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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer

ERRATUM

Replacement pages following the factual accuracy check by Roche Product Limited

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SUMMARY

Scope of the company submission

The company submission (CS) assesses the clinical effectiveness and cost effectiveness of atezolizumab (Atezo) in combination with bevacizumab (Bev), carboplatin and paclitaxel (CP) as a first-line treatment for adult patients with metastatic non-squamous, non-small cell lung cancer (NSCLC). The anticipated marketing authorisation for Atezo+Bev+CP covers all patients with first-line metastatic non-squamous NSCLC, regardless of level of programmed death-ligand 1 PD-L1 expression (an immune checkpoint protein). The scope of the CS is narrower than the anticipated marketing authorisation, focusing on two patient subgroups:

- patients with low or negative PD-L1 expression (tumour proportion score 0–49%, TC/IC 0,1,2).
- patients who have progressed on targeted therapies for epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) tumour mutations..

Thus, patients with high PD-L1 expression, who currently would be eligible to receive pembrolizumab (NICE TA531), are not included in the CS, a deviation from the NICE scope. No cost-effectiveness comparison is made by the company with pembrolizumab in PD-L1 high expression patients. The company is therefore not seeking NHS reimbursement for treatment with atezolizumab in this patient sub-group.

[redacted] Expert clinical opinion to the Evidence Review Group (ERG) concurs with this assertion.

The CS omits the comparison of Atezo+Bev+CP to chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin), with or without pemetrexed maintenance treatment (included in the NICE scope). Instead, Atezo+Bev+CP is compared to pemetrexed in combination with cisplatin / carboplatin, with or without pemetrexed maintenance treatment (also included in the NICE scope). The justification for the focus on this comparison is that it is the most commonly-used UK chemotherapy, based on clinical expert opinion sought by the company and UK market share data. Expert clinical advice to the ERG concurs with this assertion, but notes that in England pemetrexed should only be given in combination with cisplatin (based on NICE guidance, TA181). (though the ERG has identified recent audit data showing that some patients receive pemetrexed in combination with carboplatin). Patients who cannot tolerate cisplatin would therefore be treated with a carboplatin-based regimen (i.e. docetaxel

The CS also reports outcomes of response and duration of response which were also in favour of the Atezo+Bev+CP arm. Treatment with both Atezo+Bev+CP and Bev+CP was reported by patients to lead to worsening peripheral neuropathy and alopecia. However, this was attenuated over time. A clinically meaningful improvement in cough was reported by patients in both trial arms. For other measures outcomes were deemed not to be clinically meaningful and were comparable between treatment arms.

In terms of safety, the total number of adverse events was higher in the Atezo+Bev+CP group (n=6419) compared with the Bev+CP group (n=4630). However, the proportion of patients with at least one adverse event or one treatment-related adverse event was similar between groups (patients with at least one adverse event: Atezo+Bev+CP 98.2% vs Bev+CP 99.0%; patients with at least one treatment-related adverse event Atezo+Bev+CP 94.1% vs Bev+CP 95.7%). The proportion of patients experiencing treatment-related Grade 3-4 adverse events, serious adverse events and treatment-related serious adverse event were all higher in the Atezo+Bev+CP arm compared with the Bev+CP arm.

Subgroup results of the IMpower150 trial

PFS results for the subgroup of patients with low or negative PD-L1 expression favoured Atezo+Bev+CP compared to Bev+CP, though the difference between treatments was not as strongly in favour of the Atezo+Bev+CP group as it was in the total ITT population (unstratified HR 0.66, 95% CI 0.56 to 0.79 vs. unstratified HR 0.58 95% CI 0.50 to 0.68 respectively). In comparison to the ITT population (unstratified HR) the unstratified hazard ratio for the low or negative PD-L1 expression subgroup indicates slightly worse overall survival than in the ITT group (0.80 versus 0.77) with a slightly wider confidence interval which at the upper boundary extends to 0.99 therefore falling short of the line of no effect (1.0) (95% CI 0.65 to 0.99 in the low or negative PD-L1subgroup versus 0.63 to 0.93 in the ITT population).

Median investigator assessed PFS in the EGFR/ALK+ population was longer in the Atezo+Bev+CP group (10.0 months compared to 6.1 months in the Bev+CP group). The unstratified hazard ratio indicates a difference in favour of the Atezo+Bev+CP group that is slightly better than in the total ITT population (unstratified HR 0.55, 95% CI 0.34 to 0.90 vs. unstratified HR 0.58 95% CI 0.50 to 0.68 respectively). In terms of OS, median survival has not been reached in the Atezo+Bev+CP group. There is therefore more uncertainty associated with the hazard ratio for OS and the upper bound of the confidence interval crosses the line of no effect (unstratified HR EGFR/ALK subgroup 0.54, 95% CI 0.29 to

the latter show a delayed but more sustained survival benefit. Expert clinical advice to the ERG concurs with this assertion. The ERG therefore agrees that the use of a fractional polynomial methodology is reasonable in this appraisal.

Two orders of fractional polynomial model were considered for inclusion: first-order, and second order. A first order model with a P=0 would be equivalent to a Weibull model, and a first order model with P=1 would correspond to a Gompertz model. The best fitting fractional polynomial model chosen for OS and PFS was the fixed effect first order model with P1=0 (Weibull). This model was used in the ITT NMA as well as the subgroup and sensitivity analyses, for methodological consistency. Based on the information provided the ERG considers that the methods used to implement the fractional polynomial model are appropriate.

[redacted]

Summary of submitted cost effectiveness evidence

The company's submission includes a review of published cost-effectiveness evidence and a new economic model developed for this appraisal. The model estimates the cost-effectiveness of Atezo+Bev+CP for people with metastatic non-squamous NSCLC in comparison to pemetrexed + cisplatin (with or without pemetrexed maintenance).

