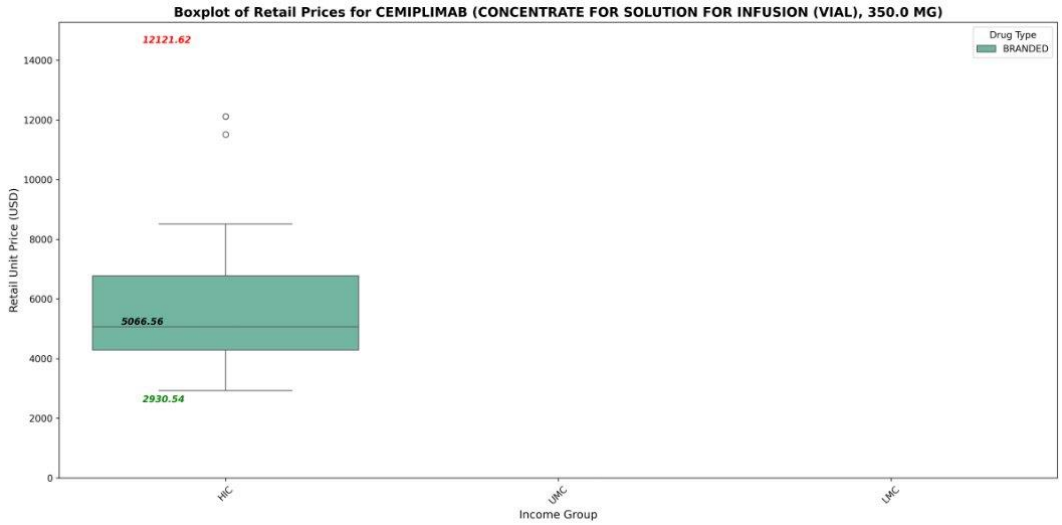
Median retail unit price (USD) for cemiplimab (concentrate for solution for infusion, 350.0 MG) across World Bank income levels*:

Income level	Median	IQR	Sample size based on number of countries
HIC	5066.56	4293.13 to 6775.30	21
UMIC	NR	NR	0
LMIC	NR	NR	0



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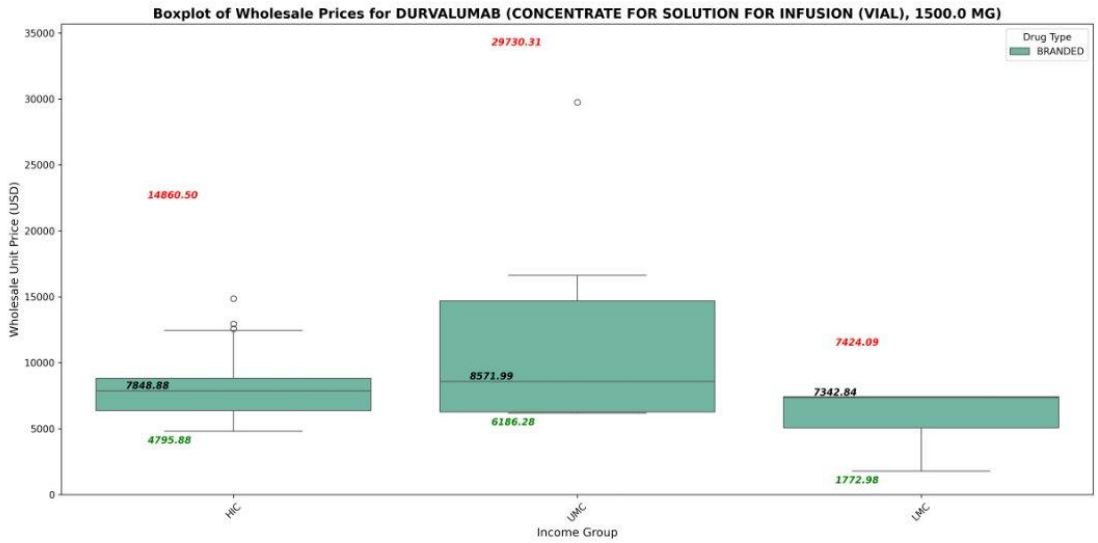
Median wholesale unit price (USD) for durvalumab (concentrate for solution for infusion, 1500.0 MG) across World Bank income levels*:

