This Evidence-to-Decision (EtD) framework addresses **atezolizumab monotherapy, cemiplimab monotherapy and pembrolizumab monotherapy** for **oncogenic-driver wild-type non-small cell lung cancer with ≥ 50% PD-L1 expression**.

# QUESTION

| **Should immune checkpoint inhibitors vs. alternative regimens be used for adult non-small cell lung cancer?** | |
|---|---|
| **POPULATION:** | adult non-small cell lung cancer (NSCLC)<br>• oncogenic-driver wild-type NSCLC with ≥ 50% 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 oncogenic-driver wild-type NSCLC with ≥ 50% PD-L1 expression:<br>• atezolizumab monotherapy (ESMO-MCBS non-curative score = 5)<br>• cemiplimab monotherapy (ESMO-MCBS non-curative score = 4)<br>• pembrolizumab monotherapy (ESMO-MCBS non-curative score = 5) |

# SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | Small | **Moderate** (atezolizumab) | **Large** (cemiplimab, pembrolizumab) | | Varies | Don't know |
| **REDUCTION IN UNDESIRABLE EFFECTS** | Increased harms and toxicity | **No/Trivial** (cemiplimab) | Small | Moderate | **Large** (pembrolizumab) | **Varies** (atezolizumab) | Don't know |
| **CERTAINTY OF EVIDENCE** | Very low | **Low** (atezolizumab, cemiplimab, pembrolizumab) | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** (atezolizumab) | **No important uncertainty or variability** (cemiplimab, pembrolizumab) | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** (atezolizumab) | **Favors the intervention** (cemiplimab, pembrolizumab) | 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<br>○ Probably no<br>○ Probably yes<br>○ **Yes**<br>○ Varies<br>○ 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 NSCLC (≥ 50% PD-L1 expression), for which three ICIs are proposed: atezolizumab, cemiplimab and pembrolizumab.<br><br>NSCLC makes up over 80% of all lung cancer cases (1). The global age-standardized incidence rate of lung cancer was estimated at 23.6 per 100,000 in 2022 and represents the leading cause of cancer-related deaths worldwide (2). The standard of care includes platinum-based chemotherapy, which has limited benefit for overall survival and is associated with a reduced quality of life in treated patients because of its cytotoxic effects (1). |

## Desirable Effects
How substantial are the desirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE |
|---|---|
| ○ Trivial or no<br>○ Small<br>○ **Moderate** (atezolizumab)<br>○ **Large** (cemiplimab, pembrolizumab)<br>○ Varies<br>○ Don't know | The application provided evidence addressing desirable effects from two randomized trials for atezolizumab monotherapy (3-5), one randomized trial for cemiplimab monotherapy (6-8) and two randomized trials for pembrolizumab monotherapy (9-13).<br><br>**Oncogenic-driver wild-type non-small cell lung cancer with ≥ 50% PD-L1 expression** |

**Atezolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression**

**Patient or population:** oncogenic driver wild-type NSCLC with high PD-L1 expression (TC3 or IC3)
**Intervention:** Atezolizumab monotherapy
**Comparison:** SoC (chemotherapeutic drug regimen with or without platinum depending on patient suitability)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | **Risk with SoC**[b] | **Risk with Atezolizumab monotherapy** | | | | |
| Overall survival (OS)<br>follow-up:<br>median 35.6 months[a] | **At 2 years** | | **HR 0.79**<br>(0.54 to 1.09)<br>[death] | 280<br>(2 RCTs) | ⨁⨁◯◯<br>Low[c,d] | Based on the point estimate, atezolizumab monotherapy may increase overall survival. Considering that a proportion of trial participants received ICIs in the subsequent |
| | 30 per 100 | **39 per 100**<br>(27 to 52) | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | The median overall survival was **13.9** months[b] | The median survival was **3.7 months more** (1.1 fewer to 11.8 more) | | | | treatment line, the effect of atezolizumab may be underestimated. |
| Progression-free survival (PFS)<br>At follow-up: 12 months | 18 per 100 | **34 per 100**<br>(24 to 44) | **HR 0.63**<br>(0.48 to 0.84)<br>[disease progression or death] | 280<br>(2 RCTs) | ⨁⨁◯◯<br>Low[e,f] | Atezolizumab monotherapy may increase progression-free survival. |
| Health-related quality of life - not reported | *see comments* | | - | - | - | Both studies measured and reported aspects of quality of life; however, reporting of total or global QoL scores was insufficient |

*__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 pooled median follow-up across studies
b. The baseline risk is derived from the pooled control group estimate of studies
c. According to protocol, crossover to receive ICIs was not permitted in the comparator arms. However, patients in IMpower 110 received ICIs as subsequent therapy in 34.7% of cases; the proportion in IPSOS was not reported. Consequently, the effect of Atezolizumab might be underestimated. Therefore, we downgraded by 1 for indirectness
d. The pooled effect estimate's CI overlaps both the line of no effect as well as the line of appreciable benefit at 0.75 (downgraded for serious imprecision)
e. Both studies were at high risk of bias due to the open-label trial design and investigator-assessed outcome reporting
f. Downgraded by 1 for imprecision. Even though the OIS criterion was met, imprecision resulted from the CI crossing the line of appreciable benefit at 0.75