Review of published economic evidence

The company conducted a systematic search for published cost-effectiveness evidence for first-line treatment of NSCLC. They reported that out of 66 economic evaluations with full publications in English, ten used data derived from the UK, of which seven were NICE technology appraisals. None of the UK economic evaluations related to the NICE decision problem for this appraisal.

Table 2 Company base case results, ITT population (PAS for Atezo and Bev, list price for all other treatments) – deterministic (Clarification Response Table 35)

Treatment	Total		Incremental analysis ICER (£/QALY)	Pairwise ICERs vs. comparator (£/QALY)
	Costs (£)	QALYs		
PEM+plat	[redacted]	[redacted]		£16,419
PEM+plat+PEM maint	[redacted]	[redacted]	£35,985	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	-

Table 3 Company base case results, PD-L1 negative/low population (PAS for Atezo and Bev, list price for all other treatments) – deterministic (Clarification Response Table 36)

Treatment	Total		Incremental analysis ICER (£/QALY)	Pairwise ICERs vs. comparator (£/QALY)
	Costs (£)	QALYs		
PEM+plat	[redacted]	[redacted]		£13,424
PEM+plat+PEM maint	[redacted]	[redacted]	£38,943	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	-

Table 4 Company base case results, EGFR/ALK positive population (PAS for Atezo and Bev, list price for all other treatments) – deterministic (Clarification Response Table 37)

Treatment	Total		Incremental analysis ICER (£/QALY)	Pairwise ICERs vs. comparator (£/QALY)
	Costs (£)	QALYs		
PEM+plat	[redacted]	[redacted]		£14,552
PEM+plat+PEM maint	[redacted]	[redacted]	£31,523	£7,014
Atezo+Bev+CP	[redacted]	[redacted]	£7,014	-

Commentary on the robustness of submitted evidence

Strengths

- The ERG considers that the company's systematic literature review of clinical effectiveness evidence is of a good standard, with comprehensive literature searches, inclusion screening, data extraction and critical appraisal.
- Overall, the ERG believes the IMpower150 RCT has been well conducted but, as an open label trial, the outcomes are susceptible to performance bias and detection bias.
- The model structure is appropriate for NSCLC and correctly implemented.
- The economic analysis complies with methodological criteria in the NICE reference case (although the decision problem does not match that in the scope, see below).

Table 6 ERG base case for ITT population (PAS for atezolizumab and bevacizumab and list price for comparators and subsequent treatments)

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
PEM+platinum w PEM maint	[redacted]	[redacted]		Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	

- the National Lung Cancer Report for 2017 (for the audit period 2016)[3] show that pemetrexed is given in combination with carboplatin as well as in combination with cisplatin.
- **Comparator 2 (PD-L1 high patients)** - No cost-effectiveness comparison is made with pembrolizumab in PD-L1 high expression patients. An indirect comparison of clinical effectiveness is presented in the CS but, based on the results [redacted] and UK clinical expert advice, a cost effectiveness comparison with pembrolizumab in PD-L1 high patients is not included in the CS. The CS states that UK clinical opinion suggests that [redacted]. Expert advice to the ERG concurs with this suggestion. The company is therefore not seeking NHS reimbursement for treatment with atezolizumab in this patient sub-group.
- **Comparator 3 (EGFR/ALK positive patients)** – the CS omits the comparison with docetaxel or pembrolizumab in patients with EGFR-or ALK-positive advanced, non-squamous NSCLC previously treated with targeted therapy. We understand that docetaxel and pembrolizumab should not be considered as comparators for people with EGFR or ALK mutations. Instead, the only comparison made is to pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed maintenance treatment. The NICE scope does not specify pemetrexed as a comparator for this patient subgroup. Expert clinical advice to the company and to the ERG suggests that pemetrexed can be considered an appropriate comparator for these patients.
- **Outcomes** – all outcomes in the scope are included in the decision problem. Time to treatment discontinuation is included in the decision problem, though not included in the scope. This is an input parameter for the economic model and is appropriate to the analysis.

ERG conclusion: The company's decision problem does not fully adhere to the NICE scope, in terms of relevant treatment comparisons. One key omission is comparison to first line chemotherapy regimens including docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with a platinum drug (carboplatin or cisplatin) (with or without pemetrexed maintenance treatment). Whilst clinical advice to the company suggests pemetrexed in combination with cisplatin is the standard of care, clinical advice to the ERG also suggests that these chemotherapy regimens may be used in combination with carboplatin for patients who cannot tolerate cisplatin.

Table 8 Company and ERG assessment of trial quality

	IMpower150	
1. Was randomisation carried out appropriately?	CS:	Yes
	ERG:	Yes
Comment:		
2. Was concealment of treatment allocation adequate?	CS:	Yes
	ERG:	Yes
Comment: Study site was not a stratification factor so the probability of the next allocation will depend on previous allocations at all the other sites. Therefore, it is unlikely that the next allocation could be guessed in advance. Furthermore each study site obtained a randomization number and treatment assignment for each eligible patient from the interactive voice/Web response system (IxRS/IWRS).		
3. Were groups similar at outset in terms of prognostic factors?	CS:	Yes
	ERG:	Yes
Comment: In the ITT population there were more patients with an ECOG performance status of 1 in the treatment arm (59.9%) than in the control arm (54.9%) but clinical advice to the ERG was that this difference is not clinically important. Arms are well balanced other than this.		
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS:	N/A (open label study)
	ERG:	No
Comment: Open label study to care providers and participants aware of treatment allocation. No evidence that outcome assessors were blind to treatment allocation.		
5. Were there any unexpected imbalances in drop-outs between groups?	CS:	No
	ERG:	No
Comment:		
6. Is there any evidence that authors measured more outcomes than reported?	CS:	No
	ERG:	No
Comment: All the key clinical effectiveness outcomes are reported. Some other patient reported outcomes (PROs) are not reported in the CS e.g. EQ-5D-3L data required for economic modelling but utility scores were provided in response to clarification question A5. The IMpower150 study protocol states that [redacted]. The CSR states that [redacted].		
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS:	Yes
	ERG:	Yes for most efficacy outcomes
Comment: An ITT analysis was conducted for efficacy outcomes. For PFS and OS appropriate censoring methods are described. [redacted]		

PGIS – Patient Global Impression of Severity; PRO – Patient reported outcome; SILC – Symptoms In Lung Cancer

3.1.5 Description and critique of company's outcome selection

The outcomes selected by the company for their decision problem and the results presented in the CS match the outcomes listed in the NICE scope. In addition, the company presents evidence on time to treatment discontinuation (TTD) which is required to inform treatment duration for atezolizumab in the economic model.

