This Evidence-to-Decision (EtD) framework addresses **ipilimumab + nivolumab** for **malignant melanoma, irrespective of PD-L1 expression**.

QUESTION

Should combination therapy vs monotherapy be used for adult malignant melanoma?	
POPULATION:	adult malignant melanoma, irrespective of PD-L1 expression
INTERVENTION:	combination therapy
COMPARISON:	monotherapy
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 malignant melanoma irrespective of PD-L1 expression: • ipilimumab + nivolumab (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 will focus on malignant melanoma (irrespective of PD-L1 expression), for which ipilimumab/nivolumab is being considered. Nivolumab and pembrolizumab (as a therapeutically equivalent alternative to nivolumab) are already listed on the WHO EML for malignant melanoma. In this EtD framework, we'll be considering the evidence for combination therapy (ipilimumab/nivolumab) compared to monotherapy (ipilimumab or nivolumab). In 2022, the global age-standardized incidence rate and cancer-related mortality rate of melanoma skin cancer was estimated at 3.2 and 0.53 per 100,000, respectively (1).

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial or no ○ Small ○ Moderate ○ **Large** (ipilimumb+nivolumab) ○ Varies ○ Don't know	The application presents multiple randomized trials as evidence for the desirable effects of combination therapy ipilimumab/nivolumab (2-7).

Ipilimumab/nivolumab compared to ICI monotherapy for malignant melanoma

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ICI monotherapy	**Risk with Ipilimumab/nivolumab**				
Overall survival (OS) follow-up: median 34.6 months[a]	**At 2 years**		**HR 0.68** (0.50 to 0.93) [death]	1133 (3 RCTs)[c]	⊕⊕⊕◯ Moderate[d,e]	Ipilimumab/nivolumab likely increases overall survival. The median overall survival in the intervention group calculated using the pooled hazard ratio underestimates the actual median overall survival reported in the relevant study publication.
	52 per 100[b]	**64 per 100** (55 to 72)				
	At 5 years					
	35 per 100[b]	**49 per 100** (38 to 59)				
	The median overall survival was **28.4** months[a]	The median overall survival was **12.8 months more** (3.9 more to 24.2 more)[f]				
Progression-free survival (PFS)	**At 2 years**		**HR 0.50**	1087	⊕⊕◯◯	Ipilimumab/nivolumab may increase progression-

follow-up: median 35.7 months[a]	24 per 100[b]	**49 per 100** (31 to 64)	(0.31 to 0.82) [disease progression or death][g]	(2 RCTs)	Low[h]	free survival.
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC QLQ-C30 Scale from: 0 to 100 follow-up: 55 weeks from baseline	The mean GHS/QoL was **-4.72** change score from baseline[b]	MD **1.08 change score from baseline lower** (3.44 lower to 1.28 higher)	-	758 (1 RCT)[i]	⊕⊕⊕◯ Moderate[j,k]	Ipilimumab/nivolumab probably results in little to no difference in Global Health Score/Quality of Life compared to ICI monotherapy.

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

Explanations

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

Magnitude of effect judgements:

Domain	Judgement per critical outcome		Judgement across desirable critical outcomes
ICIs	**Overall survival**	**Health-related quality of life**	**Overall**
Ipilimumab+nivolumab	Large	Trivial or no	Large

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 (8). Based on this recommendation, the following decision rules were considered in judging the magnitude of effects:

l. The outcomes overall survival and health-related quality of life were considered of critical importance to patients with malignant melanoma – more weight was placed on them in the decision-making process when compared to progression-free survival and adverse events.

m. 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.
n. 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.
o. 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 estimated at 13 months more in people treated with ipilimumab+nivolumab. The ESMO-MCBS Scorecard reported a score of 4 for the trial CheckMate 067. The magnitude of desirable effects for the outcome overall survival, based on the point estimate, WHO benefit thresholds and ESMO-MCBS Scorecard, was judged as large.

