Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer [ID1678]

Produced by Aberdeen HTA Group

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Andrew Walker reports that he provided consultancy advice to Roche on four projects since January 2018 that do not relate to NSCLC (covering March 2018 to date) or to the technology being assessed in this appraisal. All projects are complete, and he is not currently undertaking any work for Roche. No other competing interests to declare.

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Clare Robertson summarised and critiqued the company's definition of the decision problem and the clinical effectiveness evidence reported within the company submission. Lorna Aucott critiqued the statistical methods and analyses presented in the company submission and checked all the numerical results related to the review of the clinical effectiveness evidence. Graham Scotland with assistance from Andrew Walker critiqued the cost-effectiveness evidence submitted by the company, checked their economic model, and conducted further sensitivity analyses. Paul Manson critiqued the methods used for identifying relevant studies and checked the search strategies presented in the company submission. Gillian Price provided clinical advice during the appraisal. Miriam Brazzelli coordinated all aspects of the appraisal and acted as lead for the clinical effectiveness side of the appraisal. Graham Scotland acted as lead for the cost-effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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List of main abbreviations

NSCLC	Non-small-cell lung cancer
EGFR	Epidermal growth factor receptor
ALK	Anaplastic lymphoma kinase
CS	Company submission
TPS	Tumour proportion score
HRQoL	Health-related quality of life
EMA	European Medicines Agency
OS	Overall survival
CCOD	Clinical cut-off date
TC	Tumour cells
PFS-INV	Investigator-assessed progression free survival
DOR	Duration of response
ORR	Objective response rate
PRO	Patient-reported outcome
EORTC-QLQ	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
IHC	Immunohistochemistry
ERG	Evidence Review Group
PFS	Progression free survival
IC	Immune cells
ICER	Incremental cost-effectiveness ratio
INV	Investigator-assessed
CI	Confidence interval
Atezo	Atezolizumab
ECOG	Eastern Cooperative Oncology Group
TRAE	Treatment-related adverse event
AESI	Adverse event of special interest

Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the main aspects of the company submission and ERG's key issues

The company submission (CS) focuses on atezolizumab monotherapy as a first line treatment for patients with untreated advanced non-small-cell lung cancer (NSCLC). In a deviation from the NICE scope, the CS focuses on pembrolizumab monotherapy as the sole comparator treatment.

The key clinical effectiveness evidence is provided by one Phase III, multicentre, open-label randomised controlled trial (RCT), the IMpower110 trial. The IMpower110 trial compared atezolizumab with chemotherapy (cisplatin or carboplatin and pemetrexed, or gemcitabine) in PD-L1–selected (≥1% of tumour cells [TC] or immune cells [IC] covering ≥1% of the tumour area [TC1/2/3 or IC1/2/3]), chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC without EGFR mutations or ALK translocations. [redacted] The CS, therefore, considers data for 107 patients randomised to atezolizumab and 98 patients randomised to chemotherapy. The company reports data for the IMpower110 primary and exploratory analyses (clinical cut-off dates of September 2018 and February 2020, respectively). The primary endpoint of IMpower110 was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), duration of response (DOR).

In the absence of a direct head-to-head comparison with atezolizumab and pembrolizumab, the company conducted a network meta-analysis (NMA) of three RCTs: IMpower110, KEYNOTE-042 and KEYNOTE-024. The two KEYNOTE trials compared pembrolizumab monotherapy versus chemotherapy in 599 and 305 NSCLC patients, respectively. Different methods were used to determine PD-L1 expression across the three trials. PD-L1 expression in KEYNOTE-024 and KEYNOTE-042 was determined on TCs using the 22C3 immunohistochemistry (IHC) assay, whereas PD-L1 expression in IMpower110 was determined on TCs and ICs using the SP142 assay. KEYNOTE-024 only recruited patients whose tumours had the highest level of PD-L1 expression (TPS ≥50%), whereas IMpower110 and KEYNOTE-042 both recruited patients whose tumours had any PD-L1 expression. The company's NMA used a fractional polynomial approach (FP-NMA) for OS and PFS.

Table 1 presents a summary of the key issues identified by the ERG.

Table 1. Summary of the key issues

Issue number	Summary of issue	Report sections
Issue 1	Narrower population than that specified in the NICE final scope and choice of comparator	Sections 1.3 and 2.2.2
Issue 2	Atezolizumab effect over time	Sections 2.4 and 2.4.1
Issue 3	Assays comparability	Sections 2.3 and 2.4
Issue 4	Relative duration of treatment effects for the technology and its comparator	Section 3.2.6 and 5.3
Issue 5	Time on treatment with pembrolizumab relative to its PFS curve	Section 3.2.6
Issue 6	The validity of certain resource use frequencies in the progressive disease state of the model	Section 3.2.8

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained. In the current appraisal, a network meta-analysis found no evidence to support a meaningful difference in efficacy between the technology (atezolizumab monotherapy) and it comparator (pembrolizumab monotherapy). Therefore,

the company presented a cost comparison case which assumed equal efficacy alongside a cost-effectiveness case that applied the best estimates of relative treatment effects from the NMA. For the cost-effectiveness case, hazard ratios for pemrolizumab versus atezolizumab were applied to the selected OS and PFS curves for atezolizumab in the context of a partitioned survival model.

Overall, the technology is modelled to affect QALYs by:

- affecting overall survival and progression free survival relative to pembrolizumab monotherapy.
- Increasing the assumed duration of treatment effect compared to pembrolizumab

Overall, the technology is modelled to affect costs by:

- Having different acquisition costs compared to its comparator.
- Increasing the treatment duration relative to its comparator
- Changing the timing of progression to subsequent therapy and the progressive disease state

The modelling assumptions that have the greatest effect on the ICER are:

- The relative treatment effects, in the form of hazard ratios for OS and PFS, for pembrolizumab (the comparator) versus atezolizumab (the technology)
- The assumed duration of the treatment effect on overall survival for the technology and the comparator relative to the common comparator in the NMA (platinum-based chemotherapy) - this being longer for the technology in the company's base case
- The assumption that time on treatment with pembrolizumab equates with PFS up until the two-year stopping rule applies.

1.3 The decision problem: summary of the ERG's key issues

The ERG's key issue related to the decision problem is detailed in Table X below.

Table 2. Issue 1. Narrower population than that specified in the NICE final scope and choice of comparator

Report section	Sections 1.3 and 2.2.2
Description of issue and why the ERG has identified it as important	[redacted], the CS focuses on the IC3 (infiltrating immune cell PD-L1 expression >10%) or TC3 (tumour cell PD-L1 expression ≥50%) subpopulation; but do not report a clear breakdown of the number of patients who met IC3 and TC3 criteria. Since the NICE recommendation for pembrolizumab in untreated PD-L1 positive metastatic NSCLC is conditional on a tumour proportion score of at least 50% (TA531), the ERG is currently unclear whether pembrolizumab is the relevant comparator for the IMpower110 IC3 patients. However, in IMpower110 the number of patients in this category is likely to be small. The company also provide an exploratory analysis to assess the relative treatment effect in IMpower110 for high PD-L1 expression groups defined by different assays, including TPS ≥ 50% as defined by the 22C3 assay (used to determine PD-L1 expression in the KEYNOTE trials included in the NMA). This analysis showed a very similar magnitude of benefit for atezolizumab in both groups.
What alternative approach has the ERG suggested?	Proportions of both the TC3 and IC3 subpopulations should have been given to identify the scale of the issue.
What is the expected effect on the cost-effectiveness estimates?	This uncertainty leads to further uncertainty in the NMA that the company conducted, which feeds through to uncertainty surrounding the economic case.
What additional evidence or analyses might help to resolve this key issue?	As indicated in Table 4, Issue 3 below, a sensitivity analysis using the 22C3 TPS ≥ 50% subgroup (or TC3 subgroup) of IMpower110 in the NMA, could have helped to reduce uncertainty regarding the comparative efficacy of the two treatments in those who are eligible for pembrolizumab monotherapy according to the wording of the NICE recommendation in TA531 ('with at least a 50% tumour proportion score').

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG's key issues that relate to the clinical effectiveness evidence are detailed below in Tables 3 and 4.

Table 3. Issue 2 Atezolizumab effect over time

Report section	Sections 2.4 and 2.4.1
Description of issue and why the ERG has identified it as important	The company report log cumulative hazard plots for the trials included in their indirect comparison, which suggest that the assumption of proportional hazards may not have been met. The company tried to adopt a Fractional Polynomial (FP) approach to accommodate the possible changing relative hazards over time; but in relation to the atezolizumab pembrolizumab comparison, the direction of the effect increasingly appears to favour pembrolizumab over time. However, the comparison is complicated by different durations of follow up in the respective trials, dwindling sample sizes with increasing follow up, varying degrees of cross-over in the comparator arms of the different trials, and possibly varying degrees of immunotherapy re-challenge in the treatment arms of the trials. The above issues make it very difficult to determine if or how the relative efficacy of pembrolizumab and atezolizumab changes over time. See also issue 6 in relation to this point.
What alternative approach has the ERG suggested?	The ERG do not have a suggested alternative approach; but note that it is possible that the comparability between atezolizumab and pembrolizumab may not hold with time.
What is the expected effect on the cost-effectiveness estimates?	The company chose to use the standard random effects NMA HRs for cost-effectiveness. The ERG agree that this produces the most plausible outputs but have some remaining concern about potential for longer-term difference in effect.
What additional evidence or analyses might help to resolve this key issue?	The ERG is of the opinion that without additional and more homogeneous data between the two treatments, this uncertainty cannot be solved.

Table 4. Issue 3. Assays comparability

Report section	Sections 2.2.2 and 2.3
Description of issue and why the ERG has identified it as important	IMpower110 used assay SP142 to select IC3 (infiltrating immune cell PD-L1 expression >10%) or TC3 (tumour cell PD-L1 expression ≥50%) patients while the KEYNOTE trials used assay 22C3 to select patients with tumour proportion score ≥50%. The 22C3 assay is the most commonly used assay in UK clinical practice according to clinicians consulted by the company. The concern is how this translates into the NMA estimates, which should be developed on comparable populations across studies. IMpower110 also conducted a subgroup analysis using the 22C3 assay. While the atezolizumab/chemotherapy HRs were similar across assays, there is still a concern that the sample populations might not be fully matched. This issue relates to Issue 1 described above.
What alternative approach has the ERG suggested?	Acknowledging the double selection issue for IMpower110, selection of participants to inform the NMA could have been based on similar criteria (preferably the 22C3 assay given it is the more commonly used) or, if not possible, the proportions of both the TC3 and IC3 patients should have been given.
What is the expected effect on the cost-effectiveness estimates?	Any bias driven by lack of comparability between the IMpower110 and KEYNOTE trials populations will correspondingly lead to bias in the cost-effectiveness model.
What additional evidence or analyses might help to resolve this key issue?	IMpower110 also provides information on PD-L1 expression assed using the 22C3 assay and, therefore, a sensitivity analysis might be possible. To quantify similarity, it would be useful to identify the proportions of the TC3 and IC3 patients, separately.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

In addition to the uncertainty surround the hazard ratios from the NMA applied in the economic model, the ERG has three main issues with the company's cost-effectiveness case, as detailed in Tables 5, 6 and 7 below.

Table 5. Issue 4: the relative duration of treatment effects for the technology and its comparator

Report section	Sections 3.2.6 and 5.3
Description of issue and why the ERG has identified it as important	The company base case applies a treatment stopping rule for pembrolizumab at two years, in line with its NICE recommendation in TA521. Correspondingly they assume that this leads to loss of efficacy relative to chemotherapy from five years onward. For atezolizumab, no stopping rule is applied in line with its clinical evidence base, and therefore no loss of efficacy is assumed over the time horizon of the model. This capping of the treatment effect duration for pembolizumab is uncertain and not based on observed data, as is the added benefit of continued treatment with atezolizumab beyond two years. The capping of the pembrolizumab treatment effect, is an important determinant of the expected QALY difference between the two medicines in the cost-effectiveness model, and so the point estimate of the ICER is sensitive to changes in this assumption.
What alternative approach has the ERG suggested?	The ERG is not able to propose an alternative assumption with confidence since there are no long-term follow-up data (beyond five years) available for either medicine in this indication. Scenario analyses were performed to assess the impact of the assumption.
What is the expected effect on the cost-effectiveness estimates?	Assuming the treatment effect for permrolizumab is maintained further into the future, increases the expected QALY gain versus atezolizumab, and reduces its ICER. The ICERs in the report are not appropriate for decision making because they do not include a confidential PAS price for pembrolizumab. To give an indication of impact, increasing the treatment effect duration for pembrolizumab from 5 years to 8 years increases the deterministic point estimate of the QALY gain from 0.08 to 0.197 versus atezolizumab. However, the QALY difference remains uncertain given the uncertainty around the hazard ratios driving the difference in effects.
What additional evidence or analyses might help to resolve this key issue?	It is not an easy point to resolve given lack of longer term data available, but a more considered discussion of the assumption in light of all the available evidence and expert opinion may help to better inform the validity of the assumption.

Table 6. Issue 5: the time on treatment with pembrolizumab relative to its PFS curve

Report section	Section 3.2.6 (Treatment duration)
Description of issue and why the ERG has identified it as important	As no data were available for time on treatment with pembrolizumab, the company assumed this would follow progression free survival up to the stop rule at 2 years. However, data from the consort diagrams of the relevant KEYNOTE trials show that some patients stop treatment prior to progression and prior to two years (either due to toxicity or choice). Thus the company's assumption may overestimate treatment costs for pembrolizumab.
What alternative approach has the ERG suggested?	The ERG identified a study that provides Kaplan Meier time on treatment data for the relevant subgroups of KEYNOTE-042 which can be compared with the PFS Kaplan Meier data from the same data cut. This does suggest that time on treatment fall below PFS over the first year of follow-up, but then crosses it and runs above or very close to it in the second year. To assess the impact, the ERG has used the relative difference between the PFS and time on treatment curves from KEYNOTE-042, to adjust time on treatment in the model relative to selected PFS curve.
What is the expected effect on the cost-effectiveness estimates?	The change has a modest impact on pembrolizumab drug costs and the incremental cost of pembrolizumab compared to atezolizumab, reducing its ICER: from £560,832 per QALY gained in the company base case to £527,006 (including atezolizumab PAS, with pembrolizumab at list price).
What additional evidence or analyses might help to resolve this key issue?	Exploration of more formal methods of comparing available pembrolizumab PFS and time on treatment data, such as curve fitting to reconstructed patient level data, could better inform the relationship between the two outcomes and provide a more precise approach for the model.

Table 7. Issue 6: The validity of certain resource use frequencies in the progressive disease state of the model

Report section	Section 3.2.8 (Health care resource use)
Description of issue and why the ERG has identified it as important	The company referenced sources for GP home visits and occupational therapist visits in the progressive disease state of the model, which the ERG has been unable to trace. In addition, the ERGs clinical advisor felt that these seemed very high at 26.06 per year for application throughout time spent time in the PD state. These costs have an impact on the ICER resulting from differences in PFS between the alternatives. Those in the pembrolizumab arm spend a greater duration of time in this state of the model in the company base case.
What alternative approach has the ERG suggested?	Although the ERG has not identified an alternative source for these parameters, it prefers to reduce the frequencies based on clinical advice received.
What is the expected effect on the cost-effectiveness estimates?	Reducing the frequency of these visits by 50% has a modest impact on the incremental cost for pembrolizumab versus atezolizumab and reduces its ICER accordingly.
What additional evidence or analyses might help to resolve this key issue?	The ERG acknowledges the uncertainty around its alternative approach for these parameters, and would welcome some more clinical validation of the company's resource use frequencies as set out in Table 53 of the company submission, document B.

1.6 Summary of ERG's preferred assumptions and resulting ICER

In addition to the issues raised, the ERG identified several other minor issues that it prefers to revise. The ERGs preferred assumptions are the same as the company's except for the following:

1. No half-cycle correction for time on treatment (for both drugs), to ensure all patients receive treatment in the first cycle of the model.
2. Adjustment of pembrolizumab PFS curve to ensure it always remains below OS. This was to correct a minor issue of the PFS curve crossing the OS curve in the tail of the distribution in the company's base case (see section 4.3).
3. Pembrolizumab time to subsequent chemotherapy based on extrapolated PFS rather than applied immediately to all who discontinue at the two-year stopping point (section 4.1).
4. Pembrolizumab time on treatment adjusted relative to PFS using data from KEYNOTE-042 (as a proposed solution to issue 5 above).