3.1.7.4.1 Model fitting

Two orders of fractional polynomial model were considered for inclusion: first-order, and second order. The exponent (power level) for each order were chosen from the following set P1=0, P1=1. A first order model with a P=0 would be equivalent to a Weibull model, and a first order model with P=1 would correspond to a Gompertz model. For the second order model the following exponents were considered: P1=0 P2=0; P1=1 P2=0; P1=1; P2=1. (There is an apparent typo on page 134 which suggests P1=0 P2=1 but this is inconsistent with the rest of the CS.)

The ERG notes that only a relatively narrow range of powers (P1 and P2 in the range 0 to 1) were considered in the company's analysis. The CS states that the models used covered a broad range of hazard ratio shapes, and this was judged to be sufficiently broad to capture the variation in hazards observed in the data. Further, the CS concludes that their exclusion of higher order polynomials or further exponents is consistent with previous NICE submissions however, the reference supplied (CS appendix reference 28) is unrelated to the issue of fractional polynomial models and appears to have been cited in error. Nevertheless, the ERG notes that the hazard ratio plots for OS and PFS provided by the company for the fractional polynomial models tested (clarification question A18) do encompass a variety of shapes and are likely to capture a broad range of survival estimations. The ERG therefore agrees with the company's choice of powers.

Fixed effect versions of the five fractional polynomial models and the exponential model were fitted and evaluated for the ITT analysis for both OS and PFS.

To select the most appropriate fractional polynomial model from the first and second order models considered, the company used the deviance information criterion (DIC) to compare goodness-of-fit. The DIC is commonly used to compare the fit of Bayesian statistical models with the smallest DIC indicative of best fit. The DIC values are reported in CS appendix Table 29. The company also visually inspected the hazard curves (CS appendix Figure 11 and 13) and survival curves (CS appendix Figure 12 and Figure 14), and considered the clinical plausibility of the extrapolated survival curves.

The best fitting fractional polynomial model chosen for OS and PFS was the fixed effects model with P1=0 (Weibull). This model was used in the ITT NMA as well as the subgroup and sensitivity analyses, for methodological consistency. For completeness, the ERG would

As noted in section 3.1.6.6,

[redacted]

ERG conclusion: Treatment with Atezo+Bev+CP leads to an improvement in OS in the ITT population in comparison to Bev+CP.

3.3.3 Response rate

Objective response (shown as 'Responders' in Table 12) was defined as all those with either a complete response (CR) or a partial response (PR).

Table 12 Summary of response in the ITT population (Clinical cut-off date 22 January 2018)

	Atezo+Bev+CP n=397	Bev+CP n=393
Responders, n (%)	224 (56.4)[a]	158 (40.2)[a]
Odds ratio (95% CI)	1.94 (1.46, 2.58)	
Complete response, n (%) (95% CI)	11 (2.8) (1.4, 4.9)	3 (0.8) (0.2, 2.2)
Partial response, n (%) (95% CI)	213 (53.7) (48.6, 58.6)	155 (39.4) (34.6, 44.5)
Stable disease, n (%) (95% CI)	111 (28.0) (23.6, 32.7)	160 (40.7) (35.8, 45.8)
Progressive disease, n (%) (95% CI)	23 (5.8) (3.7, 8.6)	38 (9.7) (6.9, 13.0)
Missing or unevaluable, n (%)	39 (9.8)	37 (9.4)

Reproduced from CS Table 11

[a] CS Table 11 has an error in this row. The correct figures were supplied by the company (clarification question A7)

Below we briefly summarise the results. For full details please see CS section B.2.9 and CS Appendix D. Additional results can be found in Appendix A of the company's response to clarification questions. We summarise results for the ITT population, the EGFR/ALK positive subpopulation, and the PD-L1 low / negative subpopulation. See section 4.2.4.1.1 of this report for further information on how these populations were used to inform the fitting of baseline survival curves for atezolizumab in the economic model.

3.3.7.1 Overall survival

In the **ITT population**, as Figure 6 shows, Atezo+Bev+CP had a statistically significantly longer expected survival relative to comparison B, PEM+CIS then PLAC main + BSC, but not relative to comparison A, PEM+CARB/CIS then PEM maintenance. For the latter the credible interval crossed zero (indicating no statistically significant difference between treatments).

