This Evidence-to-Decision (EtD) framework addresses **atezolizumab + bevacizumab, durvalumab monotherapy and durvalumab + tremelimumab** for **hepatocellular carcinoma irrespective of PD-L1 expression**.

QUESTION

Should immune checkpoint inhibitors vs. alternative regimens be used for adult hepatocellular carcinoma?	
POPULATION:	adult hepatocellular carcinoma (HCC) irrespective of PD-L1 expression
INTERVENTION:	immune checkpoint inhibitors (ICIs)
COMPARISON:	alternative regimens
MAIN OUTCOMES:	overall survival; progression-free survival; health-related quality of life; adverse events (CTCAE ≥ 3)
SETTING:	treatment in the palliative 1st line setting
BACKGROUND:	application includes three ICI treatments for hepatocellular carcinoma irrespective of PD-L1 expression: • atezolizumab/bevacizumab (ESMO-MCBS non-curative score = 5) • durvalumab (ESMO-MCBS non-curative score = 4) • durvalumab/tremelimumab (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** (durvalumab, durvalumab/tremelimumab)	Moderate	**Large** (atezolizumab/bevacizumab)		Varies	Don't know
REDUCTION IN UNDESIRABLE EFFECTS	Increased harms and toxicity	**Trivial/No** (durvalumab/tremelimumab)	Small	**Moderate** (durvalumab)	Large	Varies	**Don't know** (atezolizumab/bevacizumab)
CERTAINTY OF EVIDENCE	**Very low** (atezolizumab/bevacizumab)	**Low** (durvalumab)	**Moderate** (durvalumab/tremelimumab)	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability** (durvalumab, durvalumab/tremelimumab)	**No important uncertainty or variability** (atezolizumab/bevacizumab)			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention** (atezolizumab/bevacizumab, durvalumab, durvalumab/tremelimumab)	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 HCC (irrespective of PD-L1 expression), for which three ICIs are proposed: atezolizumab/bevacizumab, durvalumab monotherapy and durvalumab/tremelimumab. HCC is the most common primary liver cancer and arises from hepatocytes. The global age-standardized incidence rate of liver cancer was estimated at 8.6 per 100,000 in 2022 and represents the third leading cause of cancer-related deaths worldwide (1). The standard of care includes sorafenib, a tyrosine kinase inhibitor, which generally is supposed to have fewer and less severe side effects than chemotherapy at least in part due to its more selective mechanism of action. However, sunitinib is not recommended by WHO as an essential medicine for this or other indications, as well as bevacizumab which is only indicated in the EML for macular degeneration.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial or no ○ **Small** (durvalumab, durvalumab/tremelimumab)) ○ Moderate ○ **Large** (atezolizumab/bevacizumab) ○ Varies ○ Don't know	The application provided evidence addressing desirable effects from one randomized trial for an atezolizumab-based treatment regimen with bevacizumab (2-4), one randomized trial for durvalumab monotherapy (5-7) and one randomized trial for durvalumab/tremelimumab (5-7).

Atezolizumab-based treatment regimens compared to SoC for HCC

Patient or population: HCC
Intervention: Atezolizumab-based treatment regimens (atezolizumab + bevacizumab)
Comparison: SoC (sorafenib)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Atezolizumab-based treatment regimens**				
Overall survival (OS) follow-up: median 15.6 months	**At 1.5 years**		**HR 0.66** (0.52 to 0.85) [death]	501 (1 RCT)[b]	⊕⊕⊕◯ Moderate[c,d,e]	Atezolizumab-based treatment regimens likely increases overall survival.
	40 per 100[a]	**55 per 100** (46 to 62)				
	The mean overall survival was **13.4** months	The mean overall survival was **6.9 months more** (2.4 more to 12.4 more)[f]				
	At 1 year					

