This Evidence-to-Decision (EtD) framework addresses **pembrolizumab + chemotherapy** for **adult head and neck squamous cell carcinoma with ≥ 1% PD-L1 expression**.

QUESTION

Should immune checkpoint inhibitors vs. alternative regimens be used for adult head and neck squamous cell carcinoma?	
POPULATION:	adult head and neck squamous cell carcinoma (HNSCC) with ≥ 1% 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 one ICI treatment for HNSCC: • pembrolizumab + 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	**Moderate**	Large		Varies	Don't know
REDUCTION IN UNDESIRABLE EFFECTS	Increased harms and toxicity	**Trivial/No**	Small	Moderate	Large	Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	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**	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 HNSCC, for which pembrolizumab + chemotherapy is proposed. The global incidence of HNSCC was estimated at 931,931 cases in 2020 and represents an important contributor to global cancer-associated morbidity and death (estimated 380,000 deaths per year) (1, 2). Approximately half of HNSCC patients will have recurrent disease; for which, the standard of care includes platinum-based chemotherapy. This regimen 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 ○ **Moderate** ○ Large ○ Varies ○ Don't know	The application presents a randomized trial as evidence for the desirable effects of pembrolizumab + chemotherapy in HNSCC (3).

Summary of findings:

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

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC[a]	**Risk with Pembrolizumab-containing treatment regimens**				
Overall survival (OS) follow-up: 2 years	17 per 100 The median OS was **10.6** months	**32 per 100** (25 to 39) The median OS was **6 months more** (3 more to 9.4 more)	**HR 0.64** (0.53 to 0.78) [survival]	477 (1 RCT)	⊕⊕⊕◯ Moderate[b]	Pembrolizumab-containing treatment regimens probably result in an increase in overall survival.

Progression-free survival (PFS) follow-up: 12 months	11 per 100	**16 per 100** (11 to 23)	**HR 0.82** (0.67 to 1.00) [survival, remission or stable disease]	477 (1 RCT)	⨁⨁◯◯ Low[c]	Pembrolizumab-containing treatment regimens may result in little to no difference in progression-free survival.
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC QLQ-C30 Scale from: 0 to 100 follow-up: 15 weeks from baseline	The mean global Health Score/Quality of Life was **0.77** change score from baseline	MD **0.4 change score from baseline higher** (3.8 lower to 4.6 higher)	-	527 (1 RCT)	⨁⨁⨁◯ Moderate[d]	Pembrolizumab-containing treatment regimens likely 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

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 risk derived from control arm of Keynote-048
b. Downgraded for indirectness; 25.2% of participants, receiving the control treatment subsequently received ICIs upon progression which might have led to an underestimation of the effect
c. Downgraded by 2 levels for very serious imprecision. The 95% CI crosses both the line of appreciable benefit and null-effect
d. Downgraded due to open-label trial design and risk of performance and detection bias

In the randomized trial, the median time from random assignment to data cutoff was 45.0 months (IQR, 41.0 to 49.2) (3). The survival benefit for pembrolizumab-containing treatments (HR 0.64, 95% CI 0.53 to 0.78) was maintained after approximately 4 years of follow-up. Study authors noted survival plateaus at approximately 4 years and 20% in patients receiving pembrolizumab-containing treatments; however, the number of patients at risk in the tails of the survival curves was very low (<10 patients at 50 months). Therefore, a judgement was made that a tail effect could potentially be ruled out.

Further, treatment for advanced disease is multimodal (i.e., surgery, radiotherapy, and chemotherapy) and patients often have worse performance status outside of clinical trials (i.e., Eastern Cooperative Oncology Group (ECOG) 2/3). In these patients, the addition of pembrolizumab to standard of care is likely to be associated with less pronounced improvements in overall survival than those observed in the Keynote-048 trial.

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 regimens	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 (4). 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 HNSCC – 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.