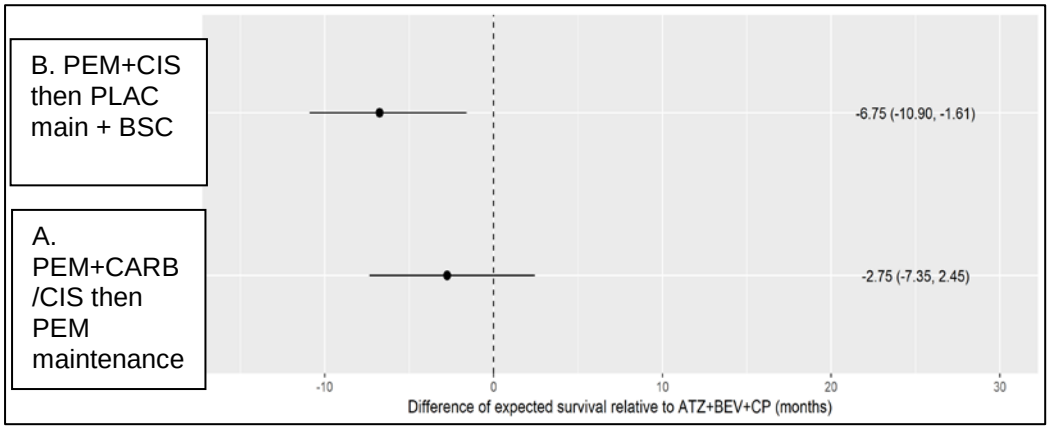
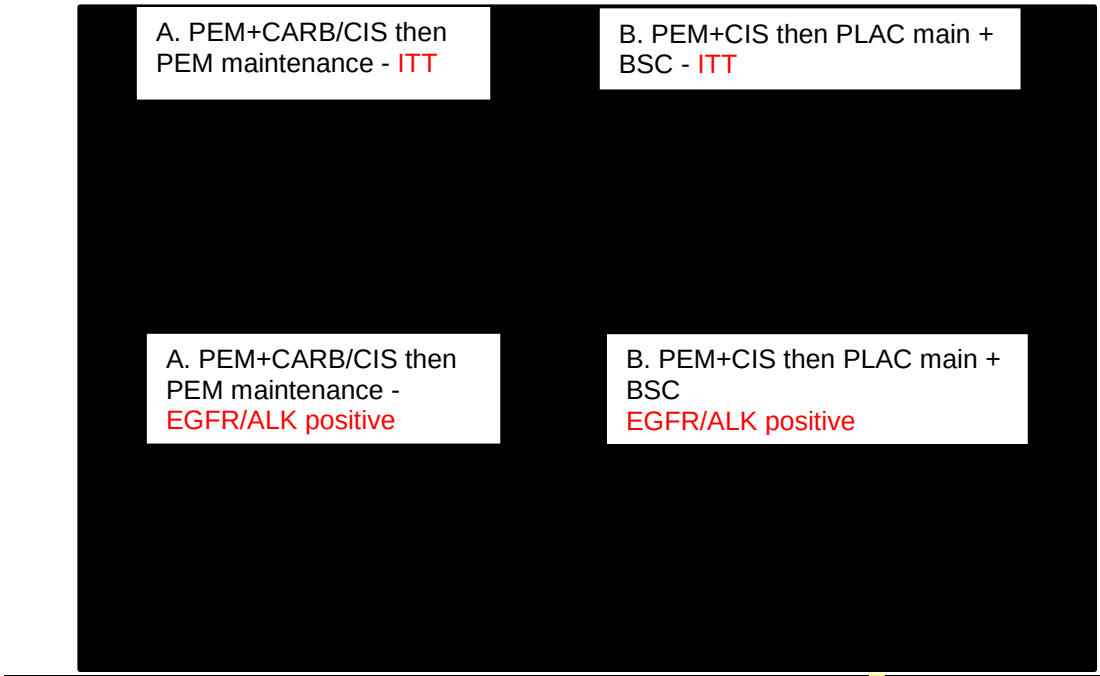


Figure 1 Forest plot of the expected mean OS difference relative to Atezo+Bev+CP (time horizon 60 months)
Reproduced from CS figure 10

[redacted]



[redacted]

PD-L1 low or negative subgroup (CS Figure 16):

- [redacted]
- [redacted]

[redacted]

3.3.7.2 Progression free survival

In the **ITT population**, the PFS results statistically favoured Atezo+Bev+CP compared to both comparator treatments. As Figure 9 shows, there was a statistically significantly longer expected PFS relative to PEM+CIS then PLAC main + BSC, and to PEM+CARB/CIS then PEM maintenance. The gain in PFS was greater compared to PEM+CIS then PLAC main + BSC.

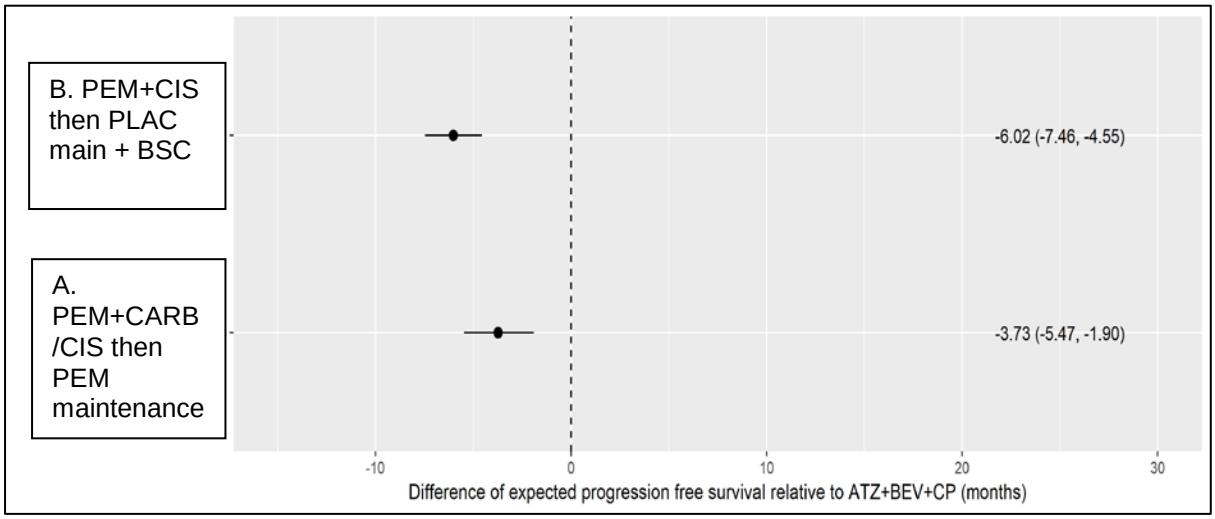
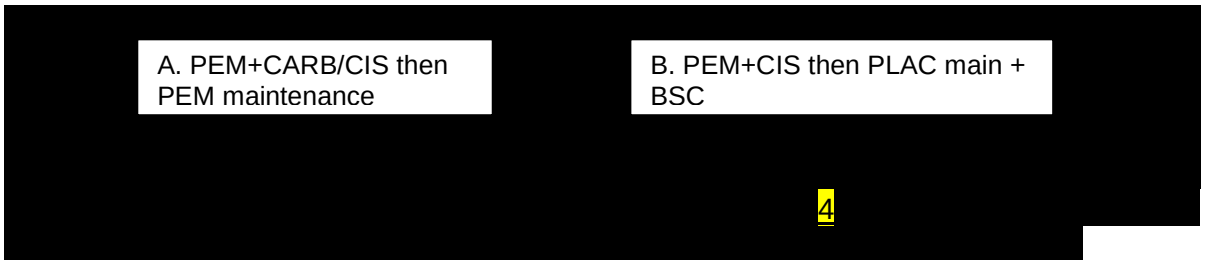