5. Assuming 50% receive subsequent therapy rather than 100%, in line with the company's clinical expert opinion that they received at the clarification stage.
6. Assuming a 50% reduction in GP home visits and therapist visits in the progressive disease health state of the model, given the ERGs inability to identify the companies applied frequencies in the stated sources and the ERGs clinical expert advice.

The impact of each individual change is documented in Table 8. These results are not appropriate for decision making as they do not include the PAS price available for pembrolizumab. A confidential appendix with the appropriate PAS price for pembrolizumab will be provided for the committee.

Table 8 Summary of the ERGs preferred assumptions and ICER (PAS price for atezolizumab, list price for pembrolizumab)

Scenario	Incremental cost (atezo versus pembro)	Incremental QALYs (atezo versus pembro)	ICER (change from company base case)
Company base case	-47,059	-0.084	560,832
1. No half cycle correction for time on treatment	-47,554	-0.084	566,728
2. Pembro PFS adjusted to always remain below OS in the tail of the distribution	-47,066	-0.084	561,530
3. Pembrolizumab time to subsequent chemotherapy based on extrapolated PFS	-46,770	-0.084	557,388
4. Pembrolizumab time on treatment adjusted relative to PFS using data from KEYNOTE-042	-44,221	-0.084	527,006
5. Assume 50% receive subsequent therapy rather than 100%	-46,768	-0.084	557,358
6. Assume 50% reduction in GP home visits and therapist visits in the progressive disease health state	-46,171	-0.084	550,242
ERG base (all combined changes)	-43,715	-0.084	521,544
ERG base (probabilistic)*	-43,080	-0.14	309,723

*Caveat: PSA does not include distributions on the relative hazards used to adjust the pembrolizumab time on treatment curve relative to its PFS curve in change number 4.

Rather than factor in changes to the assumptions about treatment effect durations in the ERG base case, several additional scenarios were conducted to explore the impact of this using the ERG base case as the reference point. These are presented in section 5.3 of the report.

As indicated, the company also provided a cost-comparison analysis which assumes equal efficacy between treatment arms. The committee may find this appropriate for decision making should they believe there is sufficient evidence to assume equal efficacy between the alternatives in the relevant population.

1 INTRODUCTION AND BACKGROUND

1.1 Introduction

The relevant health condition for this submission is untreated advanced non-small-cell lung cancer. The company's description of the prevalence, symptoms and complications of non-small-cell lung cancer (NSCLC) generally accurate and in line with the decision problem. The relevant intervention for this submission is atezolizumab monotherapy as a first line treatment.

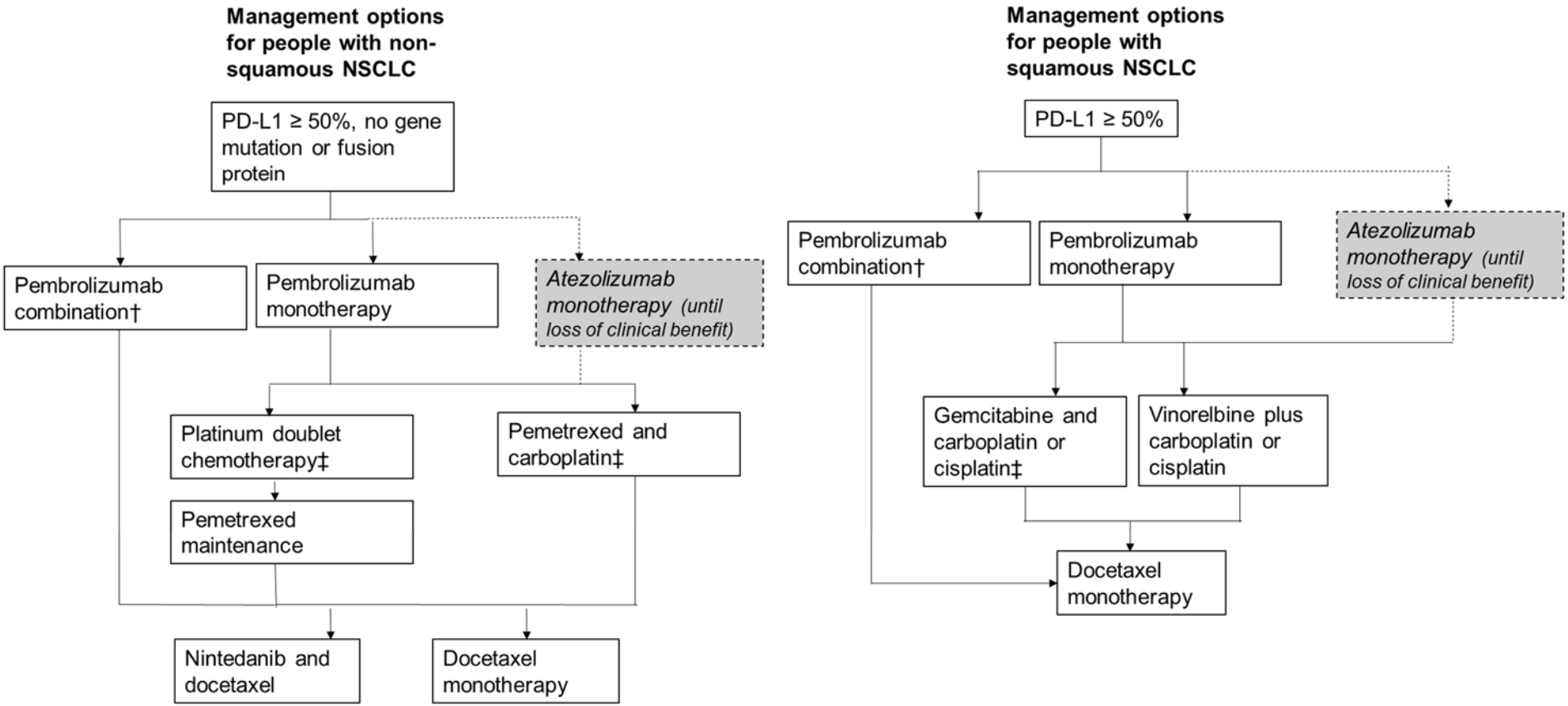
1.2 Background

Lung cancer is the UK's third most common cancer with a yearly incidence of approximately 47,200 cases.(1) NSCLC is the predominant subtype of lung cancer, accounting for 88% of all lung cancer cases in the UK in 2018.(2) NSCLC can be further divided into two major histologic types: non-squamous, representing over half of all NSCLC, and squamous, which accounts for approximately 25-30% of NSCLC cases.(3) In 2016, 70% of patients diagnosed with lung cancer in the UK had stage III or IV disease.(4) More than half of NSCLC patients are diagnosed with distant disease, which contributes to poor survival prognosis, along with advanced stage of disease at time of initial diagnosis, poor performance status and history of unintentional weight loss.(5) The 5-year survival of all treated and untreated lung cancer patients with stage IV disease is 3%, and 5-year survival rates for patients with distant metastatic NSCLC is only 6%.(6, 7) Advanced stage NSCLC has a negative impact on health-related quality of life (HRQoL). Disease-related symptoms include pain, fatigue, dyspnea, and cough, which can increase in frequency and intensity during disease progression.(8-12)

Molecular testing for epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, ROS1, or PD-L1 (programmed death-ligand 1) expression is recommended for all patients with NSCLC to inform treatment options. Determination of PD-L1 tumour expression is used to judge suitability for checkpoint inhibitor therapy and several immunohistochemistry (IHC) assays are routinely used in UK practice to identify patients who would benefit from therapy, including 22C3 (Dako), SP142 (Ventana) and SP263 (Ventana).(13, 14) In a global observation study of 2368 patients, assessed using the 22C3 test, 22% of patients had high PD-L1 expression (tumour proportion score [TPS] $\geq$50%), 52% had TPS $\geq$1%, and 48% had TPS<1%.(15) Atezolizumab, is a humanized IgG monoclonal antibody, which attaches itself to the PD-L1 protein on cancer cells, and reduces its effects by increasing the ability of the immune system to attack cancer cells and slow disease progression.(16)

The company describes the management of metastatic squamous and non-squamous NSCLC, whose tumours have PD-L1 expression ≥50%, and who do not have EGFR mutant or ALK positive NSCLC in section B.1.3.2 of the CS, and presents the current clinical care pathway based on the current NICE guideline NNG122 in Figure 1, Document B. This pathway is reproduced by the ERG as Figure 1.[17]

Figure 1. First-line treatment algorithm for adult patients with metastatic non-squamous and squamous NSCLC whose tumours have a PD-L1 expression ≥50% and who do not have EGFR mutant or ALK-positive NSCLC (including atezolizumab positioning)[17]



† Available via the Cancer Drugs Fund

‡ This combination/some of these combinations of drugs do not have a UK marketing authorisation for this indication

The grey box indicates the proposed positioning of atezolizumab

1.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 9. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 3.

Table 9 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with non-squamous or squamous untreated metastatic non-small cell lung cancer (NSCLC) with PD-L1 positive tumour expression and without epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-positive mutations.	Adult patients with [redacted].	Population in accordance with anticipated licence and trial population, i.e. metastatic NSCLC patients with high PD-L1 expression.	The CS addresses a narrower population than that specified in the NICE final scope and focuses on adult patients with [redacted]. The company state that the population addressed in the CS is in accordance with the anticipated licence for atezolizumab. The ERG clinical expert is of the opinion that patients with high PD-L1 status with a high immune background are a select group that are most likely to respond well to the study drug.
Intervention	Atezolizumab	Per final scope.	N/A	The intervention described in the CS matches that described in the NICE final scope. Atezolizumab is administered intravenously at a recommended dose of: 840 mg every two weeks, or 1200 mg every three weeks, or 1680 mg every four weeks. The initial dose should be administered over 60 minutes but, if the first infusion is well-tolerated, subsequent infusions may be delivered over 30 minutes. Treatment is recommended until loss of clinical benefit or the patient experiences unmanageable toxicity.[13] Atezolizumab is currently approved by the European Medicines Agency

				(EMA) for several indications, and an application to extend the licence [redacted] was submitted to the EMA in November 2019. The company expect marketing authorisation for this indication in [redacted]. The company provide details of atezolizumab in section B.1.2 and Appendix C of the CS.
Comparator	For people whose tumours express PD-L1 with at least a 50% tumour proportion score: • Pembrolizumab For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with or without pemetrexed maintenance treatment For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour proportion score below 50%: • Pemetrexed in combination with a	Pembrolizumab	Per final scope, pembrolizumab is the appropriate comparator with respect to the patient population, i.e. metastatic NSCLC patients with high PD-L1 expression.	The CS addresses a narrower selection of comparators than that specified in the NICE final scope. The company collected insights on prescribing patterns from 24 lung cancer consultants from NHS hospitals in England and Scotland. These data are presented in Table 3, Document B of the CS. The data indicate that pembrolizumab monotherapy is the dominant first-line standard of care, followed by pembrolizumab in combination with chemotherapy (through the Cancer Drug Fund), and with only a small number of patients being prescribed chemotherapy alone. The ERG clinical expert agrees with the company's description of the current UK clinical management options and prescribing patterns. The ERG note that for IMpower110, the company does not report a clear breakdown of the number of patients who met the IC3 definition (infiltrating immune cell PD-L1 expression $\geq$10%) and those who met the TC3 definition (tumour cell PD-L1 expression $\geq$50%) in the main CS (Documents A, B and Appendices). Since the NICE recommendation for pembrolizumab in untreated PD-L1 positive metastatic NSCLC is

	platinum drug (carboplatin or cisplatin) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%: Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)			conditional on a tumour proportion score of at least 50% (TA531), the ERG is currently unclear whether pembrolizumab is the relevant comparator for IC3 patients. However, the number of patients in IMpower110 in this category is likely to be small. The company also provide an exploratory analysis to assess the relative treatment effect in IMpower110 for high PD-L1 expression groups defined by different assays, including TPS ≥ 50% as defined by the 22C3 assay (used to determine PD-L1 expression in the KEYNOTE trials included in the NMA). This analysis showed a very similar magnitude of benefit for atezolizumab in both groups.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment health-related quality of life	Per final scope.	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment health-related quality of life	The outcomes in the CS matches the outcomes described in the final scope. The company reports primary overall survival (OS) analysis with a clinical cut-off date (CCOD) of 10th September 2018 from the IMpower110 trial, which is the key source of evidence submitted by the company. The company also reports an exploratory OS analysis with the CCOD of 4th February 2020. The exploratory analysis is of long-term follow-up data [redacted].
Subgroups	If evidence allows, subgroup analysis by: • Level of PD-L1 expression Squamous and non-squamous status	No subgroups considered.	The population under consideration for this appraisal is already limited to the highest level of PD-L1 expression and cannot be subgrouped further. The IMpower110	The ERG clinical expert has indicated that, while squamous and non-squamous patients are treated differently for some treatment options, these patients are not treated differently for immunotherapy. The ERG, therefore, has no concerns with the company decision to not carry out subgroup analysis by squamous and non-squamous patient status.

			study included patients with both squamous and non-squamous histology. However, the trial was not statistically powered to assess efficacy in either subgroup. Consequently, subgroup analysis by histology is not appropriate.	
Special considerations including issues related to equity or equality	N/A	N/A	N/A	The ERG agrees with the company that there are no anticipated equality issues related to atezolizumab

2 CLINICAL EFFECTIVENESS

2.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The ERG appraisal of the company's systematic review methods is summarised in Table 10 below.

Table 10. ERG appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D.1 of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research, CDSR and HTA organisations for evidence syntheses, and relevant conference proceedings. Details provided in Appendix D.1.1.1 of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	See Table 1, Appendix D.1.1 of the CS.
Was study selection conducted by two or more reviewers independently?	Yes	See Appendix D.1.1.3 of the CS.
Was data extraction conducted by two or more reviewers independently?	Yes	See Appendix D.1.15 of the CS
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	See Table 39, Appendix D.1.3 of the CS.
Was risk of bias assessment conducted by two or more reviewers independently?	Yes	Two reviewers independently assessed the risk of bias for each included study using the Cochrane Risk of Bias tool. Any disagreements were

		resolved through discussion or by consulting a third reviewer
Was identified evidence synthesised using appropriate methods?	Yes	NMA: See Section B.2.9.2 to B.2.9.4 , Appendix D.1.4 Appendix D.1.5 for methods and B.2.9.5 to B.2.9.7, D.1.5 for results. Heterogeneity was assessed in B.2.9.8 and D.1.6 Assumptions also investigated.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. The results are presented in Table 11.

Table 11. Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

2.1.1 Critique of evidence synthesis methods

Based on a systematic literature review, the company identified 12 relevant studies. The key evidence for the efficacy and safety of atezolizumab first-line monotherapy in advanced NSCLC is provided by one Phase III, multicentre, open-label randomised controlled trial, the IMpower110 trial.[18] In the absence of a direct head-to-head

comparison with atezolizumab and pembrolizumab, the company performed a series of indirect comparisons based on a connected network of the 12 RCTs.

2.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

2.2.1 Included studies

Details of the key clinical effectiveness evidence are provided in Table 4, Document B, of the CS and are reproduced by the ERG as Table 12.

Table 12. Key clinical effectiveness evidence

Study	IMpower110
Study design	Randomised, Phase III, global, multicentre, open-label study
Population	PD-L1–selected (≥1% of TC or IC covering ≥1% of the tumour area [TC1/2/3 or IC1/2/3]*), chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC without EGFR mutations or ALK translocations
Intervention	Atezolizumab
Comparator(s)	Cisplatin or carboplatin and pemetrexed (non-squamous) or gemcitabine (squamous)
Application for marketing authorisation	Yes
Used in the economic model	Yes
Rationale for use/non-use in the model	The IMpower110 trial comprises the relevant population, intervention, comparators and outcomes

IC: immune cells; NSCLC: non-small cell lung cancer; TC: tumour cells

The IMpower110 trial compared atezolizumab with cisplatin or carboplatin and pemetrexed, or gemcitabine in PD-L1–selected (≥1% of TC or IC covering ≥1% of the tumour area [TC1/2/3 or IC1/2/3]), chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC without EGFR mutations or ALK translocations. Patients with non-squamous disease were randomized 1:1 to receive either atezolizumab alone or pemetrexed in combination with cisplatin or carboplatin. Patients with squamous disease were randomized 1:1 to receive either atezolizumab alone or gemcitabine in combination with cisplatin or carboplatin. The intended

number of treatment cycles of chemotherapy (four or six cycles) was specified by the investigator prior to study randomization. Crossover from chemotherapy to atezolizumab was not allowed. Atezolizumab treatment continued as long as patients were experiencing clinical benefit, as assessed by the investigator, or until unacceptable toxicity or death.

