NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC [ID1210]

Pre-meeting briefing

Contains CIC and ACIC

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
Atezo+ Bev+CP	Atezolizumab + bevacizumab + carboplatin + paclitaxel
Bev+CP	Bevacizumab + carboplatin + paclitaxel
BIC	Bayesian information criterion
CDF	Cancer drugs fund
CG	Clinical guideline
CI	Confidence interval
cis	cisplatin
DOR	Duration of response
DoT	Duration of treatment
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ERG	Evidence review group
FP	Fractional polynomial
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
ITT-WT	Intention to treat wild type
maint	Maintenance treatment
NMA	Network meta-analysis
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-L1	Programmed cell death-1 ligand-1
pem	pemetrexed
PFS	Progression-free survival
plat	Platinum drug
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours
SD	Standard deviation
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TPS	Tumour proportion score

Key issues - clinical effectiveness (1)

- **Population:** Company include two patient subgroups & not the whole population covered by the anticipated marketing authorisation. Subgroups = people with PD-L1 expression TPS 0-49% and people who have progressed on targeted therapies for epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) tumour mutations. **Are these relevant subgroups?**
- **Comparator:** Company does not include chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) with a platinum drug (carboplatin or cisplatin) with or without (+/-) pemetrexed maintenance
  - Company have included pemetrexed in combination with carboplatin +/- pemetrexed maintenance. This is not recommended by NICE. **For people unable to tolerate cisplatin, is platinum combination chemotherapy containing carboplatin +/- pemetrexed maintenance the most suitable treatment option?**
  - NMA used in the ERG's base case does not include the only study that includes pemetrexed and cisplatin without maintenance (PARAMOUNT). **Would most people receive pemetrexed maintenance in clinical practice?**
  - Comparators for EGFR/ALK positive population not in line with NICE scope. **Is pemetrexed with cisplatin +/- pemetrexed maintenance the most appropriate comparator?**

[redacted]

Key issues - clinical effectiveness (2)

- **Clinical evidence:** Data from IMpower150 trial = main clinical evidence for atezolizumab + bevacizumab + carboplatin + paclitaxel (atezo+bev+CP). ITT population used, includes those with EGFR/ALK-positive mutations and all PD-L1 expression levels. Direct comparison with comparators in scope not available. Indirect treatment comparison conducted. **Is the clinical evidence appropriate for decision making?**
  - PARAMOUNT trial has different study design. **Should it be included in the NMA?**
- **Overall survival data:** Median OS has been reached in both arms for ITT and PD-L1 <50% populations but number of deaths required for final analysis not met yet so data not fully mature. Median OS not reached in EGFR/ALK positive subgroup. **Is the available data mature enough for decision making?**
- **Utility:** Is health state utility likely to be the same when on treatment with either atezo+bev+CP and pemetrexed with platinum drug +/- pemetrexed maintenance? Is the proximity to death approach appropriate?
- **Adverse events:** Is the adverse event profile acceptable, specifically the immune-related adverse events?
- **Cancer Drugs Fund:** Is atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin a candidate?

[redacted]

Key issues - cost effectiveness

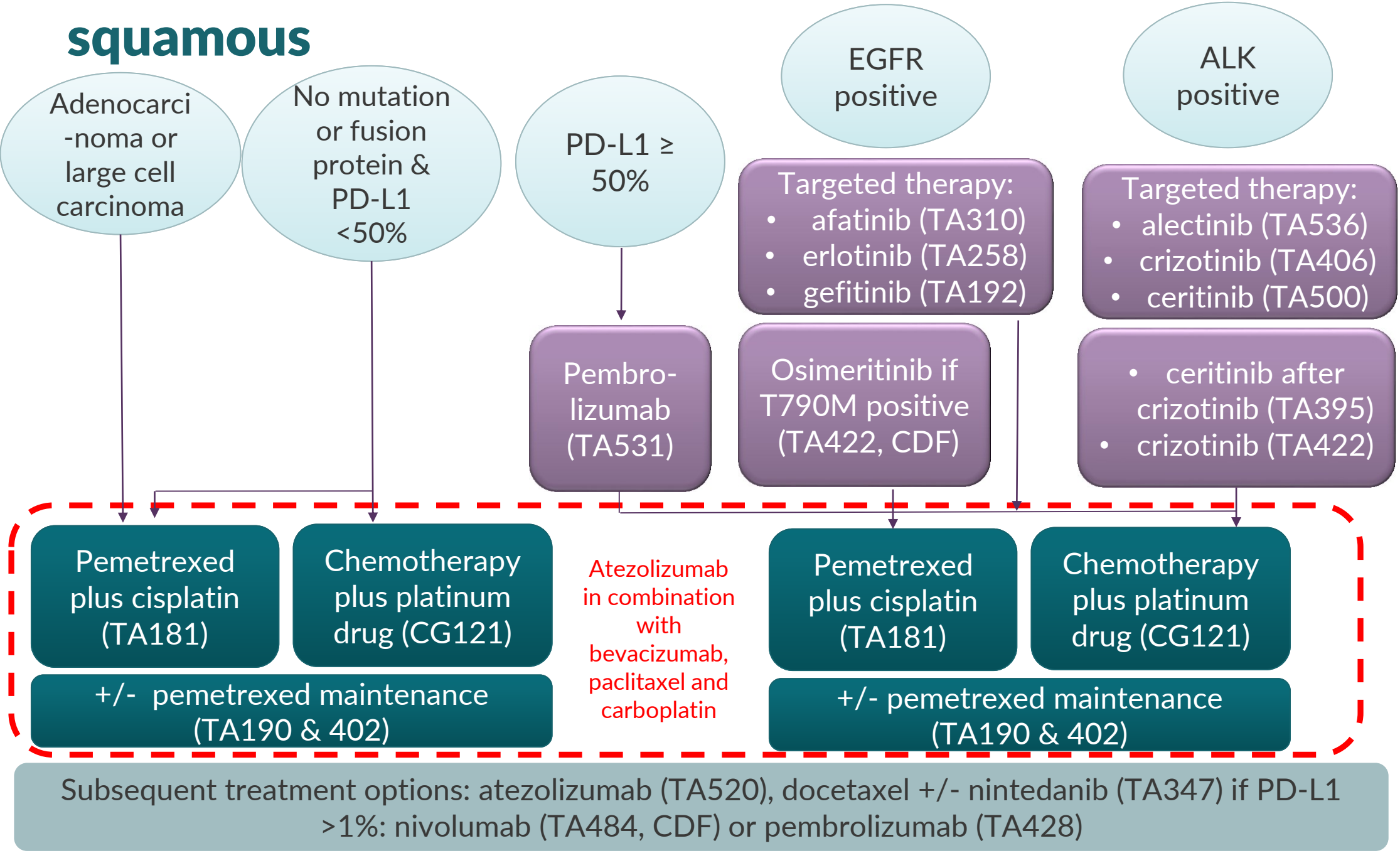
- **EGFR/ALK+ve subgroup:** Results are much more uncertain as small subgroup (n=104). **Are results for the EGFR/ALK+ve subgroup robust enough for decision making?**
- **Extrapolation of overall survival:** Is the extrapolation of OS suitable given the immaturity of the trial data? Is exponential or Weibull (more conservative survival predictions) distribution more suitable for the extrapolation?
- **Duration of treatment benefit:** Is a 5-year duration of treatment benefit for atezolizumab and bevacizumab appropriate?
  - Is a survival advantage for pemetrexed maintenance over the model time horizon realistic?
- **Utility:** Has the impact on utility value been fully captured? Should disutility for adverse events be included?
- **Subsequent therapies:** Are the subsequent therapies included in the company's model (docetaxel, nivolumab, pembrolizumab, atezolizumab) reflective of clinical practice in the UK?
- **Relevant costs and benefits:** Has the model captured all relevant costs and benefits?
  - Is a 2-year stopping rule for treatment appropriate to include in the model?
- **Results:** What are the most plausible ICERs for atezo+bev+CP in each subgroup?
- **End of life criteria:** Does atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin meet the end of life criteria?

[redacted]

Background
Non-small-cell lung cancer (NSCLC)

- Lung cancer → more than 45,000 people are diagnosed & in England in 2016, lung cancer caused over 35,500 deaths
- Mostly diagnosed at an advanced stage → cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV)
- Thirty two percent of people with lung cancer survive for more than 1 year after diagnosis
- NSCLC = estimated up to 85 to 90% of lung cancer cases
- Approximately 70% of NSCLC are of non-squamous histology and can be either large-cell undifferentiated carcinoma or adenocarcinoma
- In 2016, approximately 32,500 people were diagnosed with NSCLC in England, and around 61% had stage IIIB or stage IV disease

Treatment pathway in the UK: advanced, non-squamous



Subsequent treatment options: atezolizumab (TA520), docetaxel +/- nintedanib (TA347) if PD-L1 >1%: nivolumab (TA484, CDF) or pembrolizumab (TA428)

Atezolizumab with bevacizumab, carboplatin & paclitaxel

Mechanism of action	**Atezolizumab**: humanised IgG monoclonal antibody which directly & selectively binds to immune checkpoint protein PD-L1; **Bevacizumab:** binds to VEGF **Carboplatin:** alkylating chemotherapy **Paclitaxel:** taxane chemotherapy
Anticipated marketing authorisation	[redacted]
Administration & dosage	**Atezolizumab**: 1,200 mg every 3 weeks, **Bevacizumab:** 15 mg/kg every 3 weeks, **Carboplatin:** area under curve of 6 mg/mL/min, every 3 weeks*, **Paclitaxel:** 200 mg/m^2 every 3 weeks* (*during induction phase, 4 or 6 cycles lasting 21-day, only) all by intravenous infusion **for a maximum of 2 years in economic model**
Cost (list price)	**Atezolizumab:** £3807.69 per 20 ml vial (1,200 mg); **Bevacizumab:** £242.66 per 4 ml vial (100 mg); £924.40 per 16 ml vial (400 mg); **Carboplatin:** £6.35 per 15 ml vial (150 mg); **Paclitaxel:** £9.85 per 16.7 ml vial (100 mg) Average price per treatment cycle (3 weeks): £6,445.89 An application for a Patient Access Scheme (PAS) has been approved by Department of Health for bevacizumab. Atezolizumab has an existing PAS. These provide a simple discount to the list prices

Decision problem (1)

	Scope	Company	
Population	• People with untreated advanced, non-squamous NSCLC • People with EGFR-or ALK-positive advanced, non-squamous NSCLC who were previously treated with targeted therapy (or cannot have one)	✓ - focusing on patients with low or negative PD-L1 expression (TPS <50%, TC/IC 0,1,2) ✓	
Intervention	Atezolizumab in combination with carboplatin plus paclitaxel with or without bevacizumab	Atezolizumab in combination with carboplatin plus paclitaxel **with bevacizumab** → in line with anticipated marketing authorisation	
Outcomes	Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	✓ - also included time to treatment discontinuation	

Decision problem (2)

	Scope	Company	
Comparators	1) For untreated advanced, non-squamous NSCLC: • Chemotherapy* in combination with a platinum drug** • Pemetrexed in combination with cisplatin (adenocarcinoma or large cell carcinoma only) Both +/- pemetrexed maintenance treatment	1) x - clinical expert opinion and UK market share data suggest that pemetrexed plus platinum drug** +/- pemetrexed maintenance is the most appropriate comparator in the UK Included pemetrexed in combination with carboplatin although not recommended by NICE	
	2) Pembrolizumab (for people whose tumours express PD-L1 ≥ 50% TPS)	2) ✓/x – included in clinical section only	
	3) For EGFR-or ALK-positive advanced, non-squamous NSCLC previously treated with targeted therapy: Docetaxel or Pembrolizumab	3) x – Pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed maintenance treatment	
Subgroups	Level of PD-L1 expression	✓	

[redacted]

*Chemotherapy: docetaxel, gemcitabine, paclitaxel or vinorelbine

**Platinum drug: carboplatin or cisplatin; +/-: with or without; TPS: tumour proportion score

ERG comments on the decision problem

Population	People with PD-L1 TPS ≥ 50% & eligible to receive pembrolizumab (TA531) not included. ERG clinical expert agreed with company's justification
Intervention	Atezolizumab + carboplatin + paclitaxel (without bevacizumab) in scope but not company submission. Fine → not in anticipated marketing authorisation
Comparators	Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug, with or without pemetrexed maintenance not included • Company: focus on pemetrexed → most appropriate UK chemotherapy based on clinical expert opinion & UK market share data • ERG clinical expert agrees & highlights **pemetrexed should only be given with cisplatin (TA181).** ERG notes TA181 covers adenocarcinoma or large cell carcinoma only. Caveat not mentioned by company. NSCLC histology predominantly adenocarcinoma & squamous cell carcinoma • **People who cannot tolerate cisplatin would be treated with a carboplatin-based regimen** (i.e. docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with carboplatin), followed by maintenance treatment with pemetrexed. **Not included in the company submission** • National Lung Cancer Report (2017) → pemetrexed is given in combination with carboplatin as well as cisplatin ERG consider pemetrexed is an appropriate comparator for EGFR/ALK positive patients although not given in NICE scope or company submission

Key question: What are the appropriate comparators for EGFR/ALK positive sub-population? Is the comparison with pemetrexed plus platinum drug +/- maintenance appropriate?

Professional organisation perspective

Submission received from Royal College of Pathologists

- There is an unmet need
- PD-L1 testing status carried out already to identify people eligible for first- or second-line therapy → done with a specific companion diagnostic for pembrolizumab
- Pathologists need to know what companion diagnostic will be required → problematic if alternative antibodies and scoring systems are required → training may be required
- Investment may be needed if a different testing strategy is expected to be used

[redacted]

Clinical expert perspective

Submission received from Andrew Nicholson, Royal College of Pathologists

- Mr Nicholson also wrote the statement on behalf of the Royal College of Pathologists so expert statement reflects this

Patient expert perspective

None received yet

NHS England perspective

NHS England submission to be circulated prior to the committee meeting

[redacted]

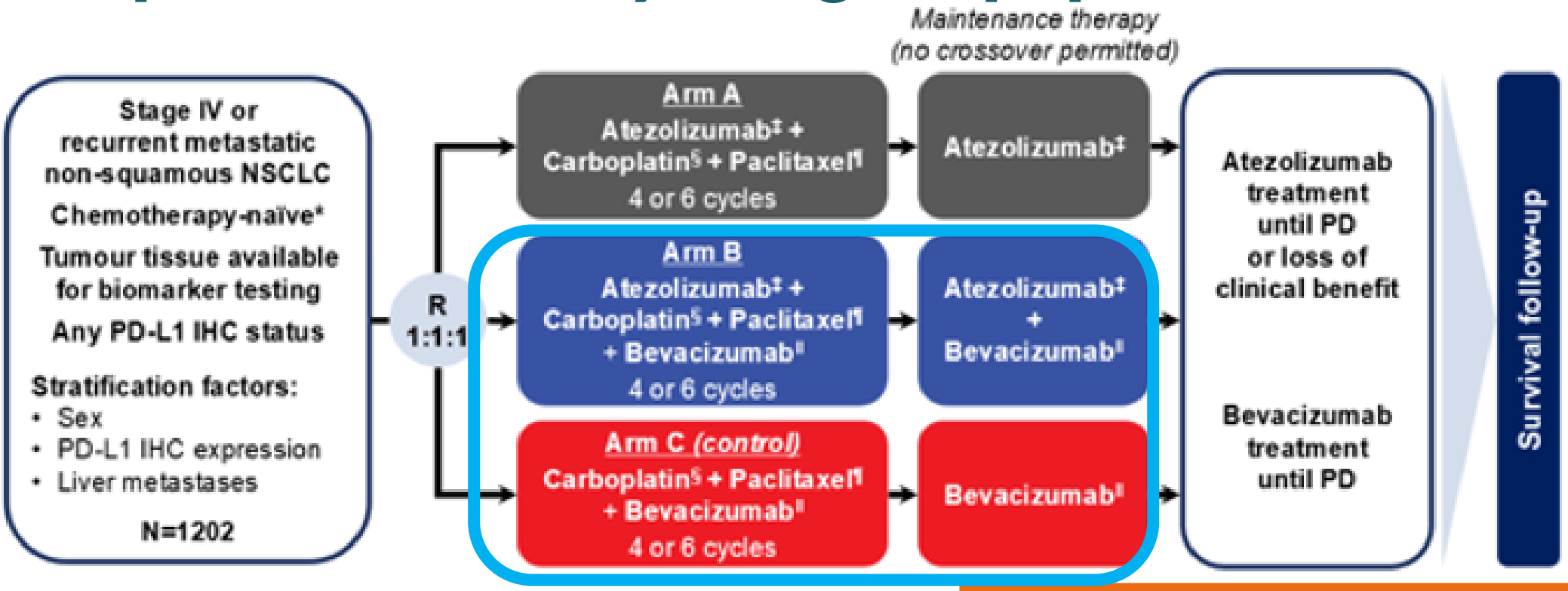
Clinical effectiveness

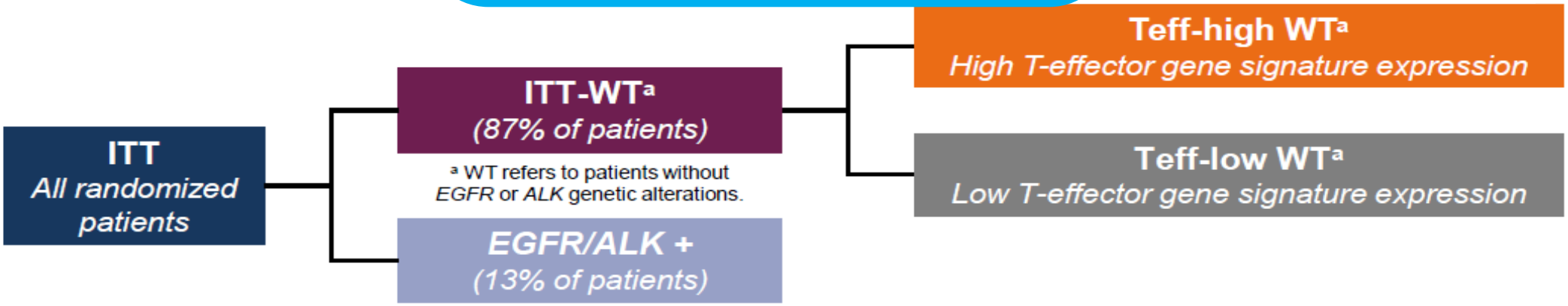
[redacted]

Company's main clinical evidence: IMpower150

Design	Randomised, open-label, phase III study
Population	• Adults with confirmed metastatic, non-squamous NSCLC with no prior treatment for metastatic non-squamous NSCLC • People with sensitising EGFR mutations or ALK-positive tumours who had experienced disease progression (during or after treatment) or intolerance to treatment with one or more EGFR or ALK TKIs, respectively. ECOG PS 0 or 1
Intervention	Atezolizumab + bevacizumab + carboplatin + paclitaxel (atezo+bev+CP)
Comparator	Bevacizumab + carboplatin + paclitaxel (bev+CP)
1◦ outcome	• Investigator-assessed PFS according to RECIST v1.1 in the Teff high wildtype (WT) & intention to treat WT (ITT-WT) population • OS in the ITT-WT population
2◦ outcomes	PFS, OS, ORR and DOR (ITT population)
Safety endpoints	Safety and tolerability of atezolizumab
Pre-planned subgroups	• PD-L1 expression subgroups • EGFK/ALK genetic alterations • Patients with liver metastases at baseline

Impower150 study design & populations





ERG comments: ITT-WT population is 87% of ITT population. [redacted] The company have used the ITT population, not ITT-WT

Key baseline characteristics in IMpower150 (1)

Population		ITT		EGFR/ALK+ve	
		Atezo+bev+CP (n=400)	Bev+CP (n=400)	Atezo+bev+CP (n=41)	Bev+CP (n=63)
Locations	240 study sites in 26 countries. **None in the UK**				
Age, years	Median (SD)	63.0 (9.5)	63.1 (9.3)	63.0 (35 to 76)	61.0 (31 to 90)
Sex, n (%)	Men	240 (60.0)	239 (59.8)	21 (51.2)	31 (49.2)
Family origin, n (%)	Asian	56 (14.0)	46 (11.5)	13 (31.7)	23 (36.5)
	Black, African or Indian American or Alaska native	6 (1.6)	13 (3.3)	0	1 (1.6)
	White	322 (80.5)	335 (83.8)	26 (63.4)	38 (60.3)
	Multiple/unknown	16 (4.1)	6 (1.5)	2 (4.8)	1 (1.6)
ECOG score, n (%)	**0**	159 (40.1)	179 (45.1)	20 (45.5)	36 (56.3)
	1	238 (59.9)	218 (54.9)	24 (54.5)	28 (43.8)
Smoking status, n (%)	Current/former	318 (79.5)	323 (80.8)	18 (43.9)	36 (57.1)
	Never	82 (20.5)	77 (19.3)	23 (56.1)	27 (42.9)

ERG comments: Arms are well balanced in the ITT population overall. Clinical advice to ERG is that ECOG performance status is a prognostic factor & difference between arms is small & not clinically important

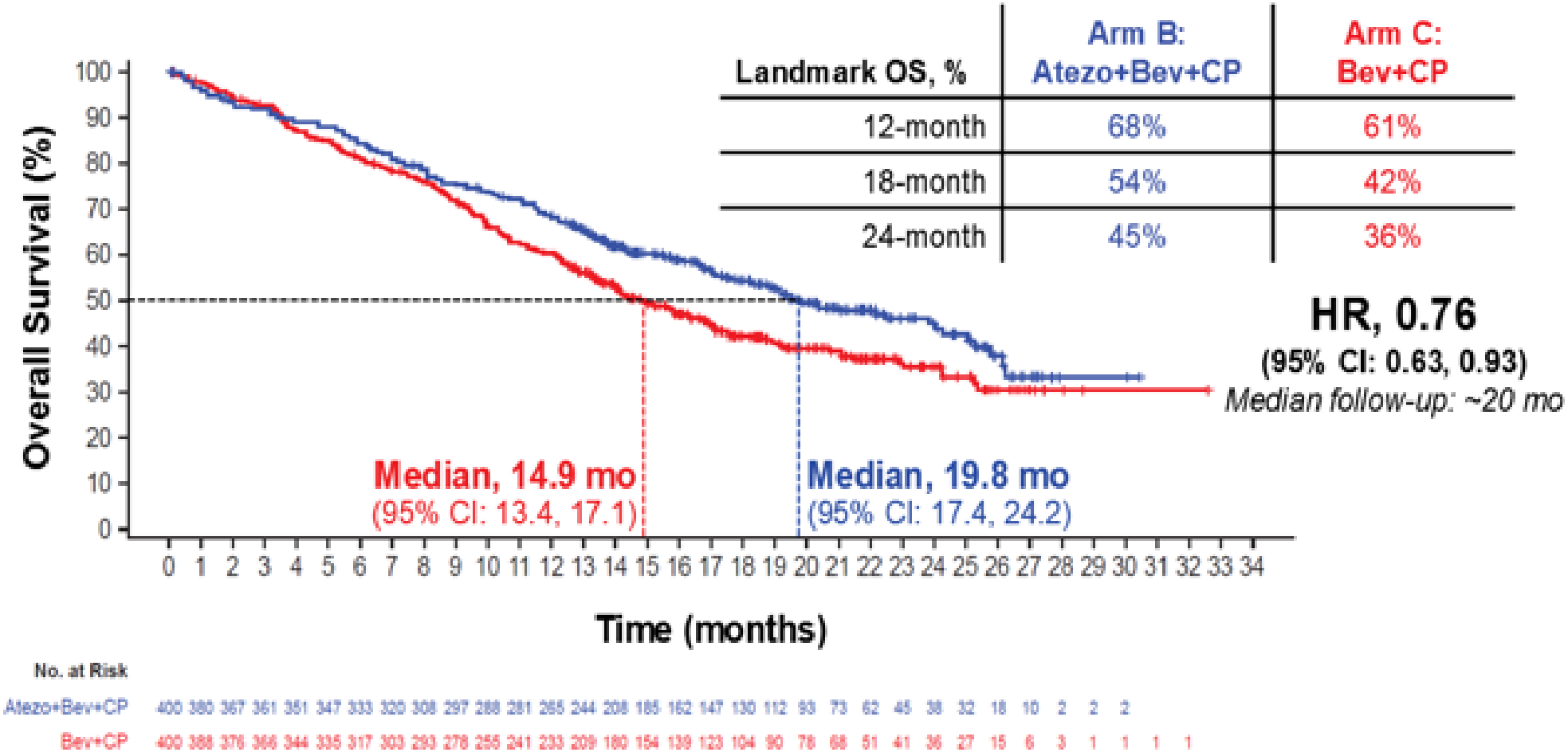
Key baseline characteristics in IMpower150 (2)