In terms of health-related quality of life, ipilimumab+nivolumab probably 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 large for ipilimumab+nivolumab when compared to monotherapy.

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

JUDGEMENT

RESEARCH EVIDENCE

○ Increased harms and toxicity
(ipilimumab+nivolumab)

Magnitude of reduction in harms and toxicity:

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

The application presents multiple randomized trials as evidence for the undesirable effects of combination therapy ipilimumab/nivolumab (2-7).

Ipilimumab/nivolumab compared to ICI monotherapy for malignant melanoma

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ICI monotherapy	**Risk with Ipilimumab/nivolumab**				
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	25 per 100	**59 per 100** (51 to 69)	**RR 2.37** (2.03 to 2.77)	1137 (3 RCTs)	⊕⊕⊕⊕ High	Ipilimumab/nivolumab results in a large increase in adverse events (CTCAE ≥ 3) compared to ICI monotherapy.

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

Additional considerations:
High certainty evidence showed that combination therapy ipilimumab+nivolumab results in a large increase in adverse events when compared to monotherapy.

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

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ○ Low ○ **Moderate** (ipilimumab+nivolumab) ○ High ○ No included studies	

Domain	Judgement per critical outcome			Judgement across critical outcomes
ICIs	Overall survival	Health-related quality of life	Adverse events	Overall
Ipilimumab/nivolumab	Moderate	Moderate	High	Moderate

Additional considerations:

Across the critical outcomes, the lowest certainty of evidence rating was 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** (ipilimumab+nivolumab)	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 (9). 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
Ipilimumab/nivolumab	Large net desirable	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.

Ipilimumab/nivolumab regimens probably result in a large increase in OS (13 months), probably results in little to no difference in health-related quality of life and result in a large increase in adverse events when compared to monotherapy. Based on this and the ESMO-MCBS Scorecard, it was judged that ipilimumab/nivolumab offers a large net desirable effect and people would have no important uncertainty or variability in how much they value the main outcomes, particularly preferring avoiding premature death.

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 (ipilimumab+nivolumab)**
○ Varies
○ Don't know

RESEARCH EVIDENCE

ICIs	Net balance	Values	Certainty of evidence	Balance of effects
Ipilimumab/nivolumab	Large net desirable	No important uncertainty or variability	Moderate	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 favors ipilimumab/nivolumab over monotherapy.

Resources required

How large are the resource requirements?