**Summary of findings:**

## Cemiplimab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression

**Patient or population:** oncogenic driver wild-type NSCLC with high PD-L1 expression (TPS ≥ 50%)
**Intervention:** Cemiplimab monotherapy
**Comparison:** SoC (platinum-based doublet chemotherapy)

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

| | | | | | | |
|---|---|---|---|---|---|---|
| Overall survival (OS)<br>follow-up:<br>median 35 months | 35 per 100 | **52 per 100**<br>(45 to 58) | **HR 0.63**<br>(0.52 to 0.77)<br>[death] | 712<br>(1 RCT) | ⨁⨁⨁◯<br>Moderate[b] | Cemiplimab monotherapy probably results in a large increase in overall survival. Considering the open-label study design and the opportunity for patients randomized to the control arm to switch to the cemiplimab arm, the magnitude of survival benefit from cemiplimab treatment may be underestimated. |
| | The median OS was **13.7** months | The median survival was **8 months more**<br>(4.1 more to 12.6 more) | | | | |
| Progression-free survival (PFS)<br>At follow-up:<br>12 months | 8 per 100 | **24 per 100**<br>(18 to 31) | **HR 0.56**<br>(0.47 to 0.67)<br>[disease progression or death] | 712<br>(1 RCT) | ⨁⨁⨁◯<br>Moderate[c] | Cemiplimab monotherapy likely results in a large increase in progression-free survival. |
| Global Health Score/Quality of Life (GHS/QoL)<br>assessed with: EORTC-QLQ C30<br>Scale from: 0 to 100<br>follow-up: 1 year from baseline | The mean global Health Score/Quality of Life was **2.2** change score from baseline | MD **5.03 change score from baseline higher**<br>(2.11 higher to 7.96 higher) | - | 563<br>(1 RCT) | ⨁⨁⨁◯<br>Moderate[d,e] | Cemiplimab 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; **MD:** mean difference; **RR:** risk ratio

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

*Explanations*

a. Baseline risk derived from the control arm of the EMPOWER-Lung 1 study
b. Downgraded by 1 due to indirectness from switching treatments in the comparator arm, with 56% of participants receiving the experimental treatment upon progression. Thus, potentially leading to an underestimated effect
c. Downgraded by 1 due to open-label trial design and potential deviation due to contextual bias
d. Downgraded by 1 due to open-label trial design and potential for performance and detection bias
e. The effect estimate and CI do not cross the line of minimal important difference of 10

**Summary of findings:**

## Pembrolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression

**Patient or population:** oncogenic driver wild-type NSCLC with high PD-L1 expression (TPS ≥ 50%)
**Intervention:** Pembrolizumab monotherapy
**Comparison:** SoC (platinum-based doublet chemotherapy)

| Outcomes | **Anticipated absolute effects*** (95% CI) | | | | Comments |
|---|---|---|---|---|---|

| | Risk with SoC | Risk with Pembrolizumab monotherapy | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | |
|---|---|---|---|---|---|---|
| Overall survival (OS)<br>follow-up:<br>median 61 months[a] | **At 2 years** | | **HR 0.66**<br>(0.57 to 0.76)<br>[death] | 904<br>(2 RCTs) | ⨁⨁⨁◯<br>Moderate[c] | Pembrolizumab monotherapy likely increases overall survival at 2 and 5 years. However, considering the open-label study design and the opportunity for treatment switching in control arms, the treatment effect might be underestimated. |
| | 30 per 100 | **45 per 100**<br>(40 to 50) | | | | |
| | **At 5 years** | | | | | |
| | 10 per 100 | **22 per 100**<br>(17 to 27) | | | | |
| | The median overall survival was **12.2** months[b] | The median survival was **6.3 months more**<br>(3.9 more to 9.2 more) | | | | |
| Progression-free survival (PFS)<br>At follow-up: 12 months | 21 per 100 | **35 per 100**<br>(17 to 54) | **HR 0.66**<br>(0.39 to 1.12)<br>[disease progression or death] | 904<br>(2 RCTs)[d] | ⨁⨁◯◯<br>Low[e,f] | Pembrolizumab monotherapy may result in an increase in progression-free survival. |
| Global Health Score/Quality of Life (GHS/QoL)<br>assessed with: EORTC-QLQ C30<br>Scale from: 0 to 100 | The mean global Health Score/Quality of Life was **-0.9** change score from baseline | MD **7.85 change score from baseline higher**<br>(2.51 higher to 13.19 higher) | - | 297<br>(1 RCT) | ⨁⨁◯◯<br>Low[g,h] | Pembrolizumab monotherapy may increase global Health Score/Quality of Life slightly. |