Population		ITT		EGFR/ALK+ve	
		Atezo+bev+CP (n=400)	Bev+CP (n=400)	Atezo+bev+CP (n=41)	Bev+CP (n=63)
EGFR status, n (%)	Positive	34 (8.5)	45 (11.3)	34 (82.9)	45 (71.4)
	Negative	353 (86.3)	345 (86.3)	6 (14.6)	16 (25.4)
	Unknown	10 (2.5)	10 (2.5)	1 (2.4)	2 (3.2)
ALK status, n (%)	Positive	11 (2.8)	20 (5.0)	11 (26.8)	20 (31.7)
	Negative	386 (96.5)	376 (94.0)	29 (70.7)	41 (65.1)
	Unknown	3 (0.8)	4 (1.0)	1 (2.4)	2 (3.2)
PD-L1 status, n (%)	< 50% TPS	352 (88.1)	351 (87.8)	38 (92.7)	60 (95.3)
	≥ 50% TPS	48 (12.0)	49 (12.3)	3 (7.3)	3 (4.8)
Non-squamous histology, n (%)	Adenocarcinoma or large cell	383 (95.8)	382 (95.6)	40 (97.6)	61 (96.8)
	Other	17 (4.3)	17 (4.3)	1 (2.4)	2 (3.2)
Liver metastases at enrolment, n (%)	Yes	67 (16.8)	69 (17.3)	5 (12.2)	10 (15.9)
	No	333 (83.3)	332 (82.8)	36 (87.8)	53 (84.1)

ERG comments: EGFR/ALK+ve population small. Differs from ITT population in proportion of males (lower), Asian participants (higher), white participants (lower) & those who had never smoked (higher). Some imbalance likely due to smaller population size & non-random nature.
Proportion with liver metastases (lower) & more people with PD-L1 ≥ 50% in the atezo+bev+CP arm

ITT population: Atezo+bev+CP significantly improves OS compared with bev+CP

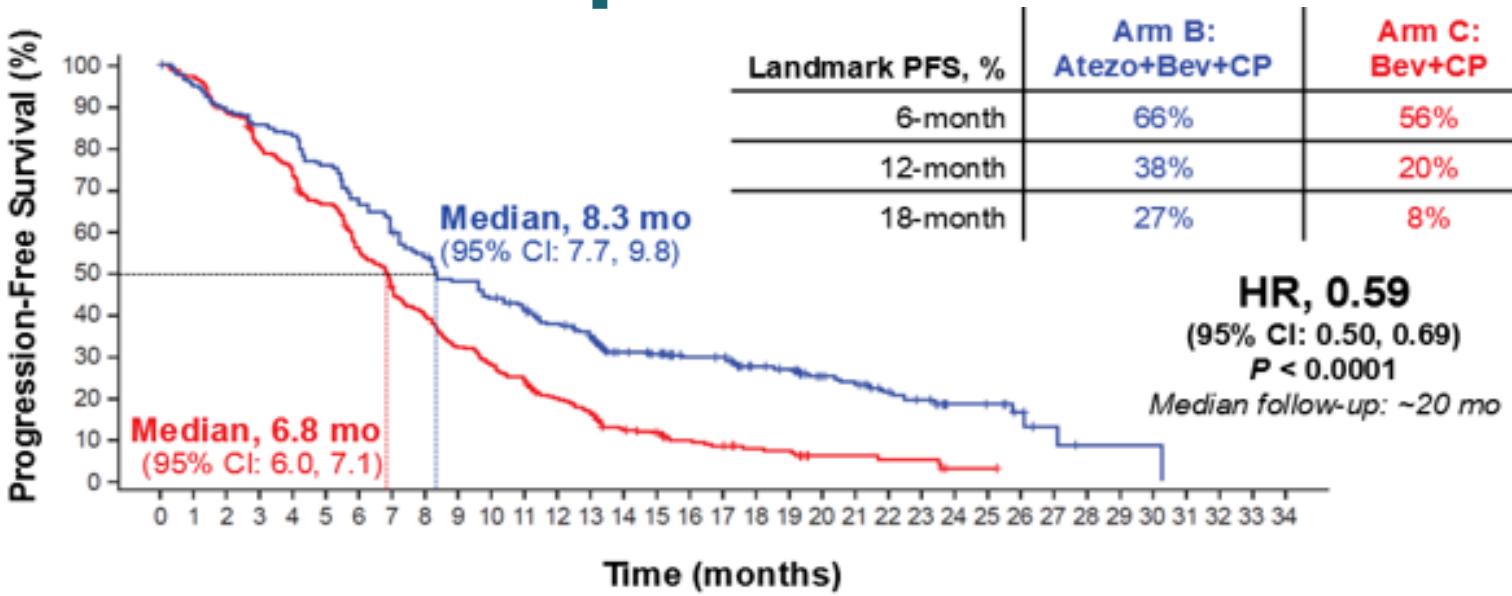
- Median OS reached in both treatment arms, however, final OS data expected in [redacted]



Landmark OS, %	Arm B: Atezo+Bev+CP	Arm C: Bev+CP
12-month	68%	61%
18-month	54%	42%
24-month	45%	36%

[redacted]

ITT population: Atezo+bev+CP significantly improves PFS compared with bev+CP



Landmark PFS, %	Arm B: Atezo+Bev+CP	Arm C: Bev+CP
6-month	66%	56%
12-month	38%	20%
18-month	27%	8%

	Atezo+bev+CP (n=400)		Bev+CP (n=400)	
Progression-free survival	Investigator assessed	Independently-reviewed	Investigator-assessed	Independently reviewed
Events, n (%)	291 (72.8)	269 (67.3)	355 (88.8)	296 (74.0)
Median PFS, months (95% CI)	8.4 (8.0 to 9.9)	8.5 (8.1 to 9.7)	6.8 (6.0 to 7.0)	7.0(6.1 to 7.8)
Investigator: HR (95% CI)	0.59 (0.50 to 0.69); p < 0.0001			
Independent: HR (95% CI)	0.67 (0.56 to 0.79); p<0.0001			

ERG comment: [redacted]

PD-L1 <50% TPS: Median OS & PFS was longer with atezo+bev+CP vs bev+CP

	Atezo+bev+CP (n = 325)	Bev+CP (n = 327)
Overall survival		
Median, months	19.1	14.9
Unstratified HR (95% CI)	0.80 (0.65 to 0.99)	
Progression-free survival (investigator-assessed)		
Median, months	8.2	6.8
Unstratified HR (95% CI)	0.66 (0.56 to 0.79)	

ERG comments: OS: slightly worse overall survival with a slightly wider confidence interval compared with total ITT population

PFS: difference between arms not as strongly in favour of atezo+bev+CP as it was in the total ITT population

[redacted]

EGFR/ALK+ve: Results should be treated with caution as small population & median OS not reached in atezo+bev+CP arm

	Atezo+bev+CP (n=41)		Bev+CP (n=63)	
Overall survival				
People with event, n (%)	13 (31.7)		33 (52.4)	
Median OS, months (95% CI)	Not estimated (17.0 to not estimated)		17.5 (10.4 to not estimated)	
Stratified HR (95% CI); p value	0.54 (0.29 to 1.03); p = 0.0578			
Progression-free survival	Investigator assessed	Independently -reviewed	Investigator assessed	Independently -reviewed
People with event, n (%)	28 (68.3)	24 (54.5)	57 (90.5)	50 (78.1)
Median PFS, months (95% CI)	10.0 (7.9 to 15.2)	9.6 (6.8 to 17.0)	6.1 (5.6 to 8.4)	5.7 (5.1 to 8.3)
Investigator-assessed: Unstratified HR (95% CI); p value	0.55 (0.35 to 0.87); p = 0.0101			
Independently-assessed HR (95% CI)	0.47 (0.28 to 0.81); p=0.0052			

ERG comment: Caution required as small population numbers & trial not stratified by EGFR/ALK+ve status → some baseline characteristics imbalances between arms. Clinical expert advice notes that people with EGFR/ALK mutations tend to have better survival & better response to pemetrexed

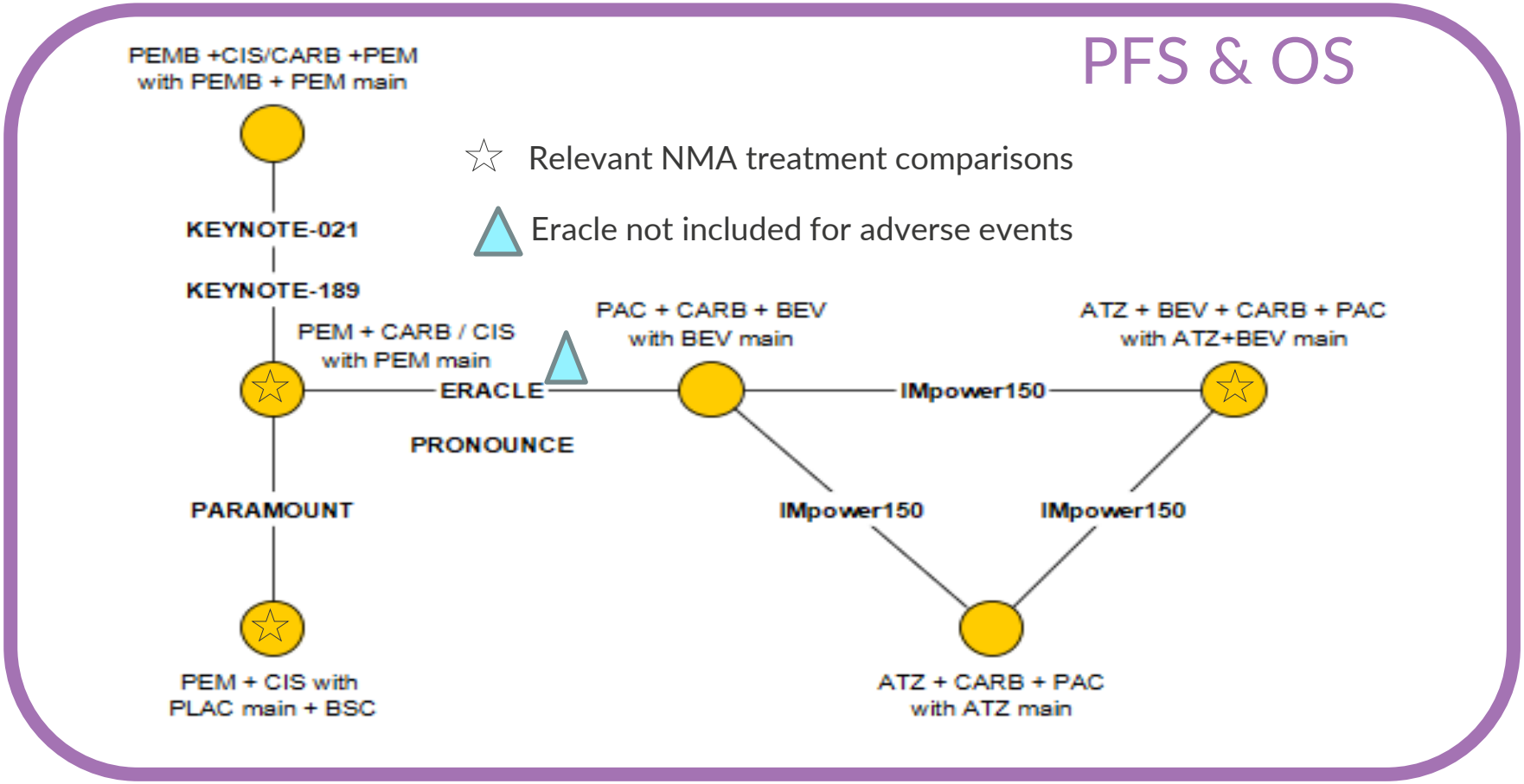
Network meta-analysis comparing atezo+bev+CP vs pemetrexed-based chemo

- No direct evidence comparing atezo+bev+CP to UK standard of care therapies
- Population: adult patients over 18 years of age with Stage IV non-squamous NSCLC who have not received prior treatment (i.e. regardless of level of PD-L1 expression)
- Subgroup analyses done for PD-L1 <50% and EGFR/ALK +ve → **assumptions required** → level of PD-L1 expression and presence of EGFR/ALK mutations are not effect modifiers for pemetrexed-based chemotherapy
- Fractional polynomial time-varying hazards estimation used for OS & PFS in base case → better captures variations in hazard ratio over time → range of polynomial models fitted
- Weibull model chosen for OS & PFS for ITT & subgroup NMA & sensitivity analyses

ERG comments: Fractional polynomial approach appropriate → clinical expert advice agrees that chemotherapy & immunotherapy have different mechanisms of action leading to different survival kinetics. Agree with choice of Weibull model. Clinical expert does not agree with assumption that EGFR and ALK status are not effect modifiers

[redacted]

Network meta-analysis comparing atezo+bev+CP vs pemetrexed-based chemo

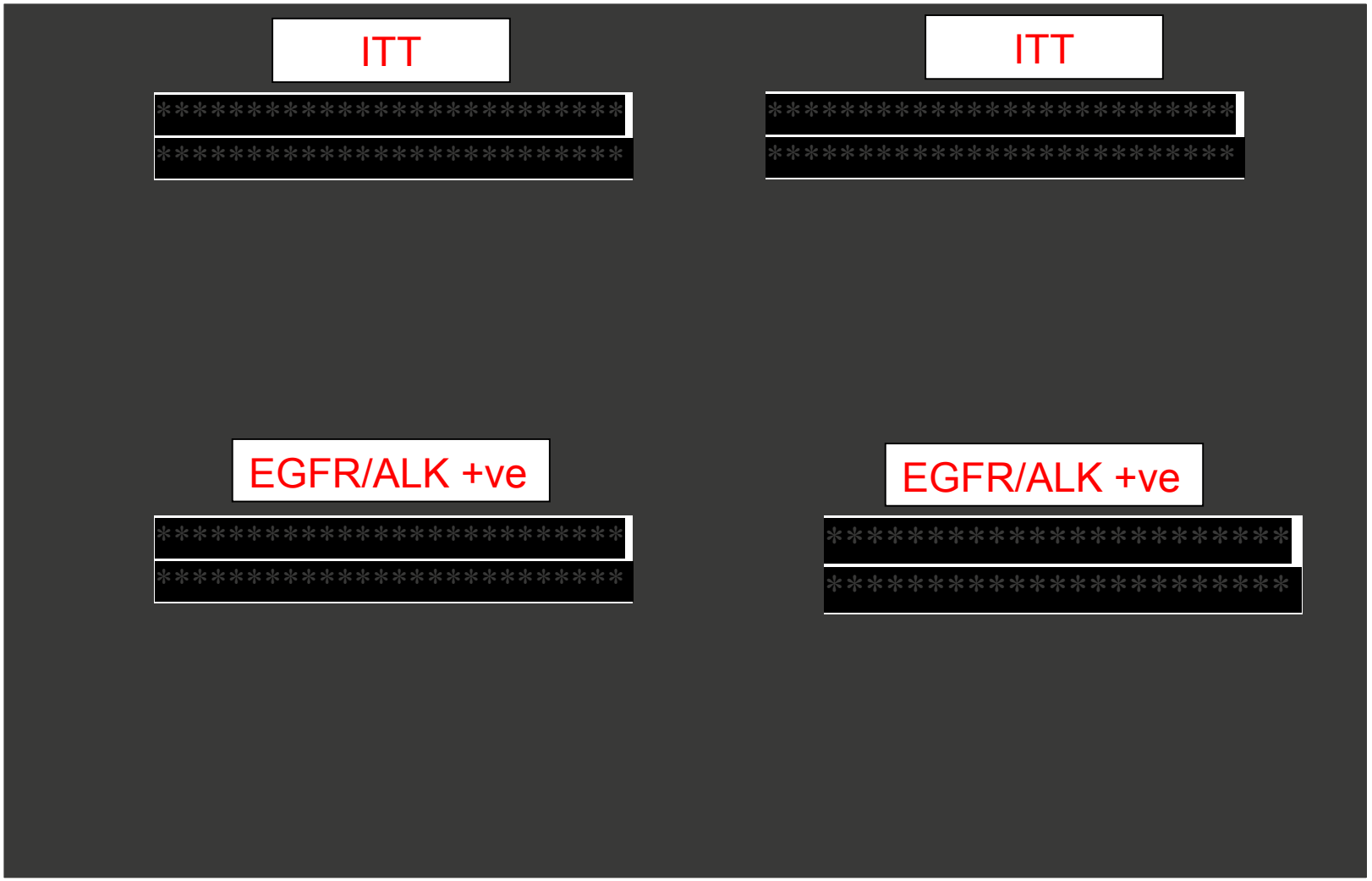


[redacted] Abbeviations: ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Atezo+bev+CP improves OS vs pemetrexed plus platinum drug with or without maintenance

PEM+ platinum drug then PEM maintenance

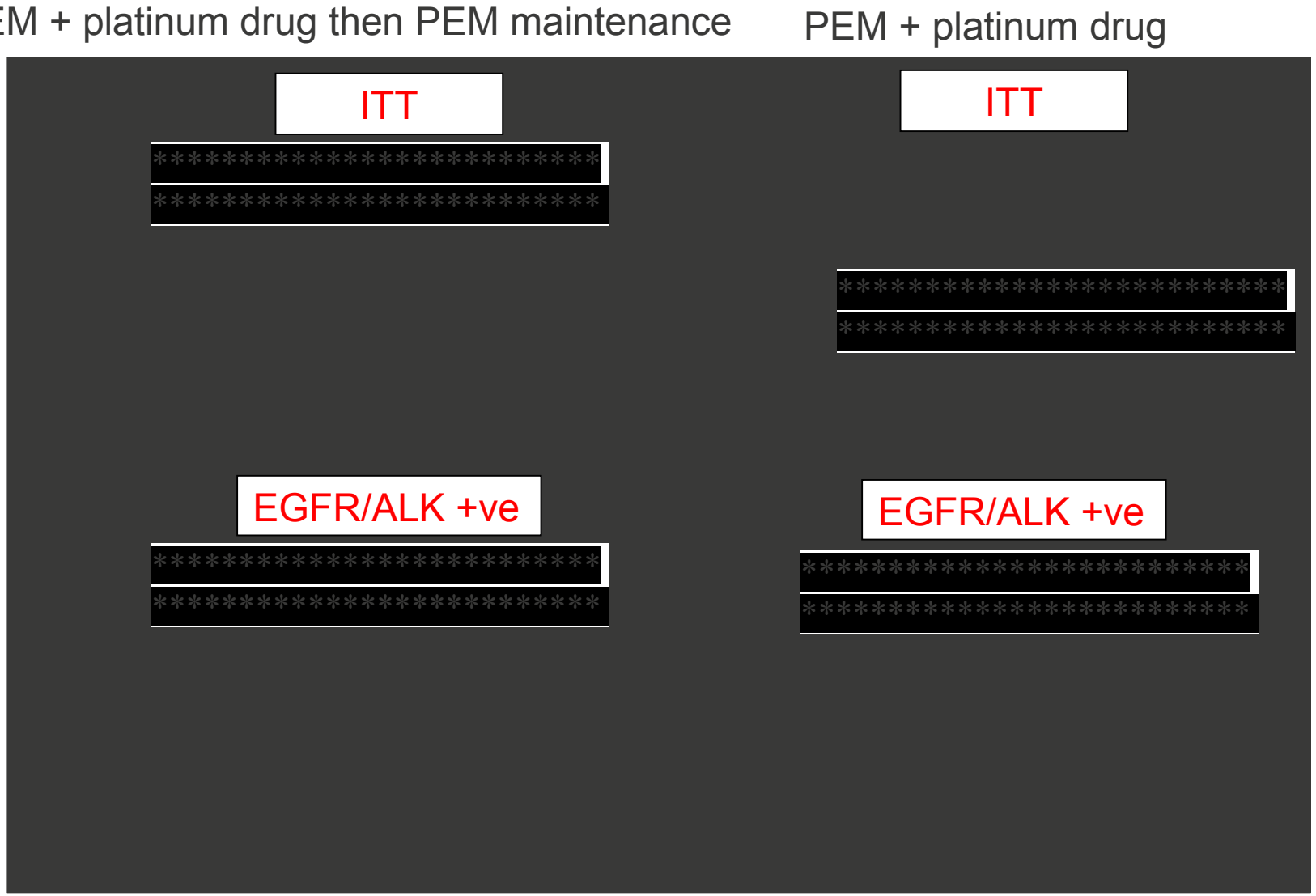
PEM + platinum drug



Please note: Results generated from NMA that includes the PARAMOUNT trial

[redacted]

Atezo+bev+CP improves PFS vs pemetrexed plus platinum drug with or without maintenance



Please note: Results generated from NMA that includes the PARAMOUNT trial

[redacted]