Progression-free survival (PFS) follow-up: median 15.6 months	21 per 100[g]	**36 per 100** (28 to 44)	**HR 0.65** (0.53 to 0.81) [disease progression or death]	501 (1 RCT)	⊕⊕⊕◯ Mdoerate[c,e]	Atezolizumab-based treatment regimens probably increase progression-free survival.
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 24 weeks from baseline	The mean global Health Score/Quality of Life was **-5,83** change score from baseline change score from baseline	MD **2.54 change score from baseline change score from baseline higher** (1.31 lower to 6.39 higher)	-	481 (1 RCT)	⊕⊕⊕◯ Moderate[h]	Atezolizumab-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

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. 18-month overall survival rate (40%) in control arm as directly reported in publication
b. IMbrave 150 (NCT03434379)
c. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process
d. In the control arm 26% subsequently received immunotherapy upon progression, and another TKI in 33%. Similarly, 32% of patients in the investigational arm received TKIs at disease progression, which is why we did not downgrade for indirectness
e. Downgraded for imprecision (confidence interval crosses defined appreciable effect at 0.75; single study only)
f. The corresponding difference in median survival time was calculated using the directly reported median survival estimate from the relevant trial's control arm and the pooled HR and CIs, assuming proportional hazards through the trial's follow-up period
g. 12-month PFS rate in control arm extracted from survival plot reported in publication
h. Downgraded for risk of performance and detection bias due to open-label design

Durvalumab monotherapy compared to SoC for HCC

Patient or population: HCC
Intervention: Durvalumab monotherapy
Comparison: SoC (sorafenib)

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Durvalumab monotherapy**				
	At 2 years					

Overall survival (OS) follow-up: median 47.9 months[a]	33 per 100[b]	**38 per 100** (32 to 44)	**HR 0.86** (0.74 to 1.01) [death]	778 (1 RCT)[c]	⊕⊕◯◯ Low[d,e,f]	Durvalumab monotherapy may increase overall survival slightly.
	At 4 years					
	15 per 100	**20 per 100** (15 to 25)				
	The median overall survival was **13.8** months	The median survival was **2.25 months more** (0.14 fewer to 4.85 more)[g]				
Progression-free survival (PFS) follow-up: median 32.4 months[h]	**At 1 year**		**HR 1.02** (0.88 to 1.19) [disease progression or death]	778 (1 RCT)	⊕⊕⊕◯ Moderate[d,i]	Durvalumab monotherapy likely results in little to no difference in progression-free survival. Cross-over in study not reported.
	33 per 100[h]	**32 per 100** (27 to 38)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 24 from baseline	The mean global Health Score/Quality of Life was **-6.08** change score from baseline[j]	mean **4.3 change score from baseline higher** (0.41 higher to 8.19 higher)[k]	-	778 (1 RCT)	⊕⊕⊕◯ Moderate[i,j]	Durvalumab monotherapy 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; **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. Weight-adjusted mean follow-up across treatment arms
b. 24- and 48-months overall survival rates in control arm directly reported in the publication
c. HIMALAYA (NCT03298451)
d. Inconsistency not applicable (single trial only); publication bias not applicable due to the prespecified selection process
e. Downgraded for imprecision by two levels (confidence interval crosses line of null effect and line of appreciable benefit at 0.75; single study only)
f. Participants received subsequent anticancer therapy in 44.0% and 45.8% in the durvalumab monotherapy and sorafenib arms, respectively. Switching upon progression, to receive ICIs in the control arm occurred at 23.4% of cases. Considering switching in the intervention arm to receive targeted therapies, we did not downgrade for indirectness
g. The corresponding difference in median survival time was calculated using the directly reported median survival estimate from the relevant trial's control arm and the pooled HR and CIs, assuming proportional hazards throughout the trial's follow-up period
h. PFS-rate in control arm extracted from survival plot reported in publication with shorter follow-up (32.4 months, weighted median) because longer follow-up publication did not report PFS data
i. Downgraded for risk of performance and detection bias due to open-label design
j. Values estimates were extracted from the graph representing the point estimates and confidence intervals, since the outcome was only reported narratively
k. Though showing statistical significance, the CI did not cross the line for minimal important difference at 10, therefore we did not downgrade for imprecision