*__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 median length of follow-up across trials
b. The risk estimate comes from Keynote-042's control group, which, due to its design, did not permit cross-over to receive ICIs and, therefore, more closely represents the baseline risk.
c. Participants in the comparator arms received ICI treatment, on- or off-trial, in 66% (Keynote-024) and 23% (Keynote-042) of cases, respectively. The suggested imbalance in trial withdrawals due to deviations from the intended intervention in the open-label trial design does not warrant a downgrade for risk of bias. However, in conjunction with the indirectness arising from patients in the control arms receiving the investigational treatment, which potentially underestimates the effect, a downgrade by 1 is justified.
d. The baseline risk comes from the pooled control group estimate of studies

e. Downgraded for unexplained inconsistency due to lack of CI overlap showing trivial/no effect and important benefit. Data from Keynote-042 are based on a predetermined subgroup analysis. Trial participant randomisation was stratified based on their PD-L1 expression.
f. The pooled effect estimate's CI overlaps both with the line of no effect and important benefit
g. Downgraded for risk of bias due to open-label study design
h. Since the OIS criterion was not met and the CI crosses the line of minimal important difference of 10, we downgraded by 1 for imprecision

**Magnitude of effect judgements:**

| Domain | Judgement per critical outcome | | Judgement across desirable critical outcomes |
|---|---|---|---|
| **ICIs** | **Overall survival** | **Health-related quality of life** | **Overall** |
| Atezolizumab | Moderate | NR | Moderate |
| Cemiplimab | Large | Trivial or no | Large |
| Pembrolizumab | Large | Small | 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 (14). 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 NSCLC – 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 rounded to 4 months more in people treated with atezolizumab, was 6.3 months more in people treated with pembrolizumab and 8 months more in people treated with cemiplimab. The ESMO-MCBS Scorecards reported a score of 4 for cemiplimab, and 5 for atezolizumab and pembrolizumab. The magnitude of effect for overall survival, based on the point estimates, WHO benefit thresholds and ESMO-MCBS Scorecards, was judged as moderate for atezolizumab, and large for pembrolizumab and cemiplimab. Since the ESMO-MCBS Scorecard for pembrolizumab was 5, the judgement for the magnitude of desirable effect moved from moderate (based on a median overall survival gain of 6.3 months) to large.

In terms of health-related quality of life, there was no to little difference for cemiplimab and a small increase for pembrolizumab. Reporting was insufficient in atezolizumab studies to quantify health-related quality of life.

| | |
|---|---|
| | The overall judgement related to the magnitude of desirable effects cannot be lower than the highest rating across critical outcomes. Therefore, the overall magnitude of desirable effects was judged as moderate for atezolizumab, and large for pembrolizumab and cemiplimab. |

## Undesirable Effects

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

| JUDGEMENT | RESEARCH EVIDENCE |
|---|---|
| ○ Increased harms and toxicity<br><br>Magnitude of reduction in harms and toxicity:<br><br>○ **Trivial or no** (cemiplimab)<br>○ Small<br>○ Moderate<br>○ **Large** (pembrolizumab)<br>○ **Varies** (atezolizumab)<br>○ Don't know | The application provided evidence addressing undesirable effects from two randomized trials for atezolizumab monotherapy (3-5), one randomized trial for cemiplimab monotherapy (6-8) and two randomized trials for pembrolizumab monotherapy (9-13).<br><br>**Oncogenic-driver wild-type non-small cell lung cancer with ≥ 50% PD-L1 expression**<br><br>**Summary of findings:** |

### Atezolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression

**Patient or population:** oncogenic driver wild-type NSCLC with high PD-L1 expression (TC3 or IC3)
**Intervention:** Atezolizumab monotherapy
**Comparison:** SoC (chemotherapeutic drug regimen with or without platinum depending on patient suitability)

| 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 monotherapy** | | | | |
| Adverse events (CTCAE ≥ 3) | 57 per 100 [a] | **46 per 100** (31 to 70) | **RR 0.81** (0.54 to 1.22) | 996 (2 RCTs) | ⊕⊕◯◯ Low[b,c] | Studies were different with respect to the age and performance status of included participants, suggesting that while the intervention leads to fewer adverse events (CTCAE ≥ 3) in young, fit patients, this advantage is potentially lost in elderly/unfit patients. |

***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. The baseline risk is derived from the pooled control group estimate of studies
b. The pooled effect estimate's CI overlaps both the line of no effect as well as the line of appreciable benefit at 0.75 (downgraded for very serious imprecision)
c. Both studies were at high risk of bias due to the open-label trial design and investigator-assessed outcome reporting

**Summary of findings:**

## Cemiplimab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression

**Patient or population:** Oncogenic driver wild-type NSCLC with high PD-L1 expression (TPS ≥ 50%)
**Intervention:** Cemiplimab monotherapy
**Comparison:** SoC (platinum-based doublet chemotherapy)