Figure 3 Forest plot of the expected PFS difference relative to Atezo+Bev+CP (time horizon 30 months)
Reproduced from CS Figure 12

The time-varying HR plots ([redacted], and CS Figure 13) show similar results to the forest plots:



EGFR/ALK positive subgroup

[redacted]

[redacted]

3.3.7.3 NMA sensitivity analyses

The scenario analysis excluding the PARAMOUNT trial improved the OS and PFS survival estimates in favour of Atezo+Bev+CP compared to PEM+CARB/CIS then PEM maintenance (the comparison to PEM+CIS then PLAC main + BSC was no longer possible with the omission of this trial) (CS Figure 18, 19, 20, 21).

The scenario analysis using a proportional hazards model (exponential fractional polynomial) showed more favourable results in favour of Atezo+Bev+CP compared to the two pemetrexed comparator regimens than was the case under the best fitting fractional polynomial model (CS Figure 22, Figure 23, Figure 24, Figure 25). It should be acknowledged, however, that the proportional hazards assumption cannot necessarily be applied to these trial data (as discussed earlier, section 3.1.7).

3.3.8 Summary of adverse events

Information on adverse events comes from the safety population of the IMpower150 trial. The safety population included all treated patients who received any amount of any component of study treatment. Patients were grouped according to whether they received any amount of atezolizumab or not. Note however that there is a minor inconsistency in the CS. CS Appendix D Figure 19 (Patient disposition in IMpower150 at the time of the updated analysis) shows 394 treated patients in both the Atezo+Bev+CP and Bev+CP arms of the trial but CS Tables 17 to 22 show only 393 patients in the safety population for the Atezo+Bev+CP group and 394 in the Bev+CP group.

The CS presents an overview of the safety profile of Atezo+Bev+CP compared with Bev+CP which is reproduced below in Table 18. The total number of adverse events was higher in the Atezo+Bev+CP group (n=6419) compared with the Bev+CP group (n=4630). However, the proportion of patients with at least one adverse event or one treatment-related adverse event was similar between groups (patients with at least one adverse event: Atezo+Bev+CP 98.2% vs Bev+CP 99.0%; patients with at least one treatment-related adverse event Atezo+Bev+CP 94.1% vs Bev+CP 95.7%). As Table 18 shows, the proportion of patients experiencing treatment-related Grade 3-4 adverse events, serious adverse events an

most patients. We note, however, that the model does not compare against carboplatin-based chemotherapy (carboplatin plus either docetaxel, gemcitabine, paclitaxel or vinorelbine) followed by pemetrexed maintenance (as per the NICE scope), which is an option for patients who cannot tolerate cisplatin. It is unclear how this omission affects the incremental cost-effectiveness results.

4.2.3 Model structure and assumptions

The company describe the key features and assumptions of their economic model in section B.3.2.2 of the CS. We reproduce their illustration of the model structure below.

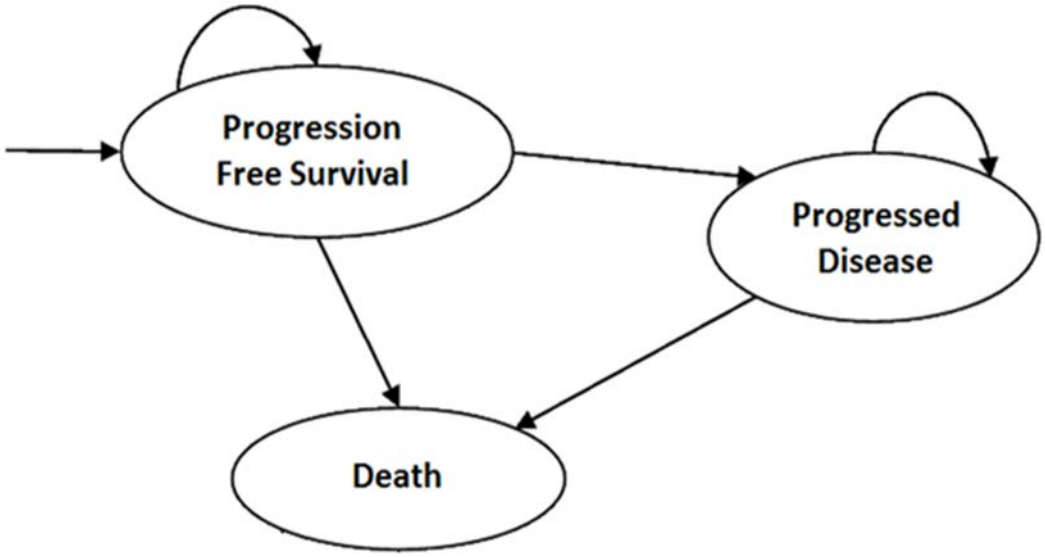


Figure 12 Economic model (reproduced from CS Figure 31)