Durvalumab/tremelimumab compared to SoC for HCC

Patient or population: HCC
Intervention: Durvalumab/tremelimumab (STRIDE regimen of single tremelimumab regular interval durvalumab)
Comparison: SoC (sorafenib)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Durvalumab/tremelimumab**				
Overall survival (OS) follow-up: median 48.2 months[a]	**At 2 years**		**HR 0.78** (0.67 to 0.92) [death]	782 (1 RCT)[c]	⊕⊕⊕◯ Moderate[d,e,f]	Durvalumab/tremelimumab likely increases overall survival.
	33 per 100[b]	**42 per 100** (36 to 47)				
	At 4 years					
	15 per 100	**23 per 100** (18 to 28)				
	The median overall survival was **13.8** months	The median overall survival was **3.9 months more** (1.2 more to 6.8 more)[g]				
Progression-free survival (PFS) follow-up: median 32.7 months[h]	**At 1 year**		**HR 0.90** (0.77 to 1.05) [disease progression or death]	782 (1 RCT)	⊕⊕◯◯ Low[d,i,j]	Durvalumab/tremelimumab may increase progression-free survival slightly.
	33 per 100[h]	**37 per 100** (31 to 43)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC-QLQ C30 Scale from: 0 to 100 follow-up: 24 weeks from baseline	The mean global Health Score/Quality of Life was **-6.08** change from baseline[k]	MD **0.35 change from baseline lower** (4.21 lower to 3.51 higher)	-	782 (1 RCT)	⊕⊕⊕◯ Moderate[j,k]	Durvalumab/tremelimumab likely results in little to no difference in global Health Score/Quality of Life compared to SoC.

*__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. Weight-adjusted mean follow-up across respective treatment arms
b. 24- and 48-months overall survival rates in control arm directly reported in publication
c. HIMALAYA (NCT03298451)
d. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process
e. Participants received subsequent anticancer therapy in 42.2% and 45.8% in the durvalumab/tremelimumab and sorafenib arms, respectively. Switching upon progression, to receive ICIs in the control arm occurred at 23.4% of cases. Considering, switching in the intervention arm to receive targeted therapies, we did not downgrade for indirectness
f. Downgraded for imprecision (CI crosses defined appreciable effect at 0.75; single study only)
g. The corresponding difference in median survival time was calculated using the directly reported median survival estimate from the relevant trial's control arm and the pooled HR and CIs, assuming proportional hazards throughout the trial's follow-up period
h. PFS-rate in control arm extracted from survival plot reported in publication with shorter follow-up (32.4 months, weighted median) because longer follow-up publication did not report PFS data
i. Downgraded for imprecision (confidence interval crosses line of null effect; single study only)
j. Downgraded for risk of performance and detection bias due to open-label design
k. Values estimates were extracted from the graph representing the point estimates and confidence intervals, since the outcome was only reported narratively

Magnitude of effect judgements:

Domain	Judgement per critical outcome		Judgement across desirable critical outcomes
ICIs	**Overall survival**	**Health-related quality of life**	**Overall**
Atezolizumab/bevacizumab	Large	Trivial or no	Large
Durvalumab monotherapy	Small	Trivial or no	Small
Durvalumab/tremelimumab	Small	Trivial or no	Small

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:

- The outcomes overall survival and health-related quality of life were considered of critical importance to patients with HCC – 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 6.9 months more in people treated with an atezolizumab-based regimen, 2.25 months more in people treated with durvalumab monotherapy and 3.9 months more in people treated with durvalumab/tremelimumab. The ESMO-MCBS Scorecards reported a score of 4 for durvalumab monotherapy, and 5 for atezolizumab-based treatment and durvalumab/tremelimumab. The magnitude of effect for overall survival, based on the point estimates, WHO benefit thresholds and ESMO-MCBS Scorecards, was judged as small for durvalumab monotherapy and durvalumab/tremelimumab, and large for the atezolizumab-based treatment regimen.

In terms of health-related quality of life, there was no to little difference for an atezolizumab-based treatment regimen, durvalumab monotherapy and durvalumab/tremelimumab.

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 durvalumab monotherapy and durvalumab/tremelimumab, and large for the atezolizumab-based treatment regimen.

