This Evidence-to-Decision (EtD) framework addresses **pembrolizumab + chemotherapy** for **triple-negative breast cancer with ≥10% PD-L1 expression (CPS ≥10).**

QUESTION

Should immune checkpoint inhibitors vs. alternative regimens be used for adult triple-negative breast cancer?	
POPULATION:	adult triple-negative breast cancer (TNBC) with ≥10% PD-L1 expression (CPS ≥10)
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 regimen for adult TNBC with ≥10% PD-L1 expression: • 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	**No/Trivial**	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 TNBC (≥10% PD-L1 expression), for which one ICI is proposed: pembrolizumab. The global age-standardized incidence rate of breast cancer was estimated at 46.8 per 100,000 in 2022, and is among the top 3 cancers in terms of incident cases and causes of cancer-related deaths worldwide (1).

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 one randomized trial as evidence for the desirable effects of pembrolizumab + chemotherapy for TNBC (≥10% PD-L1 expression) (2-4).

Pembrolizumab-based treatment regimens compared to SoC for TNBC with PD-L1 ≥ 10% expression

Patient or population: TNBC with PD-L1 ≥ 10% 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 44.1 months	34 per 100[a]	**45 per 100** (36 to 55)	**HR 0.73** (0.55 to 0.95) [death]	323 (1 RCT)[b]	⨁⨁◯◯ Low[c,d,e]	Pembrolizumab-based treatment regimens may increase overall survival.
	At 3 years					
	23 per 100	**34 per 100** (24 to 44)				

	The median OS was **16.1** months	The median OS was **6 months more** (0.8 more to 13.2 more)[f]				
Progression-free survival (PFS) follow-up: median 44.1 months	**At 1 year**		**HR 0.66** (0.50 to 0.88) [disease progression or death]	323 (1 RCT)	⊕⊕◯◯ Low[c,d,e]	Pembrolizumab-based treatment regimens may increase progression-free survival.
	23 per 100	**38 per 100** (27 to 48)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 15 weeks from baseline	The mean GHS/QoL was **-0.88** change score from baseline	MD **1.8 change score from baseline lower** (7.33 lower to 3.73 higher)	-	317 (1 RCT)	⊕⊕⊕◯ Moderate[c,e]	Pembrolizumab-based treatment regimens likely results 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. Overall survival estimates in the control arm, at specific timepoints were extracted from the respective Kaplan-Meier curves
b. Keynote-355 (NCT02819518)
c. Downgraded due to risk of reporting bias; analysis based on the 10% CPS cut-off was only introduced after the interim analysis and full accrual of participants
d. Downgraded by 1 due to imprecision; the CI crosses the line of appreciable benefit at 0.75
e. Inconsistency not applicable (single trial only); publication bias not applicable due to prespecified selection process
f. The corresponding difference in median survival time was calculated using the directly reported median survival point estimate from the relevant trial publication and the pooled HR and CIs (assuming proportional hazards throughout the trial follow-up period)

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	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 (5). 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 TNBC – 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 6 months more in people treated with pembrolizumab-containing treatment regimens. The ESMO-MCBS Scorecard reported a score of 4 for the pembrolizumab-containing treatment regimen trial. The magnitude of desirable effect 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, the pembrolizumab-containing treatment regimen likely results 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 moderate for the pembrolizumab-containing treatment regimen.

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

JUDGEMENT

○ Increased harms and toxicity

Magnitude of reduction in harms and toxicity:

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

RESEARCH EVIDENCE

The application presents one randomized trial as evidence for the undesirable effects of pembrolizumab + chemotherapy for TNBC (≥10% PD-L1 expression) (2-4).

Pembrolizumab-based treatment regimens compared to SoC for TNBC with PD-L1 ≥ 10% expression

Patient or population: TNBC with PD-L1 ≥ 10% 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	74 per 100	**78 per 100** (71 to 85)	**RR 1.06** (0.97 to 1.15)	843 (1 RCT)[b]	⊕⊕⊕◯ Moderate[a,b]	Pembrolizumab-based treatment regimens probably result in little to no difference in adverse events (CTCAE ≥ 3).

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

Explanations

a. ITT population; irrespective of PD-L1 expression status
b. Downgraded by 1 for indirectness: while a link between PD-L1 expression and incidence of irAE is not clearly established, considering its correlation with tumor response patients with CPS < 10 might have experienced the competing event of tumor progression, thus having less treatment exposure and not being considered for safety follow-up (safety was assessed among patients whose tumors expressed PD-L1 with a CPS of 10 or more and patients whose tumors expressed PD-L1 with a CPS of 1 or more)

Additional considerations:

	Moderate certainty evidence showed that pembrolizumab-containing treatment regimens probably result in no to little difference in adverse events when compared to standard of care.