The model follows a partitioned-survival approach with three health states: progression free (PF), progressed disease (PD) and death. The distribution of the cohort between the three states at each point in time is derived from PFS and OS curves, estimated from IMpower150 data and the NMA. All patients start in the PF state, at initiation of one of the modelled treatments. Patients move from PF to PD if their disease progresses, with the number of progressions per model cycle determined by the difference between the OS and PFS curves. Time to Treatment Discontinuation (TTD) curves estimated from trial data set the duration of each first-line medication. The model does not explicitly reflect subsequent lines of treatment, but an average cost for subsequent therapies in the PD state is included. Over time, patients transition to the absorbing state of death, with the number of deaths per cycle determined by the OS curve. The three-state partitioned-survival model is common in cancer appraisals and the ERG considers it appropriate in this case.

Table 1 Summary of utility values for cost-effectiveness analysis

Category	Utility	95% CI	Reference in submission	Justification
IMpower150 utilities - Proximity to death approach – Base case				
≤ 5 weeks before death	0.52	0.49 - 0.56	Section B.3.4.1	Derived from EQ-5D data collected during IMpower150 trial. Methodology as per NICE reference case.
> 5 & ≤ 11 weeks before death	0.59	0.56 - 0.61		
> 15 & ≤ 30 weeks before death	0.70	0.68 - 0.71		
> 30 weeks before death	0.73	0.72 - 0.75		
IMpower150 utilities - Pre- and post-progression - Scenario analysis				
Pre-progression	0.71	0.70 - 0.72	Section B.3.4.1	Derived from EQ-5D data collected during IMpower150 trial.
Post-progression	0.69	0.66 - 0.72		
Pembrolizumab utilities - Proximity to death approach – US publication[18] - Scenario analysis				
≤ 5 weeks before death	0.537	0.425–0.650	Section B.3.4.3	Identified from published literature
> 5 & ≤ 15 weeks before death	0.632	0.592–0.672		
> 15 & ≤ 30 weeks before death	0.726	0.684–0.767		
> 30 weeks before death	0.805	0.767–0.843		
Utilities from Nafees et al – Scenario analysis				
Progression free	0.66*	Calculated based on utility model coefficients	Section B.3.4.3	Identified from published literature
Progressed disease	0.47*			
Utilities from Chouaid et al – Scenario analysis				
Category	**Utility**	**95% CI**	**Reference in submission**	**Justification**
Progression free	0.71*	Calculated based on utility model coefficients	Section B.3.4.3	Identified from published literature
Progressed disease	0.67*			

Table reproduced from CS Table 30
*calculated based on reported regression coefficients; CI: confidence interva

the NICE committee in the NICE technology appraisal TA531 for pembrolizumab in first-line NSCLC.[12]

We conduct a scenario analysis excluding nivolumab as a second-line treatment, as this is currently recommended by NICE for use on the Cancer Drugs Fund rather than as part of routine commissioning (TA484).

The IMPower150 trial collected data on subsequent therapies for patients initially receiving Atezo+Bev+CP, however these data are not used in the company base case because these were not in line with current UK practice. The company provides a scenario analysis using these data for subsequent therapies from IMPower150.

The drug acquisition costs for the subsequent therapies are shown in Table 34 (CS Table 36). The ERG notes that the cost for pembrolizumab has been calculated based on patient weight assuming it is possible to buy part of a vial. However, this differs from the approach taken in the NICE technology appraisal TA428[17] for pembrolizumab therapy after chemotherapy for NSCLC. In that NICE appraisal, the company estimated the cost per patient receiving pembrolizumab, based on the KEYNOTE-010 trial where the average number of full 50mg vials received was 3.39 per patient, with a cost per treatment cycle of £4,453.13. The ERG suggests that this cost for pembrolizumab is more appropriate.

Table 2 Subsequent therapies after discontinuation - used in base case analysis

Post-discontinuation therapy	Treatments after Atezo+Bev+CP	Treatments after pemetrexed-based regimens	Duration of therapy (weeks)	Source for duration of therapy
Docetaxel	100%	15%	13.1[1]	Docetaxel SmPC
Nivolumab	0%	34%	26.52	NICE TA484
Pembrolizumab *	0%	34%	21.59	NICE TA428
Atezolizumab	0%	17%	35.80	NICE TA520

Table reproduced from CS Table 34

* Pembrolizumab is administered in second-line as per its license in this indication i.e. 2 mg/kg

[1] Value used in the model differs from that reported in CS Table 3

bevacizumab but list prices for comparators and subsequent treatments in Table 39, Table 40 and Table 41 below. Results with all applicable PAS price discounts are presented in a separate confidential addendum to this report.

Table 3 Company base case results, ITT population (PAS for atezolizumab and bevacizumab, list prices for other treatments) – deterministic (CS Clarification response Table 35)

Treatment	Total		Incremental analysis ICER (£/QALY)	Pairwise ICERs vs. comparator (£/QALY)
	[redacted]	[redacted]		
PEM+plat	[redacted]	[redacted]		£16,419
PEM+plat+PEM maint	[redacted]	[redacted]	£35,985	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	-

Table 4 Company base case results, PD-L1 negative/low population (PAS for atezolizumab and bevacizumab, list prices for other treatments) – deterministic (CS Clarification response Table 36)

Treatment	Total		Incremental analysis ICER (£/QALY)	Pairwise ICERs vs. comparator (£/QALY)
	[redacted]	[redacted]		
PEM+plat	[redacted]	[redacted]		£13,424
PEM+plat+PEM maint	[redacted]	[redacted]	£38,943	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	-

Table 5 Company base case results, EGFR/ALK positive population (PAS for atezolizumab and bevacizumab, list prices for other treatments) – deterministic (CS Clarification response Table 37)

Treatment	Total		Incremental analysis ICER (£/QALY)	Pairwise ICERs vs. comparator (£/QALY)
	[redacted]	[redacted]		
PEM+plat	[redacted]	[redacted]		£14,552
PEM+plat+PEM maint	[redacted]	[redacted]	£31,523	£7,014
Atezo+Bev+CP	[redacted]	[redacted]	£7,014	-

The ERG found small cost differences in the total costs for comparators in the EGFR/ALK population reported in Table 41. The results when the ERG ran the company model are shown in Table 42. This does not substantively change the estimated ICERs.