ERG comments: Limitations of the company's indirect treatment comparison

Inclusion of PARAMOUNT trial

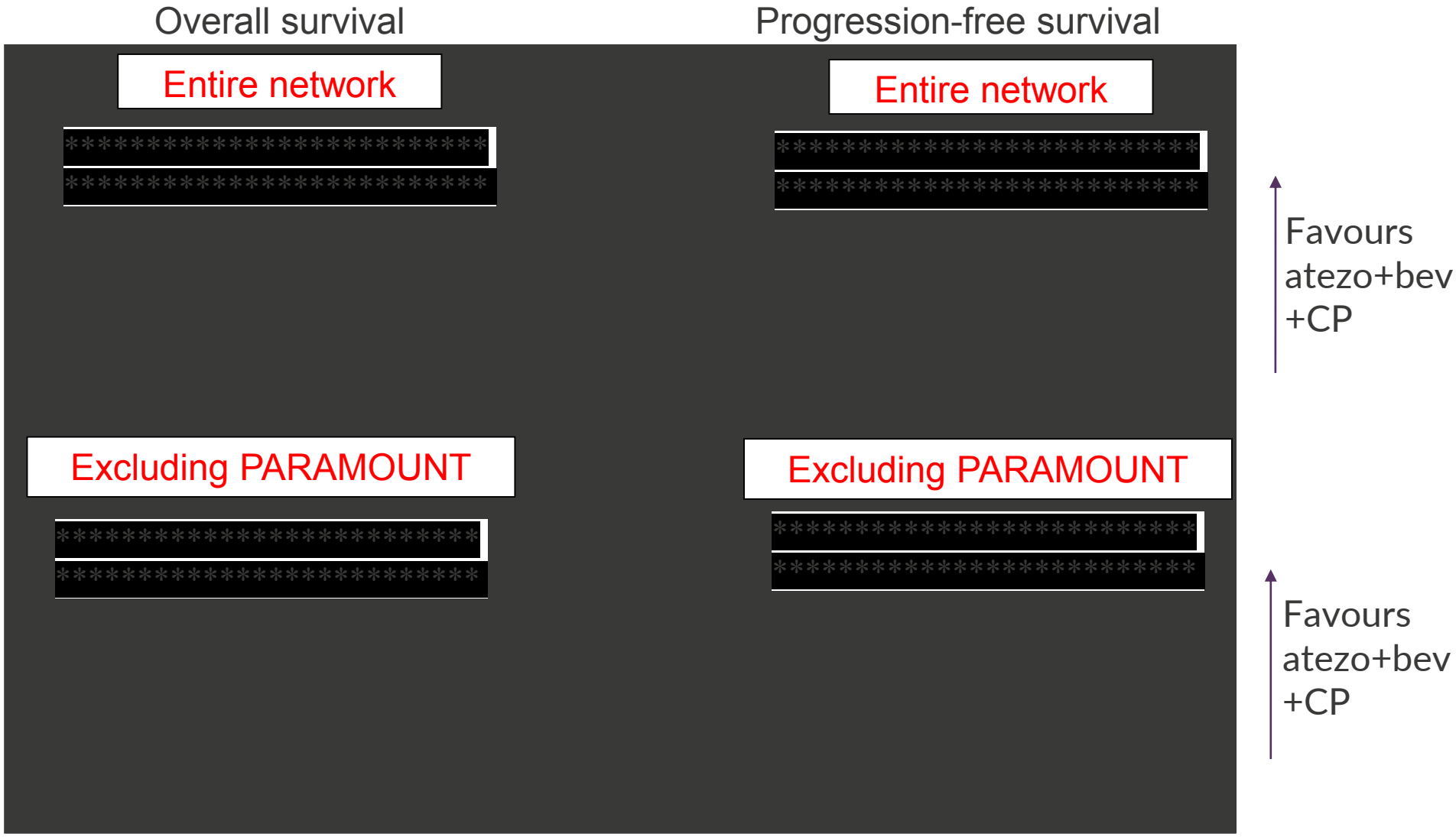
- PARAMOUNT has different study design compared to other studies in network → possible selection bias → has been excluded from the network in ERG base case & company scenario analysis
- PARAMOUNT protocol included **induction pemetrexed-based chemotherapy**
- Only those alive & achieved a certain level of response (n =539 out of 900) randomised into either pemetrexed or placebo maintenance therapy
- Results only reported for those who responded to induction therapy
- Other trials reported results for a mix of responders and non-responders
- Including PARAMOUNT enables the comparison with pemetrexed + platinum drug without pemetrexed maintenance → only study connecting pemetrexed + platinum drug to the network

Other comparators

- Trials comparing pemetrexed with other chemotherapy regimes in the NICE scope (i.e. docetaxel, gemcitabine, paclitaxel or vinorelbine) not included in company network
- ERG identified relevant evidence where other chemotherapies had been linked to pemetrexed + platinum drug in a mixed treatment comparison
- Company used a fixed effects model. ERG prefer a random effects model when PARAMOUNT is included and a fixed effects model otherwise

[redacted]

Removing PARAMOUNT from the NMA improves results for atezo+bev+CP



All figures show comparison with pem + plat + pem maintenance as excluding PARAMOUNT removes the comparison with pem + plat

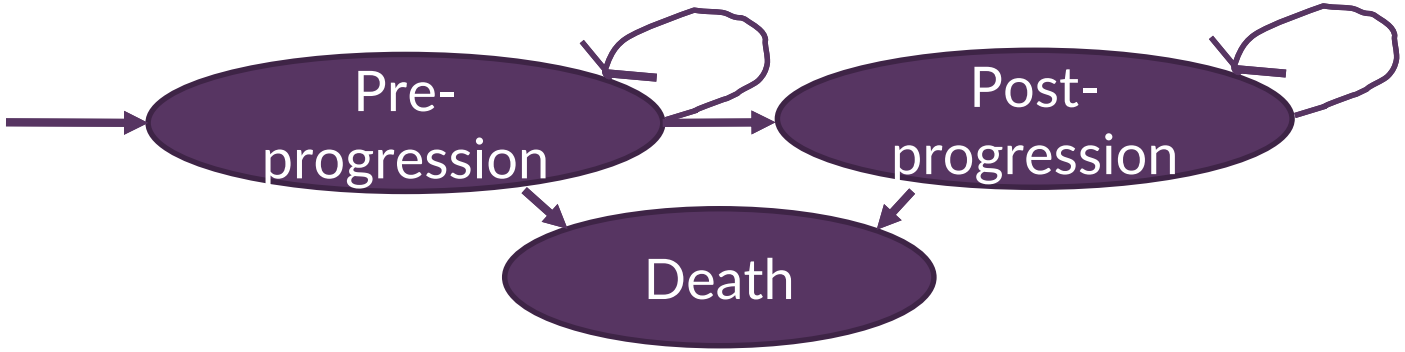
Adverse events were more common with atezo+bev+CP compared with bev+CP

Event, n (%)	Atezo+bev+CP (n=393)		Bev+CP (n=394)	
All-causality AEs	386 (98.2)		390 (99.0)	
All-causality AEs leading to discontinuation	133 (33.8)		98 (24.9)	
Treatment-related AEs	370 (94.1)		377 (95.7)	
Grade 3 or 4 treatment-related AE	223 (56.7)		191 (48.5)	
Grade 5 treatment-related AE	11 (2.8)		9 (2.3)	
Serious treatment-related AE	103 (26.2)		78 (19.8)	
Immune-mediated AEs	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4
AESI	-	49 (12.5)	-	13 (3.3)
Treatment-related AESI	182 (46.3)	42 (10.7)	70 (17.8)	8 (2.0)
SAESI	25 (6.4)	-	4 (1.0)	-
Treatment-related SAESI	22 (5.6)	-	2 (0.5)	-
AESI leading to withdrawal (any treatment)	26 (6.6)	-	3 (0.8)	-
AESI leading to any dose modification/interruption	51 (13.0)	-	16 (4.1)	-

ERG comments: Proportion of patients experiencing treatment-related grade 3-4 AEs, serious AEs and treatment-related serious AEs were all higher with atezo+bev+CP compared with bev+CP

Cost effectiveness

Company's 3 state partitioned survival model



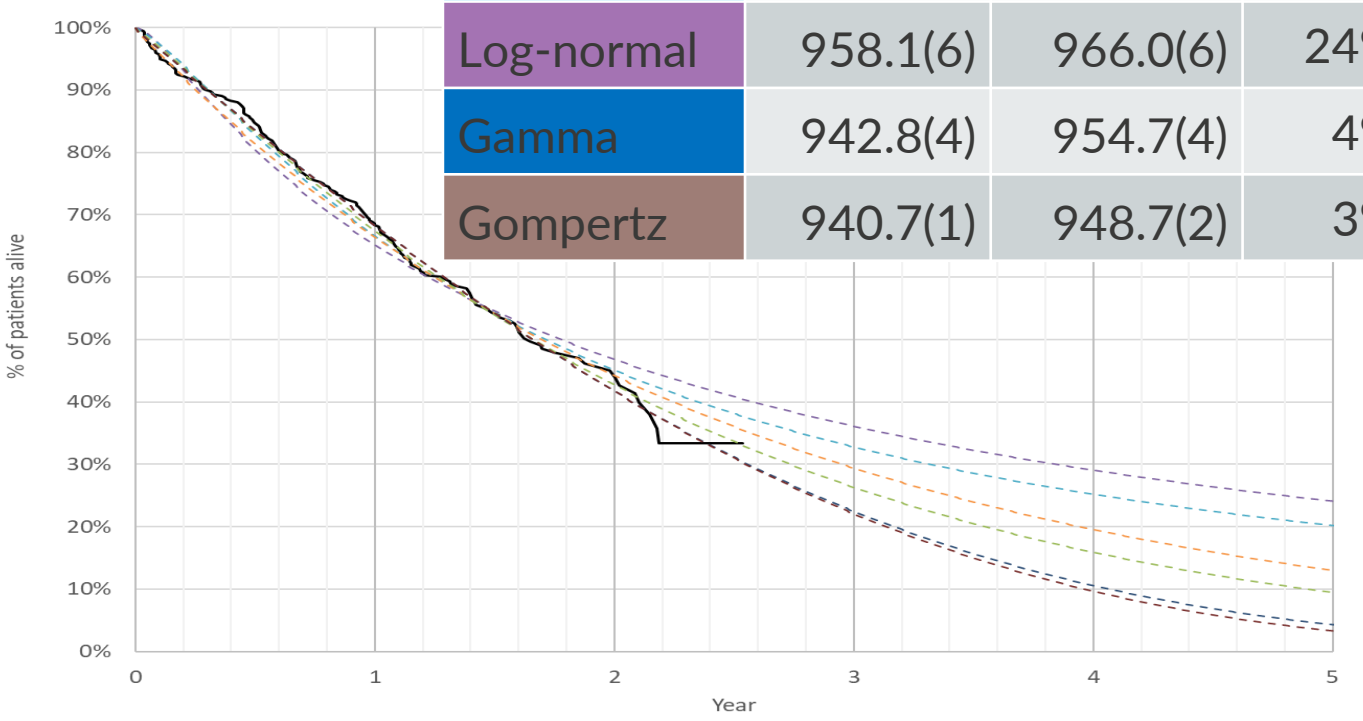
Model design	Partitioned survival model
Time horizon	20 years
Cycle length	1 week
Half cycle correction	Yes
Stopping rule	2-year stopping rule for atezo & bev Pemetrexed maintenance continues until progression
Duration of treatment effect	5 years (2 years on treatment, further 3 years after discontinuation) for atezo & bev. Pemetrexed maintenance assumed continuous benefit
Discount rate	3.5% per year
Perspective	NHS and Personal social services

ERG comment: Appropriate structure & correctly implemented. Time horizon reasonable & agree with 2 year stopping rule & 3 year treatment benefit after stopping treatment as consistent with other NICE atezolizumab & immunotherapy appraisals. PFS cap not applied in company model. Uncertainty over length of survival benefit & if survival benefit should be capped for pemetrexed maintenance

ITT population: OS estimate differs depending on distribution chosen for extrapolation

- Company report estimates of five-year survival with atezo+bev+CP from 10 UK clinicians of between 12% and 27%, with an average of 17%

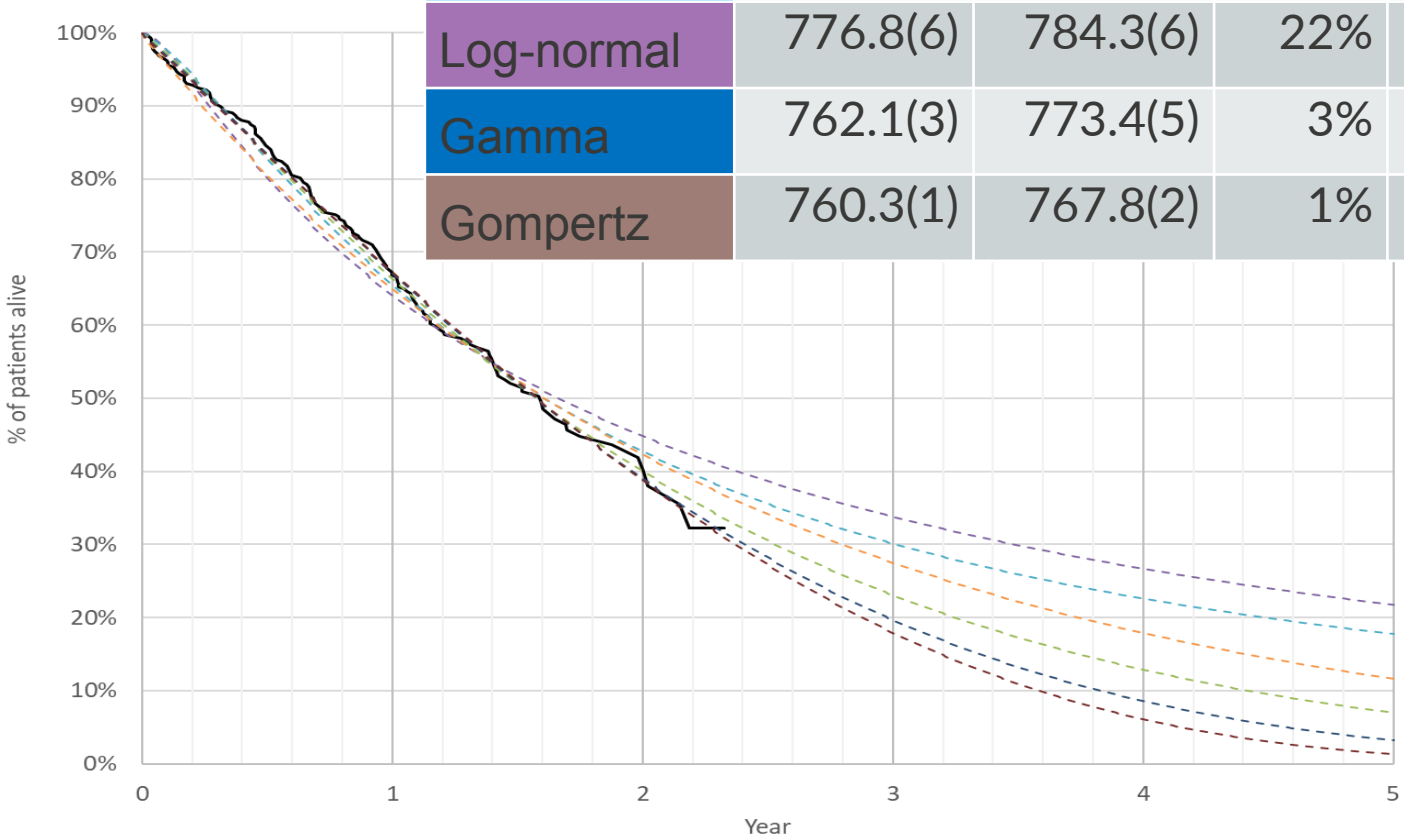
Distribution	Goodness of fit		5 & 10-year survival, respectively					
	AIC (rank)	BIC (rank)	Atezo+bev+CP		Pem+plat		Pem+plat+maint	
Exponential	942.3(3)	946.3(1)	13%	3%	2%	0%	12%	3%
Weibull	941.7(2)	949.7(3)	10%	1%	1%	0%	9%	1%
Log-logistic	947.2(5)	955.2(5)	20%	12%	5%	1%	18%	10%
Log-normal	958.1(6)	966.0(6)	24%	15%	7%	1%	21%	13%
Gamma	942.8(4)	954.7(4)	4%	0%	0%	0%	5%	0%
Gompertz	940.7(1)	948.7(2)	3%	0%	0%	0%	4%	0%



ERG comment: Gompertz, exponential and Weibull have best AIC/BIC statistics and good visual fit. Log-logistic = overly optimistic long-term projections (10% survival at 10 years). 5-year survival of 8 to 11% with comparator treatments seems reasonable & in line with NICE TA531

PD-L1 <50%: OS estimate differs depending on distribution chosen for extrapolation

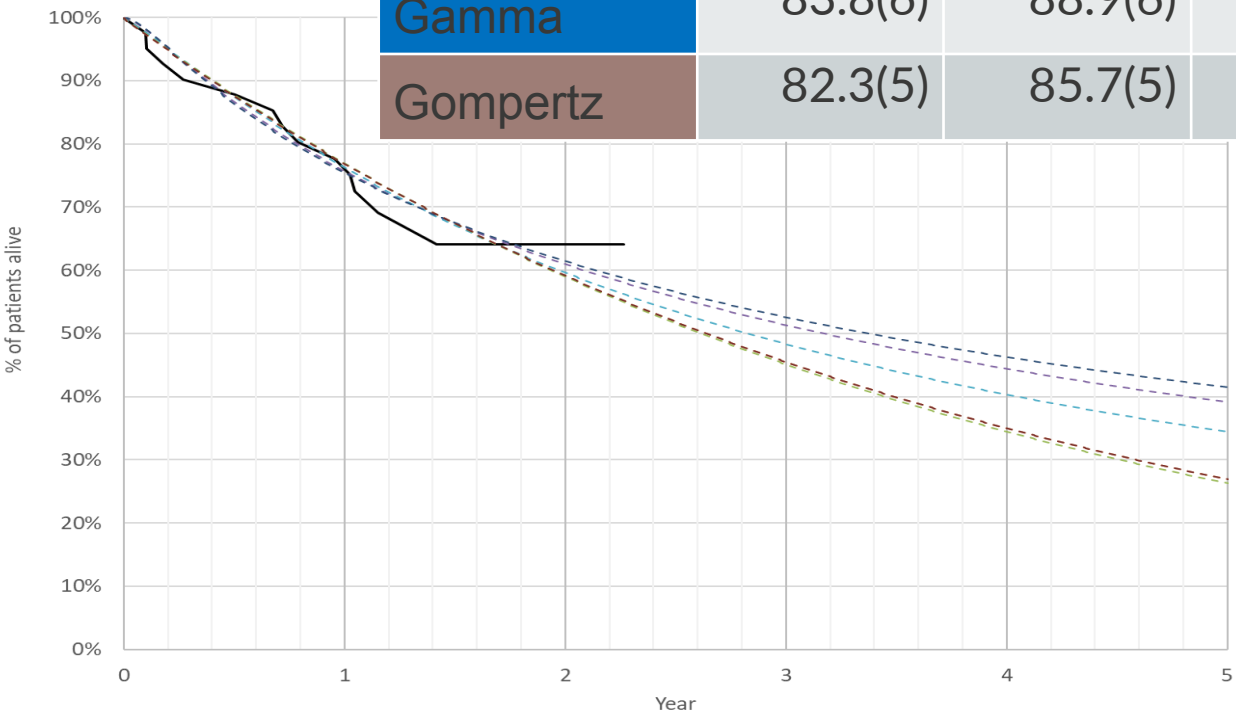
Distribution	Goodness of fit		5 & 10-year survival, respectively					
	AIC (rank)	BIC (rank)	Atezo+bev+CP		Pem+plat		Pem+plat+maint	
Exponential	763.0(4)	766.8(1)	12%	4%	3%	0%	13%	4%
Weibull	760.8(2)	768.4(3)	7%	1%	1%	0%	10%	2%
Log-logistic	765.5(5)	773.1(4)	18%	11%	6%	1%	19%	12%
Log-normal	776.8(6)	784.3(6)	22%	14%	9%	2%	21%	14%
Gamma	762.1(3)	773.4(5)	3%	0%	0%	0%	6%	0%
Gompertz	760.3(1)	767.8(2)	1%	0%	0%	0%	3%	0%



ERG comment: Gompertz, exponential and Weibull have best AIC/BIC statistics and good visual fit. Log-logistic = overly optimistic long-term projections (10% survival at 10 years). 5-year survival of 8 to 11% with comparator treatments seems reasonable & in line with NICE TA531

EGFR/ALK+ve: OS estimate differs depending on distribution chosen for extrapolation

Distribution	Goodness of fit		5 & 10-year survival, respectively					
	AIC (rank)	BIC (rank)	Atezo+bev+CP		Pem+plat		Pem+plat+maint	
Exponential	80.3(1)	82.0(1)	27%	17%	11%	3%	18%	12%
Weibull	82.3(4)	85.7(4)	26%	16%	11%	3%	18%	11%
Log-logistic	82.1(3)	85.5(3)	35%	28%	15%	9%	22%	18%
Log-normal	81.8(2)	85.2(2)	39%	33%	18%	11%	25%	21%
Gamma	83.8(6)	88.9(6)	42%	36%	20%	13%	26%	23%
Gompertz	82.3(5)	85.7(5)	27%	17%	11%	3%	18%	12%

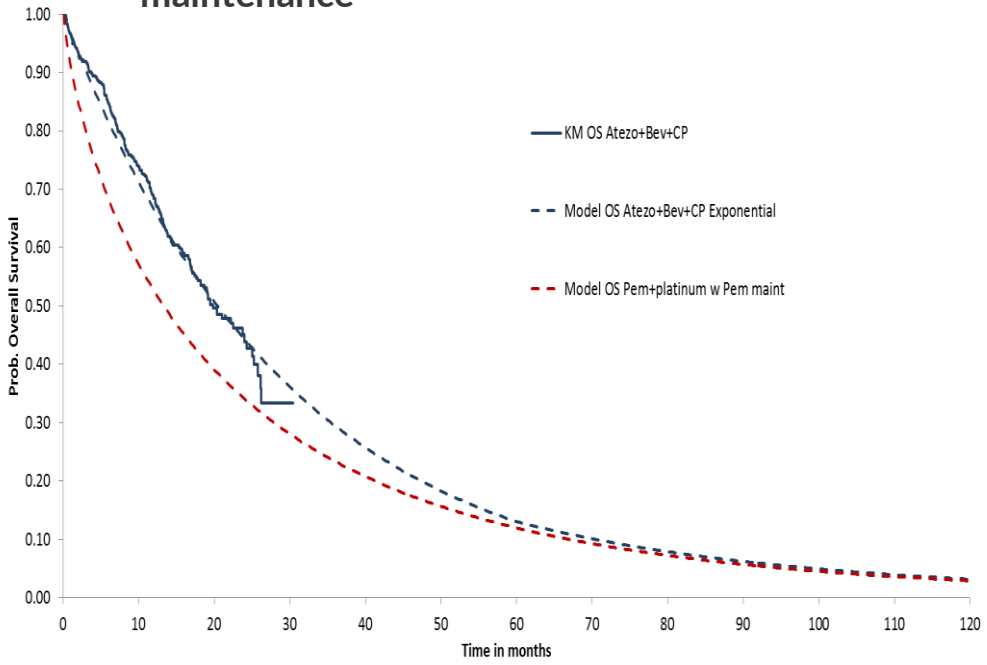


ERG comment: Difficult to differentiate on the basis of visual fit. Exponential has the best AIC and BIC statistics

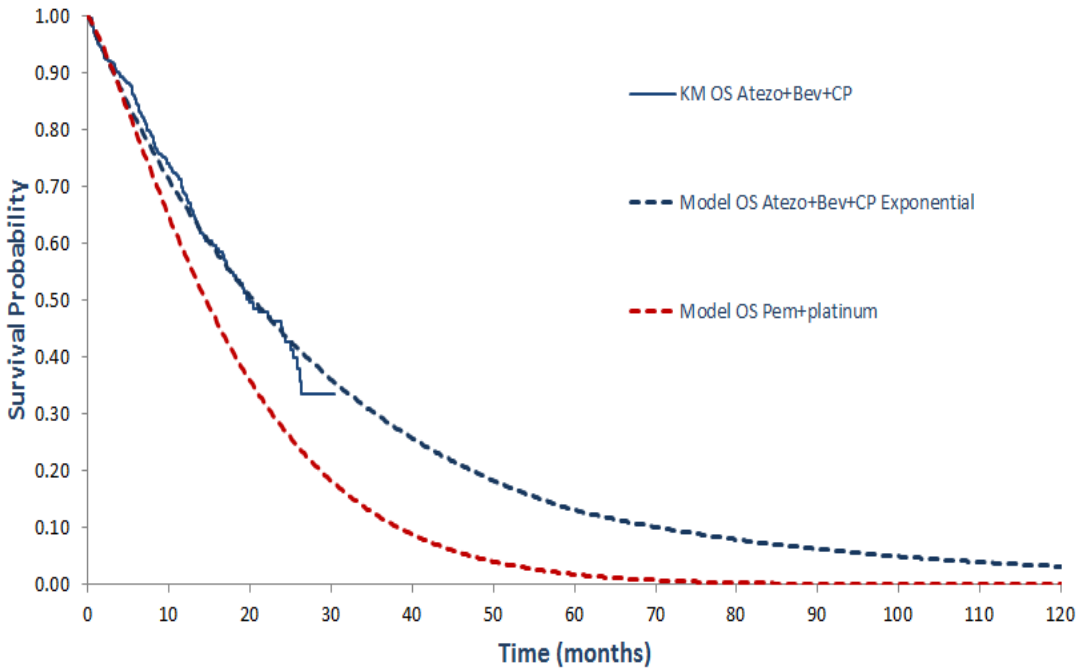
Company extrapolated OS from IMpower150 using exponential function (ITT population shown)