[redacted] The CS, therefore, considers data for 107 patients randomised to atezolizumab and 98 patients randomised to chemotherapy in IMpower110. The groups were well balanced for participant baseline characteristics, including participant demographics, ECOG performance status, HRQoL, and squamous/non-squamous status. Slightly more participants were aged under 65 years in the atezolizumab arm and the number of participants who had a previous history of tobacco use was higher in the atezolizumab arm compared with the chemotherapy arm (78/107 [72.9%] versus 54/98 [55.1%]); however, when combined with current smoking status, the ERG believe this difference is unlikely to influence the trial results (91.6% of participants had current or previous tobacco use in the atezolizumab compared with 84.7% in the chemotherapy arm). Participants in both arms were mainly white, male, with a history of tobacco use and had a baseline ECOG performance status of 1. The ERG clinical expert's opinion is that trial participants are representative of patients seen in UK practice.

The company presents details of the participant demographics and baseline characteristics in Table 6, Document B, of the CS. The ERG provide details of the demographic and baseline characteristics of patients enrolled in IMpower110, along with those of patients enrolled in the KEYNOTE-042 and KEYNOTE-024 trials, in Table 17 of this report.

The primary endpoint of IMpower110 was OS. An interim analysis was planned for the TC3 or IC3 subpopulation when approximately 96 OS events and an event-patient ratio of 45% had occurred. If the OS interim analysis was not statistically significant, the final analysis would be conducted when approximately 135 OS events had occurred in the subpopulation, and if this analysis was statistically significant, OS would be tested at planned interim and final analyses in the TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 subpopulations. The final investigator-assessed progression-free survival (PFS-INV) is presented without formal statistical testing as the company

state that secondary endpoint of PFS can only be tested formally when the primary endpoint is positive in all three PD-L1 subgroups. At clarification, the company indicated that this strict regime was put in place to control for type 1 errors at 5% level in response to several protocol participant eligibility change over the course of recruitment. Further, PFS was dropped to be a secondary outcome and tested only once OS was completed. The ERG are not entirely convinced of this approach.

The methodological quality of the IMpower110 trial was judged by the company to be at low risk of bias for all domains with the exception of blinding of outcome assessors, which was judged to be unclear (section section B.2.5 of the CS). The ERG checked the quality assessment against the study protocol (provided as an appendix to the Herbst et al 2020 New England Journal of Medicine article) and agree with the company's assessment of the methodological quality of the IMpower110 trial.[19]

2.2.2 Primary and secondary efficacy endpoints in IMpower110

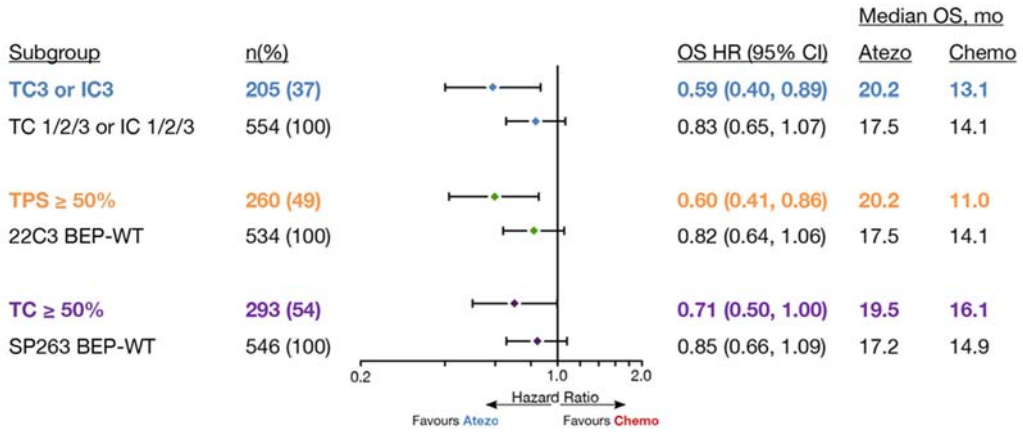
An overview of the efficacy results for the TC3 or IC3 subpopulation is presented in Table 13 below (reproduced from Table 8, Section B.2.6.1 of the CS).

Primary efficacy endpoint: overall survival

The median duration of survival follow-up was 15.7 months, with [redacted] and [redacted] death events occurring in the atezolizumab and chemotherapy arms, respectively at the time of the clinical cutoff date of 10th September 2018. Treatment with atezolizumab was associated with a 41% reduction in the risk of death compared with chemotherapy. The Kaplan-Meier estimated median OS was 7.1 months longer in the atezolizumab arm compared with the chemotherapy arm (20.2 months versus 13.1 months, respectively; stratified HR: 0.59 [95% CI, 0.40, 0.89]; p=0.0106).

The company presents OS by key subgroups within the IMpower110 TC3/IC3 subpopulation in section B.2.6.7 and Appendix G of the CS. OS favoured atezolizumab compared with chemotherapy across almost all subgroups, including patients with high PD-L1 expression across all PD-L1-IHC assays. The company present OS by the different IHC assays in Figure 14 of the CS, and this is reproduced by the ERG as Figure 2 below. The company state that improvement in OS in the atezolizumab arm compared with the chemotherapy arm is demonstrated across the IHC assays.

Figure 2: OS by high PD-L1 expression subgroups (defined by the SP142, SP263, and 22C3 assays)[20]



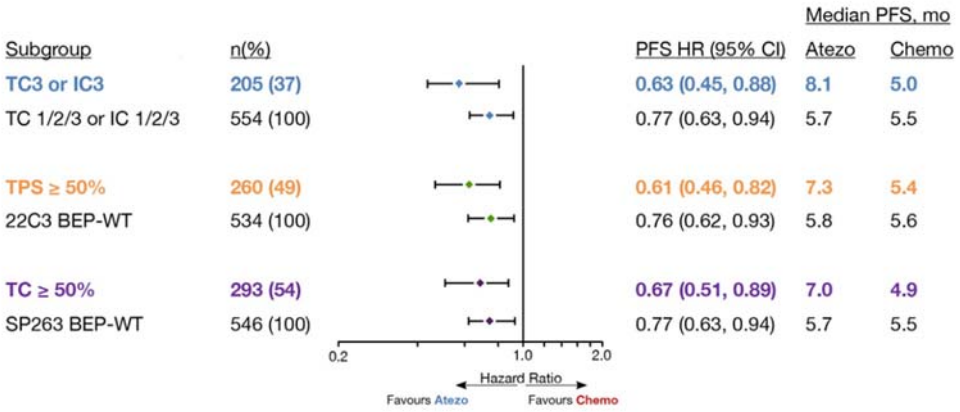
BEP: biomarker-evaluable population; CI: confidence interval; HR: hazard ratio; IC: immune cells; OS: overall survival; TC: tumour cells; TPS: tumour proportion score
Colour code: blue = SP142, orange = 22C3, purple = SP263
Note:

- TC1/2/3 or IC1/2/3 population represents the SP142-enrolled IMpower110 population without EGFR or ALK genetic alterations
- TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1
- Stratified HRs for SP142 and unstratified HRs for 22C3 and SP263

Secondary endpoints: progression-free survival, objective response rate, duration of response

The company state that PFS-INV could not be formally tested as OS had not reached statistical significance in the TC2/3 or IC2/3 subpopulation at the time of the clinical cutoff date of 10th September 2018. The company state that the p-values for PFS reported in the CS should be treated as descriptive only. At September 2018 the median PFS was 3.1 months longer in the atezolizumab arm than in the chemotherapy arm (5.0 months versus 8.1 months, respectively; stratified HR 0.63 [95% CI: 0.45, 0.88]). The company present their analysis of PFS in the PD-L1 subpopulations by the different IHC assays in Figure 27 of the CS appendices, and this is reproduced by the ERG as Figure 3 below.

Figure 3 PFS in PD-L1 subpopulations by different IHC assays[20]



Stratified HRs for SP142 TC3 or IC3-WT; unstratified HRs for all other subgroups.

Atezo: atezolizumab; BEP: biomarker-evaluable population; chemo: chemotherapy; HR: hazard ratio; PFS: progression-free survival; TC: tumour cell; WT: wild type

By considering the hazard ratios alone, the different assay give very similar results. However, the comparator groups in each of the trials may differ depending on the assay used, thereby not fully comparing like with like. While assuming that these different methods of assessing PD-L1 are comparable the company do acknowledge this limitation by suggesting that 'Sensitivity analyses may be possible with PD-L1 expression reassessed using 22C3 assay in IMpower110'. The ERG is of the opinion that such sensitivity analyses would have been beneficial. A break down further of the IC3 group would also be relevant.

Investigator-assessed confirmed ORR was higher in the atezolizumab arm compared with the chemotherapy arm (38.3% [95% CI: 29.08, 48.22] versus 28.6% [95% CI: 19.90, 38.58]), as measured by RECIST version 1.1 criteria.

[redacted]. The median duration of response was not reached in the atezolizumab arm while the chemotherapy arm was 6.7 months at the time of the analysis.

Table 13. Overview of efficacy in the TC3 or IC3 subpopulation of IMpower110[21]

Parameter	Atezolizumab	Chemotherapy
Primary Endpoint: Overall Survival		
TC3 or IC3 subpopulation	n = 107	n = 98
Patients with event (%)	[redacted]	[redacted]
Median duration of survival (95% CI) (months)		
Median OS, months	20.2	13.1
Stratified Hazard Ratio (95% CI)	0.59 (0.40, 0.89)	
p-value (Stratified log-rank)	0.0106	
Secondary Endpoints		
Progression-Free Survival		
TC3 or IC3 subpopulation	n =107	n = 98
Patients with event (%)	[redacted]	[redacted]
Median duration of PFS-INV (95% CI) (months)	8.1 (6.8, 11.0)	5.0 (4.2, 5.7)
Stratified Hazard Ratio (95% CI)	0.63 (0.45, 0.88)	
p-value (Stratified log-rank)	0.007[a]	
Objective Response Rate		
TC3 or IC3 subpopulation	n =107	n = 98
ORR (%)	38.3%	28.6%
(95% CI)	(29.08, 48.22)	(19.90, 38.58)
Duration of Response		
TC3 or IC3 subpopulation	n = 41	n = 28
Median DOR	NE	6.7
(95% CI)	(11.8, NE)	(5.5, 17.3)

CI: confidence interval; DOR: duration of response; NE: Not estimable; PFS: progression-free survival; WT: wild-type
Summaries of Time-to-Event (median, percentiles) were Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratification factors for the TC3 or IC3-WT population were: sex (male vs. female) and ECOG (0 vs. 1).
[a] p-value is descriptive only

Subsequent anti-cancer therapy

The company reports details of subsequent anti-cancer therapies in section B.2.6.3, Table 9 of the CS. A higher percentage of patients in the chemotherapy arm than in the atezolizumab arm received more than one anti-cancer therapy (46.9% versus 24.3%) and subsequent immunotherapy (29.6% versus 1.9%).). The majority of patients in the atezolizumab arm received subsequent chemotherapy.

IMpower110 TC3 or IC3 subpopulation exploratory analysis

The company present in in section B.2.7 of the CS the results of an exploratory analysis of the TC3 and IC3 subpopulations at the same time as the final analysis of OS for the TC2/3 or IC2/3, and TC1/2/3 or IC1/2/3 subpopulations (cutoff date 4th February 2020). Results of this exploratory analysis show [redacted]

The company present OS by the different IHC assays in Table 13, Document B, of the CS, which is partially reproduced by the ERG as Table 14 below. The company note that [redacted] in the atezolizumab arm compared with the chemotherapy arm was observed using the IHC assays. *The ERG have the same reservations explained earlier in the text about the comparability of the different assays.*

Table 14. OS by high PD-L1 expression subgroups as defined by the SP142, SP263, and 22C3 Assays (CCOD: 04 February 2020)[22]

Subgroups	n	HR	Atezolizumab Median OS, months	Chemotherapy Median OS, months
TC3 or IC3 (SP142)	205	[redacted]	[redacted]	[redacted]
TPS ≥50% (22C3)	260	[redacted]	[redacted]	[redacted]

Adverse reactions

The company presents the results of the IMpower110 primary and exploratory safety analyses (cutoff date 4th February 2020) in section B.2.10 of the CS, and the ERG

presents a summary of these results in Table 15 below. The safety analysis was performed on all treated patients (not just on the TC3 and IC3 subpopulations), including patients who received any amount of atezolizumab (n=286) and patients who received chemotherapy only (n=263). The median treatment duration was 5.3 months in the atezolizumab arm. In the chemotherapy arm, median treatment duration was 2.1 months for cisplatin, 2.3 months for carboplatin, 2.6 months for gemcitabine and 3.5 months for pemetrexed.[21] Fewer atezolizumab patients experienced treatment-related adverse events (TRAEs) than chemotherapy patients (60.5% versus 85.2%, respectively), with most patients experiencing Grade 3-4 TRAEs (12.9% versus 44.1% in the atezolizumab and chemotherapy arms, respectively), the most common of which were anaemia, nausea, neutropenia and thrombocytopenia (all with chemotherapy). These increased slightly in both arms for the longer available data cut, [redacted] of atezolizumab patients compared with [redacted] of chemotherapy patients. Numbers of patients experiencing serious TRAEs was lower in the atezolizumab arm compared with the chemotherapy arm (8.4% versus 15.6%, respectively in the primary analysis) and hardly changed ([redacted] versus [redacted], respectively) in the exploratory analysis. One patient (0.4%) died in the chemotherapy arm (due to pancytopenia) and no patients died in the atezolizumab arm.

A higher proportion of patients who received atezolizumab experienced adverse events of special interest events (AESIs) compared with patients who received chemotherapy (40.2% versus 16.7%, respectively). The most common AESIs (≥5%) included hepatitis (diagnosis and lab abnormality), rash, and hypothyroidism. In particular, [redacted] There were [redacted] Grade 5 AESIs, the [redacted] AESIs were Grade 1-2 and [redacted]. Immune-mediated AEs occurred more frequently among patients receiving atezolizumab than those receiving chemotherapy (40.2% versus 16.7%, respectively). Most common immune-mediated AEs (≥5% in either arm) were hepatitis and hepatic laboratory abnormalities, rash and hypothyroidism. As expected, immune-mediated AEs requiring systemic corticosteroid treatment were higher among patients treated with atezolizumab, compared with those treated with chemotherapy ([redacted] versus [redacted] respectively).

Table 15. Summary of the IMpower110 safety profile (primary and exploratory analyses)

	Primary analysis (cutoff date 10th September 2018)		Exploratory analysis (cutoff date 4th February 2020)	
	Atezolizumab n=286	Chemotherapy n=263	Atezolizumab (n=286)	Chemotherapy (n=263)
Any-cause AE, n (%)	258 (90.2)	249 (94.7)	[redacted]	[redacted]
Related AE (%)	173 (60.5)	224 (85.2)	[redacted]	[redacted]
Grade 3-4 AE, n (%)	91 (31.8)	141 (53.6)	[redacted]	[redacted]
Treatment-related Grade 3-4 AE	37 (12.9)	116 (44.1)	[redacted]	[redacted]
Serious AE, n (%)	81 (28.3)	75 (28.5)	[redacted]	[redacted]
Treatment-related serious AE	24 (8.4)	41 (15.6)	[redacted]	[redacted]
Grade 5 AE, n (%)	11 (3.8)	11 (4.2)	[redacted]	[redacted]
Treatment-related Grade 5 AE	0	1 (0.4)	[redacted]	[redacted]
AE leading to any treatment withdrawal, n (%)	18 (6.3)	43 (16.3)	[redacted]	[redacted]
Immune-mediated AE, n (%)	115 (40.2)	44 (16.7)	NR	NR
Grade 3-4 immune-mediated AE	19 (6.6)	4 (1.5)	NR	NR
Immune-mediated AE requiring use of corticosteroids, n (%)	[redacted]	[redacted]	NR	NR
Adverse events of special interest (AESIs)				
All Grade AESIs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Grade 3-4 AESIs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
All Grade AESIs requiring use of corticosteroids, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

*One more Grade 5 AE (pulmonary oedema) in the atezolizumab arm since the primary analysis
AE: adverse event; AESI: adverse event of special interest; Atezo: atezolizumab; CCOD: clinical cut-off date

Overall, the ERG agrees with the company that the safety profile of atezolizumab is similar between the primary analysis and the exploratory analysis and that no new safety signals were identified among patients enrolled in the IMpower110 trial.