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ **Low** ○ Moderate ○ High ○ No included studies	

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	Moderate	Moderate	Low

Additional considerations:

Across the critical outcomes, the lowest certainty of evidence rating was low for the pembrolizumab-containing treatment regimen.

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 (6). 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.

Pembrolizumab-containing treatment regimens may result in a moderate increase in OS (6 months), probably have trivial to no effect on health-related quality of life and probably have trivial to no effect on 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.

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**
- ○ Favors the intervention
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

ICIs	Net balance	Values	Certainty of evidence	Balance of effects
Pembrolizumab-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-containing treatment regimens.

Resources required
How large are the resource requirements?

JUDGEMENT

- ○ **Large**

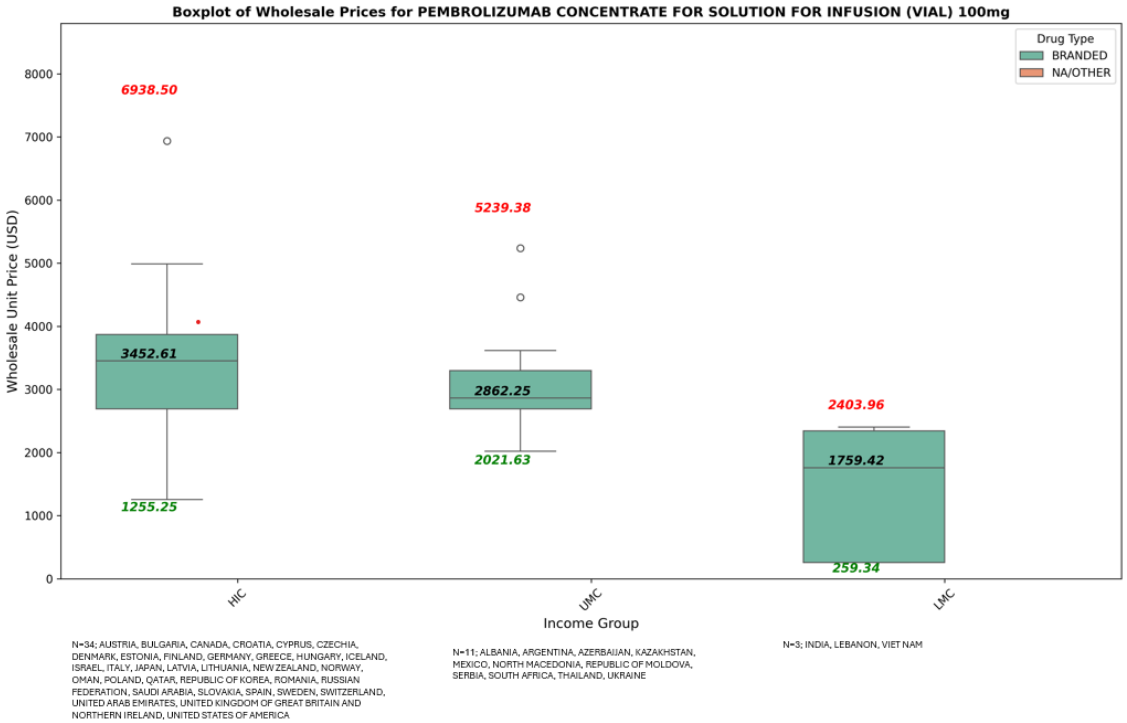
RESEARCH EVIDENCE

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

costs

- ○ Moderate costs
- ○ Negligible costs and savings
- ○ Moderate savings
- ○ Large savings
- ○ Varies
- ○ Don't know