- Comparator OS curve estimated by applying time-varying HR from the company's fractional polynomial NMA by subgroup (including PARAMOUNT trial) to subgroup specific atezo+bev+CP survival curves from IMpower150

Atezo+bev+CP versus pemetrexed + platinum drug + maintenance



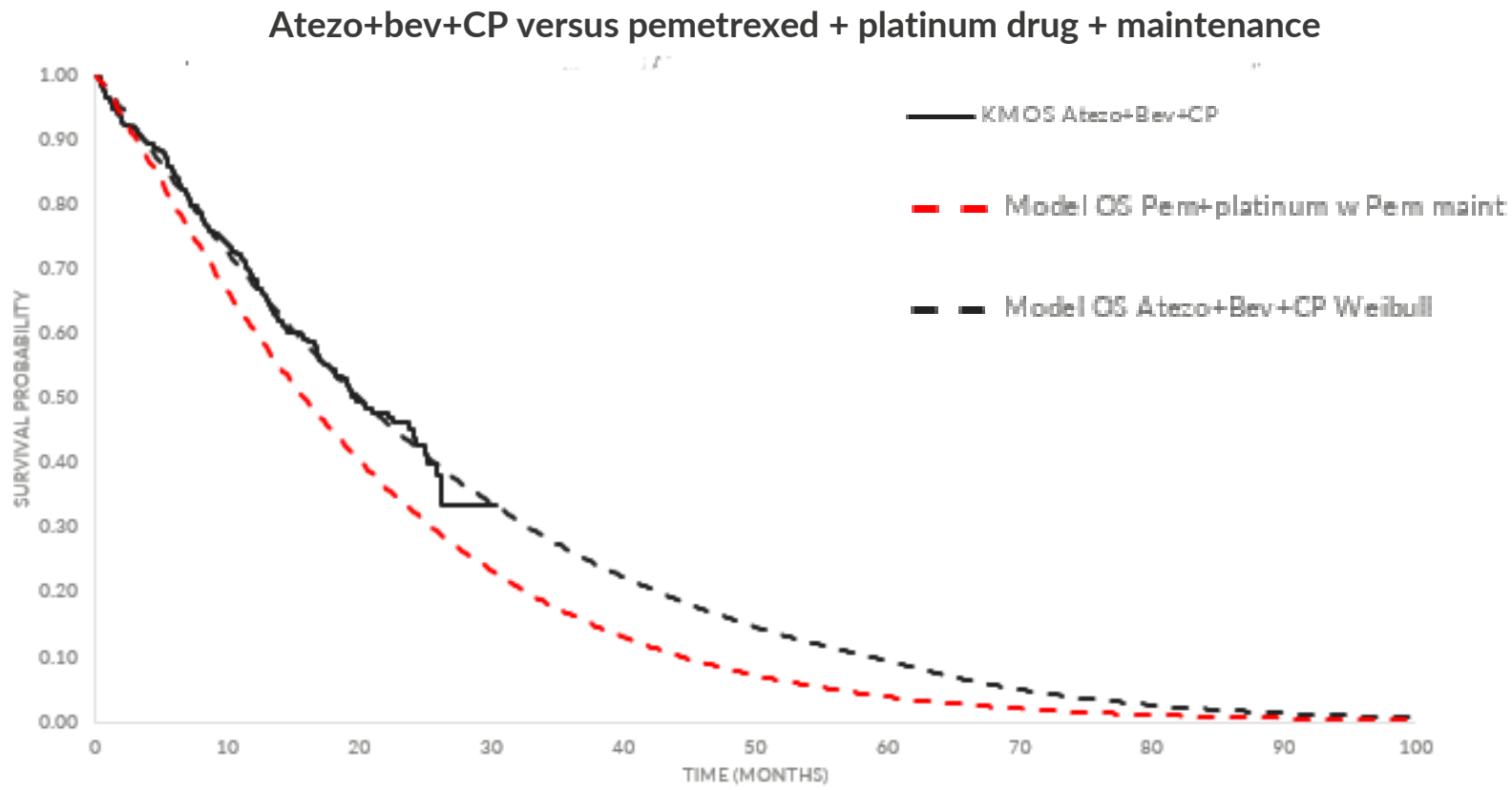
Atezo+bev+CP versus pemetrexed + platinum drug



ERG comments: Subgroup analyses are a better source for baseline survival estimates than the ITT analysis as ITT curves include those with high PD-L1. Consider ITT NMA more robust source for relative treatment effects than the subgroup NMAs as lack of evidence of effect modification for the subgroups. ERG base case = subgroup baseline survival estimates with ITT NMA estimates (excluding PARAMOUNT trial)

ERG preference: extrapolated OS using Weibull function & NMA not including PARAMOUNT

(ITT population shown)



ERG comments: Weibull distributions gives more conservative survival predictions compared with exponential distribution

[redacted]

Extrapolation of PFS is more certain as data from IMpower150 trial relatively complete

- Same approach used to fit PFS curves and to fit comparator curves to OS
- Log-logistic, Weibull and generalised gamma distributions give the best visual fit and AIC/BIC statistics for ITT and PD-L1 <50% populations
    - give a spread of projections from about 2% to 5% of people still alive and free of progression after 5 years for the ITT population
- Company & ERG used KM curve & log-logistic tail for when 20% of people remain at risk for the ITT population and PD-L1 <50% subgroup
- Log-normal, exponential or log-logistic curves best statistical and visual fit for EGFR/ALK +ve subgroup
- Company used fully parametric log normal distribution for the EGFR/ALK positive subgroup

ERG comment: Company's approach is reasonable. Model results are much less sensitive to distribution chosen for PFS than OS.
ERG use the same distributions in their base case as the company for the ITT and PD-L1 <50% subgroups. Other distributions used in scenario analyses. ERG prefers the log-logistic distribution for the EGFR/ALK positive subgroup

[redacted]

Duration of treatment effect

- Company base case = 3 year duration of treatment effect beyond treatment discontinuation for atezolizumab and bevacizumab & no cap on duration of survival effect for pemetrexed maintenance
- OS effect cap for atezo+bev+CP applied by setting the mortality rate for atezo+bev+CP equal to with-maintenance pemetrexed comparator, while maintaining the extrapolated survival advantage for pemetrexed maintenance relative to pemetrexed without maintenance

ERG comments:
High uncertainty over the persistence of survival effects after treatment is stopped but 3-year cap seems reasonable.
Consider persistent survival advantage with pemetrexed maintenance unrealistic & not consistent with committee conclusion for NICE TA402 (no evidence for post-progression survival benefit over placebo).
Likely to overestimate long-term survival gain for both atezo+bev+CP and the pemetrexed maintenance comparator and underestimate the ICER for atezo+bev+CP compared with pemetrexed plus platinum drug without maintenance.
No scenario analysis conducted to explore the impact of varying the duration of treatment effect for pemetrexed maintenance

[redacted]

2 year stopping rule

- Company included a 2 year stopping rule in the model to be consistent with previous NICE guidance for atezolizumab (TA520 and TA525) and other immunotherapies (e.g. TA531)
- IMpower150 trial did not include a 2 year stopping rule → atezolizumab & bevacizumab given until disease progression or unacceptable toxicity ([redacted])
- Approximately 20% of people still being treated with atezolizumab and 10% with bevacizumab after 2 years in IMpower150 trial
- In model, drug acquisition & administration cost set to zero after 2 years

[redacted]

Utility values were included in the company base case using the proximity to death approach

Category	Base case utilities		Source
	Mean value	95% confidence interval	
≤ 5 weeks before death	0.52	0.49 - 0.56	EQ-5D-3L data collected in IMpower150
> 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	

ERG comments: Utility impact not fully captured. No disutility included while on treatment or for adverse events in the base case. Company scenario analysis run to include AEs but assumed the same for both arms when atezo+bev+CP AE profile significantly worse. Agree, proximity to death approach has more face validity than pre/post-progression analysis & data from IMpower150 is preferred over values from published literature

All patients assumed to receive subsequent systemic anti-cancer therapy second-line in the company's model

- Second-line use of checkpoint inhibitors are not approved in people who have previously received immunotherapy first-line → as more checkpoint inhibitors are approved as initial treatment for NSCLC, the treatments given as subsequent treatment will change
- Nintedanib plus docetaxel recommended for non-squamous NSCLC that has progressed after first-line chemotherapy (TA347)
- Subsequent treatments included as an average cost in the progressed disease state and not modelled explicitly

Drug	Treatment		Duration (weeks)	Assumption
	Atezo+bev+CP	Pemetrexed comparator		
Docetaxel	100%	15%	13.1	Docetaxel SmPC
Nivolumab	0%	34%	26.52	NICE TA484 (recommended in CDF)
Pembrolizumab	0%	34%	21.59	NICE TA428
Atezolizumab	0%	17%	35.80	NICE TA520

ERG comments on company's resource use & ERG corrections to company model

- Approach taken for estimating health care resources and costs is reasonable and in line with other NICE appraisals in NSCLC
- Resource use from IMpower150 trial would have been preferred but not available
- Some minor discrepancies to some cost estimates as not updated correctly by company and some outdated sources used → the ERG has updated these in their corrections

Parameter		Company	ERG correction	Reason
Vial sharing		5%	0%	No vial sharing deemed more appropriate
Pembrolizumab cost		£3,781.28	£4,453.13	As in TA428
PFS health state cost		£61.80	£65.53	Costs updated incorrectly using incorrect index
PD health state cost		£117.00	£139.39	
Terminal care		£4,456.13	£4,556.88	
Adverse event cost	Atezo+bev+CP	£1,227.68	£1,334.27	
	PEM + platinum drug	£272.54	£289.67	
	PEM + platinum drug + PEM main	£723.78	£861.56	

Cost effectiveness results

Company's deterministic base case (with PAS for atezo and bev only)

Population & treatment	Total costs	Total QALYs	Δ costs	Δ QALYs	Fully incremental ICER (£/QALY)	Pairwise ICERs vs. comparator (£/QALY)
ITT						
Pemetrexed + plat	[redacted]	[redacted]	[redacted]	[redacted]	-	£16,419
Pemetrexed + plat + pem maint	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Atezo+bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-
PD-L1 <50%						
Pemetrexed + plat	[redacted]	[redacted]	[redacted]	[redacted]	-	£13,424
Pemetrexed + plat + pem maint	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominant
Atezo+bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-
EGFR/ALK positive						
Pemetrexed + plat	[redacted]	[redacted]	[redacted]	[redacted]	-	£14,552
Pemetrexed + plat + pem maint	[redacted]	[redacted]	[redacted]	[redacted]	£31,523	£7,014
Atezo+bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	£7,014	-

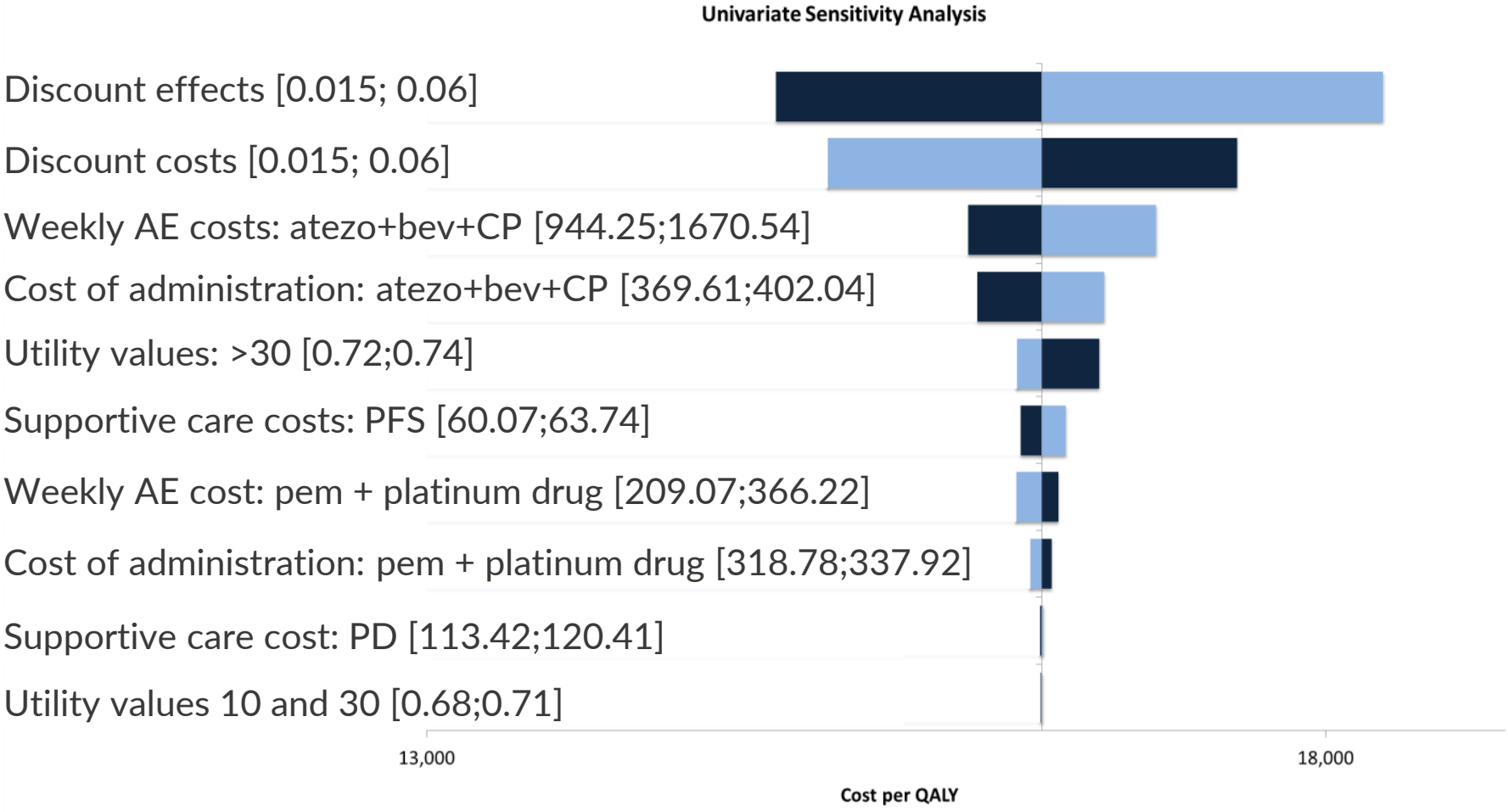
Company's probabilistic base case (with PAS for atezo and bev only)

Population & treatment	Total costs	Total QALYs	ICER £/QALY
ITT			
Pemetrexed + platinum drug	[redacted]	[redacted]	£16,658
Pemetrexed + plat drug + pem maint	[redacted]	[redacted]	Dominant
Atezo+bev+CP	[redacted]	[redacted]	-
PD-L1 <50%			
Pemetrexed + platinum drug	[redacted]	[redacted]	£13,730
Pemetrexed + plat drug + pem maint	[redacted]	[redacted]	Dominant
Atezo+bev+CP	[redacted]	[redacted]	-
EGFR/ALK positive			
Pemetrexed + platinum drug	[redacted]	[redacted]	£15,203
Pemetrexed + plat drug + pem maint	[redacted]	[redacted]	5,400
Atezo+bev+CP	[redacted]	[redacted]	-

[redacted]

Company's deterministic sensitivity analysis of atezo+bev+CP versus pemetrexed + platinum drug: ITT population with PAS for atezo and bev only

- Uncertainty over the OS or PFS extrapolations not included in the company's sensitivity analysis



[redacted]

Company's scenario analysis results vs pemetrexed + platinum drug with PAS for atezo & bev

Scenario	Base case	Scenario analysis	Base case ICER		
			ITT = £16,419	PD-L1 <50% = £13,424	EGFR/ALK +ve = £14,552
OS extrapolation	Exponential	Log-logistic	£12,376	£10,847	£12,965
		Weibull	£18,470	£15,375	£14,715
Duration of treatment effect	5 years	105 mnths (8.75 yrs)	£17,223	£14,344	£16,748
		150 mnths (12.5 yrs)	£17,522	£14,646	£17,914
		195 mnths (16.25 yrs)	£17,586	£14,717	£18,282
		240 mnths (lifetime) (20 yrs)	£17,595	£14,726	£18,351
Stopping rule	2 years	No stopping rule	£25,865	£19,866	£19,947

ERG comments: NICE TA520 committee assumed effects of atezolizumab would last 3 years after stopping treatment but noted uncertainty

[redacted]

Company's scenario analysis results vs pemetrexed + platinum drug + maint with PAS for atezo & bev

Scenario	Base case	Scenario analysis	Base case ICER		
			ITT = dominant	PD-L1 <50% = dominant	EGFR/ALK +ve = £7,014
Trials included in the NMA	PARAMOUNT included	PARMOUNT excluded	Dominant	-	-
OS extrapolation	Exponential	Log-logistic	Dominant	Dominant	£6,963
		Weibull	Dominant	Dominant	£6,918
Duration of treatment effect	5 years	105 mnths (8.75 yrs)	Dominant	Dominant	£6,582
		150 mnths (12.5 yrs)	Dominant	Dominant	£6,338
		195 mnths (16.25 yrs)	Dominant	Dominant	£6,283
		240 mnths (lifetime) (20 yrs)	Dominant	Dominant	£6,293
Stopping rule	2 years	No stopping rule	£12,234	Dominant	£14,805

[redacted]

ERG's preferred base case assumptions

- Discrepancies in the model were corrected by the ERG, see slide 42 → minor impact on results

Parameter	Subgroup	Company base case	ERG base case
Baseline OS	All	Exponential	Weibull (a plausible alternative to exponential & more conservative)
PFS extrapolation	EGFR/ALK +ve	Log-normal	Log-logistic
Survival curves & relative treatment effects	All	Subgroup-specific extrapolations for atezo arm survival curves & relative effects from subgroup NMA	Subgroup-specific survival curves for atezo arm & relative effects from ITT NMA
NMA included trials & NMA model	All	Included PARAMOUNT & used fixed effects model	Excluded PARAMOUNT & used fixed effects model
Utilities	All	IMPower150 EQ-5D time-from-death with no treatment effect	IMPower150 EQ-5D time-from-death + disutility per grade 3+ treatment related AE

ERG's deterministic base case with PAS for atezo & bev only

Population & treatment	Total costs	Total QALYs	Fully incremental ICER (£/QALY)
ITT			
Pemetrexed + plat drug + pem maint	[redacted]	[redacted]	-
Atezo+bev+CP	[redacted]	[redacted]	Dominant
PD-L1 <50%			
Pemetrexed + plat drug + pem maint	[redacted]	[redacted]	-
Atezo+bev+CP	[redacted]	[redacted]	Dominant
EGFR/ALK positive			
Pemetrexed + plat drug + pem maint	[redacted]	[redacted]	-
Atezo+bev+CP	[redacted]	[redacted]	Dominant

[redacted]

ERG's scenario analysis results: ITT population with PAS for atezo & bev only (1)

Parameter	ERG base case	ERG scenario	ICER (ERG's BC = dominant)
Baseline OS	Weibull	Exponential	Dominant
		Log-logistic	Dominant
Baseline PFS	KM + log-logistic	KM + exponential	Dominant
		KM + weibull	Dominant
TTD distribution	KM + exponential, pemetrexed follows PFS	Bev until progression (no stopping rule)	Dominant
Alternative NMA network	ITT FP excluding PARAMOUNT (fixed effects)	ITT FP including PARAMOUNT (random effects)	Dominant
		ITT excluding PARAMOUNT with exponential model	Dominant
Treatment stopping rule/ treatment effect	2 years treatment + 3 years OS effect	2 years OS effect	Dominant
		5 years OS effect	Dominant
		3 years PFS	Dominant
		No stopping rule or effect cap	£8,469

ERG's scenario analysis results: ITT population with PAS for atezo & bev only (2)

Parameter	ERG base case	ERG scenario	ICER (ERG's base case = dominant)
Utility values	IMPower150 EQ-5D, using time from death + disutilities	IMPower150 EQ-5D health states	Dominant
AE disutility	Disutilities per grade 3+ treatment related AE	No AE disutilities	Dominant
Subsequent treatments	Based on market share data	IMpower150	£3,132
		Exclude nivolumab (as CDF)	£3,670

[redacted]

End of life criteria is met

Criterion	Company				ERG	
Short life expectancy (normally < 24 months)	Undiscounted absolute life years (months)					
	Population	Pem + plat		Pem + plat + pem maint		Pem + plat + pem maint	
		Mean	Median	Mean	Median	Mean	Median
	ITT	1.53 (18.4)	1.22 (14.64)	2.18 (26.2)	1.11 (13.32)	1.72 (20.6)	1.32 (15.84)
	PD-L1 <50%	1.55 (18.6)	1.14 (13.68)	2.27 (27.2)	0.99 (11.88)	-	-
	EGFR/ALK+ve	2.04 (24.5)	0.91 (10.92)	3.15 (37.8)	0.49 (5.88)	-	-
Extension to life (normally additional 3 months)	Undiscounted life years gained (months)					
	Population	Pem + plat		Pem + plat + pem maint		Pem + plat + pem maint	
		Mean	Median	Mean	Median	Mean	Median
	ITT	1.08 (13.0)	0.48 (5.76)	0.42 (5.0)	0.59 (7.08)	0.46 (5.5)	0.32 (3.84)
	PD-L1 <50%	1.01 (12.1)	0.46 (5.52)	0.29 (3.5)	0.61 (7.32)	-	-
	EGFR/ALK+ve	3.08 (37.0)	1.73 (20.76)	1.97 (23.6)	2.15 (25.8)	-	-

[redacted] **ERG comments:** End-of-life criteria is met based on the data currently available

Equality & innovation

Equality

- The company & professional organisation identified no equality issues

Innovation

- [redacted]
- [redacted]
- [redacted]
- Atezolizumab is the first checkpoint inhibitor with a phase III combination trial to show statistically significant & clinically meaningful overall & progression-free survival benefit in all non-squamous NSCLC patients & in key subgroups**

ERG comment: Clinical advice said that atezolizumab can be considered a treatment innovation → no immunotherapy option for people in first line setting not PD-L1 ≥ 50% TPS. Regimen likely considered more attractive to clinicians if did not contain bevacizumab (cost & potential additional AEs) but atezo+CP did not show a significant survival benefit compared with bev+CP (HR=0.88, 95% CI: 0.72 to 1.08)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID1210: Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC

Document B

Company evidence submission

September 2018

File name	Version	Contains confidential information	Date
ID1210_Atezolizumab 1L non-squamous NSCLC_Document B_060918_ACIC	1	Yes	06 September 2018

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Abbreviations

ADA	Anti-drug antibodies
ADCC	Antibody dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
BEV	Bevacizumab
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CP	Carboplatin and paclitaxel
CCOD	Clinical cut-off date
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTLA	Cytotoxic T-lymphocyte associated protein-4
DES	Discrete event simulation
DIC	Deviance Information Criteria
DOR	Duration of response
DSU	Decision support unit
EAMS	Early access to medicines scheme
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	The European Organisation for Research and Treatment of Cancer
HCHS	Hospital and community health services

HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQOL	Health-related quality of life
HSUV	Health state utility values
FP	Fractional polynomials
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
INR	International normalised ratio
IPD	Individual patient data
IRF	Independent review facility
ITC	Indirect treatment comparison
ITT	Intent-to-treat population
IV	Intravenous
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma
LYG	Life years gained
MAIC	Matching adjusted indirect comparisons
MRI	Magnetic resonance imaging
NE	Not evaluable
NIHR	National Institute for Health Research
NLCA	National Lung Cancer Audit
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazards
PIM	Promising innovative medicine
PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis

PSS	Personal social services
PSSRU	Personal social services research unit
QALY	Quality-adjusted life years gained
QLQ	Quality of life questionnaire
RCT	Randomised clinical trial
RECIST	Response Evaluation Criteria in Solid Tumours
RWD	Real world data
RWE	Real world evidence
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Standard deviation
SLR	Systematic literature review
SOC	Standard of care
TKI	Tyrosine kinase inhibitor
TNF	Tumour necrosis factor
TPS	Tumour proportion score
TTD	Time to treatment discontinuation
TTO	Time trade-off
ULN	Upper limit of normal
VEGFR	Vascular endothelial growth factor receptor
WT	Wild-type

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission focuses on part of the technology's anticipated marketing authorisation as a first-line treatment of adult patients with metastatic non-squamous, non-small cell lung cancer (NSCLC). In particular, it focuses on:

- patients with low or negative PD-L1 expression (tumour proportion score 0–49%, TC/IC 0,1,2) and
- patients ineligible for, intolerable to or who have progressed on targeted therapy for EGFR or ALK tumour mutations.

