This Evidence-to-Decision (EtD) framework addresses **pembrolizumab + chemotherapy** for **ERBB-2 negative gastric/gastro-oesophageal junction adenocarcinoma (≥1% PD-L1 expression)** and **nivolumab + chemotherapy** for **ERBB-2 negative gastric/gastro-oesophageal junction adenocarcinoma (≥5% PD-L1 expression)**.

QUESTION

Should immune checkpoint inhibitors vs. alternative regimens be used for adult ERBB-2 negative, gastric/gastro-oesophageal junction adenocarcinoma?	
POPULATION:	adult ERBB-2 negative gastric/gastro-oesophageal junction adenocarcinoma (GC/GOJ)
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 one ICI-containing treatment regimens for ERBB-2 negative, GC/GOJ (≥1% PD-L1 expression): • pembrolizumab + chemotherapy (ESMO-MCBS non-curative score = 4) application includes one ICI-containing treatment regimens for ERBB-2 negative, GC/GOJ (≥5% PD-L1 expression): • nivolumab + chemotherapy (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** (pembrolizumab)	**Moderate** (nivolumab)	Large		Varies	Don't know
REDUCTION IN UNDESIRABLE EFFECTS	**Increased harms and toxicity** (nivolumab)	Trivial/No	Small	Moderate	Large	Varies	**Don't know** (pembrolizumab)
CERTAINTY OF EVIDENCE	**Very low** (pembrolizumab)	**Low** (nivolumab)	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability** (pembrolizumab, nivolumab)	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention** (pembrolizumab, nivolumab)	Favors the intervention	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 GC/GOJ (≥1% and ≥5% PD-L1 expression) for which two ICI-containing treatment regimens are proposed: pembrolizumab and nivolumab. The global age-standardized incidence rate of stomach cancer was estimated at 9.2 per 100,000 in 2022, and represents the fifth most frequent cancer worldwide and seventh leading cause of cancer-related deaths worldwide (1). The standard of care includes 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.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial or no ○ **Small (pembrolizumab)** ○ **Moderate (nivolumab** ○ Large ○ Varies ○ Don't know	The application presents evidence from two randomized trials addressing pembrolizumab + chemotherapy for GC/GOJ (≥1% PD-L1 expression) (2-6) and one randomized trial addressing nivolumab + chemotherapy for GC/GOJ (≥5% PD-L1 expression) (7-9).

Pembrolizumab-based treatment regimens compared to 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
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**				
	At 2 years					
Overall survival (OS) follow-up: median 30.2 months[a]	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**		**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.
	8 per 100[i]	**14 per 100** (11 to 19)				
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 may result in little to no difference in global Health Score/Quality of Life.

*__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 overall survival rate (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) and Keynote-062 (NCT02494583)
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 progression-free survival rate (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 trial 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 the outcome for indirectness.
k. Inconsistency not applicable (single trial only) and publication bias not applicable due to 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

Nivolumab-based treatment regimens compared to 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
Intervention: Nivolumab-based treatment regimens
Comparison: SoC

Outcomes	**Anticipated absolute effects*** (95% CI)	Relative effect	№ of participants	Certainty of the	Comments

	Risk with SoC	Risk with nivolumab-based treatment regimens	(95% CI)	(studies)	evidence (GRADE)	
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 increase overall survival.
	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,h]	Nivolumab-based treatment regimens may increase progression-free survival.
	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.