Undesirable Effects

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

JUDGEMENT

○ Increased harms and toxicity

Magnitude of reduction in harms and toxicity:

○ **Trivial or no (durvalumab/tremelimumab)**
○ Small
○ **Moderate (durvalumab)**
○ Large
○ Varies
○ **Don't know (atezolizumab/bevacizumab)**

RESEARCH EVIDENCE

The application provided evidence addressing undesirable effects from one randomized trial for an atezolizumab-based treatment regimen (2-4), one randomized trial for durvalumab monotherapy (5-7) and one randomized trial for durvalumab/tremelimumab (5-7).

Atezolizumab-based treatment regimens compared to SoC for HCC

Patient or population: HCC
Intervention: Atezolizumab-based treatment regimens (atezolizumab + bevacizumab)
Comparison: SoC (sorafenib)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Atezolizumab-based treatment regimens**				
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	63 per 100	**70 per 100** (61 to 80)	**RR 1.11** (0.97 to 1.28)	485 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	We are uncertain about the effect of atezolizumab-based treatment regimens on adverse events (CTCAE ≥ 3). Patients in the investigational arm had a substantially longer exposure to the treatment and, therefore, a higher likelihood of experiencing adverse events.

*__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. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process
b. Downgraded for risk of performance and detection bias due to open-label design
c. Downgraded by two levels for imprecision (CI crosses line of appreciable harm at 1.25 as well as the null effect line)

Durvalumab monotherapy compared to SoC for HCC

Patient or population: HCC
Intervention: Durvalumab monotherapy
Comparison: SoC (sorafenib)

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Durvalumab monotherapy**				
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution[a]	60 per 100	**44 per 100** (38 to 51)	**RR 0.73** (0.64 to 0.85)	762 (1 RCT)	⨁⨁◯◯ Low[b,c,d]	Durvalumab monotherapy may reduce 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; **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. Safety data from primary publication; no adverse events stratified by CTCAE class reported in longer-term follow-up publication
b. Inconsistency not applicable (single trial only); publication bias not applicable due to the prespecified selection process
c. Downgraded for risk of performance and detection bias due to open-label design
d. Downgraded for imprecision (confidence interval crosses defined appreciable effect; single study only)

Durvalumab/tremelimumab compared to SoC for HCC

Patient or population: HCC
Intervention: Durvalumab/tremelimumab (STRIDE regimen of single tremelimumab regular interval durvalumab)
Comparison: SoC (sorafenib)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with Durvalumab/tremelimumab**				
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution[a]	60 per 100	**58 per 100** (52 to 66)	**RR 0.98** (0.87 to 1.10)	762 (1 RCT)	⊕⊕⊕◯ Moderate[b,c,dj]	Durvalumab/tremelimumab likely results in little to no difference in adverse events (CTCAE ≥ 3) irrespective of treatment attribution.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Safety data from main publication; no adverse events stratified by CTCAE class reported in longer-term follow-up publication
b. Inconsistency not applicable (single trial only) and publication bias not applicable due to prespecified selection process
c. Downgraded for imprecision (confidence interval crosses line of null effect; single study only)
d. Downgraded for risk of performance and detection bias due to open-label design

Additional considerations:

Low certainty evidence showed that durvalumab monotherapy may result in a moderate reduction in adverse events when compared to standard of care (RR 0.73, 95% CI 0.64 to 0.85).

Based on moderate certainty evidence, durvalumab/tremelimumab likely has trivial to no effect on the reduction of adverse events (RR 0.98, 95% CI 0.87 to 1.10).

We are uncertain of the effect atezolizumab-based treatment regimens have on adverse events (RR 1.11, 95% CI 0.97 to 1.28; very low certainty evidence).

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE

○ **Very low** (atezolizumab/bevacizumab)
○ **Low** (durvalumab)
○ **Moderate** (durvalumab/tremelimumab)
○ High
○ No included studies

Domain	Judgement per critical outcome			Judgement across critical outcomes
ICIs	Overall survival	Health-related quality of life	Adverse events	Overall
Atezolizumab/bevacizumab	Moderate	Moderate	Very low	Very low
Durvalumab monotherapy	Low	Moderate	Low	Low
Durvalumab/tremelimumab	Moderate	Moderate	Moderate	Moderate

Additional considerations:

Across the critical outcomes, the lowest certainty of evidence rating was very low for atezolizumab/bevacizumab, low for durvalumab monotherapy and moderate for durvalumab/tremelimumab.