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

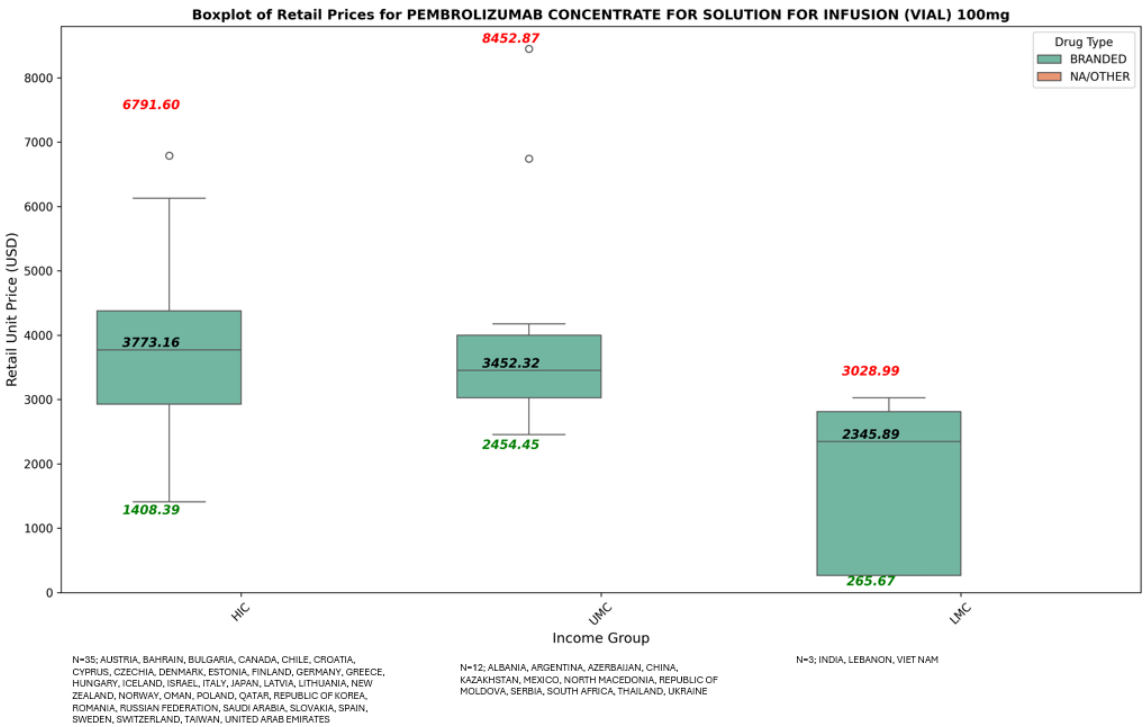


Source: author derived calculation based on most recent available wholesale prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: 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:

Direct evidence addressing the unit price for pembrolizumab was available.

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 were 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 (7).

Cost effectiveness

Does the cost-effectiveness of the intervention 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
○ Favors the intervention
○ **Varies**
○ No included studies

RESEARCH EVIDENCE

Evidence addressing cost-effectiveness of pembrolizumab plus chemotherapy for the first-line treatment of patients with PD-L1 positive metastatic TNBC was available from select countries, including Colombia (UMIC) (8) and the United States (HIC) (9).

Country	Income level	WTP threshold	ICER	Cost-effective?
United States	HIC	USD 200,000 / QALY	USD 182,732 per QALY	Yes
Colombia*	UMIC	COP 69,150,201 / QALY	NR	Yes^

* Comparator was atezolizumab plus chemotherapy.
^ 72.50% probability of being cost-effective at the stated WTP

Empirical evidence estimating cost-effective thresholds based on health expenditures per capita and life expectancy at birth was available for 174 countries (10). 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 (11). 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 inhibitor under consideration for TNBC had desirable effects, 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 checkpoint inhibitors in more settings.

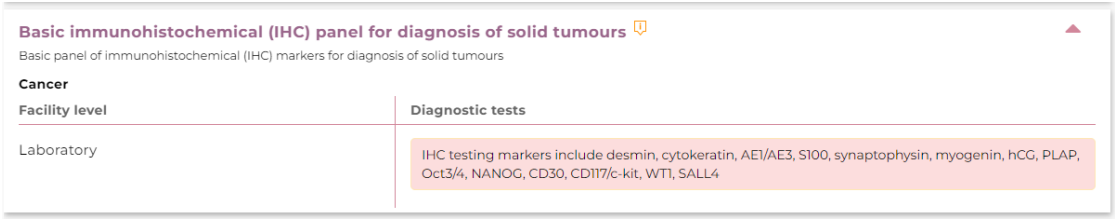
Equity
What would be the impact on health equity?

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 ICI under consideration offers desirable benefits but 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 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 (6). 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 cost of pembrolizumab 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 (12).  **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 TNBC.

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	Pembrolizumab is approved for use in 85 countries worldwide – mainly high-income countries including Canada, the United States, European Union member countries and Japan (13). 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 (14). 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 TNBC 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.

○ Varies ○ Don't know	

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