Health-related quality of life

In section B.2.6.6 of the CS, the company presents details of the impact of lung cancer treatment and symptoms on HRQoL, as measured by the Symptoms in Lung Cancer (SILC), European Organisation for the Research and Treatment of Cancer quality of life questionnaire EORTC QLQ-C30 and EORTC QLQ-LC13 tools. The ERG notes the company's statement that interpretation of patient-reported outcome (PRO) data may be limited beyond week 57 due to the low number of patients remaining on treatment and, therefore, the low number of patients expected to complete PRO assessments. The ERG have no concerns regarding the methods used to collect PRO data or participant response rates. There were no clinically meaningful improvements in mean HRQoL in either treatment arm; however, from week 24 to week 57, the decline in mean HRQoL was smaller in the atezolizumab arm than in the chemotherapy arm. Time to deterioration of lung cancer-related symptoms [redacted] in both arms. More specifically, there were non-clinically significant changes from baseline in global health status for both arms until week 24 after which the chemotherapy arm had clinically significant decline. Physical functioning had albeit not clinically important early improved function to baseline in both arms with atezolizumab having some advantage until week 20 after which the two arms were similar but not clinically different to baseline. Coughing symptoms in both arms improved, being clinically meaningful by week 42 and 48 for chemotherapy and atezolizumab respectively, but returning to baseline levels thereafter. Chest pain and fatigue, were improved in the atezolizumab arm compared to their baseline and

with the chemotherapy arm although not with any clinical meaning; chest pain and fatigue both increased after week 42 and 30 respectively, in both arms. Baseline changes in dypsnoea were not clinically meaningful for either treatment arm.[23] The chemotherapy group had raised nausea and vomiting levels compared to baseline and the atezolizumab group through out particularly early on but these were not of clinical relevance.

2.2.3 Meta-analyses

As IMpower110 was the only RCT comparing atezolizumab versus chemotherapy in treatment-naïve, high PD-L1 expression, NSCLC patients, the company did not conduct a meta-analysis.

2.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In the absence of relevant direct head-to-head data, the company conducted a network meta-analysis (NMA) based on a connected network of 12 RCTs. Details of these trials are provided in Table 10, Appendix D of the CS.

In addition to the IMpower110 trial, the company included the following Roche trials in the indirect comparison: IMpower150, IMpower130, IMpower131, and IMpower132. The remaining trials in the network included: KEYNOTE-021, KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, KEYNOTE-407, CHECKMATE-026, and CHECKMATE-227. The company present the characteristics of these trials in Table 13 of Appendix D. In order to align with the marketing authorisation, the company excluded the CHECKMATE-026 and CHECKMATE-227 trials, which assessed nivolumab versus chemotherapy, the pembrolizumab combination trials (KEYNOTE-021, KEYNOTE-189, KEYNOTE-047) and the atezolizumab combination trials (IMpower150, IMpower130, IMpower131, IMpower132) and focused on the atezolizumab monotherapy trial (IMpower110) and the two pembrolizumab monotherapy trials (KEYNOTE-024 and KEYNOTE-042). The patient target population was the PD-L1 >50% or TC3/ICT3 population with mixed histology (non-squamous or squamous). The ERG agree with the company's choice.

Details of the study design and baseline characteristics of the IMpower110 and KEYNOTE-042 and KEYNOTE-024 trials are provided in Tables 16 and 17.

The ERG is satisfied that, despite some differences, the participants' baseline characteristics are similar across the three trials in terms of age, ECOG status and disease stage. All three trials included participants with both squamous and non-squamous NSCLC and focused on patients with an absence of EGFR mutations or ALK translocations. Chemotherapy treatments varied between trials (see Table 16).

The ERG agree with the company that the definitions of OS and PFS are comparable between the trials. The methods used to assess PFS are, however, variable as the IMpower110 used progression based on investigator assessment (PFS-INV), whereas the KEYNOTE trials used blinded independent central review (PFS-IRC). The company have assumed PFS-INV and PFS-IRC are comparable for the purposes of the indirect comparison. Similarly, ORR as assessed by investigators in IMpower110 is considered comparable to ORR as assessed by an independent review committee in the other trials. The company acknowledge the limitation of these assumptions in the CS. *The ERG agree with the company that the heterogeneous methods for assessing PFS and ORR may represent a potential risk of bias.*

Different methods were used to determine PD-L1 expression across the trials.

- PD-L1 expression in KEYNOTE-024 and KEYNOTE-042 was determined on TCs using the 22C3 assay, whereas PD-L1 expression in IMpower110 was determined on TCs and ICs using the SP142 assay.

- KEYNOTE-024 only recruited patients whose tumours had the highest level of PD-L1 expression (TPS ≥50%), whereas IMpower110 and KEYNOTE-042 both recruited patients whose tumours had any PD-L1 expression.

Full details of the range of methods are presented by the company in Table 14, Appendix D of the CS, and the different assay tests and classification criteria used to determine PD-L1 expression are presented by the ERG in Table 16 in this report. The company recognises that the SP142 assay used in the IMpower110 consistently shows fewer tumour cells stained compared with the 28-8, 22C3 and SP263 assays; however, the company state that the reduced sensitivity of the SP142 assay only indicates that the assay may not detect patients with the lowest PD-L1 expression and is not less predictive than the other assays. The company also state that insights gathered from clinical experts across the country show that a patient is typically only tested with one assay and that the 22C3 assay is most prevalently used in the UK

(21 centres), followed by SP263 (5 centres) and by SP142 (1 centre), and that while variability between available assays and the limitations with SP142 are recognised, there is largely overlapping concordance across these assays and that any of them could be used to test for PD-L1 expression ahead of immunotherapy treatment. The company also cite their NSCLC atezolizumab monotherapy study OAK, a phase 3, open-label, RCT in which patients with previously treated NSCLC received atezolizumab monotherapy (n=425) or docetaxel (n=425). PD-L1 expression was evaluated using the SP142 and 22C3 assays.[24] Results showed that atezolizumab improves survival of in the TC1/2/3 or IC1/2/3 subpopulation irrespective of which assay was used.

The company presents the NSCLC definitions for 22C3, SP142, and SP263 used in the KEYNOTE studies and IMpower110 in **Error! Reference source not found.** of their clarification response.

The company present their risk of bias assessment of the trials included in the indirect comparison in Table 39, Appendix D.1.3 of the CS. The ERG has no concerns about the methodological quality of the trials included in the NMA.

Table 16. Comparison of study designs of the IMpower110, KEYNOTE-042 and KEYNOTE-024 trials

Study	IMpower110	KEYNOTE-042	KEYNOTE-024
Study design	Randomised, Phase III, global, multicentre, open-label study	Randomised, Phase III, multicentre open-label study	Randomised, Phase III, multicentre open-label study
Population	PD-L1–selected (≥1% of TC or IC covering ≥1% of the tumour area [TC1/2/3 or IC1/2/3]*), chemotherapy-naive patients with Stage IV non-squamous or squamous NSCLC without EGFR mutations or ALK translocations	Treatment-naïve, stage IV NSCLC, PD-L1 tumour proportion score ≥1% NSCLC	Chemotherapy-naïve, stage IV NSCLC, PD-L1 tumour proportion score of ≥50%, without EGFR or ALK mutations
Intervention(s)	Atezolizumab	Pembrolizumab	Pembrolizumab
Comparator(s)	Cisplatin or carboplatin and pemetrexed (non-squamous) or gemcitabine (squamous)	Carboplatin and pemetrexed (then pemetrexed maintenance for non-squamous) Carboplatin and paclitaxel (then pemetrexed maintenance for non-squamous)	Carboplatin or cisplatin and pemetrexed (non-squamous only) or Carboplatin or cisplatin and gemcitabine or carboplatin and paclitaxel
Assay used to determine PD-L1 expression	SP142 (Ventana) Subgroup efficacy analyses with 22C3 pharmDx assay and SP263	22C3 pharmDx (Agilent)	22C3 pharmDx (Dako)

Details of PD-L1 expression classification	NR	Expression was categorised by tumour presentation score, which was defined as the percentage of tumour cells with membranous PD-L1 staining	NR

Table 17. Demographics and baseline characteristics of the trials included in the NMA (IMpower110, KEYNOTE-042, KEYNOTE-024)

	IMpower100 TC3 or IC3 subpopulation		KEYNOTE-042		KEYNOTE-024	
Characteristic	**Atezolizumab n=107**	**Chemotherapy n=98**	**Pembrolizumab N=299**	**Chemotherapy N=300**	**Pembrolizumab N=154**	**Chemotherapy N=151**
Age, years						
Median	63	65.5	63.0	64.0	64.5	66.0
Range	33-79	33-87	(56.0–68.0)	(57.0–69.0)	(33-90)	(38-85)
Age group, n (%)						
<65 years	59 (55.1)	43 (43.9)	-	-	-	-
65-74 years	33 (30.8)	47 (48.0)	-	-	-	-
75-84 years	15 (14.0)	7 (7.1)	-	-	-	-
≥85 years	0	1 (1.0)	-	-	-	-
Sex, n (%)						
Male	79 (73.8)	64 (65.3)	205 (69)	210 (70)	92 (59.7)	95 (62.9)
Race, n (%)						
White	87 (81.3)	82 (83.7)	-	-	-	-
Asian	20 (18.7)	15 (15.3)	-	-	-	-

Black or African American	0	0	-	-	-	-
Multiple	0	0	-	-	-	-
Unknown	0	1 (1.0)	-	-	-	-
ECOG performance status, n (%)						
0	35 (32.7)	38 (38.8)	96 (32)	91 (30)	54 (35.1)	53 (35.1)
1	72 (67.3)	60 (61.2)	203 (68)	209 (70)	99 (64.3)	98 (64.9)
Tobacco use history, n (%)						
Never	9 (8.4)	15 (15.3)	64 (21)	67 (22)	5 (3.2)	19 (12.6)
Current	20 (18.7)	29 (29.6)	57 (19)	59 (20)	34 (22.1)	31 (20.5)
Previous	78 (72.9)	54 (55.1)	178 (60)	174 (58)	115 (74.7)	101 (66.9)
Histology at diagnosis, n (%)						
Non-squamous	80 (74.8)	75 (76.5)	192 (64)	186 (62)	125 (812)	124 (82.1)
Squamous	27 (25.2)	23 (23.5)	107 (36)	114 (38)	29 (18.8)	27 (17.9)
Disease status— no. (%)						
Locally advanced			27 (9)	35 (12)		

Metastatic			272 (91)	265 (88)		
Brain metastases			19 (6)	15 (5)	18 (11.7)	10 (6.6)
Previous treatment for non-metastatic disease— no. (%)						
Radiotherapy			40 (13)	39 (13)		
Neoadjuvant therapy			1 (<1)	5 (2)	3 (1.9)	1 (0.7)
Adjuvant therapy			8 (3)	4 (1)	6 (3.9)	3 (2.0)
Region of enrolment *— no. (%)						
Asia Pacific /East Asia	20 (18.7) *Asia Pacific	14 (14.3) *Asia Pacific	92 (31) *East Asia	94 (31) *East Asia	21 (13.6) *East Asia	19 (12.6) *East Asia
Europe	76 (71.0)	77 (78.6)	71 (24)	66 (22)	133 (86.4) *not EAST ASIA	132 (87.4) *not EAST ASIA
South America/Latin America	6 (5.6)	5 (5.1)	53 (18)	63 (21))		
North America	5 (4.7)	2 (2.0)				
Other			83 (28)	77 26)		

*

IMpower110 collected region enrolment data from Asia specific and South America, whereas KEYNOTE-024 and KEYNOTE-042 collected from East Asia and Latin America

2.4 Critique of the indirect comparison and/or multiple treatment comparison

Analyses were conducted for OS, PFS, ORR and the safety outcomes (TRAE, TRAE Grade 3+, TRSAE and withdrawal due to AEs) as having direct comparison between atezolizumab versus chemotherapy and between pembrolizumab versus chemotherapy; thus providing indirect comparison for atezolizumab versus pembrolizumab.

The patient population considered was the PD-L1 ≥ 50% or TC3/IC3 population, with mixed (non-squamous or squamous) histology. It is worth recalling that PD-L1 expression in the KEYNOTE trials was determined on **TCs** using the 22C3 assay, whereas in IMpower110 was determined on **TCs and ICs** using the SP142 assay.

The company have assumed that the different methods of assessing PD-L1 are comparable for the purpose of conducting their analyses. The ERG note the difference between the numbers of patients identified as ≥50% TPS by 22C3 and by SP142 in Figure 14, page 52 Doc B and Figure 27, page 284 of the company's Appendices. *The ERG's clinical expert opinion is that using different assays will identify slightly different patient populations, which creates uncertainty around whether these patients are suitable for both pembrolizumab and atezolizumab. Also, laboratories would not have the capacity or funding to perform multiple assays, thus decisions maybe made upon assessment with the alterative assay.*

The company has also assumed equivalence between the chemotherapy arms and between nab-paclitaxel and paclitaxel treatments. *The ERG clinical expert agrees that the appropriate chemotherapy treatments have been administered for the corresponding pathologies and, therefore, the company are correct to assume equivalence between treatments.*

For OS and PFS, analyses were conducted on both reported hazard ratio (HR) data and on individual patient survival times (reconstructed from Kaplan-Meier [KM] data for the KEYNOTE trials). The company submitted these reconstructed data at clarification. The ERG found only minor discrepancies in the reconstructed HR estimates for the KEYNOTE-042 trial compared with the originally published estimates. For OS, the published HR was 0.69 (95%CI: 0.56, 0.85) whilst the reconstructed HR was 0.70 (95%CI: 0.58, 0.86); for PFS the published HR was 0.81(95%CI: 0.67, 0.99) whilst the reconstructed HR was 0.83 (95%CI: 0.69, 1.00)]. The ERG was unable to verify these.

The possible networks are describe in the CS Appendix D.1.13 for all mixed non-squamous and squamous groups (Figure 1), the non-squamous group only (Figure 2) and the

squamous group only (Figure 3). The company for the purpose of the current evidence submission and in order to align with the marketing authorisation and reimbursement from NICE, only included IMpower110, KEYNOTE-024 and KEYNOTE-042 as assessing interventions relevant to this appraisal. The ERG are in agreement with the company's decision.

In addition to the standard HRs, the company also adjust for the effect of anti-cancer immunotherapy, using the Reserved Rank Preserving Structural Failure Time (RPSFT) method on the exploratory analyses data (CCDO: 4 February 2020). These additional analyses are presented in Appendix L, **Error! Reference source not found.** and **Error! Reference source not found.** (KM plot). They were based on data available at the 4 February 2020 cut. The company also include discount analyses at 10%, 30% and 50%, but conclude that the RPSFT estimate of OS HR is smaller and more strongly favours atezolizumab across all additional analyses: The original exploratory result was ([redacted] whilst the RPSFT result was [redacted]. The ERG consider that the underlying assumptions for cross-over adjustment methods are hard to prove and that these analyses are only useful as sensitivity analyses.[25] It is likely that the 'truth' lies somewhere between them. However, because of the different follow up lengths between the KEYNOTE and the IMpower110 trials, the company maintain that this effect increases the confounding due to subsequent therapies for the atezolizumab arms*. The ERG is of the opinion that although this may be the case, without similar analyses conducted on the KEYNOTE trials this cannot be determined with certainty.*

The company claim to adopt NMA methods in line with DSU recommendations, using a Normal distribution and identity link on the log HR's and associated standard errors for OS and PFS and a Binomial distribution and logit link for ORR and the safety outcomes.[26]

In addition, the company used a fractional polynomial approach (FP-NMA) stating that their methods follow those of Jasen et al. for OS and PFS.[27] The FP approach allows for modeling the hazard function with multiple parameters as a function of time, permitting the HR to change over time in the presence of non-proportional hazards. This approach was chosen since the profiles were potentially not parallel in the two arms (see section B.2.9.9, Figures 24 and 26), a basic assumption for proportional hazard models. *The ERG accept the company's initial rationale for presenting the FP-NMA approach.*

All outcomes were evaluated using both fixed and random effects models. The company used informative priors for the between study variances for the random models as suggested by Turner et al., 2015.[28] Models were assessed using the DIC for the non-FP models eventually favouring the random effects models for all outcomes. *The ERG consider the company approach appropriate.*

Table 18 shows the characteristics of the NMA.

Table 18. Characteristics of the company's NMA

Trials	Treatments	Population	Outcomes	Analysis methods
IMpower 110 KEYNOTE-024 KEYNOTE-042	Atezolizumab monotherapy Pembrolizumab monotherapy Chemotherapy	PD-L1 ≥50% or TC3/IC3 with mixed histology (non-squamous or squamous).	OS PFS ORR Safety outcomes (any TRAE, TRAE Grade 3+, any TRSAE, withdrawal due to AEs)	OS and PFS = time to event data allowing for time-varying HRs through the use of fractional polynomial models. ORR and safety outcomes = NMA assuming a binomial distribution and a logit-link. For all outcomes both fixed and random effects models.