Median overall survival was 6 months more in people treated with pembrolizumab-containing treatment regimens. The ESMO-MCBS Scorecard, based on the KEYNOTE-048 trial, reports a score of 4 for pembrolizumab-containing treatment regimens in the HNSCC non-curative setting. Taken together, the magnitude of desirable effects was judged as moderate in size for the outcome overall survival.

Pembrolizumab-containing treatment likely results in no to little difference 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. Given the highest rating across the critical outcomes was moderate, the magnitude of the overall desirable effects was judged as moderate in size as well.

Undesirable Effects

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

JUDGEMENT	RESEARCH EVIDENCE
○ Increased harms and toxicity Magnitude of reduction in harms and toxicity: ○ **Trivial or no** ○ Small	The application presents a randomized trial as evidence for the undesirable effects of pembrolizumab + chemotherapy in HNSCC (3). **Summary of findings:** **Pembrolizumab-containing treatment regimens compared to SoC in HNSCC with PD-L1 expression** **Patient or population:** HNSCC with PD-L1 expression (CPS ≥ 1) **Intervention:** Pembrolizumab-containing treatment regimens **Comparison:** SoC (cetuximab + cisplatin/carboplatin + 5-fluorouracil)

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

○ Moderate
○ Large
○ Varies
○ Don't know

	Risk with SoC[a]	Risk with Pembrolizumab-containing treatment regimens	(95% CI)	(studies)	the evidence (GRADE)	
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	83 per 100	**85 per 100** (79 to 92)	**RR 1.02** (0.95 to 1.10)	563 (1 RCT)	⊕⊕⊕◯ Moderate[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. Baseline risk derived from control arm of Keynote-048
b. Downgraded due to open-label trial design and risk of performance and detection bias

Additional considerations:

Moderate certainty evidence showed that pembrolizumab-containing treatment probably results in little to no difference in adverse events compared to standard of care (RR 1.02, 95% CI 0.95 to 1.10).

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

○ Very low
○ Low
○ **Moderate**
○ High
○ No included studies

RESEARCH EVIDENCE

Domain	Judgement per critical outcome			Judgement across critical outcomes
ICIs	Overall survival	Health-related quality of life	Adverse events	Overall
pembrolizumab-containing treatment regimens	Moderate	Moderate	Moderate	Moderate

Additional considerations:

Across the critical outcomes, the lowest certainty of evidence rating was moderate for pembrolizumab-containing treatment regimens. Thus, the overall certainty of the evidence of effects was judged as moderate.

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** ○ No important uncertainty or variability	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, including pembrolizumab for HNSCC (5). 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**
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.

Considering the moderate net benefit and patient perspectives from qualitative studies, it was judged that 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	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the	

ICIs	Net balance	Values	Certainty of evidence	Balance of effects
pembrolizumab-containing treatment regimens	Moderate net desirable	Probably no important uncertainty or variability	Moderate	Probably favors the intervention