*__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)
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

Magnitude of effect judgements:

Domain	Judgement per critical outcome		Judgement across desirable critical outcomes
ICIs	**Overall survival**	**Health-related quality of life**	**Overall**
Pembrolizumab-containing treatment regimen	Small	Trivial or no	Small
Nivolumab-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 (10). 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 GC/GOJ – 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 3 months more in people treated with pembrolizumab-containing treatment regimens. The ESMO-MCBS Scorecard reported a score of 4 for the Keynote-859 trial. Therefore, the magnitude of desirable effects for the outcome overall survival, based on the point estimate, WHO benefit threshold and ESMO-MCBS Scorecard, was judged as small. The median overall survival was rounded to 5 months more in people treated with nivolumab-containing treatment regimens. The ESMO-MCBS Scorecard reported a score of 4 for the nivolumab-containing treatment regimen trial. Therefore, the magnitude of desirable effects for the outcome overall survival, based on the point estimate, WHO benefit threshold and ESMO-MCBS Scorecard, was judged as moderate. In terms of health-related quality of life, pembrolizumab-containing treatment regimens may result in no to little difference (low certainty evidence) and nivolumab-containing treatment regimens likely result in no to little difference (moderate certainty evidence). 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 small for pembrolizumab-containing treatment regimens and moderate for nivolumab-containing treatment regimens.
Undesirable Effects How substantial is the **reduction** in undesirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ **Increased harms and toxicity** **(nivolumab)**	The application presents evidence from two randomized trials addressing pembrolizumab + chemotherapy for GC/GOJ (≥1% PD-L1 expression) (2-6) and one randomized trial addressing nivolumab + chemotherapy for GC/GOJ (≥5% PD-L1 expression) (7-9).

Magnitude of reduction in harms and toxicity:

○ Trivial or no
○ Small
○ Moderate
○ Large
○ Varies
○ **Don't know**

(pembrolizumab)

Pembrolizumab-based treatment regimens compared to 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
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**				
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution[c]	55 per 100	**61 per 100** (56 to 68)	**RR 1.11** (1.01 to 1.23)	2066 (2 RCTs)	⊕◯◯◯ Very low[a,b,d,e]	We are uncertain about the effects of pembrolizumab-based treatment regimens on 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. Downgraded for risk of attrition bias (larger number of patient withdrawal in both arms (24/257 and 21/250) in addition to protocol violations)
b. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process
c. Safety data from safety population; treatment-related adverse events
d. 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
e. Downgraded for imprecision (line of appreciable effect crossed by confidence interval)

Nivolumab-based treatment regimens compared to 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
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**				
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[a,b,c,d]	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. Downgraded for imprecision (line of defined appreciable effect at 0.75 or 1.25 crossed by confidence interval; single study only)
b. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process

c. Downgraded for risk of performance and detection bias due to open-label design
d. 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

Additional considerations:

We are uncertain about the effects of pembrolizumab-containing treatment regimens on adverse events (very low certainty evidence); however, nivolumab-containing treatment regimens may moderately increase adverse events when compared to standard of care (low certainty evidence).

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ **Very low (pembrolizumab)** ○ **Low (nivolumab)** ○ Moderate ○ High ○ No included studies	See table below

Domain	Judgement per critical outcome			Judgement across critical outcomes
ICIs	Overall survival	Health-related quality of life	Adverse events	Overall
Pembrolizumab-containing treatment regimens	Low	Low	Very low	Very low
Nivolumab-containing treatment regimens	Moderate	Moderate	Low	Low

Additional considerations:

Across the critical outcomes, the lowest certainty of evidence rating was very low for pembrolizumab-containing treatment regimens and low for 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**	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 (11). 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**

variability (nivolumab, pembrolizumab)

○ No important uncertainty or variability

ICIs	Net balance	Judgement
Pembrolizumab-containing treatment regimens	Small net desirable	Probably no important uncertainty or variability
Nivolumab-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.

Pembrolizumab-containing treatment regimens may result in a small increase in OS (3 months) and may have trivial to no effect on health-related quality of life; however, we are uncertain about their effect on adverse events. Based on this and the ESMO-MCBS Scorecard, it was judged that pembrolizumab-containing treatment regimens offer a small 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.

Nivolumab-containing treatment regimens likely result in a moderate increase in OS (5 months), likely have trivial to no effect on health-related quality of life and may increase adverse events moderately when compared to standard of care. Based on this and the ESMO-MCBS Scorecard, it was judged that 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.