The proposed population is narrower than the marketing authorisation as this population optimises the clinical- and cost-effectiveness of atezolizumab (Atezo) in combination with bevacizumab (Bev), carboplatin and paclitaxel (CP). The anticipated marketing authorisation for Atezo+Bev+CP covers all patients with first-line metastatic non-squamous NSCLC, regardless of level of PD-L1 expression. Details on the rationale of the proposed population are provided below.

The UK standard of care therapies in first-line metastatic non-squamous NSCLC are pemetrexed plus platinum with or without pemetrexed maintenance (recommended for patients regardless of level of PD-L1 expression) and pembrolizumab (recommended for patients with high PD-L1 expression, tumour proportion score (TPS) > 50%, TC/IC3). As the UK standard of care therapies were not included in our pivotal study IMpower150, an indirect treatment comparison (ITC) versus these therapies had to be implemented (see Section B.2.9).

Results of the ITC suggested that Atezo+Bev+CP has an expected OS and PFS benefit versus pemetrexed-based regimens in the ITT population (i.e. regardless of PD-L1 expression) (see Section B.2.9). This OS and PFS benefit compared to pemetrexed-based was consistent (i.e. similar to the ITT) in the subgroups of patients with low or negative PD-L1 expression (tumour proportion score 0–49%, TC/IC 0,1,2) and EGFR or ALK mutations. The ITC versus pembrolizumab in PD-L1 high patients demonstrated that [redacted]. Results were however associated with limitations and high uncertainty (see Section B.2.9).

Based on these results compared to pembrolizumab, UK clinical expert opinion was sought and suggested that [redacted]. As such, reimbursement is effectively not pursued in the subgroup of patients with high PD-L1 expression.

Therefore, our evidence submission focuses on the comparison to pemetrexed-based regimens. This comparison is conducted firstly in the ITT population, as this reflect the marketing authorisation and NICE reimbursement for pemetrexed-based interventions, and provides a more robust evidence base for the ITC. However, it is equally important that we compare Atezo+Bev+CP to pemetrexed-based interventions in the subgroups of patients with (i) low or negative PD-L1 expression and (ii) EGFR or ALK tumour mutations. These patient subgroups are not eligible for treatment with pembrolizumab as a first-line therapy and as such, pemetrexed-based chemotherapy is the UK standard of care for them. Hence, there is unmet need for a cancer immunotherapy option in these subgroups of patients, in which Atezo+Bev+CP demonstrates a clinically significant OS and PFS benefit.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	• People with untreated advanced, non-squamous NSCLC • People with EGFR-or ALK-positive advanced, non-squamous NSCLC who were previously treated with targeted therapy (or cannot have a targeted therapy)	• People with untreated advanced, non-squamous NSCLC, focusing on patients with low or negative PD-L1 expression (tumour proportion score 0–49%, TC/IC 0,1,2) • People with EGFR-or ALK-positive advanced, non-squamous NSCLC who were previously treated with targeted therapy (or cannot have a targeted therapy)	Restriction compared to NICE final scope, to optimise the clinical and cost-effectiveness of the atezolizumab combination
Intervention	Atezolizumab in combination with carboplatin plus paclitaxel with or without bevacizumab	Atezolizumab in combination with carboplatin plus paclitaxel with bevacizumab	The combination of atezolizumab with carboplatin and paclitaxel (without bevacizumab) will not be pursued in the anticipated marketing authorisation or in our current NICE evidence submission
Comparator(s)	1. For untreated advanced, non-squamous NSCLC: • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with or without pemetrexed maintenance treatment • Pemetrexed in combination with cisplatin (adenocarcinoma or large cell carcinoma only) o with or without pemetrexed maintenance treatment	1. For untreated advanced, non-squamous NSCLC: pemetrexed in combination with cisplatin / carboplatin, with or without pemetrexed maintenance treatment (focusing on patients with PD-L1 low or negative expression i.e. with tumour proportion score 0-49%, TC/IC 0,1,2) 2. The comparison to pembrolizumab in PD-L1 high patients is included in the clinical section of our evidence	1. Clinical expert opinion and UK market share data suggested that pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed maintenance, is the appropriate UK chemotherapy comparator in this setting (i.e. untreated advanced non-squamous NSCLC). 2. [redacted], a comparison with pembrolizumab in PD-L1 high patients is not included in the cost-effectiveness part our evidence submission

	2. Pembrolizumab (for people whose tumours express PD-L1 with at least a 50% tumour proportion score); subject to ongoing appraisal (review of TA447). 3. For EGFR-or ALK-positive advanced, non-squamous NSCLC previously treated with targeted therapy: • Docetaxel • Pembrolizumab	submission, but not in the cost-effectiveness section 3. For EGFR- or ALK-positive advanced, non-squamous NSCLC previously treated with targeted therapy: pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed maintenance treatment	3. No clinical guidance is available for which chemotherapy non-squamous EGFR/ALK+ patients should receive after targeted therapy. Clinical expert opinion was sought and suggests that pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed maintenance, is the appropriate UK chemotherapy comparator in this setting (i.e. EGFR/ALK positive advanced, non-squamous NSCLC after targeted therapy)
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Progression-free survival • Time to treatment discontinuation • Response rate • Adverse effects of treatment • Health-related quality of life	As per NICE final scope and in line with NICE reference case (1)
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the	Cost effectiveness is expressed in terms of incremental cost per quality-adjusted life year. A time horizon of 20 years is assumed, which is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The perspective taken is UK NHS and Personal Social Services.	As per NICE final scope and NICE reference case (1)

	same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account	Patient access schemes for the intervention or comparator technologies are being taken into account	
Special considerations including issues related to equity or equality	If evidence allows, subgroup analysis by level of PD-L1 expression will be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	• Subgroup analyses by level of PD-L1 expression are considered within our evidence submission • A subgroup analysis for EGFR/ALK positive patients after targeted therapy is also considered.	As per NICE final scope and evidence availability

B.1.2 Description of the technology being appraised

The technology being appraised is described in Table 2. See Appendix C for details of the summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

Table 2: Description of the technology

UK approved name and brand name	UK approved name (brand name): • Atezolizumab (Tecentriq®) • Bevacizumab (Avastin®) • Carboplatin • Paclitaxel
Mechanism of action	**Atezolizumab** is a humanised IgG monoclonal antibody which directly and selectively binds to an immune checkpoint protein called programmed death-ligand 1 (PD-L1) on the surface of both tumour cells (TC) and tumour infiltrating immune cells (IC) (2, 3). PD-L1 binds to PD-1 and B7.1 on activated T cells to inhibit T cell proliferation, cytokine production and cytolytic activity, thereby inhibiting the anti-tumour immune response (4-6). This means that binding of PD-L1 by atezolizumab may therefore enhance an anti-tumour immune response. Overexpression of PD-L1 in tumour cells has been associated with a poor prognosis in patients with several cancers (7-10). Interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathway with atezolizumab prevents down regulation of T-cell activity while allowing for the priming of new T cells (4, 11). Furthermore, atezolizumab is FcγR-binding deficient, therefore it cannot bind to Fc receptors on phagocytes and cause antibody dependent cell-mediated cytotoxicity (ADCC). This is important since ADCC-mediated depletion of tumour specific T cells could worsen autoimmunity rather than improve it (5, 12). **Bevacizumab** binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth (13). **Carboplatin** is an alkylating chemotherapy agent that disrupts DNA function and causes cell death (14). **Paclitaxel** is a taxane chemotherapy agent that inhibits microtubule structures within the cell to prevent replication and ultimately cause cell death (14).
Marketing authorisation/CE mark status	An application for a license extension of atezolizumab for the following indication was submitted to the EMA on February 12 2018. *"Atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC).*

	Patients with EGFR activating mutant or ALK-positive tumour mutations NSCLC should have received targeted therapy if clinically indicated prior to receiving atezolizumab." Marketing authorisation for this indication is expected in [redacted]. Bevacizumab, carboplatin and paclitaxel are also approved by the EMA for the first-line treatment of advanced or metastatic NSCLC other than predominantly squamous histology.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Atezolizumab is currently approved by the EMA for the following indications (2): • As monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy or who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥ 5% • As monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should have received targeted therapy if clinically indicated prior to receiving atezolizumab Bevacizumab, carboplatin and paclitaxel are also approved by the EMA for multiple indications.
Method of administration and dosage	**Atezolizumab**: Intravenous (IV) infusion, 1,200 mg every 3 weeks until loss of clinical benefit or unmanageable toxicity **Bevacizumab:** IV infusion, 15 mg/kg q3w until disease progression or unacceptable toxicity **Carboplatin:** IV infusion, AUC of 6 mg/mL/min, q3w until disease progression or unacceptable toxicity **Paclitaxel:** IV infusion, 15 mg/kg q3w until disease progression or unacceptable toxicity
Additional tests or investigations	No additional testing for the use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in treatment-naïve adult patients with metastatic, non-squamous NSCLC is required.
List price and average cost of a course of treatment	Atezolizumab: £3807.69 per 20ml vial (1,200mg) (15) Bevacizumab: £242.66 per 4ml vial (100mg); £924.40 per 16ml vial (400mg) (15) Carboplatin: £6.35 per 15ml vial (150mg) (16) Paclitaxel: £9.85 per 16.7ml vial (100mg) (16) Average price per treatment cycle (3 weeks): £6.445.89
Patient access scheme (if applicable)	Atezolizumab: [redacted] (existing PAS) Bevacizumab: [redacted] (submitted PAS)

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Lung cancer is the third most common cancer in the UK, accounting for 13% of all cancer cases, with 46,700 new lung cancer cases reported every year. It is responsible for 21% of all cancer deaths in the UK, making it the most common cause of cancer death; around 35,600 people die of lung cancer in the UK every year (17).

Lung cancer is classified by histology and can be broadly divided between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC represented 88.5% of all lung cancer cases in the UK in 2016 (18) and includes two main histological subtypes, squamous and non-squamous. Non-squamous accounts for approximately 70% of all NSCLC cases and is a collective categorisation used to define several histologic subtypes, including adenocarcinoma, large cell carcinoma and undifferentiated carcinoma (19, 20).

Lung cancer survival in the UK has changed little in the last 40 years, with only 5% of people diagnosed with lung cancer surviving for ten years or more. Out of the twenty most common cancers in England and Wales, the ten-year survival rate for lung cancer ranks the second lowest overall (21).

Table 3: Lung cancer net survival rates for patients diagnosed during 2010-11 in England and Wales

	1-year survival (%)	5-year survival (%)	10-year survival (%)
Adults	32.1	9.5	4.9
Men	30.4	8.4	4.0
Women	35.1	11.6	6.5

Most lung cancers are diagnosed at an advanced stage when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV). In 2016, 70% of patients diagnosed with lung cancer in the UK had stage III or IV disease (18). Certain metastatic sites, such as bone and liver, have been associated with a worse prognosis for patients with advanced NSCLC (22, 23). Furthermore, liver metastases in patients with advanced NSCLC have been associated with reduced response rates and progression-free survival when treated with checkpoint inhibitor monotherapy:

- In the NSCLC cohort of KEYNOTE 001, median PFS in patients with liver metastases treated with pembrolizumab was shorter compared with those without liver metastases (1.8 months [95% CI:1.4, 2.0] vs. 4.0 months [2.1, 5.1]) (24);

- In a retrospective review of Japanese patients (N=201), median PFS in patients with liver metastases treated with nivolumab was 1.2 months [95% CI:1.1, 1.5) compared with 3.3 months [95% CI: 2.7, 4.5] in those without liver metastases (25).

This may be explained by the immune suppressive tumour microenvironment in the liver that is characterised by the expression of immune inhibitory receptors, such as PD-1, CTLA-4, Tim-3, and a progressive loss of function (26, 27). Therefore, an unmet need for patients with hard to treat metastatic disease remains; innovative combination treatments may be of benefit to overcome an immune suppressive tumour microenvironment.

The high symptom burden in patients with advanced NSCLC has a highly negative impact on health-related quality of life, especially psychosocial well-being (28, 29). More than a quarter of all patients suffer from persistent depression, with lung cancer patients reporting higher levels of distress, which is likely to be a result of a significant proportion of patients presenting with advanced disease that is deemed incurable (30, 31). Furthermore, caregivers for patients with lung cancer are also associated with a detriment in quality of life (32).

For patients with locally advanced or metastatic non-squamous NSCLC, the goals of treatment are to prolong survival, control the disease and palliate symptoms while maintaining quality of life (33). Factors that influence the choice and sequence of therapies for an individual patient include histology, the presence of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations, PD-L1 expression and patient-specific factors such as age, comorbidities and personal preferences. In the first-line setting, the majority of non-mutated patients with tumours expressing high PD-L1 (TPS ≥50%) receive pembrolizumab while patients with low, negative or unknown PD-L1 status are most likely to receive platinum chemotherapy (carboplatin or cisplatin) in combination with pemetrexed, with or without pemetrexed maintenance (34). However, the benefit conferred by this chemotherapy regimen is limited, with an expected median survival of 8–14 months (35, 36).

The development of targeted therapies for ALK/EGFR oncogenic driver mutations led to a paradigm shift that is now well established; however, disease progression is still inevitable as tumour resistance invariably develops (37). Following progression or tolerability issues with targeted tyrosine kinase inhibitor (TKI) therapies, patients are likely to subsequently receive platinum-based chemotherapy, although a retrospective study reported only modest responses with a median PFS of around 4 months for erlotinib-resistant patients who received second-line chemotherapy (38). Therefore, there also remains a need for more efficacious treatment options for these patients.

There are no current guidelines outlining the appropriate chemotherapy regimen following targeted therapy. UK clinical experts confirmed to Roche[1] that the standard of care chemotherapy in these patients would be carboplatin or cisplatin in combination with pemetrexed, with or without pemetrexed maintenance; this is in accordance with ESMO guidelines (34).

Since cure is not considered a realistic outcome for most patients with advanced NSCLC, an innovative, multi-modality treatment combination with a view to inducing a prolonged period of remission, palliating symptoms and maintaining quality of life may be considered appropriate (39).

B.1.3.2 Clinical pathway of care

The information presented below is based on the current NICE guidelines for the diagnosis and management of lung cancer [CG121] (40) (see Figure 1).

First-line treatment for advanced or metastatic non-squamous NSCLC

Chemotherapy is offered to patients with non-squamous NSCLC with a good performance status and without a known mutation to an oncogenic driver. Pemetrexed in combination with cisplatin is recommended for patients with non-squamous histology [TA181] (41), although patients may also receive platinum-based doublets with a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) (34). Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug (40).

Patients whose tumours express PD-L1 with at least a 50% TPS and have no EGFR or ALK-positive mutations can receive pembrolizumab [TA531] (42). It is estimated that 27% of patients with NSCLC and no EGFR or ALK mutation in the UK have PD-L1 positive expressing tumours with at least a 50% TPS. Targeted treatments funded for ALK-positive NSCLC include crizotinib [TA406] (43), ceritinib [TA500] (44) and alectinib [TA536] (45). Gefitinib [TA192] (46), erlotinib [TA258] (47) and afatinib [TA310] (48) are funded for patients expressing an EGFR mutation. It is estimated that 17% of patients in the UK have EGFR mutant or ALK-positive NSCLC.

Although not currently approved by NICE, bevacizumab is approved by the European Medicines Agency, in addition to platinum-based chemotherapy, for the first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSCLC other than

[1] Roche Products Ltd. held an advisory board meeting with ten UK lung cancer clinical experts in March 2018. Additional advice has been obtained from four advisory board members in follow-up discussions.

predominantly squamous cell histology (13). This regimen is also included as an option in the 2016 ESMO NSCLC Guidelines (34).

Maintenance chemotherapy for advanced or metastatic non-squamous NSCLC

Pemetrexed is recommended as an option for the maintenance treatment of locally advanced or metastatic non-squamous NSCLC in adults when their disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and their Eastern Co-operative Oncology Group (ECOG) performance status is 0 or 1 at the start of maintenance treatment [TA402] (49).

Pemetrexed is also recommended as an option for the maintenance treatment of people with locally advanced or metastatic NSCLC other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel [TA190] (50).

Second-line treatment for advanced or metastatic non-squamous NSCLC

Immune checkpoint inhibitors have become available for the second-line treatment of advanced or metastatic non-squamous NSCLC in recent years (see Figure 1) (51-53). The second-line use of these checkpoint inhibitors is not approved in patients who have previously received immunotherapy in the first-line setting; therefore, the second-line use of these treatments will become virtually redundant as more checkpoint inhibitors are approved as an initial treatment for NSCLC. This has been confirmed to Roche by UK clinical experts due to the lack of sequential immunotherapy treatment data and in accordance with NHS Blueteq prescribing criteria for second-line immunotherapy.

Nintedanib in combination with docetaxel is recommended as an option for treating locally advanced, metastatic or locally recurrent non-squamous NSCLC that has progressed after first-line chemotherapy [TA347] (54). Patients who relapse after previous chemotherapy may also receive docetaxel monotherapy.

Erlotinib is recommended as an option for treating locally advanced or metastatic NSCLC that has progressed after non-targeted chemotherapy in people with:

- A delayed confirmation that their tumour is EGFR mutation-positive;
- An unobtainable result from an EGFR mutation diagnostic test because of an inadequate tissue sample or poor-quality DNA;
- A suspected EGFR mutation-positive tumour [TA374] (55).

Treatment options available for patients who progress on targeted therapy:

- Ceritinib is recommended as an option for treating ALK-positive advanced NSCLC in adults who have previously had crizotinib (but not alectinib) [TA395] (56);
- Osimertinib is recommended as an option for use within the Cancer Drugs Fund for treating locally advanced or metastatic EGFR T790M mutation-positive NSCLC in adults whose disease has progressed after first-line treatment with an EGFR tyrosine kinase inhibitor [TA416] (57).

Although no treatment options beyond second-line are included in the NICE guidance, patients who progress on targeted therapy are likely to be treated with platinum-based chemotherapy regimens (34), specifically pemetrexed in combination with cisplatin or carboplatin (with or without pemetrexed maintenance) according to expert advice obtained from UK clinical experts. Given the toxicity profile of these regimens, it is therefore likely that these patients will be fit enough to receive combination chemo-immunotherapy.

Proposed position of the technology

For the majority of non-mutated NSCLC patients, or patients with oncogenic driver mutations but have failed all available TKIs, there is a need for further improvement over the current standard of care with new agents that provide durable survival for all patients with metastatic NSCLC, regardless of PD-L1 expression. Currently, non-mutated NSCLC patients in this setting have access to pembrolizumab as a first-line treatment, only if their tumour expresses high PD-L1 mutation (>50% tumour proportion score, TC/IC 3). However, for non-mutated first-line metastatic NCSLC patients with low or negative PD-L1 expression (tumour proportion score 0–49%, TC/IC 0,1,2) or for patients with oncogenic driver mutations but have failed all available TKIs there is an unmet need for a cancer immunotherapy option.

The combination of a checkpoint inhibitor with chemotherapy and bevacizumab is an innovative option (see Section B.2.12), based on the rationale that:

- Chemotherapy may augment immune-enhancing properties of checkpoint inhibitors by several mechanisms including the generation of neo-antigens following chemotherapy induced cell death (58, 59);
- Bevacizumab may enable efficient priming and activation of T-cell responses against tumour antigens, and normalise the tumour vasculature, thereby increasing infiltration of T-cells into the tumour. Bevacizumab may also reprogramme the tumour microenvironment from immune suppressive to immune permissive (27, 60, 61) and therefore may enhance the effect of a checkpoint inhibitor.

Evidence for the efficacy of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in UK clinical practice is sourced from the IMpower150 study, in which

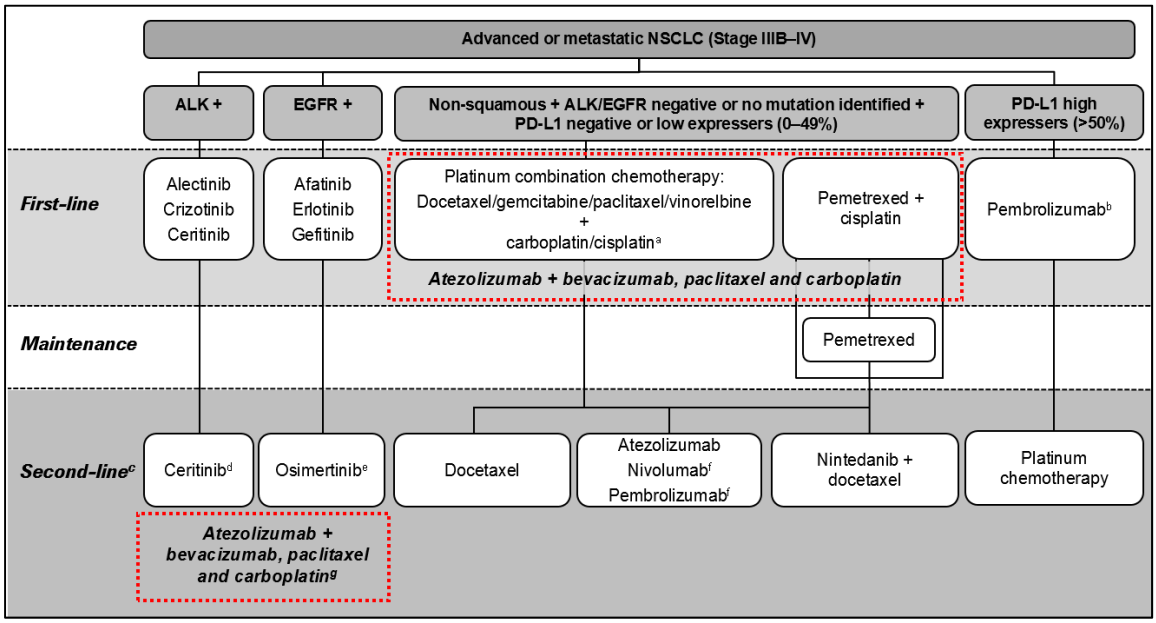
chemotherapy-naïve patients with stage IV non-squamous NSCLC were enrolled (NCT02366143) (62). Patients were enrolled regardless of PD-L1 expression, and the study included patients with EGFR mutant or ALK-positive NSCLC; these patients must have experienced disease progression after one or more targeted therapies prior to receiving the atezolizumab, bevacizumab plus chemotherapy combination.

The efficacy of Atezo+Bev+CP compared to UK standard of care was demonstrated through an ITC. Results of the ITC performed, suggested that the atezolizumab combination has an expected OS and PFS benefit versus pemetrexed-based regimens in the ITT population (i.e. regardless of PD-L1 expression) and in the subgroups of patients with low or negative PD-L1 expression and EGFR or ALK mutations. However, the ITC versus pembrolizumab in PD-L1 high patients demonstrated [redacted]. As such, [redacted], reimbursement for this subgroup of patients is not is not pursued (see Sections B.1.1 and B.2.9).