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | **Risk with SoC[a]** | **Risk with Cemiplimab monotherapy** | | | | |
| Adverse events (CTCAE ≥ 3) irrespective of treatment attribution | 52 per 100 | **46 per 100** (39 to 53) | **RR 0.89** (0.76 to 1.03) | 699 (1 RCT) | ⨁⨁◯◯ Low[b,c] | Cemiplimab monotherapy may have trivial to no effect on adverse events (CTCAE ≥ 3) irrespective of treatment attribution. |

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

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

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

*Explanations*

a. Baseline risk derived from the control arm of the EMPOWER-Lung 1 study
b. Downgraded by 1 due to open-label trial design and potential for performance and detection bias
c. Downgraded due to serious imprecision; the CI includes the null-effect-line

**Summary of findings:**

## Pembrolizumab monotherapy compared to SoC in oncogenic driver wild-type NSCLC with high PD-L1 expression

**Patient or population:** oncogenic driver wild-type NSCLC with high PD-L1 expression (TPS ≥ 50%)
**Intervention:** Pembrolizumab monotherapy
**Comparison:** SoC (platinum-based doublet chemotherapy)

| 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 monotherapy** | | | | |
| Adverse events (CTCAE ≥ 3) Irrespective of treatment attribution | 43 per 100 | **21 per 100** (16 to 29) | **RR 0.49** (0.37 to 0.66) | 1555 (2 RCTs) | ⨁⨁⨁◯ Moderate[a,b] | Pembrolizumab monotherapy probably results in a large reduction 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

**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. Downgraded for risk of bias due to open-label study design
b. The adverse events in Keynote-042 were only reported for the entire ITT population, not for the subgroup of patients with PD-L1 expression ≥ 50%. We did not judge the tumour's PD-L1 expression to lead to sufficient indirectness with respect to adverse event outcomes, justifying downgrade for indirectness

**Additional considerations:**

Moderate certainty evidence showed that pembrolizumab monotherapy probably results in a large reduction in adverse events when compared to standard of care (RR 0.49, 95% CI 0.37 to 0.66).

Based on low certainty evidence, cemiplimab monotherapy may have trivial to no effect on the reduction of adverse events (RR 0.89, 95% CI 0.76 to 1.03).

Because studies addressing adverse events for atezolizumab were different with respect to the age and performance status of included participants, data suggested that the intervention led to fewer adverse events (CTCAE ≥ 3) in young, fit patients, but not elderly/unfit patients.

## Certainty of evidence

What is the overall certainty of the evidence of effects?

**JUDGEMENT**

○ Very low
○ **Low (atezolizumab, cemiplimab, pembrolizumab)**
○ Moderate
○ High
○ No included studies

**RESEARCH EVIDENCE**

| Domain | Judgement per critical outcome | | | Judgement across critical outcomes |
|---|---|---|---|---|
| ICIs | Overall survival | Health-related quality of life | Adverse events | Overall |
| Atezolizumab | Low | NA | Low | Low |
| Cemiplimab | Moderate | Moderate | Low | Low |
| Pembrolizumab | Moderate | Low | Moderate | Low |

**Additional considerations:**

Across the critical outcomes, the lowest certainty of evidence rating was low for atezolizumab, cemiplimab and pembrolizumab.

## Values

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

| JUDGEMENT | RESEARCH EVIDENCE |
|---|---|
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>○ **Probably no important uncertainty or variability** (atezolizumab)<br>○ **No important uncertainty or variability** (cemiplimab, pembrolizumab) | 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. Five (29%) addressed lung cancer specifically (15). 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.<br><br>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 | Moderate net desirable | Probably no important uncertainty or variability |
| Cemiplimab | Large net desirable | No important uncertainty or variability |
| Pembrolizumab | 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.

Cemiplimab probably results in a large increase in OS (8 months); however, it probably has trivial to no effect on health-related quality of life and may have trivial to no effect in reducing adverse events when compared to standard of care. Based on this and the ESMO-MCBS Scorecard, it was judged that cemiplimab 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.

Pembrolizumab probably results in a moderate increase in OS (6.3 months) and large reduction in adverse events. With this, and an ESMO-MCBS score of 5, pembrolizumab was judged to have a large net desirable effect. Further, it may increase health-related quality of life. Given its positive effect on these three outcomes and the ESMO-MCBS Scorecard, it was judged that pembrolizumab 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.

| | |
|---|---|
| | For atezolizumab, considering the moderate benefit based on the point estimate (3.7 months), variable reduction in harms when compared to standard of care, lack of data related to health-related quality of life and 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)**
○ **Favors the intervention (cemiplimab, pembrolizumab)**
○ Varies
○ Don't know

**RESEARCH EVIDENCE**

| ICIs | Net balance | Values | Certainty of evidence | Balance of effects |
|---|---|---|---|---|
| Atezolizumab | Moderate net desirable | Probably no important uncertainty or variability | Low | Probably favors the intervention |
| Cemiplimab | Large net desirable | No important uncertainty or variability | Low | Favors the intervention |
| Pembrolizumab | Large net desirable | No important uncertainty or variability | Low | 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 and favors cemiplimab and pembrolizumab.