For the FP-NMA models (OS and PFS) the company assessed the 1st and 2nd order polynomials as well as the proportional hazard exponential models. The company decided the 2nd FP models gave unrealistic extrapolations. The powers explored for the 1st polynomial reflect the Exponential, Weibull and Gompertz distributions, each with advantages depending on the outcome. However, for consistency the company decided to

adopt the Weibull FP-NMA model for both OS and PFS. The ERG understand the rationale for this decision.

All the NMA models seemed to have been run using 3 chains, 5000 burn-in iterations followed by 30000 samples, thinned by a factor of 6 (the default is 1).

The ERG attempted to replicate the standard proportional hazard models comparing the interventions to chemotherapy for IMpower110 and KEYNOTE-024 and KEYNOTE-042 using the reconstructed data the company supplied. While the IMpower110 results were comparable with the CS, the replicated results did not mirror either the CS results or the published results for the KEYNOTE-024 and KEYNOTE-042 trials. The ERG also attempted to run the standard NMA and FP-NMA, using code provided in the CS and with reference to other code. However, persistent errors occurred with each and while point estimated for the NMA were similar, they had very wide credible intervals. Although the FP models after revision compiled with the company specification, HR results were not available. The company sent their R and JAGs codes just prior to the ERG report submission, but due to time constraints, the *ERG was not in the position to verify the results*. *Therefore, the company results currently can only be taken at face value.*

The NMA results for OS and PFS were conducted by the company on the estimates from both the final and the exploratory analyses although they favour the CCOD Feb 2020 for extrapolation for cost effectiveness. The ERG presume this is similar for ORR and AEs.

Heterogeneity between the pembrolizumab studies was assessed for the HRs of OS and PFS and for the OR of ORR (note: AEs were only assessed for pembrolizumab in the KEYNOTE-024 study). The only cause of concern is for PFS and this casts some doubts about the reliability of the NMA PFS results.

2.4.1 Results of the NMA

The indirect comparisons from both the standard and the FP-NMA for OS and PFS imply no significant differences between atezolizumab and pembrolizumab. Similarly, there is no evidence from the presented results for difference between atezolizumab and pembrolizumab for the other outcomes (ORR and safety outcomes).

Table 19 presents a summary of the results of the direct comparison between atezolizumab and chemotherapy. A summary of the results of the indirect comparison between atezolizumab and pembrolizumab is reported in Table 20 below.

Table 19. Direct comparison between atezolizumab and chemotherapy in the IMpower110

	Primary analysis (CCOD: 10th September 2018)	Exploratory analysis (CCOD: 4th February 2020)
OS	HR_{AC}=0.59 (0.40, 0.89)	HR_{AC}=0.76 (0.54, 1.09)
PFS	Descriptive only HR_{AC}=0.73 (0.45, 0.88)	HR_{AC}=0.59 (0.43, 0.81)
ORR	38.3% (29.08, 48.22) vs 28.6%(19.90, 38.58) OR_{AC}=[redacted] Doc B, page 42	40.2%(30.8, 50.1) vs 28.6%(19.9, 38.6)
DOR	Median not reached for atezolizumab Median time to DOR was 6.7 for chemotherapy	
AEs	**Fewer** TRAE, TRAE Grade 3+, TRSAE and AEs leading to withdrawal in the atezolizumab arm **More** Immune–mediated AEs **More** AESIs but mainly at Grade 1-2	**Fewer** TRAE, TRAE Grade 3+, TRSAE and AEs leading to withdrawal in the atezolizumab arm **More** Immune–mediated AEs **More** AESIs mainly at Grade 1-2 and AESIs requiring systemic corticosteriods

HR_{AC}: Direct comparison Hazard Rate between ATZ and Chemo
OR_{AC}: Direct comparison Odds ratio between ATZ and Chemo

Table 20. Summaries of indirect comparisons between atezolizumab (ATZ) and pembrolizumab (PEMB) for OS PFS ORR and AEs. Based on the results of the IMpower110, KEYNOTE-024 and KEYNOTE-042 trials

Primary analysis (CCOD: 10th September 2018)			
OS	NMA	[redacted]	n/s; point estimates favours ATZ
Exploratory analysis (CCOD: 4th February 2020)			
OS	NMA	[redacted]	n/s
	FP-NMA		
	3 months	[redacted]	n/s; point estimates favours ATZ.
	6 months	[redacted]	n/s
	12 months	[redacted]	n/s; point estimate favours PEMB
	2+ years	This trend towards favouring PEMB continues with time but with widening credible limits and small sample sizes indicating they may be less reliable. The company expresses a concern that IMpower has longer follow up and many participants would go onto other therapies washing out possible ATZ/chemotherapy comparison. [the ERG is of the opinion that this should be similar for both interventions since the model accounts for time].	
PFS	NMA	[redacted]	n/s; point estimate slightly favours ATZ.
	FP-NMA		
	3 months	[redacted]	n/s; but point estimate favours ATZ
	12 months	[redacted]	n/s
	2+ years	Point estimates favour PEMB but sample sizes small. Treatment cross-over is not a concern here	
ERG presume: Exploratory analysis (CCOD: 4th February 2020)			
OOR	NMA only	[redacted]	n/s
AE's	NMA only	[redacted]	IMpower110 and KEYNOTE-024
	TRAE	[redacted]	n/s but point estimate favours PEMB
	TRSAE	[redacted]	n/s but point estimate slightly favours ATZ
	TRAE>=3	[redacted]	n/s but point estimate favours ATZ
	AE withdrawal	[redacted]	Marginally n/s: point estimate favours ATZ

1. ATZ: atezolizumab; PEMB: pembrolizumab
2. HR_{AP}: Indirect comparison Hazard Rate between ATZ and PEMB
3. OR_{AP}: Indirect comparison Odds Ratio between ATZ and PEMB
4. n/s: statistically non-significant

The company's conclusions for all the models is that there is insufficient evidence of a difference between atezolizumab and pembrolizumab for OS, PFS, ORR and safety outcomes. Based on their presented figures and estimates, the ERG largely agree with the company's conclusions. However, i) there is some doubt about maintenance of the comparable effect over time based on the FP-NMA model, ii) the robustness of the PFS results may be questioned, iii) the 'withdrawal due to AEs' outcome shows borderline results in favour of atezolizumab (Figure 19, Appendix D.1.5), and iv) the differing assays in the different studies detailed earlier may be a cause of concern with respect to the homogenerity of the sample population between the trails. For this latter point, SP142 (as used in IMpower110) is not widely in use in practice (only one UK centre) and the ERG's clinical advice has suggested this is not as sensitive as 22C3, which is commonly used in clinical practice (and used in the KEYNOTE trials). A breakdown of the IC3 and TC3 groups by means of a sensitivity analysis would have been useful.

2.5 Additional work on clinical effectiveness undertaken by the ERG

Despite several attempts, the ERG was unable to replicate the FP-NMA or indeed the standard NMA for OS and PFS. Recently received code may make their finer details more transparent.

2.6 Conclusions of the clinical effectiveness section

The company's decision problem is appropriate for addressing the final scope issued by NICE in relation to this appraisal. Overall, the ERG consider the methods used to conduct the systematic review of clinical effectiveness evidence to be in line with current methodological standards.

Results of the IMpower110 trial indicate that atezolizumab has statistical benefit over chemotherapy for OS and PFS based on the data available at the September 2018 cut; but only clinical benefit for OS based on the data available at the February 2020 data cut.

While patients who received atezolizumab were more likely to experience adverse events of special interest than patients who received chemotherapy in the IMpower110 trial, no unexpected adverse events were identified. The ERG have no concerns about the safety profile of atezolizumab based on the results of the IMpower110 trial.

In the absence of direct clinical evidence, the company conducted a NMA to indirectly estimate OS, PFS, ORR and safety outcomes to compare atezolizumab and

pembrolizumab. Three trials contributed to the NMA: IMpower110 assessing atezolizumab versus chemotherapy and KEYNOTE-024 and KEYNOTE-042 assessing pembrolizumab versus chemotherapy.

The ERG currently cannot verify the results, but mostly accepts the company's interpretation of the NMA results indicating that overall atezolizumab monotherapy (using IMpowere110 data) is comparable to pembrolizumab monothereapy (using both the KEYNOTE-24 and KEYNOTE-042 data). This is indicated by the NMA HR's. However, the FP-NMA results possibly suggests that this may not be sustained with time. The company have various suggestions for this, which could be plausible but the ERG would prefer a more cautionary approach. In addition, the ERG is unclear about the homogeneity of the study populations between the trials because of the differing assays used.

COST EFFECTIVENESS

3.1 ERG comment on company's review of cost-effectiveness evidence

The company reviewed previous economic evaluations of medicines for first line locally advanced or metastatic NSCLC. The method was described in an appendix with the studies identified and an overview provided in Section B3.1 on page 82 of the submission. The search was undertaken in October 2019 and included published studies, main HTA agencies (including NCE), conference abstracts, and searching the cited studies in the published economic evaluations. The review identified 57 published papers, 7 HTAs and 30 conference abstracts. In Appendix H the company provided tables summarising the methods and results of these studies over 115 pages, before concluding on page 428, "Consideration of the caveats and limitations of previous studies will ensure the most appropriate methods are utilised in future analyses, and robust cost-effectiveness estimates are achieved in this indication." However, it is not clear from the Appendix or from Document B what these were and it is difficult to trace any specific link between the SLR and the design of the model.

It could be argued that the SLR gave the company confidence in their design, but there is a sense that this was a huge amount of effort with no very visible returns. The ERG suggests the SLR could have been more focused. For example, it could have been restricted to previous economic evaluations of PD-L1 inhibitors and the specific ways they have modelled PFS and OS. It could also have been restricted to the economic evaluations in NSCLC most closely matching the current decision problem, where one medicine with a certain mechanism of action (MoA) is 'standard of care' and the HTA considers a second medicine with a similar MoA. This could also have sought previous experience on more specific issues such as under what circumstances clinical evidence is sufficiently similar to be considered a basis for a cost comparison / cost-minimisation analysis. These could potentially have been a more productive focus of the effort and more useful in shaping the submission.

No existing economic evaluations of atezolizumab monotherapy for untreated patients with advanced NSCLC were identified. Of greatest relevance to the current decision problem, is the economic model used to inform NICE guidance on pembrolizumab monotherapy for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531).[29] The company provided a comparison of some of their own model's features against this previous model (Document B, Table 27). More in-depth comparisons were, however, limited by the redaction of key modelling details from the TA531.

3.2 Summary and critique of the company's submitted economic evaluation by the ERG

3.2.1 NICE reference case checklist

Table 21. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, 20 years is in line with previous appraisals for this indication.
Synthesis of evidence on health effects	Based on systematic review	Yes, NMA of relevant trials
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes, EQ-5D-3L measured directly from patients in IMpower110
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, patients
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, UK general population tariffs.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the	Yes

	individuals receiving the health benefit	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome; NMA, network meta-analysis		

3.2.2 Model structure

This was presented in Document B, pages 85-86. The company submission presented a three-state partitioned survival model – using parametric curves fitted to PFS and OS data from IMpower110 for atezolizumab and hazard ratios for pembrolizumab versus atezolizumab derived from the NMA applied to these reference curves. The rationale for the structure was that it is:

- Simple and intuitive
- Allows multiple extrapolations
- Is in line with NICE DSU guidance to compare the data from Impower110 to other RCTs where IPD were not available

Time to treatment discontinuation data from IMpower110 was further used to determine treatment on treatment for atezolizumab, whilst time on treatment was assumed equal to PFS for pembrolizumab up to 2 years where a stopping rule was applied in line with its recommendation from TA531. No stopping rule was applied for atezolizumab, in line with its clinical evidence base in which treatment was allowed up until the loss of clinical benefit.

The company submission included a comparison of the design and inputs to the company model compared to those used for pembrolizumab in TA531 (Document B, pages 88-89, Table 27) and this shows the design of the two economics models to be similar.

The ERG agrees the company's model structure is acceptable. Due to limited availability of data, there is some inconsistency in the approach used to model time on treatment between the two alternatives. This could potentially overestimate time on treatment for pembrolizumab relative to its derived PFS curve.

3.2.3 Population

The modelled population is in line with the TC3 or IC3 subgroup of IMpwer110 trial, [redacted] outlined in company submission (Document B, Table 1):

"Adult patients with [redacted]."

The Final Scope proposed two sub-groups, different levels of PD-L1 and histology (squamous and non-squamous). The company submission pointed out that the [redacted], so further sub-groups within this biomarker are not presented. The company also argue analysis by histology sub-group is not appropriate because the RCT was not powered to detect differences.

The ERG acknowledges seeking sub-group analysis for PD-L1 levels above 50% is not appropriate. However, other sub-groups such as histology could have been presented, even if with caveats.

3.2.4 Interventions and comparators

The intervention, atezolizumab, is applied according to its marketing authorisation: 1200mg administered intravenously every three weeks until unmanageable toxicity or loss of clinical benefit as defined in section B3.2.2.3 of the company submission. It can be noted that the definition of 'clinical benefit' allows for some use of permbrolizumab following progression according to RECIST v1.1.

The comparator in the submission was pembrolizumab monotherapy applied according to its marketing authorisation: 200mg administered intravenously every three weeks. In line with the NICE recommendation from TA531 for pembrolizumab monotherapy, the treatment duration is limited to a maximum of two years of uninterrupted treatment.

[redacted]. *However, there may be a group of patients who meet the IC3 definition of IMpower110 (infiltrating immune cell PD-L1 expression ≥ 10%) who do not meet the TC3 definition (tumour cell PD-L1 expression ≥ 50%). Since the NICE recommendation for pembrolizumab in untreated PD-L1 positive metastatic NSCLC is conditional on a tumour proportion score of at least 50% (TA531), it is*

unclear whether pembrolizumab is the revenant comparator for IC3 only patients. However, the number of patients in IMpower110 in this category is likely to be small. The company also provided an exploratory analysis to assess the relative treatment effect in IMpower110 for high PD-L1 expression groups defined by different assays, including TPS ≥ 50% as defined by the 22C3 assay (used to determine PD-L1 expression in the KEYNOTE trials) [see also Chapter 2 about comparability of assays]. This showed a very similar magnitude of benefit in this subgroup (see Figure 14 and Table 13 of the company submission, Document B) compared to the TC3 or IC3 group defined by the SP142 assay.

3.2.5 Perspective, time horizon and discounting

The perspective and approach to discounting were in line with the NICE reference case. A time horizon of 20 years was chosen for the base case analysis. Whilst generally appropriate and consistent with TA531, it can be noted that in the company base case [redacted] and [redacted] remain alive at this time point in the atezolizumab and perbrolizumab arms of the model, respectively.

3.2.6 Treatment effectiveness and extrapolation

This was presented in Document B of the company submission, Section B.3.3.

IMpower110 data were used in the model for atezolizumab, from the analysis on 4th February 2020 (minimum follow-up 24 months, median 31 months). Data for pembrolizumab were generated by applying hazard ratios estimated in the indirect comparison.

Extrapolation in the model was by parametric functions fitted to observed Kaplan-Meier data. The parametric functions considered included the most commonly used forms: Weibull, log-normal, log-logistic, exponential, generalised gamma, Gompertz.

In the company base case parametric functions were fitted from Month 0, as in Figures 28 (OS), 31 (PFS) and 35 (TTD) of the company submission (Document B). An alternative method with extrapolations fitted only to the tails of the Kaplan-Meier plots was used in sensitivity analyses (see Table 66, Document B). The ERG notes that the choice of 20% was based on a methods paper published in the Lancet in 2002, although no specific justification for the relevance of that figure to this case was given.[30] However, the ERG notes that whether a given parametric function was fitted from month 0 or from where 20% were still at risk made almost no difference to the estimated QALY difference between treatments.

The choice of parametric function for the base case was based on three factors:

1. Statistical fit to the observed data using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).
2. Curves were (i) visually inspected and (ii) validated against relevant long-term data sources available to help identify the most plausible survival model.
3. Opinion was sought from three clinicians to validate the extrapolation approach taken and determine which of the extrapolations better represent UK clinical practice.

The ERG agrees these were the appropriate methods to use to make the selection.

Overall survival

Based on the AIC and BIC statistics (Document B, Table 28), visual inspection, and clinical plausibility of the extraploations, the alternative parametric functions were ranked. These rankings are provided in Table 30 of the company submission, document B (reproduced below as Table 22).