The proposed positioning of the atezolizumab plus bevacizumab combination in the treatment pathway is indicated in Figure 1 below. Based on the anticipated marketing authorisation, the clinical efficacy observed in IMpower150, and the results of an ITC versus UK standard of care therapies (see Sections B.1.1 and B.2.9), the Atezo+Bev+CP combination will provide an innovative treatment option, versus pemetrexed-based chemotherapy regimens, for:

1. Chemotherapy-naïve patients with advanced non-squamous NSCLC with low or negative PD-L1 expression (tumour proportion score 0-49%, TC/IC 0,1,2)
2. Patients with EGFR or ALK mutation that have developed resistance to or progressed on targeted therapy (having exhausted all available options).

Figure 1: Proposed position of the technology in the advanced or metastatic NSCLC treatment pathway (based on NICE guidance CG121)



[a]Single-agent chemotherapy with a third-generation drug offered if a platinum combination cannot be tolerated; [b]PD-L1 expression ≥50% TPS; [c]Patients who progress following non-targeted therapy may receive an ALK or EGFR tyrosine kinase inhibitor as a second-line treatment if an actionable mutation is identified or suspected; [d]Certinib after crizotinib failure; not suitable after first-line alectinib; [e]EGFR T790M mutation-positive only; [f]PD-L1 positive patients only; [g]Atezolizumab+bevacizumab, paclitaxel and carboplatin would be available as a second-line treatment option for patients who progress on targeted therapy (after exhausting all available options) and are ineligible for osimertinib, i.e. non T790Mpatients

B.1.4 Equality considerations

No equality issues have been identified.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Table 4: Clinical effectiveness evidence

Study	**IMpower150 (NCT02366143)** (62) **Study publications:** • Primary analysis, ESMO-IO 2017, Reck M et al. (63) • Primary manuscript, N Engl J Med, Socinski M et al. (64) • Key subgroups efficacy, AACR 2018, Kowanetz M et al. (65) • Updated overall survival analysis, ASCO 2018, Socinski M et al. (66) • Patient-reported outcomes, ASCO 2018, Reck M et al. (67)				
Study design	Randomised, open-label, Phase III study				
Population	• Age ≥18 years' old • ECOG PS 0 or 1 • Histologically or cytologically confirmed metastatic non-squamous NSCLC • 'All-comer' patient population, i.e. patients were eligible regardless of their PD-L1 expression level and included those with EGFR mutant or ALK-positive disease • No prior treatment for metastatic non-squamous NSCLC allowed, except for patients with sensitising EGFR mutations or ALK-positive tumours who had experienced disease progression (during or after treatment) or intolerance to treatment with one or more EGFR or ALK TKIs, respectively				
Intervention(s)	Atezolizumab+bevacizumab+carboplatin+paclitaxel				
Comparator(s)	Bevacizumab+carboplatin+paclitaxel				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	IMpower150 was a registration Phase III trial providing efficacy and safety evidence for the combination of atezolizumab, plus bevacizumab, carboplatin and paclitaxel (Atezo+Bev+CP). Data from IMpower150 were used to inform the efficacy and safety of Atezo+Bev+CP in the economic model. The efficacy and safety of relevant comparators (UK standard of care therapies in this indication) was informed through indirect treatment comparisons.				
Reported outcomes specified in the decision problem	Overall survival, progression-free survival, response rate, adverse effects of treatment, health-related quality of life				
All other reported outcomes	Time to treatment discontinuation				

ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; q3w, every 3 weeks; TKI, tyrosine kinase inhibitor

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Unless otherwise stated, information on the IMpower150 study was sourced from the clinical study reports (68, 69).

B.2.3.1 Study design

IMpower150 is a Phase III, open-label, randomised study to investigate the efficacy and safety of atezolizumab (Atezo) in combination with carboplatin+paclitaxel (CP), with or without bevacizumab (Bev) compared with Bev+CP in chemotherapy-naïve patients with stage IV non-squamous NSCLC (Figure 2).

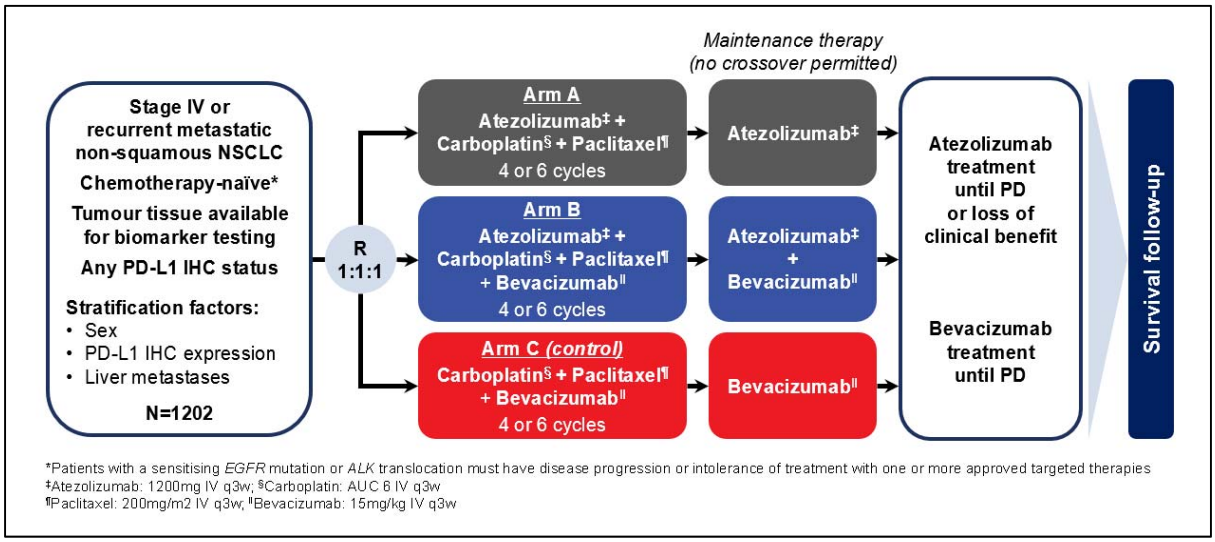
Eligible patients (N=1202) were randomly assigned in a 1:1:1 ratio to one of three treatment arms:

- **Arm A (n=402):** Atezo+CP induction (four or six 21-day cycles) followed by atezo maintenance (21-day cycles)
- **Arm B (n=400):** Atezo+Bev+CP induction (four or six 21-day cycles) followed by Atezo+Bev maintenance (21-day cycles)
- **Arm C (n=400):** Bev+CP induction (four or six 21-day cycles) followed by bev maintenance (21-day cycles)

The principal question of IMpower150 is to assess whether the addition of atezolizumab to Arm C adds clinical value, i.e. Arm B vs. Arm C. The analysis of Arm A vs. Arm C was triggered when a significant overall survival benefit was observed in Arm B compared with Arm C. However, comparing Arm A with Arm C failed to show a statistically significant survival benefit (HR=0.88, 95% CI: 0.72, 1.08; p=0.2041) (66), therefore marketing authorisation was applied for Atezo+Bev+CP (Arm B) only. As such, data for Arm A is not included in this appraisal. Moreover, the IMpower150 study was not designed or powered to compare Arm A vs. Arm B.

All patients were tested for PD-L1 expression during screening but the results did not determine entry criteria. Furthermore, patients with EGFR mutant or ALK-positive NSCLC were enrolled provided they were chemotherapy-naïve and had either progressed on or had been intolerant to appropriate targeted therapy. Therefore, IMpower150 enrolled an all-comers population. Stratification factors included gender, PD-L1 expression, and the presence of liver metastases given the poor prognosis in this patient population.

Figure 2: IMpower150 study design schematic



The co-primary endpoints of IMpower150 were overall survival (OS) and progression-free survival (PFS), as determined by the investigator using Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1).

The co-primary OS and PFS endpoints in IMpower150 were assessed in all randomised patients without an ALK or EGFR genetic mutation, known as the intention-to-treat wild type population (ITT-WT), which accounted for 87% of the total study population.

The primary analysis of the co-primary PFS endpoint in IMpower150 was also assessed in a subgroup of patients who had a specific T-effector (Teff) gene signature (defined by mRNA expression of 3 genes, *PD-L1*, *CXCL-9* and *IFNγ*). This was included in the study design as the Teff gene signature appeared to be a more sensitive biomarker of PFS benefit for monotherapy atezolizumab vs. docetaxel than PD-L1 immunohistochemistry expression in the second-line NSCLC study (OAK) (70). However, since the Atezo+Bev+CP combination demonstrated a clinically meaningful improvement in outcomes regardless of Teff gene signature status, this biomarker was not deemed to be clinically relevant and therefore this data did not impact the anticipated marketing authorisation. As such, these data will not be included in the economic model or discussed further in this submission.

IMPORTANT INFORMATION RELEVANT TO THIS APPRAISAL

- This appraisal evaluates the clinical effectiveness of the combination of Atezo+Bev+CP, compared with Bev+CP (i.e. **Arm B vs. Arm C** only from study IMpower150) and, more importantly, compared to UK standard of care therapies via indirect treatment comparisons (ITCs). Since Arm A did not show a statistically significant survival benefit over Arm C, marketing authorisation was only applied for Arm B, therefore data for Arm A vs. Arm C are not considered in this appraisal. Study IMpower150 was not designed or powered to compare Arm A vs. Arm B.
- While the co-primary endpoints were analysed in the ITT-WT population, the anticipated marketing authorisation is based **on the entire ITT population**, i.e. including those patients with EGFR mutant and ALK-positive NSCLC. Therefore, data presented in the appraisal and included in the economic model will be that of the ITT population, to reflect the anticipated marketing authorisation and the decision problem from NICE. Comparisons in relevant subgroups of the ITT population (in terms of PD-L1 expression and presence of EGFR or ALK tumour mutations) will also be considered.
- Data for patients with the **Teff gene signature will not be presented or included** in the economic model since the Atezo+Bev+CP combination demonstrated a clinically

B.2.3.2 Summary of study methodology

	IMpower150 (NCT02366143) (64)
Settings and locations of data collection	1202 patients were randomised at 240 study sites in 26 countries. **<u>Countries, number of patients (centres)</u>** • United States 266 (61) • Spain 138 (20) • Germany 94 (17) • Japan 93 (15) • Australia 88 (16) • Ukraine 74 (13) • France 72 (12) • Italy 50 (11) • Chile 44 (3) • Netherlands 39 (12) • Russia 37 (5) • Taiwan 34 (10) • Brazil 27 (9) • Portugal 23 (6) • Latvia 17 (2) • Belgium 16 (2) • Switzerland 14 (3) • Austria 12 (2) • Argentina 10 (7) • Bulgaria 10 (2) • Mexico 9 (3) • Peru 9 (3) • Singapore 9 (1) • Slovakia 8 (3) • Canada 6 (1) • Lithuania 3 (1)
Trial design	IMpower150 is a Phase III, open-label, randomised study of atezolizumab in combination with carboplatin+paclitaxel with or without bevacizumab

	compared with bevacizumab+carboplatin+paclitaxel in chemotherapy-naïve patients with stage IV non-squamous NSCLC
Eligibility criteria	**Inclusion criteria** • Age ≥18 years' old • ECOG PS 0 or 1 • Histologically or cytologically confirmed, stage IV non-squamous NSCLC • No prior treatment for Stage IV non-squamous NSCLC o Patients with a sensitising mutation in the EGFR gene or an ALK fusion oncogene had to have experienced PD (during or after treatment) or intolerance to treatment with one or more targeted therapies • Patients who had received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy for non-metastatic disease had to have experienced a treatment-free interval of at least 6 months from randomisation since the last chemotherapy, radiotherapy, or chemoradiotherapy • Patients with a history of treated asymptomatic CNS metastases were eligible, provided they met all of the following criteria: o Only supratentorial and cerebellar metastases allowed o No ongoing requirement for corticosteroids as therapy for CNS disease o No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomisation o No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study • Known PD-L1 tumour status as determined by an IHC assay performed by a central laboratory on previously obtained archival tumour tissue or tissue obtained from a biopsy at screening • Measurable disease as defined by (RECIST v1.1) • Adequate haematologic and end-organ function, defined by the following laboratory results o ANC ≥1500 cells/μL without granulocyte colony-stimulating factor support o Lymphocyte count ≥500/μL o Platelet count ≥100×10^9/L o Haemoglobin ≥9.0 g/dL o INR or aPTT ≤1.5 x ULN o AST, ALT, and alkaline phosphatase ≤2.5 x ULN, except: - Documented liver metastases: AST and/or ALT ≤5 x ULN - Documented liver or bone metastases: alkaline phosphatase ≤5 x ULN o Serum bilirubin ≤1.25 x ULN o Serum creatinine ≤1.5 x ULN • For both female patients and male patients, agreement to remain abstinent or use highly effective form(s) of contraception and to continue its use for 5 months after the last dose of atezolizumab and/or 6 months after the last dose of bevacizumab or paclitaxel, whichever was later

	• Able and willing to provide written informed consent and to comply with the study protocol **<u>Key exclusion criteria (please refer to CSR for further detail)</u>** • Active or untreated CNS metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments • Leptomeningeal disease • Malignancies other than NSCLC within 5 years prior to randomisation, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS>90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localised prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent) • Positive test for HIV; patients with active hepatitis B or hepatitis C; active tuberculosis • Severe infections within 4 weeks prior to randomisation, including, but not limited to, hospitalisation for complications of infection, bacteraemia, or severe pneumonia • Received therapeutic oral or IV antibiotics within 2 weeks prior to randomisation • Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to randomisation, unstable arrhythmias, or unstable angina **Exclusion criteria related to medications** • Treatment with any approved anti-cancer therapy, including hormonal therapy, within 3 weeks prior to initiation of study treatment; TKIs approved for treatment of NSCLC discontinued >7 days prior to randomisation • Treatment with any other investigational agent with therapeutic intent within 28 days prior to randomisation • Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-PD-1, and anti-PD-L1 therapeutic antibodies • History of autoimmune disease • Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumour necrosis factor [anti-TNF] agents) within 2 weeks prior to randomisation **Exclusion criteria related to bevacizumab** • Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg) • Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomisation • History of haemoptysis (≥one-half teaspoon of bright red blood per episode) within1 month prior to randomisation

	• Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation) • Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for >2 weeks prior to randomisation • Clear tumour infiltration into the thoracic great vessels is seen on imaging • Clear cavitation of pulmonary lesions is seen on imaging **Exclusion criteria related to chemotherapy** • Known history of severe allergic reactions to platinum-containing compounds or mannitol • Known sensitivity to any component of paclitaxel • Grade ≥2 peripheral neuropathy as defined by NCI CTCAE v4.0 (paclitaxel)
Trial drugs and concomitant medications	**Trial drugs** Eligible patients were randomised in a 1:1:1 ratio to receive Atezo+CP (Arm A), Atezo+Bev+CP (Arm B), and Bev+CP (Arm C). No crossover was permitted from the control arm (Arm C) to either of the experimental arms (Arms A and B). **Atezolizumab:** IV, 1200 mg q3w until loss of clinical benefit, in combination with: • **Bevacizumab:** IV, 15 mg/kg q3w until disease progression or unacceptable toxicity, PLUS; • **Carboplatin:** IV, AUC of 6 mg/mL/min, q3w until disease progression or unacceptable toxicity, PLUS; • **Paclitaxel:** IV, 15 mg/kg q3w until disease progression or unacceptable toxicity **Concomitant medications** **Permitted concomitant medications included:** • Premedication with antihistamines for any atezolizumab infusions after Cycle 1 • Palliative radiotherapy (e.g., treatment of known bony metastases) provided it did not interfere with the assessment of tumour target lesions • Prophylactic or therapeutic anticoagulation therapy • Corticosteroids (≤10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease • Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency Caution was exercised when the following were co-administered with atezolizumab: • Systemic corticosteroids and TNF-α inhibitors: alternatives, including antihistamines, were considered first by the treating physician but if these were not feasible, systemic corticosteroids and TNF-α inhibitors could be administered, except in the case of patients for whom CT scans with contrast were contraindicated **Prohibited concomitant medications:** • Denosumab

	• Any live, attenuated vaccine within 4 weeks prior to randomisation, during treatment, or within 5 months after the last atezolizumab dose • Use of steroids to premedicate patients for whom CT scans with contrast were contraindicated
Primary outcome	**Co-primary endpoint:** • Investigator-assessed PFS according to RECIST v1.1 in the Teff high WT and the ITT-WT population • OS in the ITT-WT population
Other outcomes used in the economic model/specified in the scope	**Secondary endpoints:** • PFS, OS, ORR, DOR from the ITT population **Safety endpoints:** • Safety and tolerability of atezolizumab **Patient-reported outcomes:** • Time to deterioration in patient-reported lung cancer symptoms of cough, dyspnoea, chest pain, or arm/shoulder pain, using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13) • Change from baseline in PROs of HRQoL, lung cancer−related symptoms, and functioning as assessed by the EORTC QLQC30 and QLQ-LC13
Pre-planned subgroups	**Pre-planned subgroup analyses** PFS efficacy of Atezo+Bev+CP in key patient populations: • PD-L1 expression subgroups (including TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3, and TC0/1/2 and IC0/1/2) • Patients with EGFR/ALK genetic alterations • Patients with liver metastases at baseline

ADA, anti-drug antibodies; ALK, anaplastic lymphoma kinase; ALT, alanine transaminase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; AUC, area under the curve; CNS, central nervous system; CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth-factor receptor; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-3L, EuroQoL 5 Dimensions 3-Level; HRQoL; health-related quality of life; INR, international normalised ratio; IRF, Independent Review Facility; IV, intravenous; MRI, magnetic resonance imaging; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, three-times weekly; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitor; TNF-α, tumour necrosis factor-α; ULN, upper limit of normal

B.2.3.3 Patient demographics and baseline characteristics

In the ITT population, patient demographics and baseline characteristics were in general balanced among the treatment arms. The arms were well balanced with respect to stratification factors by sex, presence of liver metastases at baseline and PD-L1 expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1).

As expected, among ITT patients who were tested for EGFR and ALK genetic alterations, the majority were EGFR wild type and ALK translocation negative. In comparison to the ITT population, the EGFR mutant and ALK-positive subgroup had a higher proportion of females

(53.1% vs. 40.1%), Asians (35.8% vs. 12.5%), and patients who had never smoked (51.2% vs. 19.6%).

Table 5: Patent demographics and baseline characteristics in IMpower150 (ITT population)

	Atezo+Bev+CP n=400	Bev+CP n=400
Mean age, years (SD) Median age, (range)	63.0 (9.5) 63.0 (31–89)	63.1 (9.3) 63.0 (31–90)
Male, n (%)	240 (60.0)	239 (59.8)
Race, n (%) American Indian or Alaska native Asian Black or African American White Multiple Unknown	 3 (0.8) 56 (14.0) 3 (0.8) 322 (80.5) 3 (0.8) 13 (3.3)	 1 (0.3) 46 (11.5) 12 (3.0) 335 (83.8) 0 6 (1.5)
ECOG PS, n (%) 0 1	n=397 159 (40.1) 238 (59.9)	n=397 179 (45.1) 218 (54.9)
Smoking status, n (%) Never Current Previous	 82 (20.5) 90 (22.5) 228 (57.0)	 77 (19.3) 92 (23.0) 231 (57.8)
Non-squamous histology detail, n (%) Adenocarcinoma Adenocarcinoma with neuroendocrine features Adenosquamous Bronchioloalveolar carcinoma Large cell Sarcamatoid Undifferentiated NA Unknown	 378 (94.5) 3 (0.8) 1 (0.3) 2 (0.5) 5 (1.3) 1 (0.3) 7 (1.8) 1 (0.3) 2 (0.5)	 377 (94.3) 3 (0.8) 1 (0.3) 2 (0.5) 5 91.3) 1 (0.3) 7 (1.8) 1 (0.3) 2 (0.5)
EGFR mutation status, n (%) Positive Negative Unknown	 34 (8.5) 353 (86.3) 10 (2.5)	 45 (11.3) 345 (86.3) 10 (2.5)
EML4-ALK rearrangement status, n (%) Positive Negative Unknown	 11 (2.8) 386 (96.5) 3 (0.8)	 20 (5.0) 376 (94.0) 4 (1.0)
KRAS mutation status, n (%) Positive Negative Unknown	 46 911.5) 60 (15.0) 294 (73.5)	 38 (9.5) 77 (19.3) 285 (71.3)
Liver metastases at enrolment from IxRS, n (%) Yes	 67 (16.8)	 69 (17.3)

No	333 (83.3)	332 (82.8)
PD-L1 IHC stratification factor from IxRS, n (%)		
TC0/1/2 and IC0/1	299 (74.8)	301 (75.3)
TC0/1/2 and IC2/3	53 (13.3)	50 (12.5)
TC3 and any IC	48 (12.0)	49 (12.3)

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EML4-ALK, *EML4*-anaplastic lymphoma kinase; IC, tumour-infiltrating immune cell; IHC, immunohistochemistry; IxRS, Interactive Voice/Web Response System; PD-L1, programmed death-ligand-1SD, standard deviation; TC, tumour cell

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Unless otherwise stated, information for IMpower150 is sourced from the protocol and clinical study report (68, 71). The participant flow for IMpower150 is presented in Appendix D.

Determination of sample size

The primary endpoint of PFS was analysed in the Teff-high WT population and in the ITT-WT population, and the primary endpoint of OS was analysed in the ITT-WT population. Treatment comparisons were tested by first comparing Atezo+Bev+CP (Arm B) vs. Bev+CP (Arm C); Atezo+CP (Arm A) was compared with Arm C if a statistically significant difference in OS was observed between Arm B and Arm C in the ITT-WT population.

This study enrolled approximately 1200 patients. The ITT-WT population included approximately 1080 patients, assuming 10% prevalence for sensitising EGFR mutations or ALK-positive NSCLC disease. The Teff-high WT population included approximately 540 patients, assuming 50% prevalence with the chosen Teff cut-off.

The sample size of this study was based on the number of events required to demonstrate efficacy with regard to both PFS and OS (co-primary endpoints) for the comparison of the Arm B vs. Arm C.

Analysis plan

The final PFS analysis was conducted when both of the following criteria were met:

- Approximately 516 PFS events had occurred in Arms B and C in the ITT-WT population;
- The last patient had enrolled in the study.

At the time of the final PFS analysis (henceforth referred to as the interim analysis; clinical cut-off date [CCOD] 15 September 2017), there was significantly fewer than 370 OS events

in the ITT-WT population Arms B and C combined (310 events had been observed). Consequently, per the statistical analysis plan and protocol, a nominal α of 0.01% (negligible impact on overall type I error rate) was spent on the OS analysis at the time of the interim analysis. At the time of the second interim OS analysis (henceforth referred to as the updated analysis; CCOD 22 January 2018), 376 events had been observed.

The final OS analysis for the primary comparison of Arm B vs. Arm C will be conducted when there are approximately 507 OS events in the ITT-WT population (Arms B and C combined). This number of events corresponds to a minimum detectable difference in HR of approximately 0.83 in the ITT-WT population. The OS final analysis is expected to occur [redacted].

Analysis populations

- The ITT population is defined as all randomised patients, regardless of receipt of the assigned treatment.
- The ITT-WT population is defined as the ITT population excluding patients with an activating EGFR mutation or ALK translocation.
- The Teff-high WT population is defined as the Teff-high population excluding patients with an activating EGFR mutation or ALK translocation.