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**

RESEARCH EVIDENCE

ICIs	Net balance	Values	Certainty of evidence	Balance of effects
Pembrolizumab-containing treatment regimens	Small net desirable	Probably no important uncertainty or variability	Very low	Probably favors the intervention
Nivolumab-containing treatment regimens	Moderate net desirable	Probably no important uncertainty or variability	Low	Probably favors the intervention

Additional considerations:

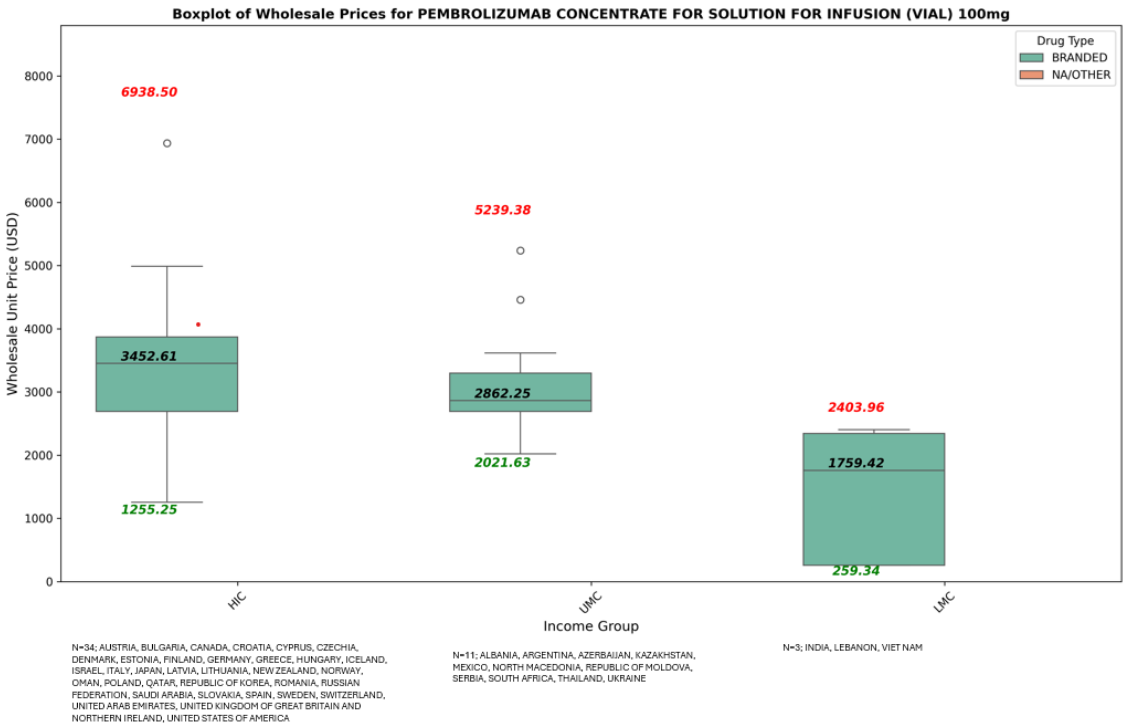
A judgement based on the net balance between desirable and undesirable effects, patient values and the certainty of evidence was made that the balance of effects probably favors pembrolizumab- and nivolumab-containing treatment regimens.

intervention (nivolumab, pembrolizumab) ○ Favors the intervention ○ Varies ○ Don't know	

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*:

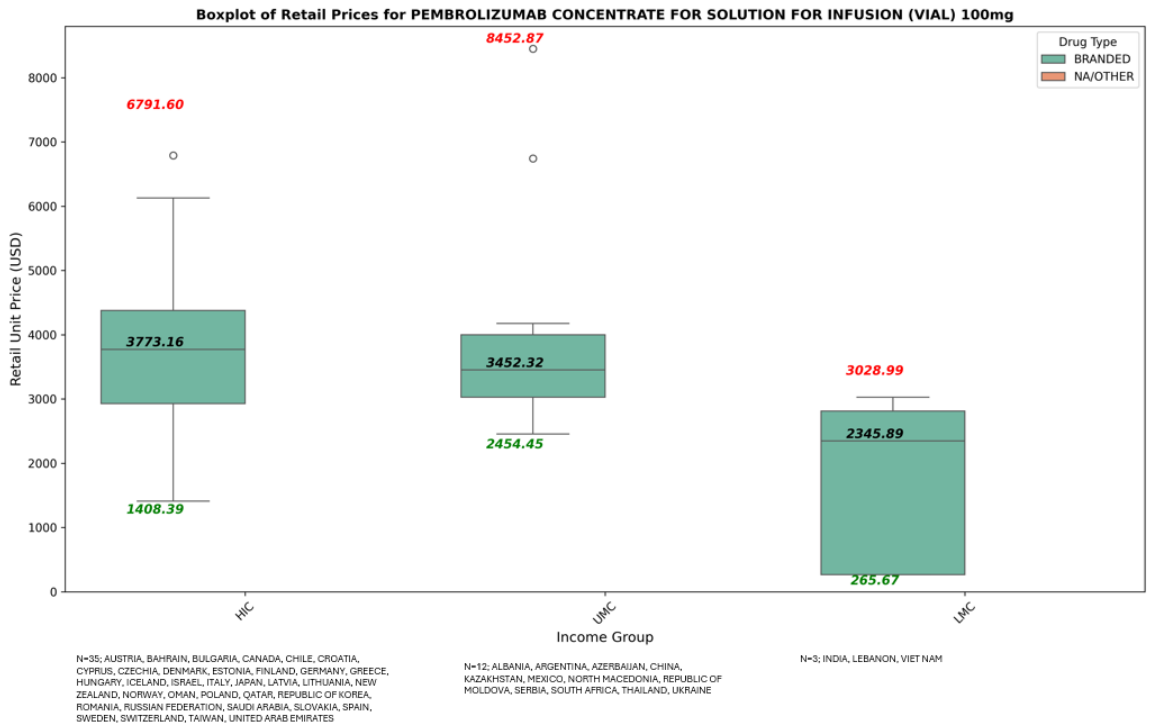
Income level	Median	IQR	Sample size based on number of countries
HIC	3452.61	2692.68 to 3871.57	34
UMIC	2862.25	2693.96 to 3299.45	11
LMIC	1759.42	259.34 to 2343.91	3



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*:

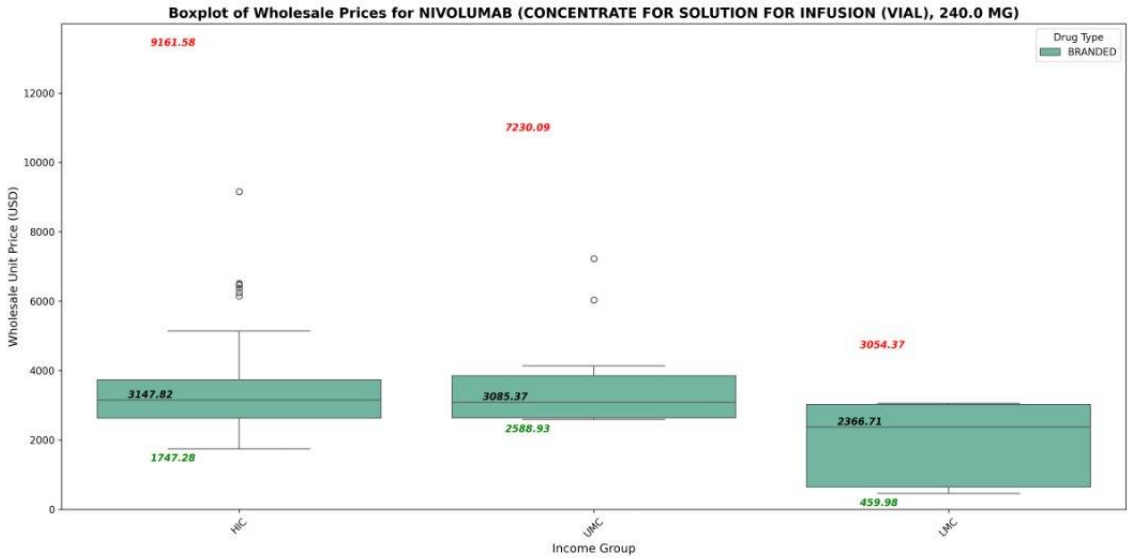
Income level	Median	IQR	Sample size based on number of countries
HIC	3773.16	2928.38 to 4377.63	35
UMIC	3452.32	3027.62 to 4001.05	12
LMIC	2345.89	265.67 to 2812.69	3