## Resources required

How large are the resource requirements?

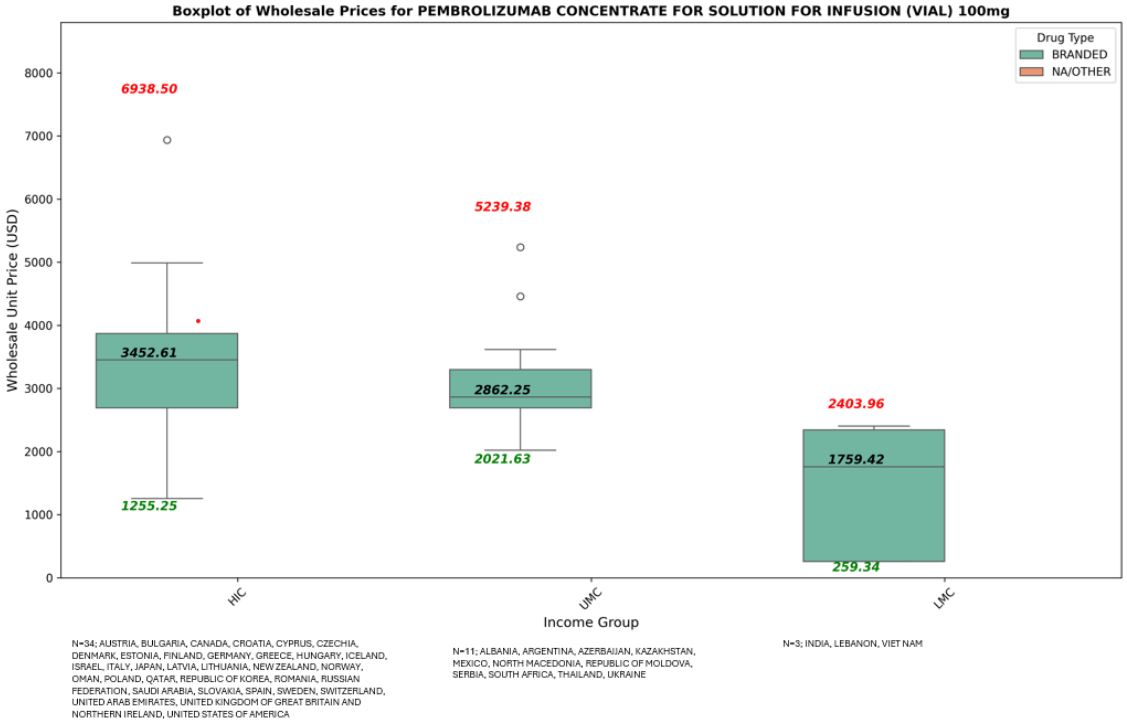
**JUDGEMENT**

**RESEARCH EVIDENCE**

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

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

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

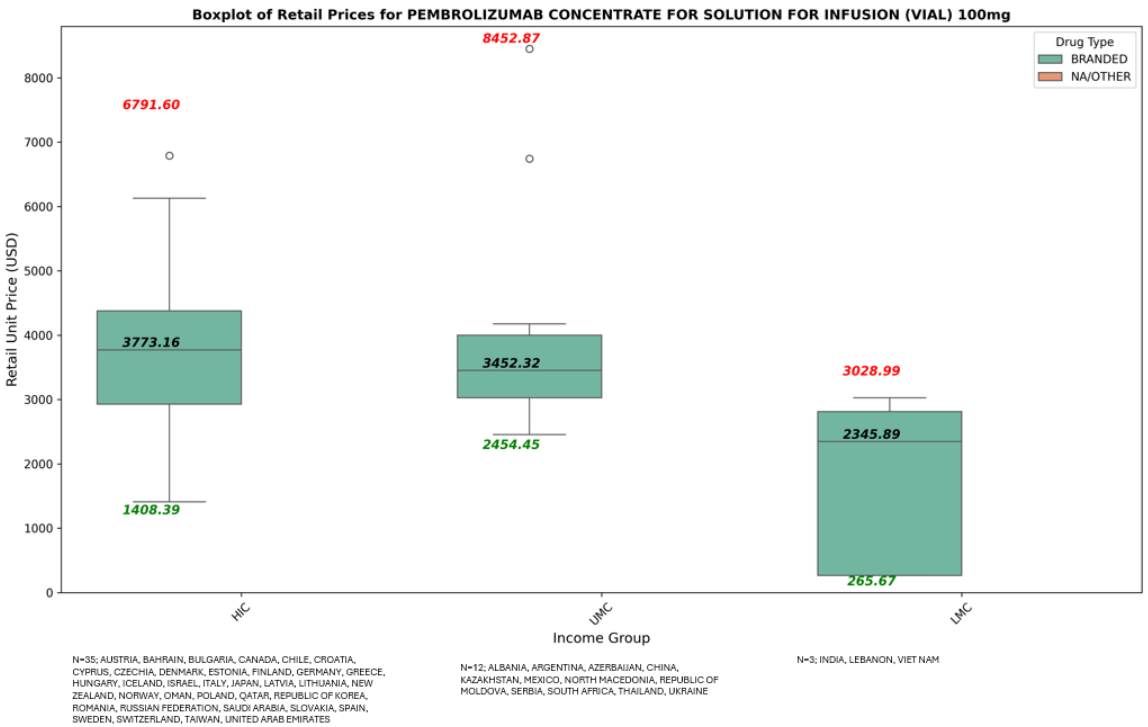



Source: author derived calculation based on most recent available wholesale prices (as of November 2024) extracted from GlobalData Price Intelligenc (POLI) and Eversana NAVLIN Price & Access datasets. Latest publicly available country-specific prices may be accessed via sources listed here, where available: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

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