Table 6 ERG rerun of company base case for the EGFR/ALK positive population (PAS for atezolizumab and bevacizumab, list prices for comparators and subsequent treatments) – deterministic

Treatment	Total		Incremental analysis ICER (£/QALY)	Pairwise ICERs vs. comparator (£/QALY)
	[redacted]	[redacted]		
PEM+plat	[redacted]	[redacted]		£14,430
PEM+plat+PEM maint	[redacted]	[redacted]	£36,206	£4,758
Atezo+Bev+CP	[redacted]	[redacted]	£4,758	-

ERG conclusion: Except for the EGFR/ALK positive population, other base case results reported in the company's clarification response were reproducible when the ERG ran the company's model.

4.3.2 Company's sensitivity analyses

The company's sensitivity analysis comprised of probabilistic sensitivity analysis (PSA), one-way sensitivity analyses and scenario analyses. The company reports these set of analysis in the CS section B.3.8 and updates them in Appendix D of the company's clarification response.

4.3.2.1.1 Company's probabilistic sensitivity analyses

The CS reports PSA performed on the base case analysis to assess parameter uncertainty (CS section B3.8.1) with 1000 samples.

The mean values, distributions around the means, and sources used to estimate the parameters are detailed in Appendix R of the CS. Joint uncertainty over parameters estimates used to estimate relative treatment effects on OS and PFS are sampled from the CODA output from the NMA. The company used the normal distribution for all other parameters varied in the PSA. A more standard approach is to use the gamma distribution for costs and the beta distribution for utilities. In addition, the company uses arbitrary variations for some of the input parameters of costs of +/- 5%. The ERG is of the opinion that 95% confidence intervals are more appropriate and if these CIs are not available varying by +/-25% or 30% of the base case input parameters is preferable.

4.4.1 ERG corrections to company base case and scenarios

The company base case results for the three populations with ERG corrections are shown in Table 47 - Table 49, with PAS price for atezolizumab and bevacizumab and list price for comparators and subsequent treatments. The ERG corrections (Table 44) only have a minor impact on the results. We show equivalent results with all available PAS discounts in a separate confidential addendum, respectively.

Table 7 ERG corrected company base case for ITT population (PAS for Atezo & Bev only) - deterministic

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
PEM+platinum	[redacted]	[redacted]	-	£14,467
PEM+platinum w PEM maint	[redacted]	[redacted]	£37,184	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	

Table 8 ERG corrected company base case for PD-L1 low/negative population (PAS for Atezo & Bev only) - deterministic

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
PEM+platinum	[redacted]	[redacted]	-	£11,513
PEM+platinum w PEM maint	[redacted]	[redacted]	£39,876	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	

Table 9 ERG corrected company base case for EGFR/ALK positive population (PAS for Atezo & Bev only) - deterministic

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
PEM+platinum	[redacted]	[redacted]	-	£14,547
PEM+platinum w PEM maint	[redacted]	[redacted]	£37,024	£4,563
Atezo+Bev+CP	[redacted]	[redacted]	£4,563	

Table 50 and Table 51 show the ERG corrections to the company scenario analyses for the ITT population with PAS discounts for atezolizumab and bevacizumab only.

Table 10 ERG corrected company scenarios for ITT population, comparison with pem+plat (PAS for Atezo & Bev only) - deterministic

Scenario		Atezo+Bev+CP		Pem+platinum		ICER
		Total QALYs	Total costs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£15,784
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	£11,728
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£19,214
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£12,041
	Gompertz	Does not converge				
PFS distribution	KM with Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£16,766
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£16,614
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	£14,803
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£16,050
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£14,460
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	£16,958
TTD distribution	KM with Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	£15,585
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	£13,687
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	£16,236
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	£12,604
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	£18,936
	Gompertz	Does not converge				
Alternative NMA network	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	ITT exclude KEYNOTE	[redacted]	[redacted]	[redacted]	[redacted]	£14,596
	ITT exclude PARAMOUNT	Does not converge				
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	£17,595
	NMA - Fract Poly (RE)	[redacted]	[redacted]	[redacted]	[redacted]	£14,540
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	£23,915

Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	£14,976
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	£15,213
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	£15,265
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	£15,272
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	£15,058
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	£14,956
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	£16,246
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	IMpower150	[redacted]	[redacted]	[redacted]	[redacted]	£21,399
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	£14,589

Table 11 ERG corrected company scenarios for ITT population, comparison with pem+plat with pem maintenance (PAS for Atezo & Bev only) - deterministic

Scenario		Atezo+Bev+CP		Pem+platinum +maintenance		ICER
		[redacted]	[redacted]	[redacted]	[redacted]	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
PFS distribution	KM with Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
TTD distribution	KM with Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gompertz	[redacted]				[redacted]
Alternative NMA network	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ITT exclude KEYNOTE	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ITT exclude PARAMOUNT	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	NMA - Fract Poly (RE)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	£6,042

Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IMpower150	[redacted]	[redacted]	[redacted]	[redacted]	£139
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

4.4.2 ERG base case and scenarios

Results for the ERG base case analysis for the ITT population are shown in Table 52 (PAS for atezolizumab and bevacizumab only). This analysis uses NMA results excluding the PARAMOUNT trial, so results are only available verses the comparator with pemetrexed maintenance. Equivalent results for the PD-L1 low/negative and EGFR/ALK positive populations are shown in Table 53 and Table 54.