JUDGEMENT

○ **Large costs**
○ Moderate costs
○ Negligible costs and

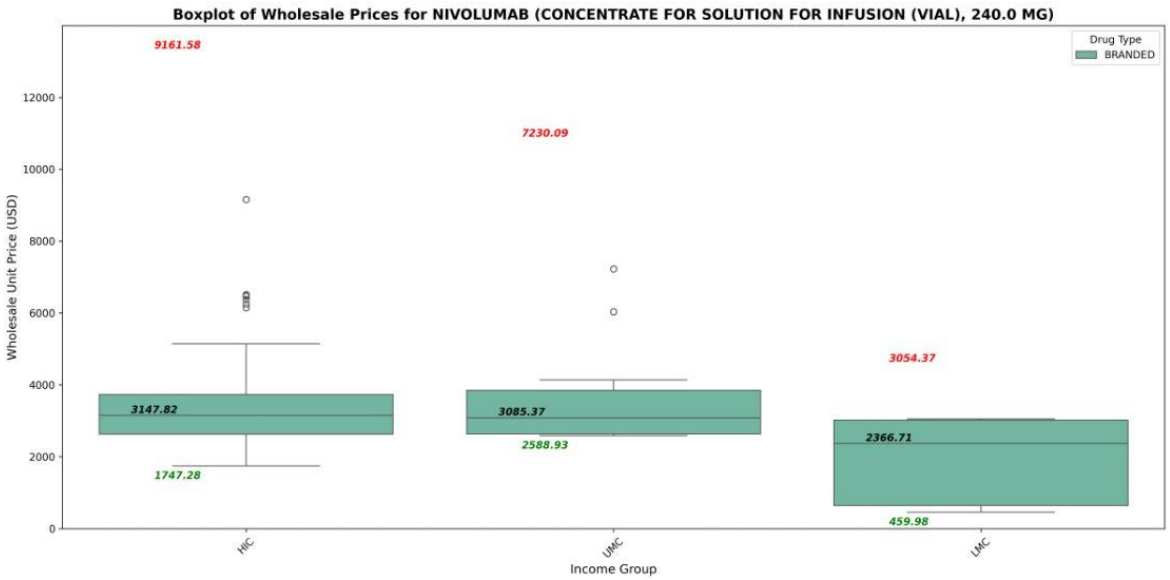
RESEARCH EVIDENCE

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

Income level	Median	IQR	Sample size based on number of countries
HIC	3147.82	2632.86 to 3734.15	37

savings
○ Moderate savings
○ Large savings
○ Varies
○ Don't know

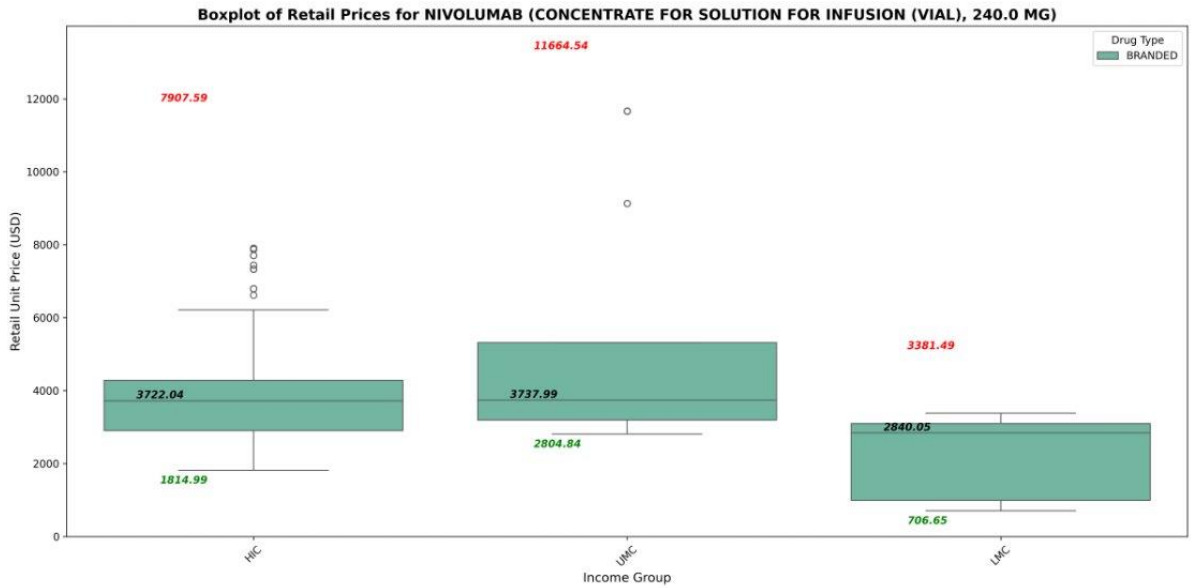
UMIC	3085.37	2639.78 to 3848.65	8
LMIC	2366.71	643.98 to 3021.01	3



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 vial) across World Bank income levels*:

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



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

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

Income level	Median	IQR	Sample size based on number of countries
HIC	14197.18	12370.89 to 17464.71	36
UMIC	12451.31	11104.59 to 13445.63	8
LMIC	3447.07	1840.58 to 8859.21	2

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

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

Income level	Median	IQR	Sample size based on number of countries

HIC	16025.41	13773.54 to 20420.17	35
UMIC	13986.11	13462.27 to 16059.71	7
LMIC	4426.49	2333.14 to 9523.03	2

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

Additional considerations:

Direct evidence addressing the unit price of ipilimumab and nivolumab was available.