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) across World Bank income levels*:

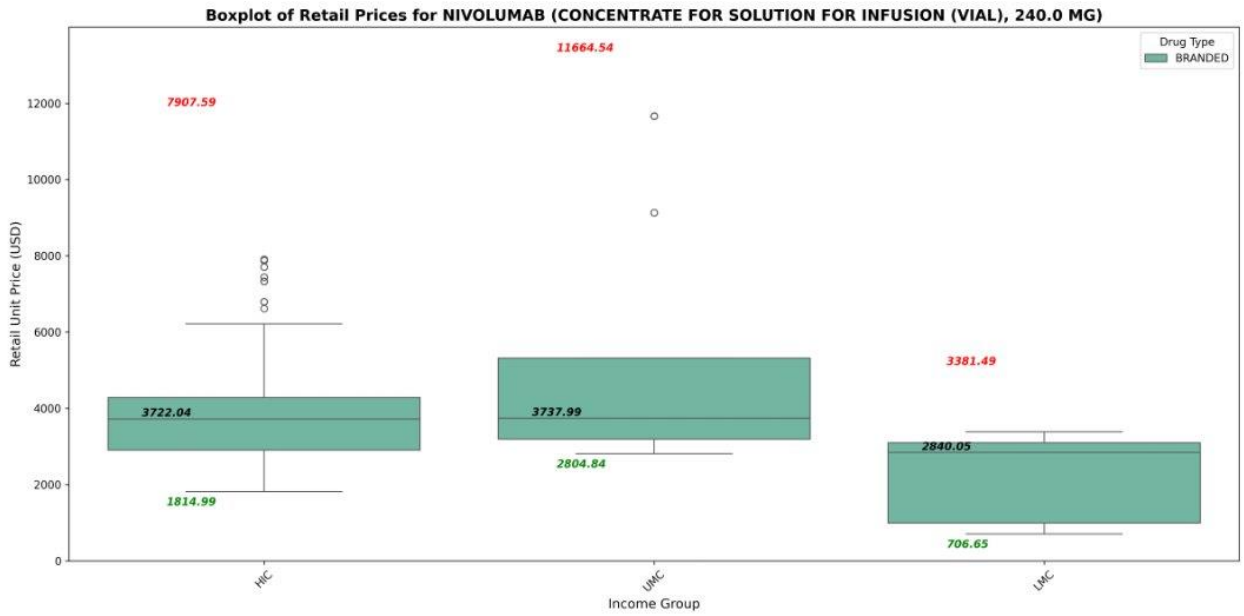
Income level	Median	IQR	Sample size based on number of countries
HIC	3147.82	2632.86 to 3734.15	37
UMIC	3085.37	2639.78 to 3848.65	8
LMIC	2366.71	643.98 to 3021.01	3



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-source

Median retail unit price (USD) for nivolumab (concentrate for solution for infusion, 240 mg) 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

Additional considerations:

Direct evidence addressing the unit price for pembrolizumab and nivolumab was available.

Relative to other EML medicines, the costs of pembrolizumab and nivolumab at the current unit pricing are large across World Bank income levels. Within an income level, there was substantial variation in prices which can be in part attributed to pricing dynamics at the country level and the limited number of countries informing each income level. These small sample sizes reduce our confidence in the estimates, especially for LMICs for which data from only three countries were available. Further, there were no data available for LICs.