Table 12 ERG base case for ITT population (PAS for atezolizumab and bevacizumab and list price for comparators and subsequent treatments)

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
PEM+platinum w PEM maint	[redacted]	[redacted]		Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	

Table 13 ERG base case results for PD-L1 population (PAS for atezolizumab and bevacizumab and list price for comparators and subsequent treatments)

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
PEM+platinum w PEM maint	[redacted]	[redacted]		Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	

Table 14 ERG base case results for EGFR/ALK population (PAS for atezolizumab and bevacizumab and list price for comparators and subsequent treatments)

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
PEM+platinum w PEM maint	[redacted]	[redacted]		Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	

The results of scenarios around the ERG ITT base case are shown in Table 55. Although these analyses do not reflect agreed price discounts for pemetrexed maintenance or for some subsequent treatments, they do indicate which parameters the model is most sensitive to: extrapolations of overall surival and treatment duration, the use of a stopping rule for atezolizumab and bevacizumab as part of Atezo+Bev+CP and the costs of subequent treatments.

Table 15 ERG scenarios for ITT (PAS for Atezolizumab and Bevacizumab and list price for comparators and subsequent treatments)

Description		Atezo+Bev+CP		PEM+platinum+PEM Maintenance		ICER
		Total QALYs	Total costs	Total QALYs	Total costs	
OS distribution	Weibull (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
PFS distribution	KM+log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	KM + Exponential	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	KM+weibull	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
TTD distribution	KM + Exponential Pemetrexed follows PFS (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Bevacizumab until progression	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Alternative NMA network/ model	ITT FP excluding PARAMOUNT (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ITT FP (RE)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ITT Excluding PARAMOUNT + PH	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Treatment stopping rule/ treatment effect	2 years treatment + 3 years OS effect (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	2 years OS	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	5 years OS	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	3 years PFS	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	No stopping rule or effect cap	[redacted]	[redacted]	[redacted]	[redacted]	£8,469
Utility values	IMPower150 EQ-5D, using time from death + disutilities (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IMPower150 EQ-5D health states	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
AE disutility	Disutilities per grade 3+ treatment related AE (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	No AE disutilities	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IMpower150	[redacted]	[redacted]	[redacted]	[redacted]	£3,132
	Exclude nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	£3,670

4.4.3.4 NMA

Given concerns about potential bias due to patient selection, we think it is appropriate to exclude the PARAMOUNT study from the NMA. The company's choice of survival curves for PFS and TTD are reasonable and appropriate.

4.4.3.5 Health utility

The company's approach to health state utility values is reasonable and consistent with the NICE reference case and with previous NICE technology appraisals. However, the ERG considers that the differences in treatment related adverse events between treatments have not been fully captured and it is unclear whether patients treated with Atezo + Bev. + CP have the same health state utility values whilst on treatment as those treated with pemetrexed + platinum (with or without pemetrexed maintenance).

4.4.3.6 Health resources and costs

The approach taken by the company for estimating health care resources and costs is reasonable and in line with previous NICE technology appraisals for NSCLC. There are some minor discrepancies to some of the cost estimates as they have not been updated correctly.

5 End of life

End of life criterion 1 - "The treatment is indicated for patients with a short life expectancy, normally less than 24 months". Table 56 reports the mean and median undiscounted life years from the company's model. The mean estimates for pemetrexed plus platinum with pemetrexed maintenance therapy exceed 24 months. The ERG's discounted estimates for pemetrexed maintenance therapy are less than 24 months in the ITT population (Table 57).

Table 16 Company base case undiscounted life years

Absolute life years (undiscounted)	**PEM+platinum**		**PEM+platinum with PEM maint**	
	Mean OS	Median OS	Mean OS	Median OS
ITT	1.53	1.22	2.18	1.11
PD-L1	1.55	1.14	2.27	0.99
EGFR/ALK +ve	2.04	0.91	3.15	0.49

Table 17 ERG base case undiscounted life years

Absolute life Years (undiscounted)	PEM+platinum with PEM maint	
	Mean OS	Median OS
ITT	1.72	1.32

End of life criterion 2 – "There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment". Table 58 reports the company's modelled incremental mean and median undiscounted life years gained. For all populations the estimates exceed 3 months.

Table 18 Company modelled undiscounted life years gained

Life years gained (undiscounted)	Versus Pem+platinum		Versus PEM+platinum w PEM maint	
	Mean OS	Median OS	Mean OS	Median OS
ITT	1.08	0.48	0.42	0.59
PD-L1	1.01	0.46	0.29	0.61
EGFR/ALK +ve	3.08	1.73	1.97	2.15

The ERG's modelled undiscounted life years gained estimate is also greater than 3 months in the ITT population (Table 59).

Table 19 ERG modelled undiscounted incremental life years gained

LY gained (undiscounted)	Versus PEM+platinum w PEM maint	
	Mean OS	Median OS
ITT	0.46	0.32

ERG conclusion: Atezo+Bev+CP meets both of the end-of-life criteria based on the ERG's modelled estimates in the ITT population. However, it does not appear to meet all of the end of life criteria when compared to pemetrexed plus platinum with pemetrexed maintenance therapy using the company's modelled estimates.

6 Innovation

The CS provides a lengthy justification for why atezolizumab should be considered a treatment innovation for the first line treatment of metastatic NSCLC (CS section B.2.12). The justification centres on a suggested unmet need for an improvement of efficacy in first-line treatments for non-squamous metastatic NSCLC, and specifically the need for further treatment options for patients with low or negative PD-L1 expression and in patients with an EGFR or ALK mutation who are ineligible for, intolerable to or have progressed on targeted therapy.