| Income level | Median | IQR | Sample size based on number of countries |
|---|---|---|---|
| HIC | 3773.16 | 2928.38 to 4377.63 | 35 |
| UMIC | 3452.32 | 3027.62 to 4001.05 | 12 |

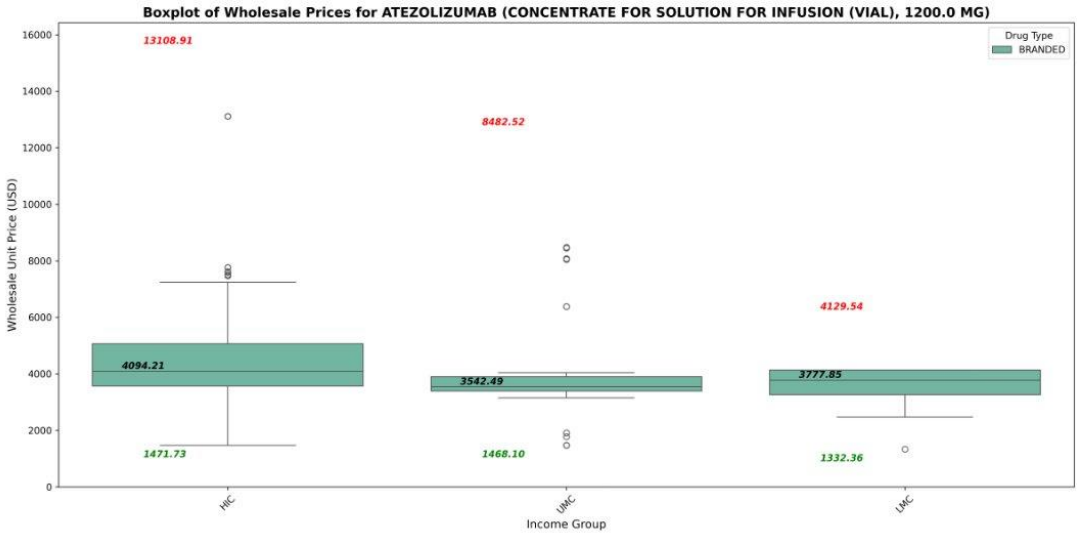
| | | | |
|---|---|---|---|
| LMIC | 2345.89 | 265.67 to 2812.69 | 3 |




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

Median wholesale unit price (USD) for atezolizumab (concentrate for solution for infusion, 1200.0 MG) across World Bank income levels*:

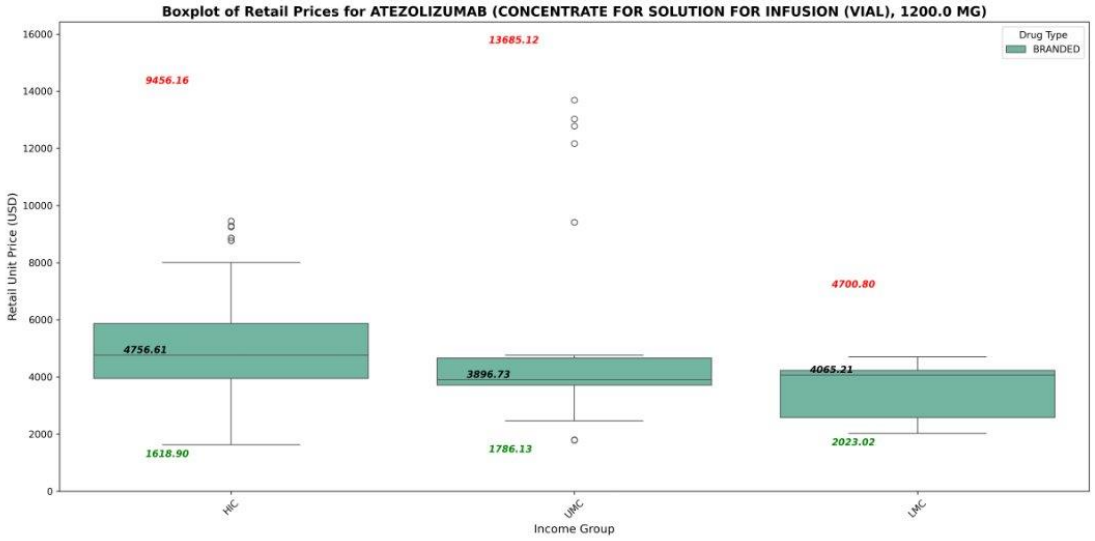
| Income level | Median | IQR | Sample size based on number of countries |
|---|---|---|---|
| HIC | 4094.21 | 3571.64 to 5064.84 | 36 |
| UMIC | 3542.49 | 3390.50 to 3894.29 | 12 |
| LMIC | 3777.85 | 3260.60 to 4129.54 | 5 |