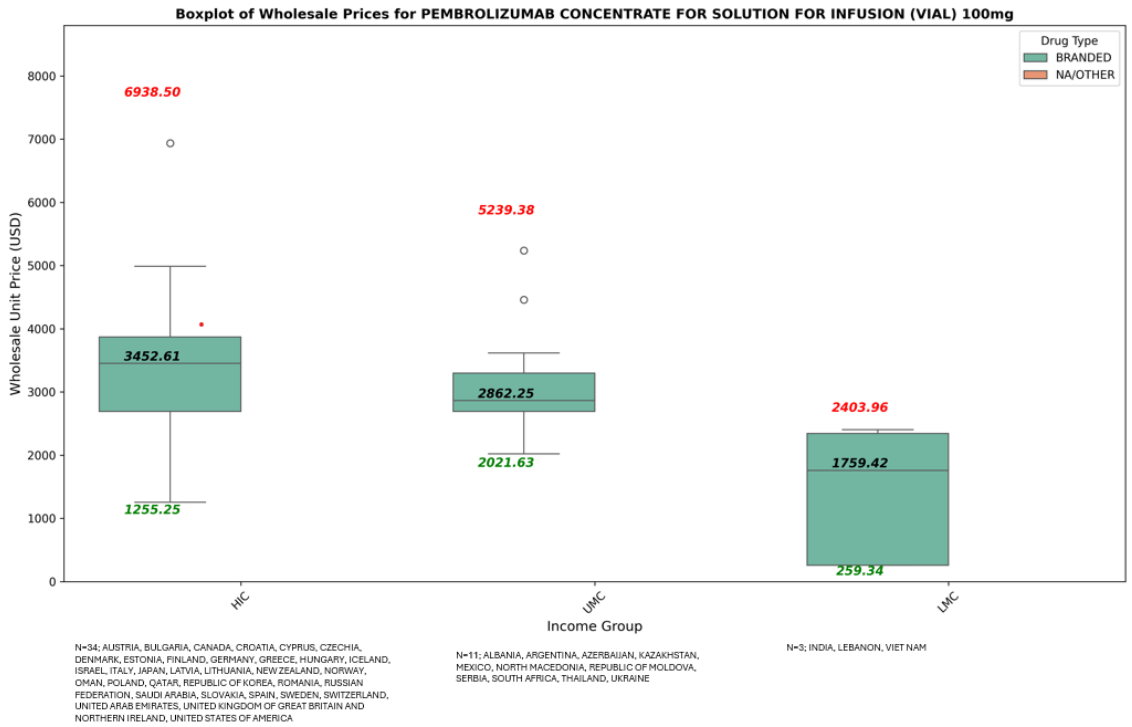
comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the interventio n** ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** A judgement based on the net balance between desirable and undesirable effects, patient values and the certainty of evidence was made that the balance of effects probably favors pembrolizumab-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*:

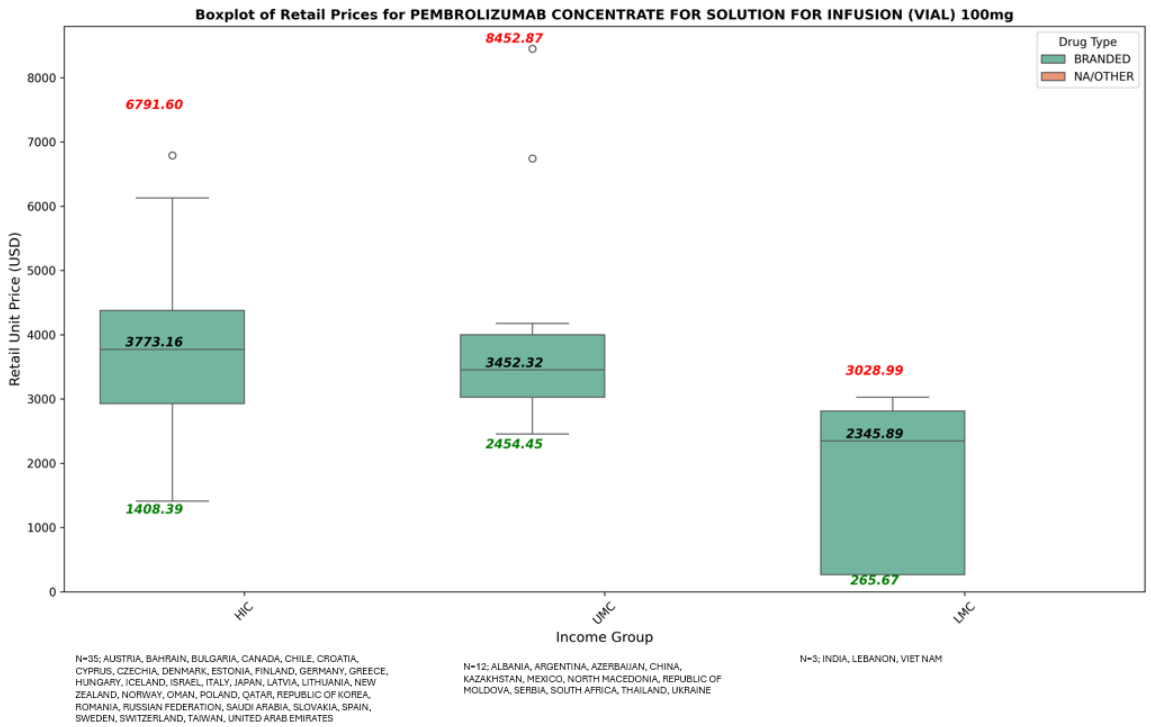
Income level	Median	IQR	Sample size based on number of countries
HIC	3452.61	2692.68 to 3871.57	34
UMIC	2862.25	2693.96 to 3299.45	11
LMIC	1759.42	259.34 to 2343.91	3