Nonetheless, harnessing pricing dynamics is needed to promote implementation and affordable use of pembrolizumab and nivolumab 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 (12).

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 comparison ○ Probably favors the intervention ○ Favors the intervention ○ **Varies** ○ No included studies	Evidence addressing cost-effectiveness of pembrolizumab versus chemotherapy was available from select countries, including China (UMIC) (13) and France (HIC) (14). **Country** | **Income level** | **WTP threshold** | **ICER** | **Cost-effective?** China (CPS ≥ 1) | UMIC | USD 35,864 / QALY | USD 72,762 / QALY | No China (CPS ≥ 10) | UMIC | USD 35,864 / QALY | USD 34,813 / QALY | Yes France (CPS ≥ 10) | HIC | € 140,000 | € 107,406 / QALY | Yes Evidence addressing cost-effectiveness of nivolumab versus chemotherapy was available from select countries, including China (UMIC) (15), Japan (HIC) (16) and the United States (HIC) (17). **Country** | **Income level** | **WTP threshold** | **ICER** | **Cost-effective?** China | UMIC | USD 31,498 / QALY | USD 278,658 / QALY | No Japan | HIC | USD 150,000 / QALY | USD 327,161 / QALY | No United States* | HIC | USD 100,000 / QALY | USD 944,089 / QALY | No * Lifetime horizon Evidence addressing cost-effectiveness of pembrolizumab compared to nivolumab was available from select countries, including China (UMIC), the United States (HIC) and the United Kingdom (HIC). The study reported that pembrolizumab was more cost-effective that nivolumab from the Chinese healthcare system perspective, but that nivolumab was more cost-effective in the United States and United Kingdom (18). Empirical evidence estimating cost-effective thresholds based on health expenditures per capita and life expectancy at birth was available for 174 countries (19). 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. **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 (20). 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 checkpoint inhibitors under consideration for GC/GOJ had 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?

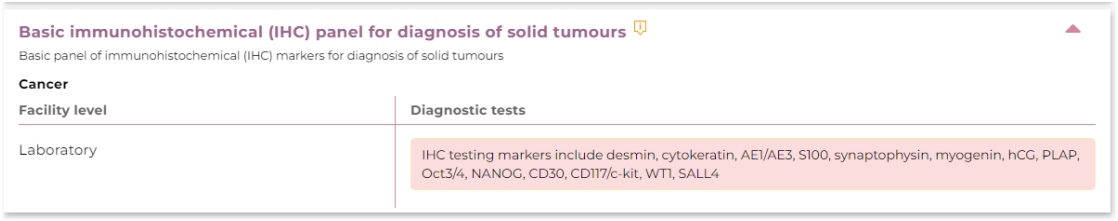
JUDGEMENT	RESEARCH EVIDENCE
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Additional considerations:** Despite checkpoint inhibitors being accessible in many HICs, the WHO EML is a global list and the impact on LMICs and LICs was considered. 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	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 (11). 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.

know	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 (21).  **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 GC/GOJ.

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	Pembrolizumab is approved for use in 85 countries worldwide – mainly high-income countries including Canada, the United States, European Union member countries and Japan (22). Data on the availability, out-of-pocket costs, and accessibility of pembrolizumab for melanoma, non-small cell lung cancer, colorectal cancer and renal cell carcinoma were available from the 2023 update to the ESMO Global Consortium Study (23). In HICs, pembrolizumab for melanoma was “almost always available to patients at no cost or on a subsidized basis”. In LMICs and LICs, when available, however, pembrolizumab 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 non-small cell lung cancer, 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

○ Probably available in most settings ○ Available in most settings ○ Varies ○ Don't know	indirect evidence regarding the extent of pembrolizumab availability for GC/GOJ across World Bank income settings. **Additional considerations:** Pembrolizumab- and nivolumab-containing regimens are approved for use in many countries; however, on-the-ground access outside of HICs is limited.

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