Table 22. Company rankings of OS distributions for atezolizumab based on AIC/BIC, visual fit and clinical plausibility (source: Table 30, Document B of the CS).

Parametric distribution	Atezo AIC (rank)	Atezo BIC (rank)	Visual fit to KM	Clinical plausibility	Ranking
Exponential	6	6	~	~	-
Weibull	2	2	✓	✓	1
Log-Logistic	1	1	✓	~	~
Log-Normal	3	3	~	×	-
Gen Gamma	5	5	✓	~	2
Gompertz	4	4	✓	×	-

The ERG has reservations about the importance of the rankings based on AIC and BIC. The difference in AIC/BIC figures for the five highest ranked curves were minimal, which could be taken as evidence that all these distributions offer plausible fits to the observed data. Visual fit was assessed subjectively. In Document B two of the six curve fits were presented; the other four were located in Appendix N, pages 562-563. The company's judgement was that the exponential and log-normal were the poorest fits (indicated by their failure to achieve a tick in Table 2 above).

The ERG agrees with the company that the exponential appears to have the poorest fit to the observed data, but find little to choose between the visuals fits of other curves.

The company report that the three UK clinicians they consulted reached a consensus that the Weibull best reflected their expectations, but no supporting evidence was provided for why they believed this. From Table 30 of the company submission, use of external data did not appear to play a role in curve selection.

The level of OS at each time point with each extrapolation was set out in Table 29 of the company submission (Document B) reproduced as Table 23 below.

Table 23. Percentage of patients alive with alternative parametric OS distributions for atezolizumab (source, Company submission, document B, Table 29)

Months	Exponential	Weibull	Gamma	Log-logistic	Log-Normal	Gompertz
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
126	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Having selected the Weibull as base case with generalised gamma as the second choice, the company submission then turned to external data as validation. Two sources were quoted, both giving longer-term data on pembrolizumab outcomes:

- 'Flatiron data', which the company clarified to be 'real world data' on use of pembrolizumab for the relevant indication in the USA. This showed pembrolizumab OS at 3 years of 32% (confidence interval from 27% to 38%). The company submission compares that to the Weibull estimates of [redacted] for atezolizumab and [redacted] for pembrolizumab but the only comment is that the atezolizumab estimate is within the confidence interval for pembrolizumab.
- Garon et al (described as real-world data in section B.3.3.2.1 of Document B) is a report of the 5-year results of KEYNOTE-001 clinical study.[31] In the context of a study of the use of pembrolizumab in a broader population with NSCLC, this included some patients with PD-L1 over 50% who were previously untreated and therefore appear to match the license for atezolizumab considered here. This showed 5-year OS with pembrolizumab was 29.6%.

It was not clear whether these two studies represented all the available evidence on longer-term OS as no literature review was reported. Neither data source is described in the company submission to allow a judgement on its reliability and relevance as a source of data to judge likely OS in NHS patients. For example, Flatiron was not described at all, although

the company provided some more details on it in response to the clarification letter, and note that it has been used in previous appraisals of atezolizumab to validate OS extraploations. Garon et al. is based on only 27 cases (from Figure 1, panel C of the original publication) which is a small sample size for judging OS.[31]

The company believe these data validate their choice of the Weibull, but there is a degree of uncertainty. As noted above, the Flatiron data show pembrolizumab has an OS of [redacted] after three years but the base case model in this submission predicts [redacted]. However, the five-year Garon data are consistent with the Weibull based five-year projections for permbrolizumab ([redacted]). Of relevance to the discussion of OS is the recent announcement that five year data from the KEYNOTE-024 trial have now been analysed.[32] Although no publication was available at time of writing, it has been announced that the five year OS rate was 31.9%, which is reasonably consistent with the pembrolizumab OS projections when applying the company's preferred hazard ratios to the generalised gamma or log-logistic curves for atezolizumab ([redacted] and [redacted] survival at five years).

The company submission reports the log normal and Gompertz were excluded as they were 'too optimistic' beyond 120 months, but no supporting evidence was provided. Both of these distributions do, however, appear to result in five-year OS projections for pembrolizumab above [redacted].

Overall, the company's justification for its base case parametric function seemed unconvincing to the ERG. Visual fit selection was based on judgements that were not explained. Key clinical opinion was summarised as favouring the Weibull with no other explanation. External supporting data, which should have been central to the judgement, seemed to be brought in after the selection had been made and divergences between projections and observed external data are not explored in any depth.

Nevertheless, the ERG believe that the Weibull offers a reasonable base case, and that the generalised gamma and log-logistic offer the most relevant alternatives for scenario analysis. In light of the recent five-year data announced for KEYNOTE-024, the ERGs clinical advisor was of the opinion that the change in OS between 36 months and 60 months predicted by the Weibull appeared quite steep, and tended towards favouring the generalised gamma curve.

Progression-free survival

The company's approach was presented in Document B, section B.3.3.3.

The same general approach was used as for the overall survival modelling i.e. fitting parametric functions to the Kaplan-Meier data (starting Month 0) from IMpower110, then applying a hazard ratio derived from the indirect comparison for permbrolizumab. The same criteria were used for selecting a parametric function for the base case.

On AIC and BIC, four curves appeared to offer a similarly good fit to the observed data: log-logistic, log-normal, generalised gamma, and Gompertz.

The ERG agrees that the exponential and Weibull do offer a poorer fit to the observed data than the other four distributions.

For visual fit, the company's judgement was that exponential and Weibull also performed poorly on this assessment, but the other functions provided a satisfactory fit (presented in Document B, Figures 31-33 and Appendices N.1.2, Figures 40 to 42).
The ERG agrees.

In terms of clinical plausibility, little information is presented in the company submission but the Gompertz was ruled out because clinicians found the predictions beyond 5 years implausible.

It would have been helpful to know why the clinicians thought the Gompertz predictions were implausible.

The company selected the generalised-gamma as this was consistent with the parametric fit for time on treatment (see below). However, it was emphasised that log-logistic and log-normal were very similar.

The ERG agrees with the rationale.

Relative treatment effects (pembrolizumab versus atezolizumab)
The ERG appraised the company's NMA in Section 2.4 of this report. The HRs were estimated by the company followed DSU guidance. The company noted proportional hazards (PH) may not hold and estimated HRs based on fractional polynomials. The ERG accepts this was an appropriate method, but the ERG describe problems in reproducing the company's results.

In the methods section for the economics model, the company said that OS and PFS estimates for pembrolizumab were generated by applying hazard ratios from the ITC, without specifying which ones were used (pages 91-92, Document B). It was not clear if this referred to HRs using random effects (assuming PH) or fractional polynomials (assuming PH did not apply) and the ERG asked for more detail in Clarification Question B1. The company responded to say they used the random effects HRs in the economics base case (Company's Response to CQs, page 22). They explained, "We observed that the fitting of the curves is not ideal for both PFS and OS when the fractional polynomial model is used. This causes implausible results for this comparison."

The ERG has been able to confirm this and does not believe FP HRs should be used in the model.

Capped treatment effect

The company submission did not include a specific section on this topic in Document B. However, it was assumed in the company base case that as pembrolizumab has a maximum duration of treatment of two years, then the treatment effect should be capped at five years. From this point the hazard of mortality in the pembrolizumab arm was set to the hazard for the chemotherapy arm of the NMA. For atezolizumab, which has no stopping rule, the company assumes no cap to the treatment effect in terms of OS in the base case. With the company base case curve selections, these assumptions cause the permbrolizumab OS curve to converge with and then drop below the atezolizumab OS curve from about 93 months.

In a sensitivity analysis, a treatment effect cap of eight years was applied for atezolizumab (Document B, page 94). The justification for this was that if the cap for atezolizumab was set at 5 years this would suggest no additional benefit for treatment beyond two years, which the company suggest is unreasonable. Eight years was selected as a longer time than five years. The company note that in this alternative scenario, the OS curves converge and overlap from about 90 months onwards, which the company interested as being consistent with clinicians' opinions that the two products were comparable in terms of efficacy.
The company describes the cap at eight years as the 'worst case scenario' for atezolizumab but also provides a sensitivity analysis with a cap at five years for atezolizumab (to match pembrolizumab).

The ERG notes that the difference between pembrolizumab and atezolizumab is 0.08 QALYs in the base case, 0.14 when the atezolizumab cap is at 8 years and 0.2 when the atezolizumab cap is at 5 years (all favouring pembrolizumab).

The ERG agrees that atezolizumab is likely to have a longer treatment duration than pembrolizumab, but relative benefits versus pembrolizumab beyond five years remain an area of uncertainty. The company argue that to use the same cap on treatment benefit would imply no additional benefit to treating for more than two years with atezolizumab, but the ERG point out that no evidence was presented in the company submission confirming a longer treatment effect duration with treatment extended beyond two years. Hence, it is possible that after two years of treatment the immunological effect of treatment has reached a maximum achievable. Therefore, the same duration of treatment effect as for pembrolizumab is also a possible, albeit pessimistic scenario.

Given how central the issue of treatment effect capping is to the estimate of QALY gains, a specific section in the company submission giving more detailed consideration to these issues would have been helpful.

For PFS, the company base case assumed no capping of the treatment effect for atezolizumab or pembrolizumab versus chemotherapy. The company submission included one diagram (Document B, Figure 34) showing the effect of capping the treatment effect at five years for both atezolizumab and pembrolizumab. No explanation or interpretation of this scenario was supplied. However, the model provided the functionality to test this, and the company did provide a scenario in response to the clarification letter, which capped the PFS treatment effect at five years for pembrolizumab.

Treatment duration

In the company's economic model, atezolizumab was modelled as it was used in the RCT (Document B, section B.3.2.2.3) defined as: "until unmanageable toxicity or loss of clinical benefit as defined by the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG Performance Status that was attributed to disease progression

- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that could not be managed by protocol-allowed medical interventions
- Patients must have provided written consent to acknowledge deferring other treatment options in favour of continuing study treatment at the time of initial radiographic progression per RECIST v1.1"

Pembrolizumab was modelled to time of progression with an upper limit on the duration of treatment of two years. While this is not stated in the licensed use of pembrolizumab, an upper limit of 35 cycles was used in the RCT protocol for KEYNOTE-024 and NHS England stated this would be their criterion for funding pembrolizumab in this role. The Summary of Product Characteristics for pembrolizumab states that "Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity".[33] It also notes that "It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed."

The company submission did not use an equivalent 'stop rule' for atezolizumab for three reasons:

1. To impose a stop rule on atezolizumab would not be consistent with the IMpower110 RCT evidence
2. There is a lack of rationale for a stop rule at two years
3. The company identified re-challenge as the biggest unmet medical need and believes that extending the IO availability to allow (re-challenge or) continued treatment would be a valuable option for some patients. However, the company was not aware on any available data about re-challenge (CS, section B.3.3.5)

They cited support by clinicians for their approach, given that re-challenge was not permitted.

As stated, time to treatment discontinuation data for atezolizumab were taken from the IMpower110 RCT (Document B, section B.3.3.4). The standard set of six parametric functions was considered to extrapolate this beyond the time period observed in the RCT. The selection was made on the basis of goodness-of-it and clinical plausibility; the company reports the three clinicians said a maximum of 10% of patients would still be on treatment after 5 years (page 103, Document B). The company judged the generalised-gamma to meet these criteria to the greatest extent, with the Weibull as the next best alternative.

The generally ERG agrees with the selections.

For pembrolizumab, the company reported that data on time to treatment discontinuation are not available. PFS data were used instead with an assumption of 'treat to progression' up to 2 years when the imposed 'stop rule' applies.

However, assuming treatment depends only on progression may underestimate discontinuation because stopping as a result of adverse events or patient preference is not included. This could make pembrolizumab seem more expensive than if the model had been based on actual time on treatment data.

In fact, the ERG notes that the following data are reported for pembrolizumab:
KEYNOTE 024[34]

- *In the supplementary appendix to Reck 2016, the CONSORT diagram showed that 80/154 patients had discontinued pembrolizumab at median follow-up of 11.2 months. Of the 80, 57 had stopped for reasons that would be captured in PFS but 23 had stopped for other reasons including 17 with adverse events.*
- *Reck 2016 also reported that at median follow-up of 11.2 months, the median duration of treatment was 7 months, while median PFS was 10.3 months.*
- *Reck 2019 reported median treatment duration with pembrolizumab in KEYNOTE 024 of 7.9 months at a median follow-up was 25.2 months.*

KEYNOTE 042[35]

- *In the consort diagram in the report of the RCT (Mok 2019 NEJM), of 298 patients with PD-L1 of 50% or more, 298 received pembrolizumab and 217 had discontinued. Of the 217, 149 discontinued for reasons that would be captured in PFS, but a further 68 stopped for other reasons including 61 with adverse events.*
- *Mok (2019 NEJM) also reports that after a median follow-up of 12.8 months, median PFS was 7.1 months for pembrolizumab while the median number of doses administered was 9 (equates to approximately 6.5 months).*

The ERG notes that considering the data above for the two pembrolizumab RCTs, a PFS-based definition of treatment discontinuation (as used in the company submission for atezolizumab) would likely underestimate the hazard of discontinuing pembrolizumab at least in the short term.

Subsequently, the ERG has identified a published paper by Velcheti et al which reports a post hoc analysis of time-on-treatment from KEYNOTE-024 and the PD-L1 ≥50% group in

KEYNOTE-042.[36] Whilst the KEYNOTE-024 time on treatment (ToT) data reported by Velcheti et al comes from the later data cut (median follow-up was 25.2 months) when comparable PFS data were not available, the reported ToT data for KEYNOTE-042 is directly comparable with the PFS data reported by Mok et al., 2019.[35] The ERG therefore extracted and compared data from the published curves on the proportion of patients remaining on treatment and the proportion progression free at set follow-up times (Table 4). Whilst this shows that time on treatment falls slightly below PFS in the first 6 months, it then crosses it and runs slightly above it from 12-21 months, before dropping off steeply just before 24 months when patients would complete their 35 cycles. Thus, the company's assumption of treatment continuing in line with PFS to 2 years for pembrolizumab is unlikely to bias the ICER substantially. Nevertheless, the ERG has tested the impact of adjusting pembrolizumab time on treatment relative to its derived PFS curve using the relative differences in the hazard of discontinuing and the hazard of progression or death between the extracted timepoints in Table 24.

Table 24. Extracted PFS and time on treatment data from KENOTE-042.

KEYNOTE 042 Time on Treatment		**KEYNOTE 042 Progression free survival**		**Model projection of Pembro PFS and ToT**	**Relative hazards by timepoint (Treatment discontinuation versus progression or death)***
Time (months)	Proportion	Time (months)	Proportion	Proportion	
0.0	1.000	0.0	1.000	[redacted]	
3.0	0.672	3.0	0.714	[redacted]	1.18
6.0	0.520	6.0	0.565	[redacted]	1.09
9.0	0.434	9.0	0.445	[redacted]	0.75
12.0	0.376	12.0	0.378	[redacted]	0.89
15.0	0.340	15.0	0.316	[redacted]	0.56
18.0	0.301	18.0	0.287	[redacted]	1.27
21.0	0.262	21.0	0.258	[redacted]	1.30
23.5	0.221	23.5	0.226	[redacted]	1.28
24.0	0.066	24.0	0.223	[redacted]	95.80

* Rate of treatment discontinuation over the rate of progression or death (PFS) between the extracted time points

3.2.7 Health related quality of life

This was presented in Section B.3.4 of Document B of the company submission, starting from page 108.

EQ-5D-3L was collected in the IMpower110 RCT. In the submission, values at baseline were provided for 97 TC3 or IC3 patients on atezolizumab (out of 107 randomised to this arm) and for 87 TC3 or IC3 patients on chemotherapy (of 98 randomised). In total there was a baseline value for 184 patients out of 205 randomised (90%).

The baseline utilities, using the UK tariff, were Provided in Table 40 of Document B (Reproduced in Table 25 below):

Table 25. Summary of baseline utilities (Source: Table 40 of the company submission, document B).

N	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
184	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline and a follow-up EQ-5D observation were available for 84 patients on atezolizumab (of 107) and 79 patients on chemotherapy (of 98); combined, this gave data for 163 patients out of 205 (80%).

Post-baseline, 1528 observations were available in 163 patients (just over 9 observations per patient on average).

The ERG note that 21 patients have no EQ-5D-3L values at baseline (21/205, 10%). In terms of patients who had baseline and at least one follow-up, 42 patients were not included (205 minus 163) so it appears a further 21 patients had a baseline but no follow-up data. It was unclear what assumptions were made about missing data in the analyses. No reasons why data were missing were presented. There was no comparison of baseline characteristics of patients with and without EQ-5D (1) at baseline and (2) at follow-up.