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



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:

Relative to other EML medicines, the costs of pembrolizumab at the current unit pricing are large across World Bank income levels. It was noted that country costs for pembrolizumab correlate with income level, with the highest median wholesale and retail prices observed in high-income countries. Further, 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 was available. Further, there were no data available for LICs.

Nonetheless, harnessing pricing dynamics is needed to promote implementation and affordable use of pembrolizumab 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 (6).

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 for the first-line treatment of patients with recurrent or metastatic head and next squamous cell carcinoma was available from select countries, including Argentina (UMIC) (7), China (UMIC) (2), Colombia (UMIC) (8), and the United States (HIC) (1). Whether pembrolizumab was found to be cost-effective depended in part on local willingness-to-pay thresholds, which are often based on a country's per capita gross domestic product. Therefore, the cost-effectiveness of pembrolizumab is anticipated to vary across settings.

Country	Income level	WTP threshold	ICER	Cost-effective?
United States	HIC	USD 100,000 / QALY	USD 86,827 / QALY	Yes
Argentina	UMIC	AR 1,676,122 / QALY	AR 170,985 / QALY	Yes
China	UMIC	USD 28,130 / QALY	USD 65,186 / QALY	No
Colombia	UMIC	COP 69,150,201 / QALY	COP 61,078,685 / QALY	Yes

Empirical evidence estimating cost-effective thresholds based on health expenditures per capita and life expectancy at birth was available for 174 countries (9). 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 (10). 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 for pembrolizumab, a judgement on the cost-effectiveness was made based on select examples and empirically derived cost-effective thresholds. While pembrolizumab-containing treatment regimens has moderate desirable effects in HNSCC, at the current price, it is 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 pembrolizumab in more settings.

Equity
What would be the impact on health equity?

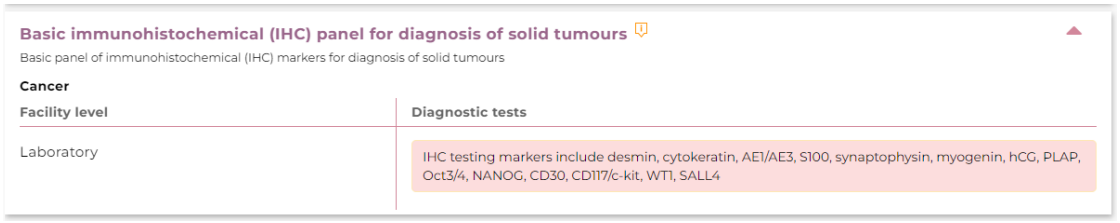
JUDGEMENT	RESEARCH EVIDENCE
○ **Reduced** ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Additional considerations:** Despite pembrolizumab being accessible in many HICs, the WHO EML is a global list and the impact on LMICs and LICs was considered. Given pembrolizumab was judged to have moderate net benefit and is not accessible to patients globally because of its prohibitively high price, a judgement was made that health equity would be reduced. On the other hand, if price decreased substantially, access to pembrolizumab 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, including pembrolizumab for HNSCC (5). 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, including pembrolizumab, due to its modest benefit in combination with chemotherapy compared to chemotherapy standard of care. Pembrolizumab is 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 pembrolizumab-containing treatment when compared to chemotherapy risks 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 (11).  **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 intervention is already implemented in many high-income settings. Beyond the large cost, another barrier to implementation is the diagnostic work up, including staging of cancer and PDL1 expression.