Values

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

JUDGEMENT

○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ **Probably no important uncertainty or variability** (durvalumab, durvalumab/tremelimumab)
○ **No important uncertainty or variability** (atezolizumab/bevacizumab)

RESEARCH EVIDENCE

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
Atezolizumab/bevacizumab	Large net desirable	No important uncertainty or variability
Durvalumab monotherapy	Small net desirable	Probably no important uncertainty or variability
Durvalumab/tremelimumab	Small 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.

Atezolizumab/bevacizumab probably results in a large increase in OS (6.9 months) and probably has trivial to no effect on health-related quality of life. We are uncertain on its effect on adverse events (very low certainty evidence) when compared to standard of care. Based on the large increase in OS and the ESMO-MCBS Scorecard, it was judged that atezolizumab/bevacizumab 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.

Durvalumab/tremelimumab probably results in a small increase in OS (3.9 months), probably has trivial to no effect on health-related quality of life and probably has trivial to no effect on adverse events. Given the small increase in OS and the ESMO-MCBS Scorecard, it was judged that durvalumab/tremelimumab offers 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.

Durvalumab monotherapy may result in a small increase in OS (2.25 months), probably has trivial to no effect on health-related quality of life and may reduce adverse events. Based on this and the ESMO-MCBS Scorecard, 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

○ Favors the comparison
○ Probably favors the comparison
○ Does not favor either the intervention or the comparison
○ **Probably favors the intervention (atezolizumab/bevacizumab, durvalumab, durvalumab/tremelimumab)**
○ Favors the intervention
○ Varies

RESEARCH EVIDENCE

ICIs	Net balance	Values	Certainty of evidence	Balance of effects
Atezolizumab/bevacizumab	Large net desirable	No important uncertainty or variability	Very low	Probably favors the intervention
Durvalumab monotherapy	Small net desirable	Probably no important uncertainty or variability	Low	Probably favors the intervention
Durvalumab/tremelimumab	Small net desirable	Probably no important uncertainty or variability	Moderate	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 atezolizumab/bevacizumab, durvalumab monotherapy and durvalumab/tremelimumab.

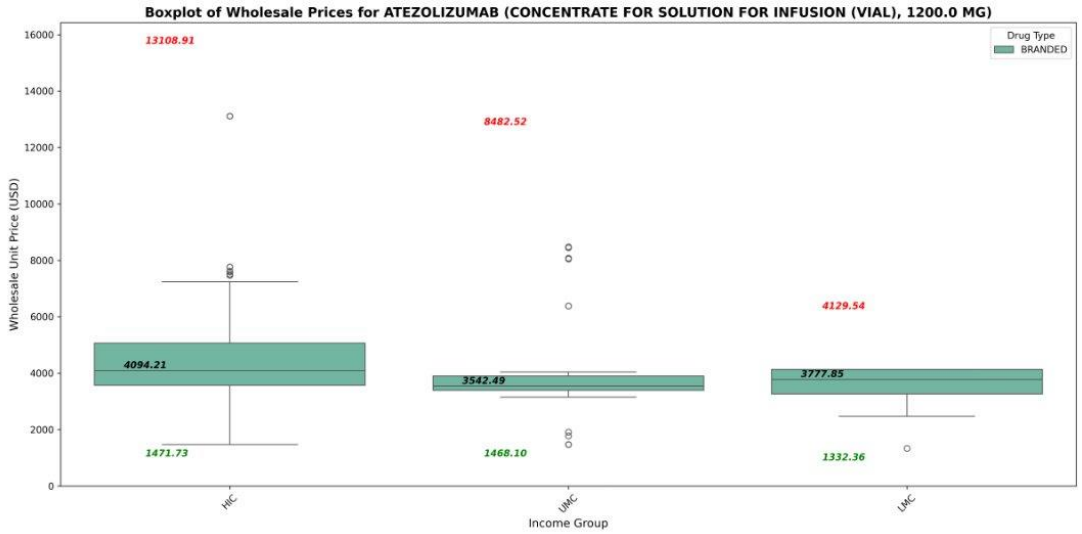
○ Don't know	

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 atezolizumab (concentrate for solution for infusion, 1200.0 MG) across World Bank income levels*:

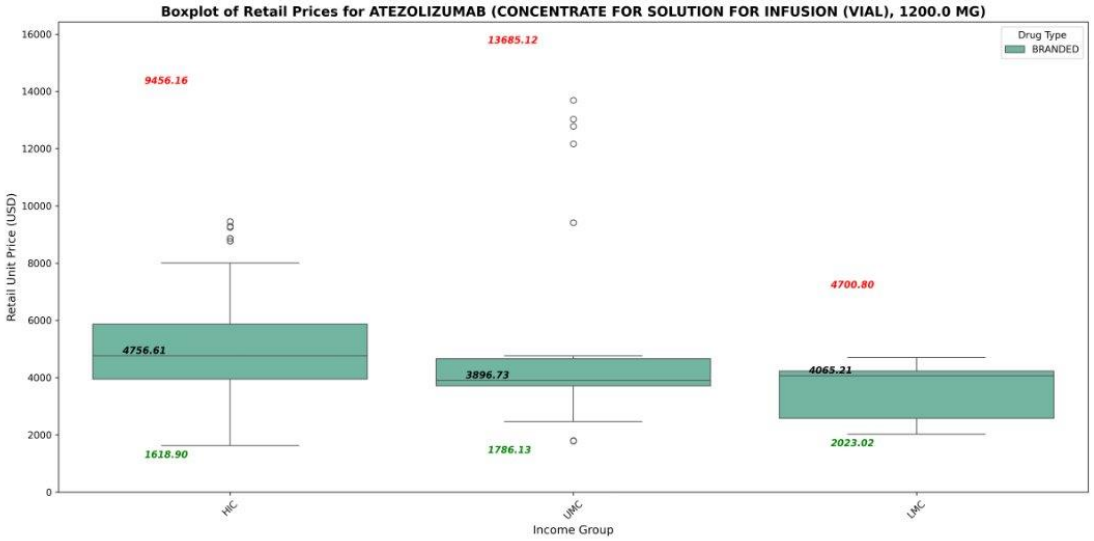
Income level	Median	IQR	Sample size based on number of countries
HIC	4094.21	3571.64 to 5064.84	36
UMIC	3542.49	3390.50 to 3894.29	12
LMIC	3777.85	3260.60 to 4129.54	5



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 atezolizumab (concentrate for solution for infusion, 1200.0 MG) across World Bank income levels*:

Income level	Median	IQR	Sample size based on number of countries
HIC	4756.61	3947.13 to 5869.36	36
UMIC	3896.73	3708.80 to 4664.18	12
LMIC	4065.21	2576.75 to 4230.30	6