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*:

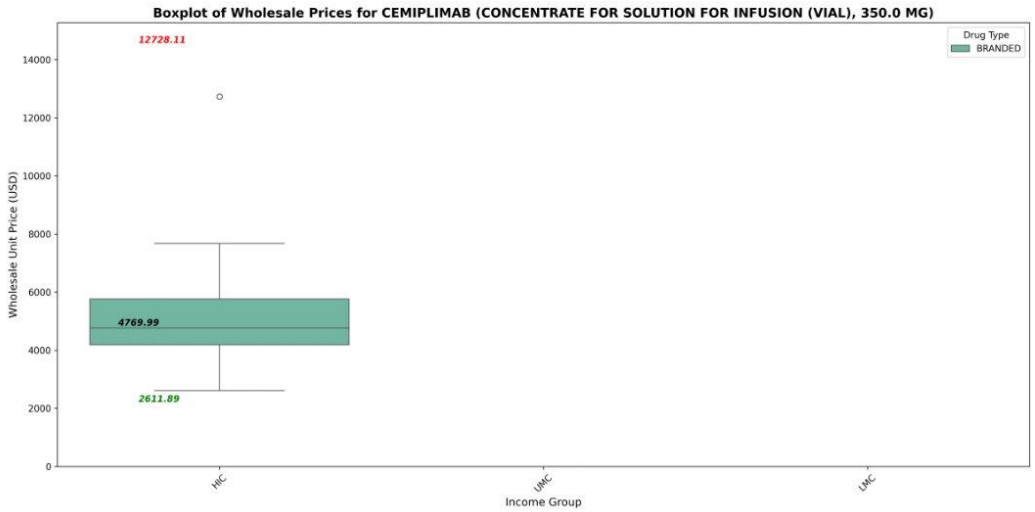
| Income level | Median | IQR | Sample size based on number of countries |
|---|---|---|---|
| HIC | 4756.61 | 3947.13 to 5869.36 | 36 |
| UMIC | 3896.73 | 3708.80 to 4664.18 | 12 |
| LMIC | 4065.21 | 2576.75 to 4230.30 | 6 |




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 cemiplimab (concentrate for solution for infusion, 350.0 MG) across World Bank income levels*:

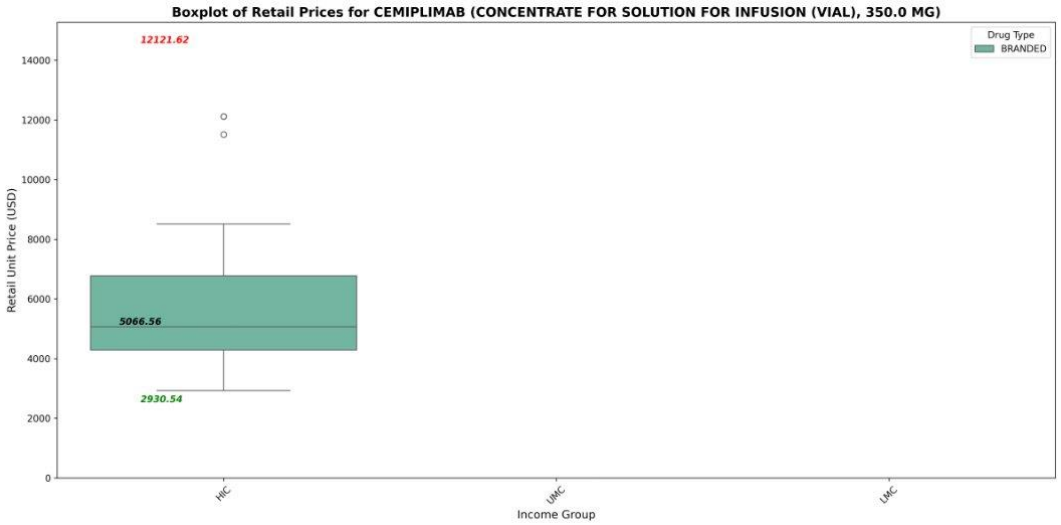
| Income level | Median | IQR | Sample size based on number of countries |
|---|---|---|---|
| HIC | 4769.99 | 4183.03 to 5760.73 | 25 |
| UMIC | NR | NR | 0 |
| LMIC | NR | NR | 0 |