Relative to other EML medicines, the costs of ipilimumab and nivolumab at the current unit pricing are large across World Bank income levels. It was noted that the cost of two immunotherapies (i.e., ipilimumab + nivolumab) is prohibitively expensive when compared to one PD-1 checkpoint inhibitor, for which the cost is already extremely large. The small sample sizes reduce our confidence in the estimates, especially for LMICs for which data from less than five countries were available. Further, there were no data available for LICs.

Nonetheless, harnessing pricing dynamics is needed to promote implementation and affordable use of combination therapy at the country level.

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 nivolumab+ipilimumab compared to nivolumab was available from the United States (HIC) (10).

Country	Income level	WTP threshold	ICER	Cost-effective?
United States*	HIC	USD 100,000 / QALY	USD 76,169 / QALY	Yes

* Based on cost-utility

Empirical evidence estimating cost-effective thresholds based on health expenditures per capita and life expectancy at birth was available for 174 countries (11). 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 ICIs across World Bank income settings without compromising efficacy and safety, alternative dosing strategies have been proposed (12). 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 a select example and empirically derived cost-effective thresholds. While the combination therapy under consideration for malignant melanoma irrespective of PD-L1 expression had large net 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?

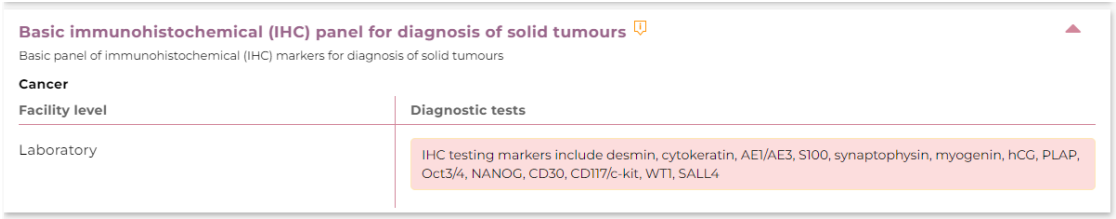
JUDGEMENT	RESEARCH EVIDENCE
○ **Reduced** ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Additional considerations:** Despite checkpoint inhibitors being accessible in many HICs, the WHO EML is a global list and the impact on LMICs and LICs was considered. Because the ICI under consideration offers desirable benefits but is not accessible to patients globally because of 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**	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 (9). 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

○ Don't know	improved symptom burden and quality of life and decreased psychological distress. **Additional considerations:** Empiric evidence from the patient perspective provides support for the acceptability of immune checkpoint inhibitors. These immune checkpoint inhibitors are likely not acceptable to most health decision makers and health systems, especially those in LMICs and LICs, due to cost. The large costs associated with these checkpoint inhibitors when compared to other anti-cancer treatments risk diverting resources from health budgets at the expense of other essential medicines.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Diagnostic requirements – immunohistochemistry companion tests – to identify patients with the indication approved for treatment. The WHO Essential Diagnostics List includes a basic panel for immunohistochemical (IHC) markers for diagnosis of solid tumors, but the panel does not include IHC testing markers for PDL1 (13).  **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 malignant melanoma.

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**	Pembrolizumab is approved for use in 85 countries worldwide – mainly high-income countries including Canada, the United States, European Union member countries and Japan (14). Data on the availability, out-of-pocket costs, and accessibility of nivolumab for melanoma were available from the 2023 update to the ESMO Global Consortium

most settings ○ Probably available in most settings ○ Available in most settings ○ Varies ○ Don't know	Study (15). In HICs, nivolumab for melanoma was “almost always available to patients at no cost or on a subsidized basis”. In LMICs and LICs, when available, however, nivolumab was “generally provided only at full cost as an out-of-pocket expenditure for patients”. **Additional considerations:** Nivolumab-containing regimens are approved for use in many countries; however, on-the-ground access outside of HICs is limited.

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