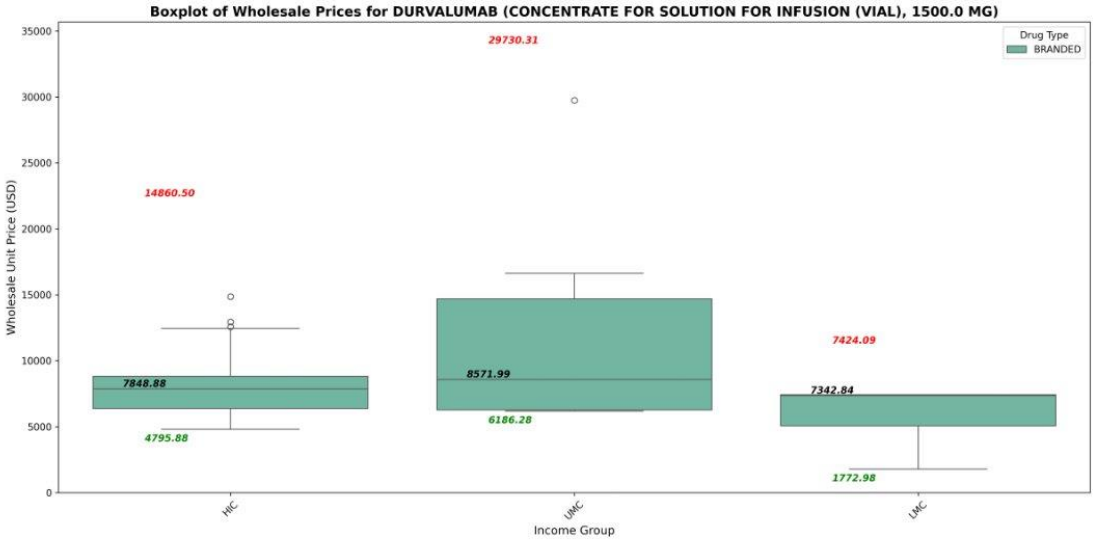


Source: author derived calculation based on most recent available retail prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: 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 durvalumab (concentrate for solution for infusion, 1500.0 MG) across World Bank income levels*:

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

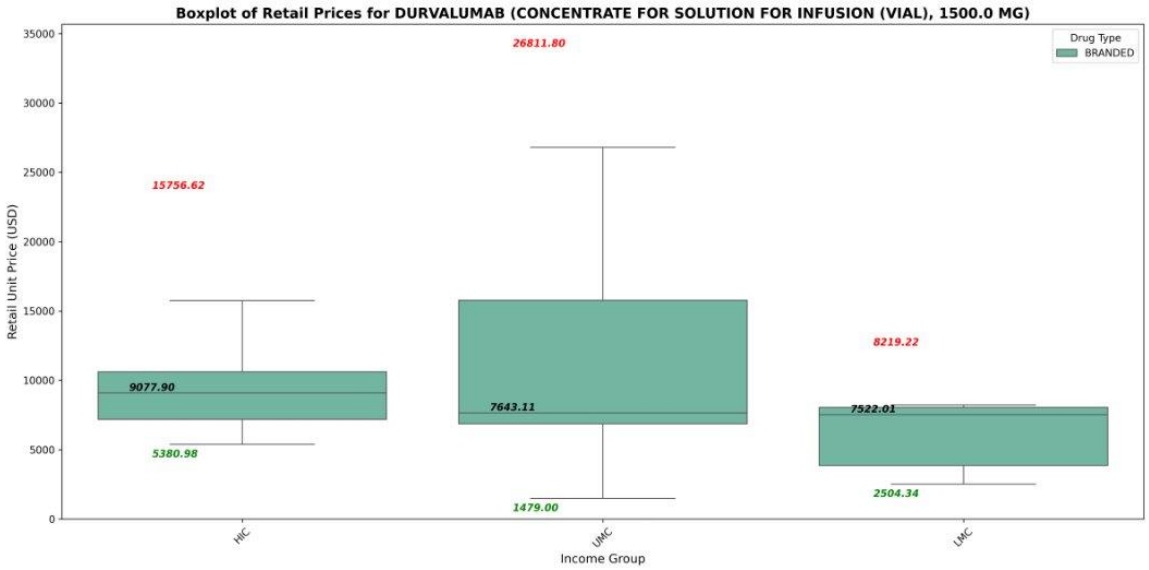
LMIC	7342.84	5054.37 to 7424.09	3



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

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

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



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

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

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

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

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

Income level	Median	IQR	Sample size based on number of countries

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

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

Additional considerations:

Direct evidence addressing the unit price for atezolizumab, durvalumab and tremelimumab was available.

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

Nonetheless, harnessing pricing dynamics is needed to promote implementation and affordable use of atezolizumab and durvalumab 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 atezolizumab plus bevacizumab compared to sorafenib as first-line treatment for unresectable hepatocellular carcinoma was available from the United States (HIC) (10, 11). In this HIC setting, the ICER exceeded WTP thresholds and the ICI was not considered cost-effective.