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 cemiplimab (concentrate for solution for infusion, 350.0 MG) across World Bank income levels*:

| Income level | Median | IQR | Sample size based on number of countries |
|---|---|---|---|
| HIC | 5066.56 | 4293.13 to 6775.30 | 21 |
| 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, cemiplimab and pembrolizumab was available.

Relative to other EML medicines, the costs of atezolizumab, cemiplimab and 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 pembrolizumab 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. Further, there were no data available for LICs. Compared to pembrolizumab and atezolizumab, data for cemiplimab in non-HIC settings were not reported in the data source.

Nonetheless, harnessing pricing dynamics is needed to promote implementation and affordable use of atezolizumab, cemiplimab and 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 (16).

## Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE |
|---|---|

| | |
|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ **Varies**<br>○ No included studies | A systematic review addressing the cost-effectiveness of pembrolizumab for the treatment of NSCLC identified 24 cost-effectiveness studies from China, France, Singapore, Switzerland, United Kingdom and United States, all of which are HICs or UMICs (17). Whether or not pembrolizumab was found to be cost-effective was associated at least in part with the selection of model parameters, willingness-to-pay thresholds, and treatment strategies.<br><br>Empirical evidence estimating cost-effective thresholds based on health expenditures per capita and life expectancy at birth was available for 174 countries (18). 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 pembrolizumab across World Bank income settings without compromising efficacy and safety, alternative dosing strategies have been proposed (19). 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 three checkpoint inhibitors under consideration for oncogenic-driver wild-type non-small cell lung cancer with ≥ 50% PD-L1 expression had moderate 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**<br>○ Probably reduced<br>○ Probably no impact<br>○ Probably | **Additional considerations:**<br><br>Despite checkpoint inhibitors being accessible in many HICs, the WHO EML is a global list and the impact on LMICs and LICs was considered. |

| | |
|---|---|
| increased<br>○ Increased<br>○ Varies<br>○ Don't know | Because the ICIs under consideration offer moderate 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. |

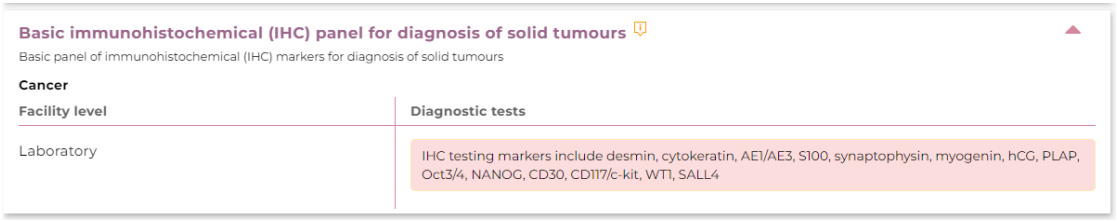
## Acceptability

Is the intervention acceptable to key stakeholders?

| JUDGEMENT | RESEARCH EVIDENCE |
|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ **Varies**<br>○ 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. Five (29%) addressed lung cancer specifically (15). 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.<br><br>**Additional considerations:**<br><br>Empiric evidence from the patient perspective provides support for the acceptability of immune checkpoint inhibitors.<br><br>Atezolizumab, cemiplimab and pembrolizumab 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<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ **Varies**<br>○ Don't know | Diagnostic requirements – immunohistochemistry companion tests – to identify patients with the indication approved for treatment.<br><br>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 (20).<br><br>  <br>**Basic immunohistochemical (IHC) panel for diagnosis of solid tumours**<br>Basic panel of immunohistochemical (IHC) markers for diagnosis of solid tumours<br>**Cancer**<br>**Facility level** / **Diagnostic tests**<br>Laboratory<br>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.<br><br>**Additional considerations:**<br><br>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 NSCLC. |

## 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<br>○ **Probably not available in most settings**<br>○ Probably available in most settings<br>○ Available in most settings<br>○ Varies<br>○ 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 (21).<br><br>Data on the availability, out-of-pocket costs, and accessibility of pembrolizumab for melanoma, NSCLC, colorectal cancer and renal cell carcinoma were available from the 2023 update to the ESMO Global Consortium Study (22). 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 NSCLC, 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 cemiplimab availability for NSCLC across World Bank income settings.<br><br>**Additional considerations:**<br><br>Atezolizumab, cemiplimab and pembrolizumab are approved for use in many countries; however, on-the-ground access outside of HICs is limited. |

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