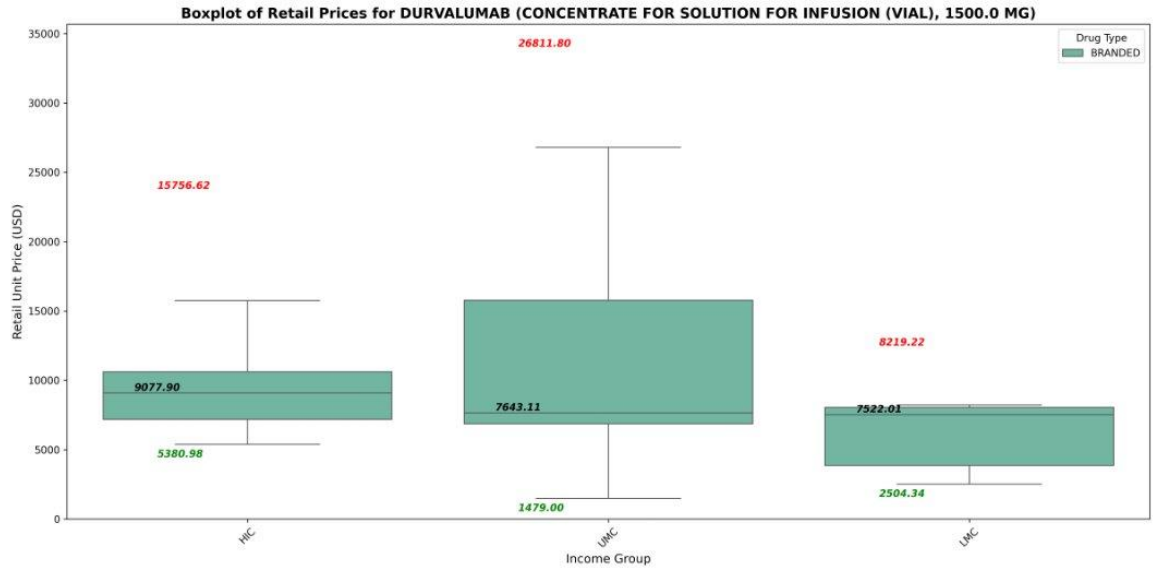
Income level	Median	IQR	Sample size based on number of countries
HIC	7848.88	6364.79 to 8808.71	36
UMIC	8571.99	6266.52 to 14678.40	9
LMIC	7342.84	5054.37 to 7424.09	3



Source: author derived calculation based on most recent available wholesale prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: https://www.who.int/teams/health-product-and-policy-standards/medicines-selection-ip-and-affordability/affordability-pricing/med-price-info-source

Median retail unit price (USD) for durvalumab (concentrate for solution for infusion, 1500.0 MG) across World Bank income levels*:

Income level	Median	IQR	Sample size based on number of countries
HIC	9077.90	7179.67 to 10624.14	34
UMIC	7643.11	6855.05 to 15764.25	7
LMIC	7522.01	3857.16 to 8044.91	3



Source: author derived calculation based on most recent available retail prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: https://www.who.int/teams/health-product-and-policy-standards/medicines-selection-ip-and-affordability/affordability-pricing/med-price-info-source

Median wholesale unit price (USD) for tremelimumab (concentrate for solution for infusion, 300.0 MG) across World Bank income levels*:

Income level	Median	IQR	Sample size based on number of countries
HIC	24284.41	20895.89 to 26102.48	16
UMIC	NR	NR	0
LMIC	NR	NR	0

Source: author derived calculation based on most recent available wholesale prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: https://www.who.int/teams/health-product-and-policy-standards/medicines-selection-ip-and-affordability/affordability-pricing/med-price-info-source

Median retail unit price (USD) for tremelimumab (concentrate for solution for infusion, 300.0 MG) across World Bank income levels*:

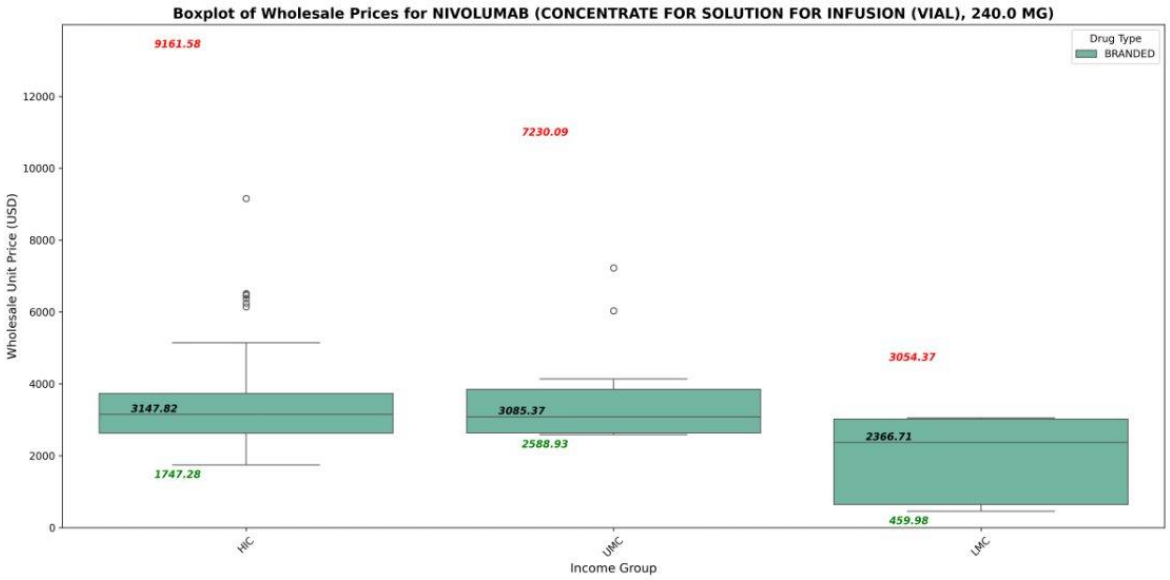
Income level	Median	IQR	Sample size based on number of countries

HIC	29678.14	22542.01 to 32777.13	15
UMIC	NR	NR	0
LMIC	NR	NR	0

Source: author derived calculation based on most recent available retail prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: https://www.who.int/teams/health-product-and-policy-standards/medicines-selection-ip-and-affordability/affordability-pricing/med-price-info-source

Median wholesale unit price (USD) for nivolumab (concentrate for solution for infusion, 240 mg vial) across World Bank income levels*:

Income level	Median	IQR	Sample size based on number of countries
HIC	3147.82	2632.86 to 3734.15	37
UMIC	3085.37	2639.78 to 3848.65	8
LMIC	2366.71	643.98 to 3021.01	3



Source: author derived calculation based on most recent available wholesale prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: https://www.who.int/teams/health-product-and-policy-standards/medicines-selection-ip-and-affordability/affordability-pricing/med-price-info-

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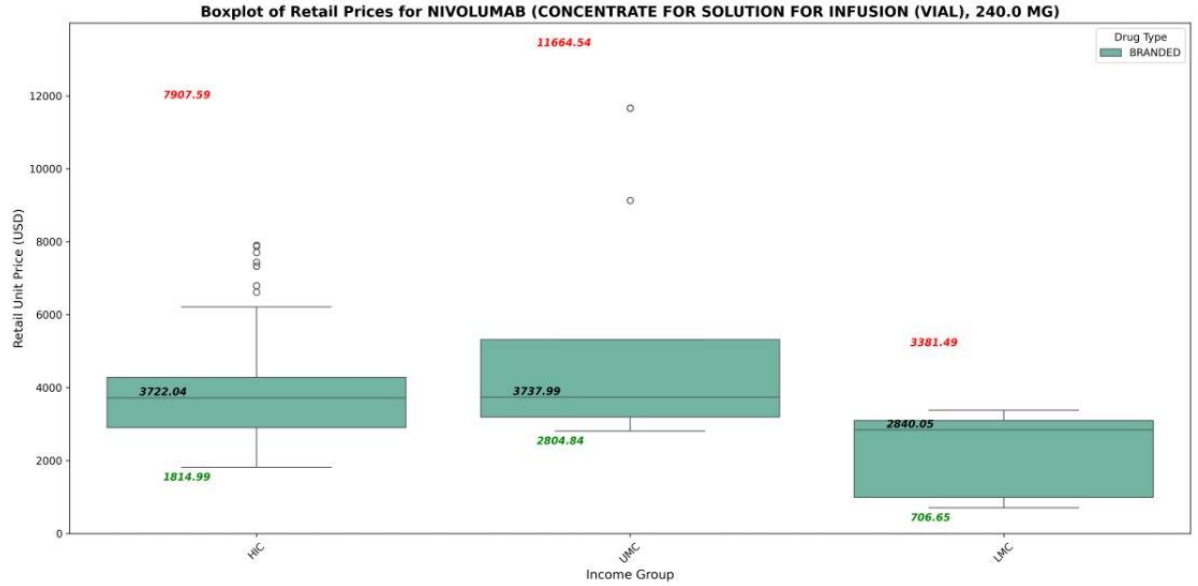
Median retail unit price (USD) for nivolumab (concentrate for solution for infusion, 240 mg vial) across World Bank income levels*:

Income level	Median	IQR	Sample size based on number of countries
HIC	3722.04	2906.20 to 4281.61	37
UMIC	3737.99	3189.56 to 5313.62	8
LMIC	2840.05	989.32 to 3094.72	3



Source: author derived calculation based on most recent available retail prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: https://www.who.int/teams/health-product-and-policy-standards/medicines-selection-ip-and-affordability/affordability-pricing/med-price-info-source

Median wholesale unit price (USD) for branded ipilimumab (concentrate for solution for infusion, 200 mg vial) across World Bank income levels*:

Income level	Median	IQR	Sample size based on number of countries
HIC	14197.18	12370.89 to 17464.71	36
UMIC	12451.31	11104.59 to 13445.63	8

LMIC	3447.07	1840.58 to 8859.21	2

Source: author derived calculation based on most recent available wholesale prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: https://www.who.int/teams/health-product-and-policy-standards/medicines-selection-ip-and-affordability/affordability-pricing/med-price-info-source

Median retail unit price (USD) for branded ipilimumab (concentrate for solution for infusion, 200 mg vial) across World Bank income levels*:

Income level	Median	IQR	Sample size based on number of countries
HIC	16025.41	13773.54 to 20420.17	35
UMIC	13986.11	13462.27 to 16059.71	7
LMIC	4426.49	2333.14 to 9523.03	2

Source: author derived calculation based on most recent available retail prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: https://www.who.int/teams/health-product-and-policy-standards/medicines-selection-ip-and-affordability/affordability-pricing/med-price-info-source

Additional considerations:

Direct evidence addressing the unit price for pembrolizumab, cemiplimab, durvalumab, tremelimumab, nivolumab and ipilimumab was available.

Relative to other EML medicines, the costs of these cancer medicines at the current unit pricing are large across World Bank income levels. The number of countries informing the UMIC and LMIC income levels was limited. These small sample sizes reduce our confidence in the estimates in non-HIC countries and may reflect, in part, variability in access to these cancer medicines. Further, there were no data available for LICs.

Nonetheless, harnessing pricing dynamics is needed to promote implementation and affordable use of these cancer medicines at the country level. Of note, biosimilar entry for pembrolizumab is anticipated in the next 3 to 5 years (2028 to 2023). Given its dominant role in several critical indications, it likely has the largest potential for cost reduction (21).

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the	A systematic review addressing the cost-effectiveness of pembrolizumab for the treatment of NSCLC identified 24 cost-effectiveness studies from China, France, Singapore, Switzerland, United Kingdom and United States, all of which are HICs or UMICs (22). Whether or not pembrolizumab was found to be cost-effective was associated at least in part with the selection of model parameters, willingness-to-pay thresholds, and treatment strategies. Empirical evidence estimating cost-effective thresholds based on health expenditures per capita and life expectancy at birth was available for 174 countries (23). As of 2019, the following cost-effectiveness thresholds in USD per QALY were estimated for each country income level. The authors noted that their empirically derived thresholds were lower than those used in many countries. If used, they may result in more conservative health decision-making.

comparison
○ Probably favors the intervention
○ Favors the intervention
○ **Varies**
○ No included studies

Income level	Range	Median	IQR	Sample size based on number of countries	Cost-effective?
HIC	$5480–$95958	$18,218	$10229–$43175	54	Varies
UMIC	$1108–$10638	$4,355	$2886–$5301	48	No
LMIC	$190–$3249	$745	$451–$1389	49	No
LIC	$87–$320	$163	$131–$229	23	No

To help achieve cost-effective use of pembrolizumab across World Bank income settings without compromising efficacy and safety, alternative dosing strategies have been proposed (24). They include electronic rounding, hybrid dosing, lower dose selection, interval extension and shortening of treatment duration. The scientific basis for these alternative dosing strategies is growing and is based on evidence from both clinical trials and pharmacokinetic studies.

Additional considerations:

In the absence of a *de novo* cost-effectiveness model that considers diverse income settings and alternative dosing strategies, a judgement on the cost-effectiveness was made based on select examples and empirically derived cost-effective thresholds.

While the four checkpoint inhibitors under consideration for oncogenic-driver wild-type non-small cell lung cancer irrespective of PD-L1 expression had moderate to large net desirable effects, at the current price, they are likely not cost-effective in most settings, particularly in LMICs and LICs, and when diagnostic requirements are considered.

Clinically proven alternative dosing strategies may be an important step in helping achieve cost-effective use of these checkpoint inhibitors in more settings.