Data reported in this submission will focus on the ITT population, i.e. including those patients with EGFR- and ALK-positive mutations and regardless of Teff gene signature status, in order to reflect the anticipated marketing authorisation and the decision problem from NICE. Please refer to Table 13 for data on the ITT-WT population.

The safety population included all treated patients, defined as randomised patients who received any amount of any component of study treatment. For the safety analyses, patients were grouped according to whether any amount of atezolizumab was received, including when atezolizumab was received in error.

Primary hypothesis

PFS is defined as the time from randomisation to the first documented progressive disease (PD) as determined by the investigator with the use of RECIST v1.1 or death from any cause, whichever occurred first. Data for patients who were alive and who did not experience PD at the time of analysis were censored at the date of the last tumour assessment. Data for patients with no post-baseline tumour assessment were censored at the date of randomisation plus 1 day.

OS is defined as the time from randomisation to death from any cause. Data for patients who were not reported as having died at the time of analysis were censored at the date last known to be alive. Data for patients who did not have post-baseline information were censored at the date of randomisation plus 1 day.

The null and alternative hypotheses regarding PFS and OS can be phrased in terms of the survival functions $S_B(t)$ for Arm B and $S_C(t)$ for Arm C:

- H_0: $S_B(t) = S_C(t)$ vs. H_1: $S_B(t) > S_C(t)$.

The HRs, λB/λC (where λB, and λC represent the hazard of having a PFS or death in the Atezo+Bev+CP and Bev+CP arms, respectively), comparing the treatment effect between the two treatment arms, was estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test, and the 95% CI was provided.

KM methodology was used to estimate median PFS and OS and to construct survival curves for each treatment arm for a visual description of the difference among arms. The Brookmeyer-Crowley methodology was used to construct the 95% CI for the median PFS and OS.

Handling of missing data and censoring methods

An overview of the analysis (and censoring, if applicable) methods used for the efficacy parameters in IMpower150 is summarised below.

Table 6: Summary of analysis methods for efficacy parameters

Endpoint	Definition	Censoring	Methodology
PFS per RECIST v1.1 by investigator in Teff-high WT and ITT-WT populations	Time from randomisation to first documented PD or death from any cause, whichever occurred first.	• Patients who were alive and who did not experience PD at time of analysis were censored at date of the last tumour assessment • Patients with no post-baseline tumour assessment were censored at date of randomisation plus 1 day	Kaplan-Meier methodology, stratified log-rank test, and stratified Cox regression
OS in ITT-WT population	Time from randomisation to death from any cause	• Patients who were not reported as having died at time of analysis were censored at the date last known to be alive • Patients who did not have post-baseline information were censored at the date of randomisation plus 1 day	Same methods as for PFS co-primary endpoint in the ITT-WT population
PFS and OS in PD-L1 TC2/3 or IC2/3 WT and TC1/2/3 or IC1/2/3 WT populations	Same as above	Same as above	Similar methods as for co-primary endpoints
PFS and OS in ITT populations	Same as above	Same as above	Similar methods as for co-primary endpoints
ORR (confirmation not required) per RECIST v1.1 by investigator in Teff-high WT and ITT-WT populations	Proportion of patients with an objective response, either CR or PR	N/A	Clopper-Pearson method for 95% CI of response rates and stratified Cochran-Mantel-Haenszel test for difference in rates
DOR (confirmation not required) per RECIST v1.1 by investigator	Time from the first documented objective response to documented PD or death from any cause, whichever occurred first	• Patients who were alive and who did not experience PD at time of analysis were censored at the date of the last tumour assessment. • If no tumour assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR was censored at the date of the first occurrence of the objective response	Kaplan-Meier methodology Comparisons between treatment arms using stratified and unstratified log-rank test are for descriptive purposes only
PFS per RECIST v1.1 by IRF in Teff-high WT and ITT-WT populations	Time from randomisation to the first documented PD	Same as for PFS as assessed by investigator	Same as for PFS as assessed by investigator

	as determined by IRF or death from any cause, whichever occurred first		
OS at 1- and 2-year landmark time points in Teff-high WT and ITT-WT populations	Same as above	Same as above	Kaplan-Meier methodology with 95% CI calculated with the standard error derived from the Greenwood formula. 95% CI for the difference in OS rates between the two treatment arms was estimated using the normal approximation method, with standard errors computed using the Greenwood methods

CR, complete response; DOR, duration of response; IC, tumour-infiltrating immune cell; IRF, independent review facility; ITT-WT, intention-to-treat wild type; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed-death ligand-1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TC, tumour cell; Teff, T-effector gene signature

Summary of statistical analyses

Data management

Data entered manually were collected via electronic data capture using electronic case report forms (eCRFs). eCRFs were completed by designated, trained site staff. Study monitors performed source data verification of data entered into eCRFs to ensure data were accurate, complete and verifiable from source documents.

Patients used ePRO devices provided by an ePRO vendor to capture patient-reported outcome (PRO) data. Data were transmitted automatically after entry to a centralised database at the ePRO vendor.

Patient withdrawals

Within the ITT population a total of 204 patients (51%) in the Atezo+Bev+CP arm and 244 patients (61%) in the Bev+CP arm discontinued treatment. Further information on reasons for discontinuation is detailed in Appendix D.

Table 7: Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
IMpower150 (NCT02366143)	Null and alternative hypotheses regarding PFS and OS phrased in terms of the survival functions $S_B(t)$ (Atezo+Bev+CP) and $S_C(t)$ (Bev+CP) H_0: $S_B(t) = S_C(t)$ vs. H1: $S_B(t) > S_C(t)$.	Kaplan-Meier methodology, stratified log-rank test, and stratified Cox regression	Sample size = 1200 516 PFS events corresponds to a minimum detectable difference in HR of approximately 0.70 in the Teff-high WT population and 0.78 in the ITT-WT population 507 OS events corresponds to a minimum detectable difference in HR of approximately 0.83 in the ITT-WT population	Data management: EDC via eCRFs and ePRO devices Treatment discontinuations: Atezo+Bev+CP: 204 (51%) Bev+CP: 244 (61%)

eCRF, electronic case report form, ePRO, electronic patient reported outcome; HR, hazard ratio; ITT-WT, intention-to-treat wild type; PFS, progression-free survival; OS, overall survival; Teff, T-effector gene signature

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Critical appraisal of the included randomised clinical trials was performed using established risk of bias tools recommended for HTA submissions. The complete quality assessment is presented in Appendix D. A summary is presented below.

Table 8: Clinical effectiveness evidence quality assessment

Study question	IMpower150 (NCT02366143)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	N/A (open label study)
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A (open label study)
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

B.2.6 Clinical effectiveness results of the relevant trials

The data discussed in this section has been taken from the updated analysis (CCOD 22 January 2018) where available (68); additional data from the interim analysis (CCOD 15 September 2017) is also presented where necessary, i.e. PFS analysis (69).

At the interim analysis, 517 death or PD events had been observed among ITT-WT patients for Arms B and C; the stratified HR was 0.62 (95% CI: 0.52, 0.74; p<0.0001), indicating a statistically significant and clinically meaningful benefit in PFS with Atezo+Bev+CP compared with Bev+CP (64, 69). At the updated analysis, IMpower150 met the OS co-primary endpoint of demonstrating a statistically significant and clinically meaningful improvement in OS with Atezo+Bev+CP compared with Bev+CP in the ITT-WT population (HR=0.78; 95% CI: 0.64, 0.96; p=0.0164, median OS 19.2 vs. 14.7 months) (68).

However, in accordance with the proposed marketing authorisation, this section will focus on the efficacy of Atezo+Bev+CP in the total ITT population (i.e., including patients with EGFR mutant and ALK-positive NSCLC). Please refer to Table 13 for a summary of the efficacy data for all endpoints in the ITT-WT population. The marketing authorisation submission included EGFR mutant and ALK-positive patients due to the high unmet medical need in this population and clinical opinion on the strength of this data.

Investigator-assessed progression-free survival – ITT population

At the clinical cut-off of the interim analysis (minimum follow-up time of 9 months), 598 death or PD events had been observed among ITT patients for the Atezo+Bev+CP and Bev+CP arms (event/patient ratio of 66.8% and 82.8% respectively). The stratified HR for investigator-assessed PFS was 0.61 (95% CI: 0.52, 0.72), indicating a clinically meaningful benefit with Atezo+Bev+CP compared with Bev+CP (69).

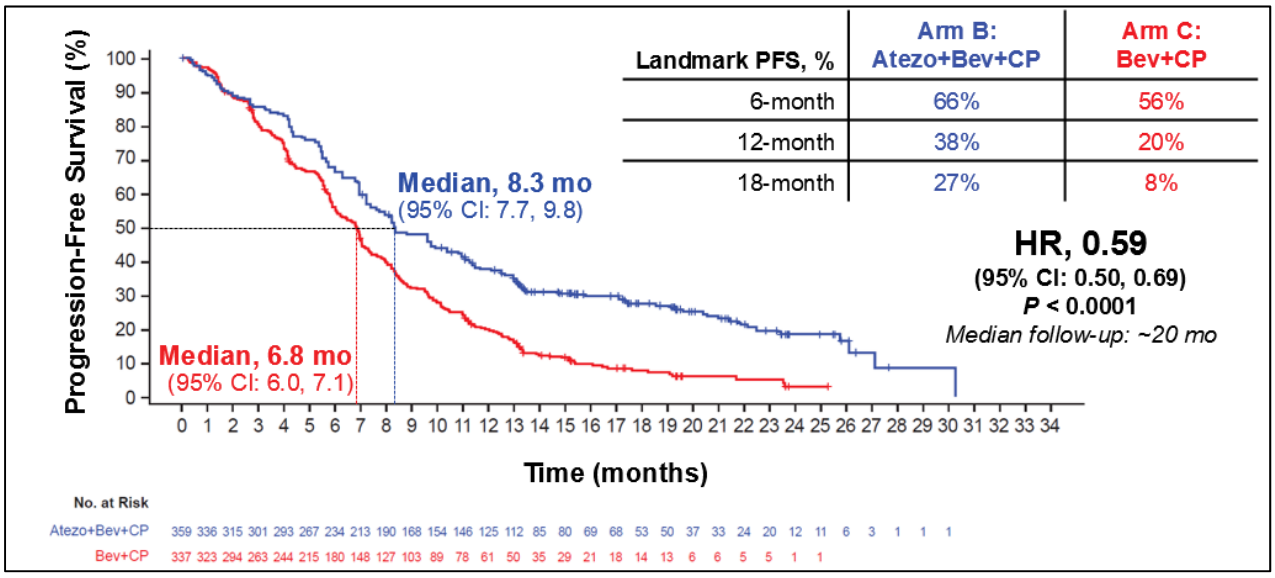
At the time of the updated analysis (minimum follow-up time of 13.5 months), the stratified HR improved to 0.59 (95% CI: 0.50, 0.69). The median duration of PFS was greater in the Atezo+Bev+CP arm (8.4 months, 95% CI: 8.0, 9.9) compared with the Bev+CP arm (6.8 months, 95% CI: 6.0, 7.0) (68).

Table 9: Investigator-assessed progression-free survival in the ITT population of IMpower150 (updated analysis)

	Atezo+Bev+CP n=400	Bev+CP n=400
Patients with event, n (%)	291 (72.8)	355 (88.8)
Median PFS, months (95% CI)	8.4 (8.0, 9.9)	6.8 (6.0, 7.0)
Stratified HR (95% CI) p value	0.59 (0.50, 0.69) p<0.0001*	

HR, hazard ratio; PFS, progression-free survival
CCOD: 22 January 2018
*for descriptive purposes only

Figure 3: KM curve – investigator-assessed progression-free survival in the ITT population of IMpower150 (updated analysis)



CCOD: 22 January 2018

Overall survival – ITT population

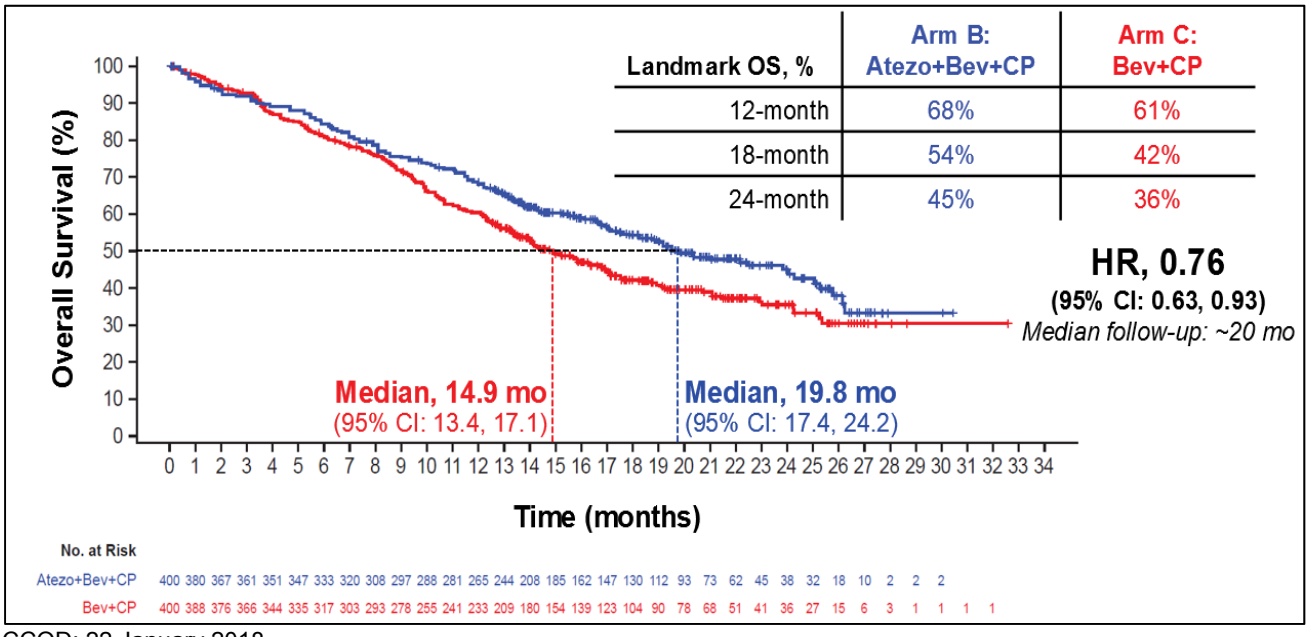
As of the CCOD of 22 January 2018 for the updated analysis, 422 total deaths had been observed across the two treatment groups, for an overall event/patient ratio of 52.8%. OS data from the second interim analysis showed a clinically meaningful improvement with Atezo+Bev+CP compared with Bev+CP. The stratified HR was 0.76 (95% CI: 0.63, 0.93), corresponding to a 24% relative reduction in the risk of death associated with Atezo+Bev+CP compared with Bev+CP in the ITT population. Median OS was 4.9 months longer in the Atezo+Bev+CP arm (19.8 months, 95% CI: 17.4, 24.2) than the Bev+CP arm (14.9 months, 95% CI 13.4, 17.1). The landmark event-free rate was higher in the Atezo+Bev+CP arm compared with the Bev+CP arm at 12 months (68.4% vs. 60.6%) and 24 months (45.1% vs. 35.5%) after randomisation (68).

Table 10: Overall survival in the ITT population of IMpower150 (updated analysis)

	Atezo+Bev+CP n=400	Bev+CP n=400
Patients with event, n (%)	192 (48.0)	230 (57.5)
Median OS, months (95% CI)	19.8 (17.4, 24.2)	14.9 (13.4, 17.1)
Stratified HR (95% CI) p value	0.76 (0.63, 0.93) p=0.0060	

HR, hazard ratio; OS, overall survival
CCOD: 22 January 2018

Figure 4: KM curve – overall survival in the ITT population of IMpower150 (updated analysis)



CCOD: 22 January 2018

Objective response rate

In the ITT population, the proportion of patients with a confirmed objective response (CR or PR) was higher in the Atezo+Bev+CP arm (56.4%, 95% CI: 51.4, 61.4) compared with the Bev+CP arm (40.2%, 95% CI: 35.3, 45.2; odds ratio [OR]=1.94, 95% CI: 1.46, 2.48). More patients in the Atezo+Bev+CP arm compared with the Bev+CP arm had a CR (2.8% vs. 0.8%) or a PR (53.7% vs. 39.4%). Conversely, more patients in the Bev+CP arm had the best objective response of SD (40.7% vs. 28.0%) or PD (9.7% vs. 5.8%) (68).

Table 11: Summary of ORR in the ITT population of IMpower150 (updated analysis)

	Atezo+Bev+CP n=397	**Bev+CP n=393**
Responders, n (%)	28 (68.3)	57 (90.5)
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)

CCOD: 22 January 2018

Duration of response

Treatment with Atezo+Bev+CP resulted in prolonged DOR compared with Bev+CP. Among confirmed responders, the median DOR was longer in the Atezo+Bev+CP arm (11.5 months) compared with the Bev+CP (6.0 months). The stratified HR was 0.41 (95% CI: 0.32, 0.53). Of note, 39.3% of responders in the Atezo+Bev+CP arm vs. 11.4% in the Bev+CP arm had an ongoing response at the time of the updated analysis CCOD (68).

Table 12: Duration of confirmed response in the ITT population of IMpower150 (updated analysis)

	Atezo+Bev+CP n=224	**Bev+CP n=158**
Patients with event, n (%)	136 (60.7)	140 (88.6)
Patients with ongoing response at CCOD, n (%)	88 (39.3)	18 (11.4)
Median DOR, months (95% CI)	11.5 (8.9, 15.7)	6.0 (5.5, 6.9)
Stratified HR (95% CI) p value	0.41 (0.32, 0.53) p<0.0001	

DOR, duration of response
CCOD: 22 January 2018

Efficacy summary and comparison between populations

The benefit of Atezo+Bev+CP compared with Bev+CP demonstrated across all endpoints in the ITT population of IMpower150 was also observed in the ITT-WT population.

Table 13: Summary of efficacy – all populations of IMpower150 (updated analysis)

	ITT population		ITT-WT population	
	Atezo+Bev+CP	**Bev+CP**	**Atezo+Bev+CP**	**Bev+CP**
Overall survival	**n=400**	**n=400**	**n=359**	**n=337**
Patients with event, n (%)	192 (48.0)	230 (57.5)	179 (49.9)	197 (58.5)
Median OS, months (95% CI)	19.8 (17.4, 24.2)	14.9 (13.4, 17.1)	19.2 (17.0, 23.8)	14.7 (13.3, 16.9)
Hazard ratio (95% CI) p value	0.76 (0.63, 0.93) p=0.0060		0.78 (0.64, 0.96) p=0.0164	
Progression-free survival	**n=400**	**n=400**	**n=359**	**n=337**
Patients with event, n (%)	291 (72.8)	355 (88.8)	298 (88.4)	263 (73.3)
Median PFS, months (95% CI)	8.4 (8.0, 9.9)	6.8 (6.0, 7.0)	6.8 (6.0, 7.1)	8.3 (7.7, 9.8)
Hazard ratio (95% CI) p value	0.59 (0.50, 0.69) p<0.0001*		0.59 (0.50, 0.70) p<0.0001	
Objective response rate	**n=397**	**n=393**	**n=356**	**n=332**
Responders, n (%)	28 (68.3)	57 (90.5)	197 (55.3)	134 (40.4)
Odds ratio (95% CI)	1.94 (1.46, 2.58)		1.83 (1.35, 2.49)	
Complete response, n (%) (95% CI)	11 (2.8) (1.4, 4.9)	11 (2.8) (1.4, 4.9)	9 (2.5) (1.2, 4.7)	2 (0.6) (0.1, 2.2)
Partial response, n (%) (95% CI)	213 (53.7) (48.6, 58.6)	213 (53.7) (48.6, 58.6)	188 (52.8) (47.5, 58.1)	132 (39.8) (34.5, 45.3)
Duration of response	**n=224**	**n=158**	**n=197**	**n=134**
Patients with event, n (%)	136 (60.7)	140 (88.6)	120 (60.9)	116 (86.6)
Patients with ongoing response at CCOD, n (%)	88 (39.3)	18 (11.4)	77 (39.1)	18 (13.4)
Median DOR, months (95% CI)	11.5 (8.9, 15.7)	6.0 (5.5, 6.9)	11.5 (8.9, 16.2)	6.4 (5.7, 7.0)
HR (95% CI) p value	0.41 (0.32, 0.53) p<0.0001		0.45 (0.34, 0.59) p<0.0001	

HR: stratified analysis; p value: log-rank
DOR, duration of response; OS, overall survival; PFS, progression-free survival
CCOD: 22 January 2018

Patient-reported outcomes

Data for patient reported outcomes were presented at the American Society of Clinical Oncology annual meeting in 2018 (67).

PRO questionnaire completion rates for the EORTC QLQ-C30 at baseline were 90.6%, and 91.8% in Arms B and C, respectively, and remained at ≥70% completion until Cycle 20 in the Bev+CP arm and Cycle 25 in the Atezo+Bev+CP arm (67, 69).

Patient-reported global health status, physical functioning and disease burden symptom scores were comparable between treatment arms at baseline (Cycle 1 Day 1); patients reported generally moderate to high functioning and minimal symptom burden. Patients also reported generally minimal lung cancer symptom burden (i.e., cough, dyspnoea,

arm/shoulder pain, chest pain, fatigue), thus limiting the opportunity to demonstrate a large magnitude of improvement within the PRO symptom scores.

Patient-reported HRQoL and physical functioning

Patients on average did not report a clinically meaningful worsening of global health status or physical functioning scores (≥10-point decrease in mean score) at any point through Cycle 13 of treatment at which point there are fewer than 25% of patients in the baseline sample of the Bev+CP arm, therefore comparisons between arms should be interpreted with caution. Mean global health status and physical functioning scores decreased numerically (worsened) during Cycles 2 to 6 and then increased numerically (improved) following completion of chemotherapy (Cycles ≥6).

Patient-reported treatment-related symptoms

Overall, patients did not report clinically meaningful worsening (≥10-point increase from baseline) at any point on treatment for multiple treatment-related symptoms including fatigue, constipation, diarrhoea, nausea/vomiting, haemoptysis, dysphagia, and sore mouth through Cycles 13, and 18 for the Bev+CP and Atezo+Bev+CP arms, respectively. A clinically meaningful worsening was observed across treatment arms for both patient-reported peripheral neuropathy and alopecia; large mean increases from baseline (≥60-point increase for alopecia; ≥30-point increase for peripheral neuropathy) were seen initially in both treatment arms and attenuated over time at similar time points across arms.

Patient-reported lung cancer-related symptoms

No differences were observed between treatment arms in the time to deterioration of each individual lung cancer symptom, i.e., cough, dyspnoea single-item, dyspnoea multi-item, chest pain, and pain in arm/shoulder. Median time-to-deterioration was not reached in any arm across symptom scores for analyses conducted in the ITT population. Furthermore, mean patient-reported lung cancer–related symptom scores decreased in all treatment arms from baseline through Cycle 13, with patients in all arms demonstrating a clinically meaningful improvement in coughing scores.

Summary of patient-reported outcomes

The prolonged PFS and improved OS observed with Atezo+Bev+CP vs Bev+CP in the IMpower150 study was achieved while baseline HRQoL and physical functioning were maintained, despite a higher incidence of treatment-related adverse event (see Section B.2.10). The PRO data reflect a minimal treatment burden across arms; treatment-related

symptom scores numerically decreased and, in most cases, returned to baseline following the completion of chemotherapy.

Overall, the PRO data support the positive benefit-risk profile demonstrated in the clinical data with Atezo+Bev+CP in metastatic non-squamous NSCLC.

B.2.7 Subgroup analyses

Pre-planned subgroup analyses were carried out by baseline risk factors in the ITT population, including by PD-L1 expression, patients with EGFR mutant and ALK positive NSCLC and the presence of liver metastases. Efficacy results from the subgroup analyses of IMpower150 have been published (65) and are summarised in Appendix E.