In the company submission, three approaches to modelling utility values were considered, but one of these (the 'proximity to death' approach) was discarded because of wide, overlapping confidence intervals and counter-intuitive results.

The ERG accepts 'proximity to death' was not the best approach in this case given the diminishing numbers of patients contributing observations with increasing proximity to death, and the counterintuitive results generated.

The two models considered further were (1) pre-progression and post-progression, and (2) on treatment and off-treatment.

For the pre- and post-progression approach, data were available:

- Pre-progression for [redacted] patients on atezolizumab (of 107, [redacted]) and [redacted] patients on chemotherapy (of 98, [redacted]) patients
- Post-progression for [redacted] and [redacted] patients respectively

Results were presented in Table 42 of Document B (page 110), reproduced as Table 26 below.

Table 26. Health state utility values by progression status (Source: Table 42, Company submission, Document B)

Label	Estimate	SE	Lower limit 95% CI	Upper limit 95% CI
Pre progression				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]
Post progression				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]

The ERG notes that post-progression values in particular are based on small numbers with only [redacted] atezolizumab patients and [redacted] chemotherapy patients who progressed providing an EQ-5D value. Given the small numbers, the ERG also asked the company to present pre- and post-progression utilities for the wider population of IMpower110 at the clarification stage. The company provided this in their response (see company response to question B10 of the clarification letter), and it showed consistency with pooled results in Table 6.

Patients initially receiving atezolizumab appeared to have a higher post-progression utility value, although the p-value for the treatment by progression status interaction was not reported. This could, however, suggest that patients continue to derive some benefit after the RECIST criteria for progression in the RCT were met. This would support the idea that radiological progression and progression defined by symptom increase are not the same. The company, however, applied pulled values in the model, suggesting this to be conservative.

Using pooled values, progression of disease gave a decline in utility of [redacted]. There is some evidence that this [redacted].[37] This would also support the idea that radiological progression can occur before symptom increase in some patients.

The second approach to modelling utility values was by whether patients were on or off treatment; this was presented in Document B (section B.3.4.1.2). The results are reproduced in Table 27 below.

Table 27. Health state utility values by on/off treatment (Source: Table 44, Company submission, Document B)

Label	Estimate	SE	Lower limit 95% CI	Upper limit 95% CI
On treatment				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment				
Atezo (Arm A)	[redacted]	[redacted]	[redacted]	[redacted]
Chemo (Arm B)	[redacted]	[redacted]	[redacted]	[redacted]
Arm A and B pooled	[redacted]	[redacted]	[redacted]	[redacted]

As for the pre- and post-progression approach, some estimates are based on small numbers (off treatment there are values for [redacted] patients who had been on atezolizumab and [redacted] who had been on chemotherapy).

The ERG notes that point estimates of 'off treatment' utility appear more consistent between the treatment arms as compared to post-progression utility values, which could suggest greater homogeneity in the patient experience in the former compared to the latter.

Both approaches considered the stratification factors from the IMpower110 RCT in the models as potential explanatory variables (i.e. ECOG status, sex, histology). The company reports no statistically significant effects were seen for these variables.

The company selected the pre- and post-progression approach as their base-case. The justification was that although the main alternative, the on/off treatment approach, had the advantage of allowing for continued benefit after progression, it had the disadvantage of causing an artificial drop in utility when pembrolizumab reached its two-year maximum duration funded by NHS England.

The ERG agrees that this is an issue; however, the alternative approach of applying the utility drop associated with radiographic progression has its own limitations. It is possible that the observed post-progression values disproportionately reflect the health related quality of life of patients who have progressed radiographically but are yet to experience a significant deterioration in symptoms, which could result in the post-progression values overestimating average utility over time in the progressive disease state.

In addition, the drop in utility values from TA531 (NICE's guidance on pembrolizumab in this indication) was 0.11 on progression, (0.778 minus 0.668).[29] By contrast, the IMpower110 based figure gives a decline of [redacted]. The difference between pre- and post-progression for the two seemingly similar medicines suggests the true figure is uncertain. However, the company provided a scenario analysis that utilised the KENOTE-024 utility data, and this in fact moves the ICER in atezolizumab's favour.

It was assumed that any disutility from adverse events was captured in the EQ-5D data collected in IMpower110 (page 129, Document B). Whilst this is an uncertain assumption do the degree of missing data, it is unlikely to important consideration in the comparison between atezolizumab and pembrolizumab which are similarly well tolerated.

3.2.8 Resources and costs

Drug acquisition and administration

For pembrolizumab, the dosing assumed was 200mg every three weeks, with list price matching the one quoted in Section 2 of TA531 (£5,260 per cycle).

In terms of administration a cost was assumed for each infusion (hospital visit). This was the same as for TA531, at £183.54.
As an infusion takes 30 minutes, this seems plausible.

Adverse events

For adverse events, only grade 3 or 4 events were considered. For atezolizumab, any type of event with an incidence of 2% or more was included, but for pembrolizumab the threshold was higher: the incidence had to be 10% or more. This was because due to the way data from KEYNOTE-024 were presented.

It was unclear to the ERG why adverse event data were only taken from KEYNOTE-024, excluding the relevant patients from KEYNOTE-042.

Tables 56 and 57 of the company submission (Document B, page 125) show the number of events and the assumed treatment cost per event:

The company say the approach is conservative, since the definitions used include more adverse events for atezolizumab, but it would have been helpful to see a like-with-like comparison in the base case and the scenario described above as a sensitivity analysis. However, the ERG is generally satisfied with the approach, and would not expect differences in adverse event frequencies to be a substantial driver of the cost difference between the alternative medicines being compared.

Health care resource use

The company said that PD-L1 testing is part of routine practice and would not have a differential impact on the comparators being considered (would apply equally to atezolizumab and pembrolizumab), so the cost of testing was not included in the model (Document B, page 126).

The ERG agrees that the rationale (applies equally to all treatments) is sensible.

Resource use assumptions were set out for pre-progression and post-progression states per year and unit costs were then attached (Company submission, Tables 53 and 54, page 122, Document B). The assumed resource use either used data from TA531, the NICE Clinical Guideline on lung cancer diagnosis and a management (CG 121) or a Marie Curie report into the cost of end of life care.[29, 38, 39]

The data from TA531 seem relevant. The ERG is slightly concerned by the use of resource use assumptions from a clinical guideline because these could be seen as planned or aspirational levels rather than a description of the current service. In addition, the publication is now quite old, as is the Marie Curie report which was used to inform GP contact frequency in the progressive disease state. The ERG could not trace the company's number of 26.09 (fortnightly) GP home visits or occupational therapist visits per annum in the PD state from the references provided, and has some concern that these may not be applicable for the entire duration of time in the PD state.[39] The ERG's clinical advisor was also skeptical of the these assigned frequencies. However, having not been able to identify a better source for these parameters, the ERG explore the impact of reducing them by 25% and 50% in scenario analysis. Ideally, it would have been preferable to have some real world data on resource use frequencies or clinical validation for those health care resource use parameters obtained from older sources.

In addition to the health state costs, terminal care costs were applied in the model as a one of cost upon entry to the death state. These were applied equally in both arms of the model (only timing will affect any small differences between arms due to discounting).

The ERG agrees that this approach is reasonable and is consistent with other appraisals.

Subsequent therapy

For costing of subsequent therapies, the company used the same approach as in TA531, where the regimen received was assumed to be platinum-doublet chemotherapy (page 119, Document B). This was justified with reference the NICE's treatment pathway website and to usual care in the NHS.[40]

The assumed regimens were outlined in Table 48 of the company submission (Document B, page 120). 100% of progressed patients were assumed to receive one regimen of chemotherapy.

The ERG's clinical adviser has confirmed that assuming all patients who are subsequently treated receive platinum-doublet chemotherapy is plausible in the NHS. However, the ERG questioned the assumption that 100% of patients initially treated with first line immunotherapy will subsequently receive chemotherapy and asked the company to explore this further at the clarification stage. The company duly consulted three practicing oncologists who suggested that 50-70% of patients on first line IO monotherapy would receive subsequent treatment, and provided a scenario in response to the clarification letter that applied 50%. The impact on the ICER was minimal.

It can be noted that the subsequent treatments applied in the PD state of the model are not fully aligned with the treatments received following progression on atezolizumab in the IMpower110 trial. Of those receiving subsequent treatment in IMpower110 following progression on atezolizumab, the majority received chemotherapy, although subsequent immunotherapy and targeted therapies were reported for a small proportion of patients (Company submission, Table 12, document B). However, a similar picture was observed in the KENOTE trials of pembrolizumab. The ERG do not consider the differences in modelled subsequent treatments compared to the immunotherapy arms of the respective trials to be a major issues. Of potentially greater importance, for determining the comparative efficacy of permbrolizumab versus atezolizumab in the NMA, is the degree of crossover to immunotherapy from the chemotherapy arms of respective trials.

4 COST EFFECTIVENESS RESULTS

4.1 Company's cost effectiveness results

The company presented an incremental cost-effectiveness analysis and a cost comparison (assuming equal efficacy for atezolizumab and pembrolizumab) – both at list prices and including an approved patient access scheme (PAS) price for atezolizumab. Neither set of results is appropriate for decision making because a confidential PAS price is also available for permbrolizumab.

The company expressed a preference for the cost comparison approach given the lack of significant difference in efficacy from the NMA. This was supported by the clinical experts they consulted, who highlighted the lack of evidence to support a meaningful difference in efficacy or safety between atezolizumab and pembrolizumab in this indication.

Nevertheless, the confidence intervals on the hazard ratios from the NMA are relatively wide and do not rule out the possibility of a meaningful difference. Therefore, it is appropriate that the company have explored both approaches.

In the base case cost-effectiveness analysis at list prices (Company submission, document B, Table 60), atezolizumab offered slightly less QALYs [redacted].

Applying the PAS discount to atezolizumab reduced the lifetime cost in the pembrolizumab arm from [redacted] to [redacted] (Company submission, document B, Table 61). Pembrolizumab at list price cost an additional £47,059 for 0.08 additional QALYs, an ICER of £560,832, putting atezolizumab in the south west quadrant relative to permbrolizumab. The company submission estimates that the incremental cost per QALY (pembrolizumab versus atezolizumab) only falls below £30k if pembrolizumab is discounted by at least [redacted] and below £20k per QALY at a minimum discount of [redacted]

The QALY difference is driven primarily by a small difference of 0.14 life years favouring pembrolizumab. The cost difference is driven primarily by differences in drug acquisition costs, [redacted].

The company's cost comparison results are provided in Table 62 (at list prices) and Table 63 (including the atezolizumab PAS) of the company submission (document B).

The ERG questioned the small difference in progressive disease costs despite the stated assumption of equal efficacy.

In response to the clarification letter, the company indicated that this was due to subsequent treatment costs being conditioned on time to treatment discontinuation, for which atezolizumab has its own separate curve, whilst pembrolizumab time on treatment is assumed equal to PFS up to the two year stopping point.

Whilst it may be reasonable to assume that subsequent treatment occurs upon discontinuation of atezolizumab (allowing for some post-progression treatment), it may be less so in the longer term where the TTD curve falls below PFS. Furthermore, the application of further treatment costs upon stopping pembrolizumab at two years lacks clinical validity. In this context, it may be more appropriate use the PFS curve to determine the proportion of patients initiating further treatment over time. However, the company's method only affects the timing of subsequent treatment costs in the context of their model, and so the impact on the cost difference would be minimal. Nevertheless, the ERG explored the impact of conditioning the timing of subsequent treatment costs on the PFS curve for permbrolizumab beyond two years. Further, the ERG assessed the impact on the cost comparison of assuming that 50% (rather than 100%) of patients who commence treatment on atezolizumab or pembrolizumab receive subsequent chemotherapy. This is in line with the advice the company received from clinical experts at the clarification stage.

4.2 Company's sensitivity analyses

The company presented probabilistic sensitivity analysis for the cost-effectiveness base case. This indicated a high degree of uncertainty around the small incremental QALY, whilst the incremental cost was dependent on whether the list price or PAS price was applied to atezolizumab. The scatter plot and CEAC are provided for the PAS price case below. The probabilistic results with the appropriate PAS price included for pembrolizumab are provided

by the ERG in a confidential appendix. There was an error in the computation of the CEAC provided by the company in their submission, which they updated at the clarification stage. However, the probabilities of cost-effectiveness for the two treatments still did not sum to one in the updated figure. Therefore, the ERG has recomputed the CEAC provided below using 2,500 probabilistic iterations.

Figure 4. Incremental Cost-Effectiveness Plane (PAS price for atezolizumab) (Source: Figure 17 of the company's response to the clarification letter)

Figure 5. Cost-Effectiveness Acceptability Curves - (PAS price for atezolizumab)

The company further provided a large number of scenario analyses, which they added to at the clarification stage based on ERG requests, and updated the Table to include measures of net monetary benefit and net health benefits at cost-effectiveness thresholds of £20,000 and £30,000. The updated table using the PAS price for atezolizumab (list price for pembrolizumab) is provided as Table 28 below. Under all the scenarios explored, atezolizumab produced the highest net benefits at the applied thresholds.

Omissions from the scenario analyses were application of the time dependent hazard ratios from the fractional polynomial NMA, and variation in the assumed treatment effect duration for pembrolizumab. The ERG acknowledges the implausible extrapolations produced for pembrolizumab when applying the FP NMA HRs in the company model but explores the impact of extending the treatment effect duration of pembrolizumab in Chapter 5.

Table 28. Scenario analyses results pembrolizumab vs. atezolizumab* (PAS price) (Source: Table 13 of the company's response to the clarification letter)

Parameter	Value	Atezo Mono			Pembro mono			Pembro Mono vs. Atezo Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER*	NMB* WTP £30K	NMB* WTP £20K	NHB* WTP £30K	NHB* WTP £20K
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,059	560,832*	-44,542*	-45,381*	-1.5*	-2.3*
Distribution OS	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	48,475	476,303*	-45,422*	-46,439*	-1.5*	-2.3*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,481	401,488*	-43,933*	-45,116*	-1.5*	-2.3*
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	47,186	536,154*	-44,546*	-45,426*	-1.5*	-2.3*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,445	405,563*	-43,935*	-45,105*	-1.5*	-2.3*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.29	48,869	170,602*	-40,276*	-43,140*	-1.3*	-2.2*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	48,235	461,996*	-45,103*	-46,147*	-1.5*	-2.3*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,010	565,197*	-44,514*	-45,346*	-1.5*	-2.3*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,386	392,050*	-43,760*	-44,969*	-1.5*	-2.2*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	47,090	538,405*	-44,466*	-45,340*	-1.5*	-2.3*

	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	47,358	402,037*	-43,824*	-45,002*	-1.5*	-2.3*
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.29	48,746	170,678*	-40,178*	-43,034*	-1.3*	-2.2*
Distribution PFS	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	59,018	645,357*	-56,275*	-57,189*	-1.9*	-2.9*
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	51,166	576,877*	-48,505*	-49,392*	-1.6*	-2.5*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,451	561,842*	-44,917*	-45,762*	-1.5*	-2.3*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,549	552,459*	-44,022*	-44,864*	-1.5*	-2.2*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,559	563,118*	-44,079*	-44,906*	-1.5*	-2.2*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	45,394	507,668*	-42,711*	-43,606*	-1.4*	-2.2*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.09	45,574	523,873*	-42,964*	-43,834*	-1.4*	-2.2*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,866	552,201*	-43,374*	-44,205*	-1.4*	-2.2*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,883	553,930*	-43,398*	-44,226*	-1.4*	-2.2*
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,885	554,118*	-43,401*	-44,229*	-1.4*	-2.2*
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	45,925	558,277*	-43,457*	-44,280*	-1.4*	-2.2*
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	55,120	656,895*	-52,603*	-53,442*	-1.8*	-2.7*