Country	Income level	WTP threshold	ICER	Cost-effective?
United States	HIC	USD 150,000 / QALY	USD 169,223 / QALY *	No
United States	HIC	USD 150,000 / QALY	USD 322,500 / QALY	No

* ICUR

Evidence addressing cost-effectiveness of durvalumab plus tremelimumab compared to sorafenib as first-line treatment for unresectable hepatocellular carcinoma was available from the United States (HIC) (12). In this HIC setting, the ICER did not exceed the WTP threshold and the ICI was considered cost-effective.

Country	Income level	WTP threshold	ICER	Cost-effective?
United States	HIC	USD 150,000 / QALY	USD 106,307 / QALY	Yes

Empirical evidence estimating cost-effective thresholds based on health expenditures per capita and life expectancy at birth was available for 174 countries (13). 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	Depends
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 immune checkpoint inhibitors across World Bank income settings without compromising efficacy and safety, alternative dosing strategies have been proposed (14). 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 immune checkpoint inhibitors under consideration for HCC had small to large net desirable effects, at the current price, they are likely not cost-effective in most settings, particularly in LMICs and LICs, and when diagnostic requirements are considered.

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

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE
○ **Reduced** ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	**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 small to large net 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.

○ Varies ○ Don't know	

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 (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 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. Atezolizumab and durvalumab 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 (15). **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 HCC.

Availability

What is the regulatory status, market availability and on-the-ground availability/access of the medicine to patients?

JUDGEMENT	RESEARCH EVIDENCE
○ Not available in most settings ○ **Probably not available in most settings** ○ Probably available in most settings ○ Available in most settings ○ Varies ○ Don't know	Pembrolizumab is approved for use in 85 countries worldwide – mainly high-income countries including Canada, the United States, European Union member countries and Japan (16). 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 (17). 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 atezolizumab and durvalumab availability for hepatocellular carcinoma across World Bank income settings. **Additional considerations:** Atezolizumab and durvalumab are approved for use in many countries; however, on-the-ground access outside of HICs is limited.

REFERENCES SUMMARY

1. Globocan. Age-Standardized Rate (World) per 100 000, Incidence and Mortality, Both Sexes, in 2022 2022 [Available from: https://gco.iarc.fr/today/en/dataviz/bars?mode=cancer&group_populations=1&types=0_1&sort_by=value1.
2. Cheng A-L, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. Journal of Hepatology. 2022;76(4):862-73.
3. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382(20):1894-905.
4. Galle PR, Finn RS, Qin S, Ikeda M, Zhu AX, Kim T-Y, et al. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. The Lancet Oncology. 2021;22(7):991-1001.
5. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid. 2022;1(8):EVIDoa2100070.
6. Sangro B, Chan SL, Kelley RK, Lau G, Kudo M, Sukeepaisarnjaroen W, et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Ann Oncol. 2024;35(5):448-57.
7. Sangro B, Galle PR, Kelley RK, Charoentum C, De Toni EN, Ostapenko Y, et al. Patient-Reported Outcomes From the Phase III HIMALAYA Study of Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. J Clin Oncol. 2024;42(23):2790-9.
8. 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.
9. 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).
10. Su D, Wu B, Shi L. Cost-effectiveness of Atezolizumab Plus Bevacizumab vs Sorafenib as First-Line Treatment of Unresectable Hepatocellular Carcinoma. JAMA Network Open. 2021;4(2):e210037-e.
11. Zhang X, Wang J, Shi J, Jia X, Dang S, Wang W. Cost-effectiveness of Atezolizumab Plus Bevacizumab vs Sorafenib for Patients With Unresectable or Metastatic Hepatocellular Carcinoma. JAMA Network Open. 2021;4(4):e214846-e.
12. Liao W, Xu H, Hutton D, Wu Q, Yang Y, Feng M, et al. Cost-effectiveness analysis of durvalumab plus tremelimumab as first-line therapy in patients with unresectable hepatocellular carcinoma. Ther Adv Med Oncol. 2024;16:17588359241274625.
13. 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.
14. 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.
15. World Health Organization. WHO Model List of Essential In Vitro Diagnostics 2024 [Available from: https://edl.who-healthtechnologies.org/.
16. 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/.
17. 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.