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	Pembrolizumab is approved for use in 85 countries worldwide – mainly high-income countries including Canada, the United States, European Union member countries and Japan (12). 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 (13). 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 indirect evidence regarding the extent of pembrolizumab availability for HNSCC across World Bank income settings. **Additional considerations:** Pembrolizumab is approved for use in many countries; however, on-the-ground access outside of HICs is limited.

know	

REFERENCES

1. Borse RH, Ramakrishnan K, Gandhi J, Dhankhar P, Chirovsky D. Cost-effectiveness of pembrolizumab for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma in the United States. J Med Econ. 2022;25(1):954-65.
2. Xin W, Ding H, Fang Q, Zheng X, Tong Y, Xu G, et al. Cost-effectiveness of pembrolizumab for treatment of platinum-resistant recurrent or metastatic head and neck squamous cell carcinoma in China: an economic analysis based on a randomised, open-label, phase III trial. BMJ Open. 2020;10(12):e038867.
3. Harrington KJ, Burtness B, Greil R, Soulières D, Tahara M, de Castro G, Jr., et al. Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study. J Clin Oncol. 2023;41(4):790-802.
4. Jenei K, Aziz Z, Booth C, Cappello B, Ceppi F, de Vries EGE, et al. Cancer medicines on the WHO Model List of Essential Medicines: processes, challenges, and a way forward. The Lancet Global Health. 2022;10(12):e1860-e6.
5. Yip R, Arnolda G, Lamprell K, Nic Giolla Easpaig B, Chittajallu R, Delaney G, et al. Experience of patients considering or using checkpoint inhibitors in cancer treatment: a systematic review of qualitative research. J Immunother Cancer. 2024;12(1).
6. Schouten A. Addressing the Financial Implications of PD-1/PD-L1 Immune Checkpoint Inhibitors: A Policy Analysis of Access and Inclusion on the WHO Model List of Essential Medicines 2025 [Available from: https://cdn.who.int/media/docs/default-source/2025-eml-expert-committee/addition-of-new-medicines/a.22-pd1-pdl1-icis_financial-impact-report.pdf?sfvrsn=7378e942_1.
7. Wurcel V, Chirovsky D, Borse R, Altuna JI, Carabajal F, Gandhi J. Cost-Effectiveness of Pembrolizumab Regimens for the First-Line Treatment of Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma in Argentina. Adv Ther. 2021;38(5):2613-30.
8. Urrego-Reyes J, Lopez C, Marrugo A C, Wurcel V, Khandelwal A, Patel A, et al. EE199 Cost-Effectiveness of Pembrolizumab for the First-Line Treatment of Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma in Colombia. Value in Health. 2023;26(6):S95.
9. Pichon-Riviere A, Drummond M, Palacios A, Garcia-Marti S, Augustovski F. Determining the efficiency path to universal health

coverage: cost-effectiveness thresholds for 174 countries

based on growth in life expectancy and health expenditures. Lancet Glob Health. 2023;11.
10. Malmberg R, Zietse M, Dumoulin DW, Hendrikx JJMA, Aerts JGJV, van der Veldt AAM, et al. Alternative dosing strategies for immune checkpoint inhibitors to improve cost-effectiveness: a special focus on nivolumab and pembrolizumab. The Lancet Oncology. 2022;23(12):e552-e61.
11. World Health Organization. WHO Model List of Essential In Vitro Diagnostics 2024 [Available from: https://edl.who-healthtechnologies.org/.
12. CPP Investments. CPPIB Acquires Partial Royalty Interest in KEYTRUDA® (pembrolizumab) from LifeArc 2019 [Available from: https://www.cppinvestments.com/newsroom/cppib-acquires-partial-royalty-interest-keytruda-pembrolizumab-lifearc/.
13. Cherny NI, Trapani D, Galotti M, Saar M, Bricalli G, Roitberg F, et al. ESMO Global Consortium Study on the availability, out-of-pocket costs, and accessibility of cancer medicines: 2023 update. Ann Oncol. 2025;36(3):247-62.