Distribution TTD	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,041	548,696*	-43,524*	-44,363*	-1.5*	-2.2*
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	35,726	425,770*	-33,209*	-34,048*	-1.1*	-1.7*
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	35,866	427,431*	-33,348*	-34,188*	-1.1*	-1.7*
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	37,358	445,211*	-34,840*	-35,679*	-1.2*	-1.8*
	KM with Exponential tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	57,250	682,279*	-54,733*	-55,572*	-1.8*	-2.8*
	KM with Weibull tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,510	554,282*	-43,992*	-44,832*	-1.5*	-2.2*
	KM with Log-normal tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	37,683	449,090*	-35,166*	-36,005*	-1.2*	-1.8*
	KM with Gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,536	566,506*	-45,018*	-45,857*	-1.5*	-2.3*
	KM with Log-logistic tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	38,132	454,439*	-35,615*	-36,454*	-1.2*	-1.8*
	KM with Gompertz tail	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	36,104	430,267*	-33,586*	-34,425*	-1.1*	-1.7*
Pembro treatment duration assumption	Set it equal to atezo actual treatment duration up to two years, when pemro	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	51,873	618,203*	-49,356*	-50,195*	-1.6*	-2.5*

	is discontinued													
Utility method	IMpower110 (On/Off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.03	47,059	1,433,902*	-46,075*	-46,403*	-1.5*	-2.3*
	IMpower110 (Proximity to death)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.11	47,059	441,166*	-43,859*	-44,926*	-1.5*	-2.2*
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,059	591,720*	-44,674*	-45,469*	-1.5*	-2.3*
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	47,059	22,209,162*	-46,996*	-47,017*	-1.6*	-2.4*
	KEYNOTE-024	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.05	47,059	864,808*	-45,427*	-45,971*	-1.5*	-2.3*
Time horizon	5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.12	55,315	453,856*	-51,658*	-52,877*	-1.7*	-2.6*
	10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.14	49,792	363,872*	-45,687*	-47,055*	-1.5*	-2.4*
	15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.10	47,830	456,515*	-44,687*	-45,735*	-1.5*	-2.3*
NMA	FE model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.06	37,862	677,054*	-40,811*	-41,442*	-1.4*	-2.1*
Administration schedule	Q6W vs. Q4W atezo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	48,555	578,658*	-46,038*	-46,877*	-1.5*	-2.3*
Capping of treatment benefit	Atezo OS treatment effect capped at 96 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.14	47,464	345,711*	-43,345*	-44,718*	-1.4*	-2.2*

	Atezo OS treatment effect capped at 60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.2	48,022	234,870*	-41,888*	-43,933*	-1.4*	-2.2*
# Pembro PFS cap	Pembro PFS and OS cap at 60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,403	597,908*	-45,025*	-45,818*	-1.5*	-2.3*
# half cycle correction	No half-cycle correction for drug and administration costs in the progression-free state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	47,554	566,728*	-45,037*	-45,876*	-1.5*	-2.3*
# % of patients receiving subsequent therapy	50% of patients receive subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	46,768	557,358*	-44,251*	-45,090*	-1.5*	-2.3*
# Utilities	Utility values for the whole ITT WT population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.07	47,059	636,699*	-44,842*	-45,581*	-1.5*	-2.3*
# half cycle correction, % of patients receiving	All three changes as suggested by	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.07	47,263	639,448*	-45,045*	-45,784*	-1.5*	-2.3*

subsequent therapy and utilities	the ERG and described in the previous three scenarios													

*pembro versus atezo: high ICER indicates atezo is worth funding; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; KM, Kaplan Meier; NMA, network meta-analysis; HR, hazard ratio; FE, fixed effects; #, new scenario analyses provided

NMB, net monetary benefit, NMB is calculated as: *(incremental gain in QALYs x threshold) – incremental cost*. A positive incremental NMB indicats that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Negative NMB and negative NHB mean atezo is worth funding

4.3 Model validation and face validity check

As noted in previous sections, the company selected time to event curves using measures for statistical fit, visual inspection, and clinical plausibility based on consultation with experts. The company also note validation against all available evidence.

With respect to model quality control, the company note that this was carried out by an external consultancy, including cell by cell formula and reference checking, and model functionality checks.

In addition, the ERG has carried out its own formula and cell referencing checks and has identified no material errors. Further functionality checks were applied by the ERG, such as: setting hazard ratios to one and checking OS and PFS were equalised; setting all utilities to one to ensure QALYs equalled life years; and equalising all the parameters expected to drive differences in costs and effects (based on the model description) and confirming the model showed zero difference between treatments with these settings. These checks all generated results consistent with expectation. One minor bug was identified in the pembrolizumab cohort trace which seemed to allow PFS to exceed OS in the tails of the selected distribution. The ERG assessed the impact of overriding the PFS curve with the OS curve where this occurred, and it had minimal impact on the cost-effectiveness results.

The validity of the company's fitted survival curves was discussed in Chapter 3 above (see 3.2.6).

5 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

5.1 Exploratory and sensitivity analyses undertaken by the ERG

Based on the arguments set out in the critique of the company's case (Chapter 3), the ERG conducted several further scenario analyses to explore the impact of remaining uncertainties on the company's cost effectiveness findings. The scenarios assessed are set our below.

List of cost-effectiveness analysis scenarios assessed by the ERG (see Table 29 for results):

1. Correcting pembrolizumab PFS to remain below OS at all times.
2. Increasing the treatment effect duration cap for pembrolizumab from 5 years, to 6, 7 and 8 years
3. Combination of 2 with selection of generalized gamma OS reference curve
4. Combination of 2 with selection of the log-logistic OS reference curve
5. Subsequent treatment costs conditioned on the PFS curve for pembrolizumab, rather than treatment discontinuation.
6. Pembrolizumab time on treatment adjusted relative to PFS using data from KENOTE-042
7. 25% and 50% reductions in progressive disease GP and therapist costs.
8. Application of pembrolizumab HRs from the random effects NMA using the Impower110 September 2018 data cut.

List of cost-comparison scenarios assessed by the ERG (see Table 30 for results):

1. Subsequent treatment costs conditioned on the PFS curve for pembrolizumab, rather than treatment discontinuation.
2. 50% (rather than 100%) of patients who commence treatment on atezolizumab or pembrolizumab receive subsequent chemotherapy.
3. 1 and 2 combined with efficacy equalized

5.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The results of the further scenario analysis conducted by the ERG are provided in Table 29 (cost-utility model) and Table 30 (cost comparison) below. Atezolizumab continues to provide positive incremental net benefits at the thresholds of £20k and £30k across all scenarios explored (at PAS price for atezolizumab, list price for pembrolizumab). Of the

scenarios explored, the ICER and incremental net benefits are most sensitive to the assumed treatment effect durations for pembrolizumab and the Impower110 data cut used to inform the NMA. It can be noted that when the earlier cut from IMpower110 is used, the direction of the QALY difference switches in atezolizumab's favour. The ICER and net benefits are also modestly sensitive to the adjusted time on treatment for pembrolizumab as per scenario 6. The other scenarios result in only small changes to the ICER and incremental net benefits. The cost comparison results were insensitive to the additional scenarios explored by the ERG (Table 30).

Table 29. ERG scenario analyses results atezolizumab versus pembrolizumab* (PAS price)

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.08	-47,059	560,832	44,542	45,381	1.5	2.3
1. Pembrolizumab PFS	Adjusted to always remain below OS in the tail of the distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-47,066	561,530	44,552	45,390	1.5	2.3
2. Pembrolizumab treatment effect duration cap	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.132	-47,475	360,717	43,527	44,843	1.5	2.2
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.168	-47,795	284,012	42,746	44,429	1.4	2.2
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.197	-48,047	243,532	42,128	44,101	1.4	2.2
3. OS ggamma with Pembrolizumab treatment effect duration cap	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.143	-47,661	333,588	43,375	44,803	1.4	2.2
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.186	-48,030	258,679	42,460	44,317	1.4	2.2
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.220	-48,327	219,549	41,723	43,924	1.4	2.2
4. OS log-logistic with Pembrolizumab treatment effect duration cap	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.177	-47,956	271,668	42,660	44,425	1.4	2.2
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.222	-48,346	217,594	41,681	43,903	1.4	2.2
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.258	-48,655	188,291	40,903	43,487	1.4	2.2
5. Pembrolizumab time to subsequent therapy	Based on PFS curve rather than assumed TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-46,770	557,388	44,253	45,092	1.5	2.3

6. Pembrolizumab time on treatment	Adjusted relative to PFS using data from KENOTE-042	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-44,221	527,006	41,704	42,543	1.4	2.1
	Adjusted relative to PFS using data from KENOTE-042 + removal of half cycle correction for time on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-45,024	536,580	42,507	43,346	1.4	2.2
7. PD health state costs.	25% reduction in PD GP and therapist costs.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-46,615	555,537	44,098	44,937	1.5	2.2
	25% reduction in PD GP and therapist costs.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-46,171	550,242	43,653	44,493	1.5	2.2
8. Pembrolizumab HRs	Random effects NMA, IMpower110 Sept 2018 data cut	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.441	-58,042	-131,592	71,274	66,864	2.4	3.3

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; NMA, network meta-analysis; HR, hazard ratio; TTD, time to treatment discontinuation.

NMB, net monetary benefit, NMB is calculated as: *(incremental gain in QALYs x threshold) – incremental cost*. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Table 30. ERG cost comparison scenario analyses results atezolizumab versus pembrolizumab (atezolizumab PAS price)

Parameter	Value	Atezolizumab	Pembrolizumab	Atezolizumab vs. Pembrolizumab
		Costs	Costs	Incremental savings
Base case		[redacted]	[redacted]	(52,078)
1. Pembrolizumab time to subsequent therapy	Based on PFS curve rather than assumed TTD	[redacted]	[redacted]	(51,682)
2. Use of subsequent chemotherapy	50% rather than 100%	[redacted]	[redacted]	(£51,792)
3. 1 and 2 combined with		[redacted]	[redacted]	(£51,594)

5.3 ERG's preferred assumptions

The ERGs preferred assumptions for their base case are the same as the company's except for the following:

1. No half-cycle correction for treatment costs, to ensure all patients receive
2. Pembrolizumab PFS adjusted to remain below OS at all times
2. Pembrolizumab time to subsequent chemotherapy based on extrapolated PFS rather than applied to all who discontinue at the two-year stopping point
3. Pembrolizumab time on treatment adjusted relative to PFS using data from KEYNOTE-042
4. 50% receive subsequent therapy rather than 100%, in line with the company's clinical expert opinion.
5. 50% reduction in GP home visits and therapist visits in the progressive disease health state, given the ERGs inability to identify the companies applied frequencies in the stated sources and the ERGs own clinical expert advice.

The impact of applying these changes cumulatively is provided in Table 31 below. Whilst the changes reduce the ICER for pembrolizumab versus atezolizumab somewhat, it remains highly uncertain given the uncertainty surrounding the QALY gain which is driven by wide confidence intervals surrounding the hazard ratios from the NMA. The probabilistic output with the ERG base case settings are provided in Table 32, Figure 6, and Figure 7. Note, the ERG have not incorporated distributions for the adjustments made to the time on treatment curve for pembrolizumab relative to its PFS curve (these are applied deterministically).

Regarding the assumption of loss of efficacy for pembrolizumab relative to chemotherapy from 5 years onwards, this seems to be quite a pessimistic assumption in the context of the recently reported 5 year data from the KEYNOTE-024 study, where the reported HR for OS (versus chemotherapy) was 0.62 (0.48–0.81), compared with a hazard ratio of 0.63; 95% CI (0.47 to 0.86) reported at a median follow-up of 25 months (Reck 2019).[41, 42] This suggests no obvious loss in relative efficacy for pembrolizumab versus chemotherapy by 5 years follow-up, and so complete loss from 5 years would seem like an unlikely scenario. However, it can be noted that in KEYNOTE-024, patients randomized to pembro who completed two years of therapy or stopped pembrolizumab after achieving complete response and then had progressive disease, were eligible for a second course of pembrolizumab monotherapy. It is the ERG's understanding that such re-challenge would not be permitted in the NHS in England, and so the applicability of these results to the NHS is questionable. Thus, given the ongoing lack of certainty around the duration of treatment effect for pembrolizumab and atezolizumab, the ERG provides a range of scenarios below, using the ERG base case as the reference point in Table 33.

It can be noted that as the treatment effect duration for pembrolizumab increases, the QALY gain increases while the incremental cost remains relatively stable. However, the QALY difference remains highly uncertain in all these scenarios given the uncertainty around the HRs for permbrolizumab versus atezolizumab.

Table 31. Incremental changes leading to the ERGs base case (atezolizumab versus pembrolizumab)

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
Company base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-47,059	560,832	44,542	45,381	1.5	2.3
+ Half cycle correction for time on treatment	removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-47,554	566,728	45,037	45,876	1.5	2.3
+Pembrolizumab PFS	Adjusted to remain below OS in the tail of the distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-47,561	567,432	45,046	45,885	1.5	2.3
+Pembrolizumab time to subsequent therapy	Based on PFS curve rather than assumed TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-47,278	564,058	44,764	45,602	1.5	2.3
+Pembrolizumab time on treatment	Adjusted relative to PFS using data from KENOTE-042	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-44,758	533,989	42,243	43,081	1.4	2.2
+Subsequent therapy	50% receive it rather than 100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-44,608	532,198	42,093	42,931	1.4	2.1
+ PD health state costs. (ERG base)	50% reduction in PD GP and therapist visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-43,715	521,544	41,200	42,038	1.4	2.1

ICER, incremental cost-effectiveness ratio; **LYs**, life years; **QALYs**, quality-adjusted life years; **TTD**, time to treatment discontinuation.

NMB, net monetary benefit, NMB is calculated as: *(incremental gain in QALYs x threshold) – incremental cost*. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

Table 32. ERG base case – atezolizumab versus pembrolizumab (probabilistic)

	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER (£/QALY)
Pembro	[redacted]	[redacted]	[redacted]	-43,080	-0.21	-0.14	309,723
Atezo	[redacted]	[redacted]	[redacted]				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years,							

*Caveat: PSA does not include distributions on the relative hazards used by the ERG to adjust the pembrolizumab time on treatment curve relative to its PFS curve

Figure 6. ERG base case cost-effectiveness scatter plot (atezolizumab versus pembrolizumab)

[redacted]

Figure 7. ERG base case cost-effectiveness acceptability curves

Table 33. Exploration of the duration of treatment effect with reference to the ERG base case (atezolizumab versus pembrolizumab)

Parameter	Value	Atezo Mono			Pembro mono			Atezo Mono vs. Pembro Mono						
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. QALYs	Inc. Costs	ICER	Inc. NMB WTP £30K	Inc. NMB WTP £20K	Inc. NHB WTP £30K	Inc. NHB WTP £20K
ERG base		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.084	-43,715	521,544	41,200	42,038	1.4	2.1
Pembro treatment effect duration	6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.132	-44,000	334,336	40,052	41,368	1.3	2.1
	7 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.168	-44,222	262,780	39,173	40,856	1.3	2.0
	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.197	-44,397	225,034	38,478	40,451	1.3	2.0
Atezolizumab treatment effect duration	8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.137	-44,016	320,598	39,897	41,270	1.3	2.1
Atezolizumab and pembrolizumab treatment effect durations	Atezo 8; pembro 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.185	-44,306	239,495	38,756	40,606	1.3	2.0
	Atezo 8; pembro 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.222	-44,528	200,879	37,878	40,095	1.3	2.0
	Atezo 8; pembro 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.251	-44,704	178,334	37,184	39,690	1.2	2.0

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

NMB, net monetary benefit, NMB is calculated as: *(incremental gain in QALYs x threshold) – incremental cost*. A positive incremental NMB indicates that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.;

NHB, net health benefit calculated as: *incremental gain in QALYs – (incremental cost / opportunity cost threshold).* A positive NHB implies that overall population health would be increased as a result of the new intervention

5.4 Conclusions of the cost effectiveness section

Overall, the ERG believes the company have presented a reasonable economic case given the lack of evidence to identify a meaningful difference in efficacy or safety between the medicines being compared. However, there are substantial uncertainties around the case, and a meaningful difference between the drugs cannot be ruled out based on the available evidence. Whilst changes to key parameters such as time on treatment and the assumed duration of treatment effect for pembrolizumab have a substantial effect on the ICER, the difference in QALYs remains highly uncertain in across all scenarios given the uncertainty surrounding the hazard ratios from the NMA.

Key issues in the cost-effectiveness case that would benefit from further scrutiny and discussion include:

1. The expected duration of treatment effects for pembrolizumab versus chemotherapy in the context of a two-year stopping rule and no re-challenge for progressive disease
2. The expected gains in treatment effect duration that might be achievable with atezolizumab with no stopping rule
3. The expected difference between time on treatment and progression free survival for pembrolizumab
4. The health care resource use frequencies and health state costs for the progressive disease state of the company model.

As the cost-effectiveness case or cost comparison case is predicated on the validity NMA, further clarity on the comparability of high PD-L1 cohorts identified using the SP142 assay (as per IMpower110) and the 22C3 assay (as per the KEYNOTE trials) would be beneficial.

6 END OF LIFE

Based on the evidence and modelling provided, it is unlikely that NICE end of life criteria will apply in the context of this appraisal, on the grounds that the [redacted]*, and there is insufficient evidence to support a meaningful difference in life expectancy between the two treatments.*

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