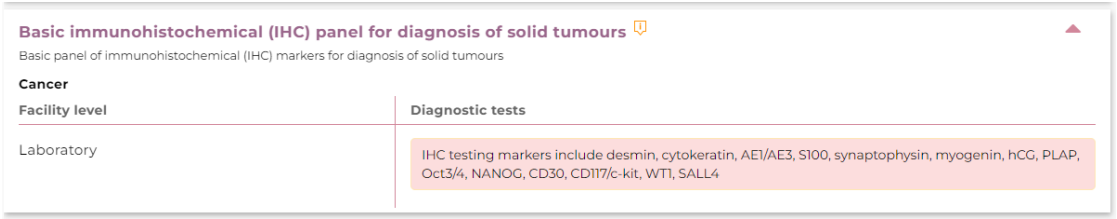
Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ **Reduced** ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Additional considerations:** Despite checkpoint inhibitors being accessible in many HICs, the WHO EML is a global list and the impact on LMICs and LICs was considered. Because the ICIs under consideration offer desirable benefits but are not accessible to patients globally because of their prohibitively high price, a judgement was made that health equity would be reduced. On the other hand, if price decreased substantially, access in disadvantaged populations would improve and health equity would increase.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	A systematic review of qualitative research identified 17 studies published between 2017 and 2022 that addressed the experience of patients considering or using checkpoint inhibitors in cancer. Five (29%) addressed lung cancer specifically (20). Overall, patients viewed immune checkpoint inhibitors positively when compared to other anti-cancer treatments, noting newfound hope, fewer or more manageable treatment-related side effects, and among those experiencing treatment success, improved quality of life when compared to chemotherapy and radiation therapy. Of note, hope is key for cancer patient acceptance of further treatment and is associated with improved symptom burden and quality of life and decreased psychological distress. **Additional considerations:** Empiric evidence from the patient perspective provides support for the acceptability of immune checkpoint inhibitors. These immune checkpoint inhibitors are likely not acceptable to most health decision makers and health systems, especially those in LMICs and LICs, due to cost. The large costs associated with these checkpoint inhibitors when compared to other anti-cancer treatments risk diverting resources from health budgets at the expense of other essential medicines.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Diagnostic requirements – immunohistochemistry companion tests – to identify patients with the indication approved for treatment. The WHO Essential Diagnostics List includes a basic panel for immunohistochemical (IHC) markers for diagnosis of solid tumors, but the panel does not include IHC testing markers for PDL1 (25).  **Basic immunohistochemical (IHC) panel for diagnosis of solid tumours** Basic panel of immunohistochemical (IHC) markers for diagnosis of solid tumours **Cancer** **Facility level** | **Diagnostic tests** Laboratory | IHC testing markers include desmin, cytokeratin, AE1/AE3, S100, synaptophysin, myogenin, hCG, PLAP, Oct3/4, NANOG, CD30, CD117/c-kit, WT1, SALL4 Additional considerations for healthcare-worker training, resources for the management of side-effects and monitoring capabilities. **Additional considerations:** The interventions are already implemented in many high-income settings. Beyond the large cost, another barrier to implementation is the need for diagnostic companion tests. Immunohistochemistry is an important component of the application of immune checkpoint inhibitor treatment in NSCLC.

Availability What is the regulatory status, market availability and on-the-ground availability/access of the medicine to patients?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ Not available in most settings ○ **Probably not available in most settings** ○ Probably available in most settings ○ Available in most settings ○ Varies ○ Don't know	Pembrolizumab is approved for use in 85 countries worldwide – mainly high-income countries including Canada, the United States, European Union member countries and Japan (26). Data on the availability, out-of-pocket costs, and accessibility of pembrolizumab for melanoma, NSCLC, colorectal cancer and renal cell carcinoma were available from the 2023 update to the ESMO Global Consortium Study (27). In HICs, pembrolizumab and nivolumab for melanoma was "almost always available to patients at no cost or on a subsidized basis". In LMICs and LICs, when available, however, pembrolizumab and nivolumab was "generally provided only at full cost as an out-of-pocket expenditure for patients". Although pembrolizumab for melanoma was almost always actually available in HICs (accessibility with a valid prescription), there was important variation in the actual availability across UMICs, LMICs and LICs. Outside of HICs, pembrolizumab for NSCLC, colorectal cancer and renal cell carcinoma was more commonly provided as an out-of-pocket expenditure for patients than not – often at full cost to the patient. These data provide indirect evidence regarding the extent of cemiplimab and durvalumab availability for NSCLC across World Bank income settings. **Additional considerations:** Cemiplimab-, durvalumab-, nivolumab- and pembrolizumab-containing regimens are approved for use in many countries; however, on-the-ground access outside of HICs is limited.

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