Median OS was longer with Atezo+Bev+CP compared with Bev+CP in all PD-L1 expression subgroups analysed, demonstrating a numerical and clinically meaningful improvement consistent to that observed in the overall ITT population. The point estimates of the OS HR in the TC3 or IC3, TC2/3 or IC2/3 and TC1/2/3 or IC1/2/3 groups were 0.67, 0.78, and 0.73, respectively. A numerical improvement in OS was observed in the subgroup with low or negative PD-L1 expression (TC0/1/2 and IC0/1/2; median: 19.1 months vs. 14.9 months; unstratified HR: 0.80; 95% CI: [0.65, 0.99]).

For the ITT-WT population (relevant to the comparison with pembrolizumab reported in B.2.8), median OS was longer with Atezo+Bev+CP compared with Bev+CP in all PD-L1 expression subgroups analysed, demonstrating, a numerical and clinically meaningful improvement. Median OS was longer for Atezo+Bev+CP compared with Bev+CP in patients with high levels of PD-L1 expression (i.e. TC or IC3, equivalent to patients with TPS >50%) (median OS 25.2 months vs. 15.0 months, unstratified HR=0.70, 95% CI: 0.43, 1.13).

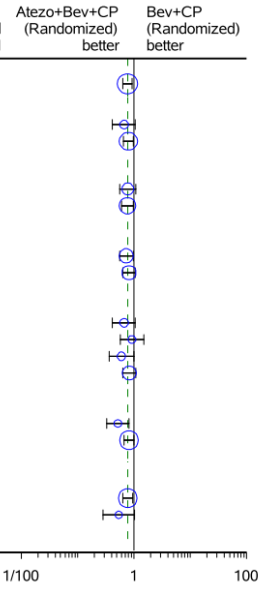
Among EGFR mutant and ALK-positive NSCLC patients, a total of 46 death events had been observed in the Atezo+Bev+CP and Bev+CP arms for an overall event/patient ratio of 44.2%. The unstratified HR was 0.54 (95% CI: 0.29, 1.03); median survival could not be estimated for the Atezo+Bev+CP arm and was 17.5 months (95% CI: 10.4, NE) in the Bev+CP arm.

Liver metastases, a known poor prognostic factor for NSCLC, was included as a stratification factor in IMpower150. Patients with liver metastases at enrolment demonstrated a clinically meaningful OS benefit for Atezo+Bev+CP (n=52) vs. Bev+CP (n=57); the unstratified HR (95% CI) for OS was 0.52 (0.33, 0.82).

PFS subgroup analysis was consistent with the OS subgroup analysis and can be found in Appendix E.

Figure 5: Summary of key subgroup analysis of overall survival – ITT population

Baseline Risk Factors	Total n	Bev+CP (Randomized) (N=400) n	Events	Median (Months)	Atezo+Bev+CP (Randomized) (N=400) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	800	400	230	14.9	400	192	19.8	0.77	(0.63, 0.93)
TC3 or IC3 vs TC0/1/2 and IC0/1/2									
TC3 or IC3	148	73	40	13.2	75	32	25.2	0.67	(0.42, 1.06)
TC0/1/2 and IC0/1/2	652	327	190	14.9	325	160	19.1	0.80	(0.65, 0.99)
TC2/3 or IC2/3 vs TC0/1 and IC0/1									
TC2/3 or IC2/3	273	133	72	15.0	140	67	22.5	0.78	(0.56, 1.09)
TC0/1 and IC0/1	526	266	158	14.9	260	125	19.2	0.77	(0.61, 0.97)
TC1/2/3 or IC1/2/3 vs TC0 and IC0									
TC1/2/3 or IC1/2/3	404	195	104	16.4	209	92	24.0	0.73	(0.55, 0.97)
TC0 and IC0	396	205	126	14.3	191	100	17.1	0.82	(0.63, 1.06)
TC/IC 4 Incremental Subgroups									
TC3 or IC3	148	73	40	13.2	75	32	25.2	0.67	(0.42, 1.06)
TC2/3 or IC2/3 exclude TC3 or IC3	125	60	32	16.7	65	35	17.6	0.92	(0.57, 1.49)
TC1/2/3 or IC1/2/3 exclude TC2/3 or IC2/3	137	67	36	16.4	70	25	24.0	0.60	(0.36, 1.01)
TC0 and IC0	390	200	122	14.4	190	100	17.1	0.83	(0.64, 1.08)
Liver Metastasis at Enrollment									
Yes	109	57	47	9.4	52	31	13.3	0.52	(0.33, 0.82)
No	691	343	183	17.0	348	161	20.4	0.82	(0.66, 1.01)
EGFR Wild Type/ALK Negative									
Yes	696	337	197	14.7	359	179	19.2	0.78	(0.64, 0.96)
No	104	63	33	17.5	41	13	NE	0.54	(0.28, 1.03)



B.2.8 Meta-analysis

Only one RCT (IMpower150) has investigated the efficacy and safety of Atezo+Bev+CP. As such, a meta-analysis could not be conducted and an indirect treatment comparison (ITC) was considered to be appropriate.

B.2.9 Indirect and mixed treatment comparisons

Key information for the indirect and mixed treatment comparisons

- An indirect treatment comparison (ITC) was necessary to enable Atezo+Bev+CP to be compared with UK standard of care therapies in first-line non-squamous metastatic NSCLC. The ITC followed NICE DSU recommendations and appropriate methodology.
- A network-meta analysis (NMA) was only feasible for the comparison vs. pemetrexed-based regimens. A fractional polynomial NMA approach was implemented to account for the different mechanism of action between cancer immunotherapy and chemotherapies, as well as the presence of non-proportional hazards between Atezo+Bev+CP and pemetrexed-based chemotherapy.
- For pembrolizumab, no common treatment arm was available to enable a comparison within the NMA. As such, a matching adjusted indirect comparison (MAIC) was conducted to enable the comparison to pembrolizumab in PD-L1 high patients (>50% tumour proportion score, TC/IC 3)
- Results of the NMA demonstrate that there is a clinically meaningful expected survival difference in the ITT population in favour of Atezo+Bev+CP versus pemetrexed-based

regimens in terms of both OS and PFS. NMA results in the subgroups of patients with PD-L1 low or negative expression or EGFR/ALK mutation are consistent with the ITT analyses, demonstrating a difference in favour of Atezo+Bev+CP versus pemetrexed-based treatments.

- NMA scenario analyses excluding the PARAMOUNT study from the network of evidence, which is likely to introduce selection bias in favour of pemetrexed plus platinum with pemetrexed maintenance due to different study design and different inclusion criteria, demonstrate a more consistent and clinically plausible benefit for Atezo+Bev+CP versus pemetrexed plus platinum with pemetrexed maintenance
- The MAIC versus pembrolizumab in PD-L1 high patients demonstrated that [redacted] Results of the MAIC are however associated high uncertainty and with limitations. These result primarily from the differences in study populations and the fact that OS and PFS data were not presented separately in KEYNOTE-024 for squamous and non-squamous patients, leading to potentially conservative estimates for Atezo+Bev+CP.
- Nonetheless, as is common in ITCs, the ITC analyses (NMA and MAIC) are associated with a series of uncertainties and limitations, relating primarily to the availability of evidence, the comparability of the identified studies, limitations relating to subgroup comparisons and the extrapolation of modelled outcomes. These are discussed at the end of Section B.2.9.

In the absence of head-to head trial evidence of Atezo+Bev+CP vs. UK relevant comparators of interest, an ITC was necessary to enable a comparison to be made for the purposes of this submission.

Systematic literature review

A SLR was conducted to identify relevant studies to inform indirect comparisons between the interventions of interest. The search strategy was pre-specified in terms of population, interventions, comparisons, outcomes, and study design, and is outlined in Appendix D.

Comparators of interest

The comparators of interest included in the SLR reflect the comparators considered in the decision problem addressed in this submission (please see Section B.1.1). The following comparators of interest were included for the current evidence submission, in patient populations aligned with their marketing authorisation and reimbursement from NICE:

Table 14: Comparators of interest

Comparator of interest	Patient population
Atezo+Bev+CP	Patients regardless of PD-L1 expression (ITT), including patients with low or negative PD-L1 expression (TC/IC0,1,2) and patients with EGFR or ALK mutations
Pemetrexed plus platinum (carboplatin or cisplatin)	
Pemetrexed plus platinum (carboplatin or cisplatin) plus pemetrexed maintenance	
Pembrolizumab	PD-L1 high patients (>50% tumour proportion score, TC/IC 3)), excluding patients with EGFR or ALK mutations

Please note that additional interventions were included in the eligibility criteria for the SLR, to account for ongoing trials of atezolizumab combinations in first-line NSCLC, as well as for upcoming comparator interventions in first-line NSCLC. However, these interventions are not included in the scope of this appraisal; the relevant studies were taken into account in the SLR for the purpose of informing future updates of the NMA network of evidence.

Criteria used in trial selection

The inclusion and exclusion criteria and the study selection process are described in Appendix D (please see Section D.1.1 for the PICOS eligibility criteria and PRISMA flow diagram). Please note that some key assumptions were made in the eligibility criteria for the SLR and NMA (these are also reported in Appendix D):

- Pemetrexed plus platinum (either carboplatin or cisplatin) was considered as one intervention in the SLR and NMA. This is consistent with the NMA conducted in the recent pembrolizumab NICE appraisal in this indication (42), whilst it was also validated with ten UK clinicians through an advisory board and subsequent follow-up.
- Pemetrexed maintenance therapy was assumed to be administered after pemetrexed plus platinum (either carboplatin or cisplatin). This is not entirely aligned with the NICE recommendation for pemetrexed maintenance therapy (only recommended after pemetrexed plus cisplatin) (49). However, the same assumption was taken in the recent pembrolizumab NMA (42), so this was a pragmatic approach in the structure of our network of evidence, which would ensure consistency across NICE appraisals in this indication. This assumption of clinical similarity between the regimens was also validated by ten UK clinical experts, during an advisory board organised by Roche.

- IMpower150 included untreated patients with Stage IV non-squamous NSCLC, while many recent published first-line NSCLC studies include populations of mixed histology and stages (Stage IIIB and Stage IV). This is something that had to be accounted for. As such within the SLR and NMA, studies of mixed populations (e.g. different stages, types or histology of carcinoma) were only eligible if outcomes were reported separately for the population of interest or at least 90% of patients within the study population cohort have Stage IV non-squamous NSCLC. This was considered appropriate in order to not disregard recent and relevant evidence, whilst also ensuring comparability of the included studies.

Network meta-analysis (NMA) feasibility assessment

Table 15 shows the trials identified in the SLR, which were considered in a feasibility assessment for a NMA.

Table 15: Trials considered in the feasibility assessment and the interventions assessed in each trial

Trial identifier	**ATZ+CARB+PAC+BEV then ATZ+BEV maintenance ***	ATZ+CARB+PAC then ARZ maintenance	PAC+CARB+BEV then BEV maintenance	**PEM+CIS/CARB then PEM maintenance ***	PEMB+CARB+PEM then PEMB and PEM maintenance	**PEM+CIS then PLAC and BSC maintenance ***	**PEMB ***	Standard Chemo
IMpower150	x	x	x					
ERACLE			x	x				
KEYNOTE-021				x	x			
KEYNOTE-024							x	x
KEYNOTE-189				x	x			
PARAMOUNT				x		x		
PRONOUNCE			x	x				

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo
* Interventions in bold represent UK-relevant comparators

A NMA feasibility analysis was conducted for each outcome of interest. The outcomes of interest that were considered in the NMA are the following:

- Overall survival (OS)
- Progression free survival (PFS)

- Duration of response
- Time to treatment discontinuation (TTD)
- Objective response rate (ORR)
- All Grade ≥3 adverse effects
- Treatment-related adverse effects
- Treatment-related adverse effects leading to discontinuation
- Health-related quality of life (HRQoL)

The NMA feasibility analysis demonstrated that from the identified studies, a connected network of evidence was only feasible for the comparison vs. pemetrexed-based regimens, assuming that all of the trials are comparable and provide sufficient data to contribute to a NMA. Six of the seven identified trials contribute to the connected network via one or more common comparators.

The comparison with pembrolizumab in PD-L1 high patients (>50% tumour proportion score, TC/IC 3) (72) was not feasible via a NMA, as study KEYNOTE-024 was not able to be connected to the network of evidence. Therefore, a MAIC was conducted to enable the comparison with pembrolizumab in PD-L1 high patients. The MAIC vs. pembrolizumab is described later in this section.

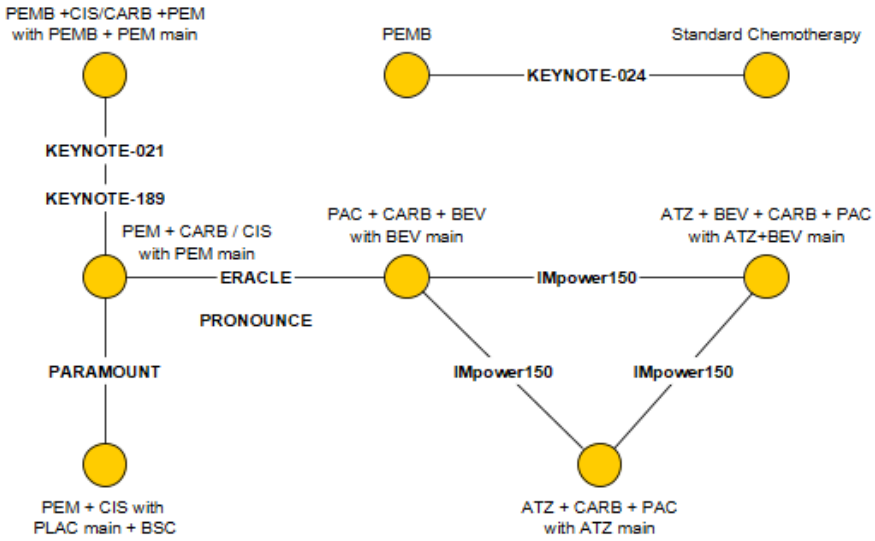
From the identified studies, following the NMA feasibility assessment (see Appendix D), the following connected networks were constructed:

1. OS – network with 6 studies: IMpower150, ERACLE, PRONOUNCE, PARAMOUNT, KEYNOTE-189, and KEYNOTE-021. This network was analysed using time-to-event data and fractional polynomial (FP) method (see “Methods of analysis” later in this Section for full context and details).
2. PFS – network with 6 studies: same studies as above. This network was also analysed using time-to-event data and FP method (see “Methods of analysis” later in this Section for full context and details).
3. ORR – network with 5 studies: IMpower150, ERACLE, PRONOUNCE, KEYNOTE-189, and KEYNOTE-021. This was analysed using standard NMA with response as a binomial outcome.
4. Adverse events leading to discontinuation – network with 4 studies: IMpower150, PRONOUNCE, KEYNOTE-189, and KEYNOTE-021. PARAMOUNT only reported these types of events for the maintenance phase and was therefore not considered comparable. This network was analysed using standard NMA with adverse events as a binomial outcome.

Please see in Figure 6 to Figure 8 below the connected networks of studies for each outcome of interest. Study names in grey (Figure 7 and Figure 8) denote that these studies were not included and did not contribute to the connected network. This is a result of the NMA feasibility assessment for each outcome of interest, presented in detail in Appendix D.

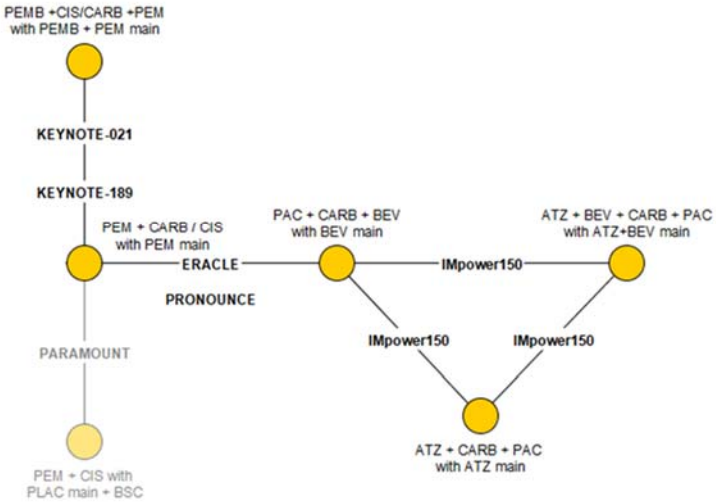
There were insufficient data to create a network for 1-year survival, duration of response, TTD, treatment related AEs, grade ≥3 AEs and HRQoL. Please see Appendix D for more details on the NMA feasibility assessment for these outcomes.

Figure 6: Network of studies informing the NMA – OS and PFS



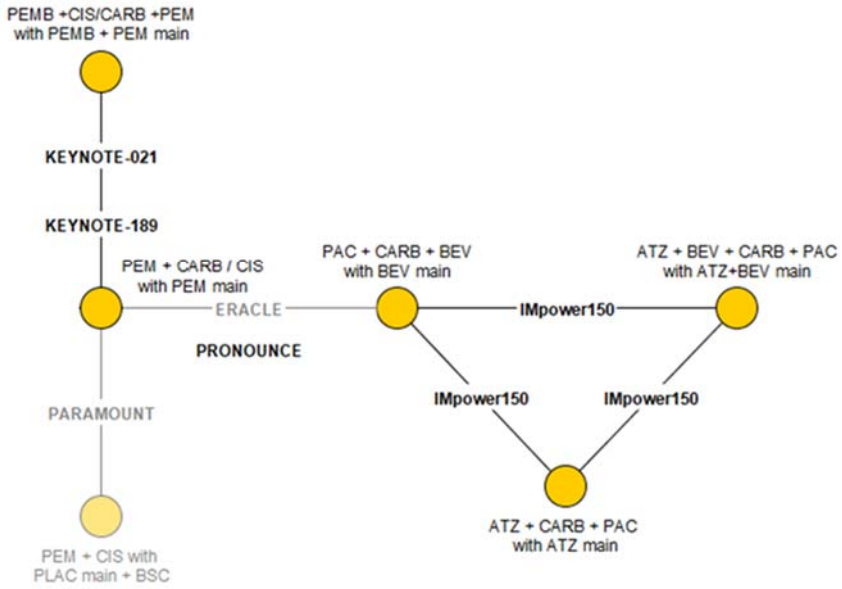
ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 7: Network of studies informing the NMA – Objective response rate (ORR)



ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 8: Network of studies informing the NMA - AEs leading to discontinuation



ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

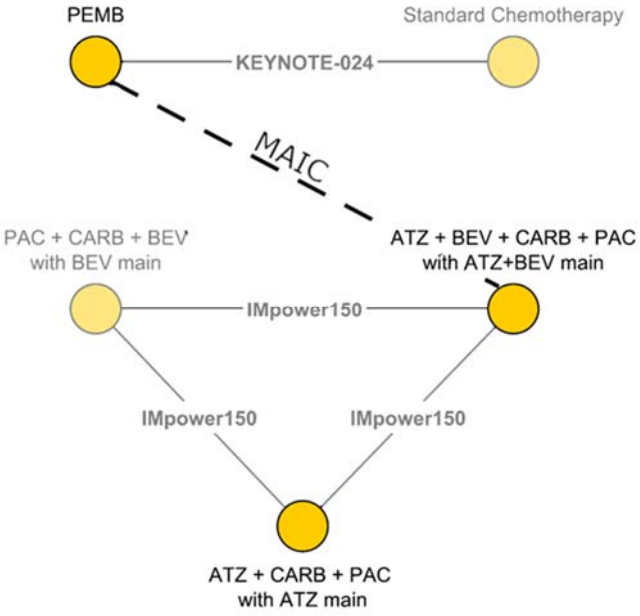
MAIC – comparison with pembrolizumab

For the comparison with pembrolizumab, the identified study (KEYNOTE-024) included a control arm of five standard of care (SOC) chemotherapy treatments. However, baseline characteristics and outcome data are not available for each of these arms separately. The only way KEYNOTE-024 could be included in the main network is to assume that all

chemotherapy regimens are equivalent. This assumption was not considered to be appropriate and therefore, this study does not share a common treatment arm with any of the other trials and sits outside of the main network.

However, the comparison between Atezo+Bev+CP in IMpower150 and pembrolizumab in KEYNOTE-024 in patients with high PD-L1 expression (>50% tumour proportion score, TC/IC 3) is explicitly included in the NICE final scope and as such is important for the current NICE evidence submission. As such, the comparison between IMpower150 and KEYNOTE-024 in this subgroup of patients was conducted via a MAIC, following the NICE DSU recommendations (73). A schematic of the network for the MAIC comparison is shown in Figure 9. More details on the MAIC are provided in Appendix D.

Figure 9: Network diagram for the MAIC analysis in patients with PD-L1 high expression (>50% tumour proportion score, TC/IC 3)



ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; MAIN, maintenance; PAC, paclitaxel; PEMB, pembrolizumab.

Other outcomes were also considered in the comparison to pembrolizumab in PD-L1 high patients: objective response rate, discontinuation due to adverse events, treatment-related adverse events, and adverse events (Grade ≥3). These were considered binary outcomes and a standard generalized linear model approach was implemented following NICE DSU recommendations (73).

NMA versus pemetrexed-based interventions – networks and analyses performed

Base case network - ITT population

The primary population of interest for the NMA versus pemetrexed-based interventions is adult patients over 18 years of age with Stage IV non-squamous NSCLC who have not received prior treatment (i.e. regardless of level of PD-L1 expression). This population is considered in the ITT NMA versus pemetrexed-based interventions and reflects the ITT population of IMpower150, as well as the anticipated license for Atezo+Bev+CP. The ITT population also reflects the marketing authorisation and NICE reimbursement for pemetrexed-based interventions, as well as the population in the studies including pemetrexed-based chemotherapy. As such, the ITT population provides a more robust evidence base for the NMA. For analyses of safety data and adverse events, data for the safety population were used. Figure 6 - Figure 8 present the base case networks of evidence for each outcome of interest.

NMA subgroup analyses

NMA subgroup analyses were conducted versus pemetrexed-based interventions for the outcomes of OS and PFS, given that these outcomes are the key drivers in the economic model. The subgroup analyses were conducted for the following populations, which are key subgroups of interest in our NICE evidence submission (see Section B.1.1):

- Patients with low or negative PD-L1 expression, to account for the subgroup of patients that are not eligible for pembrolizumab as a first-line therapy for advanced or metastatic NSCLC. This is effectively the subgroup of patients for whom pemetrexed-based chemotherapy is standard of care in the UK, and have an unmet need for a cancer immunotherapy option
- Patients with EGFR/ALK mutation, as this is a subgroup of interest explicitly stated in the final scope from NICE

Subgroup results in terms of PD-L1 expression were reported only in IMpower150 and KEYNOTE-189, out of the studies included in the network. Results for EGFR/ALK positive patients were reported in IMpower150 only and these patients were excluded from the KEYNOTE studies.

As such and in order to be able to perform the above subgroup NMAs, an assumption had to be made for the remaining studies including pemetrexed-based interventions (ERACLE, PARAMOUNT, PRONOUNCE). This assumption is that level of PD-L1 expression and the presence of EGFR/ALK mutations are not effect modifiers for pemetrexed-based chemotherapy in these studies. This was necessary in order for a connected network to be

established and to be able to conduct a comparison between Atezo+Bev+CP and pemetrexed-based regimens within these patient subgroups, which are of interest to our NICE evidence submission.

The assumption that EGFR mutation is not an effect modifier for chemotherapy efficacy is supported by the literature (74, 75). With regards to the level of PD-L1 expression not being an effect modifier for chemotherapy, the OAK study in second-line NSCLC and KEYNOTE-189 in first-line NSCLC have demonstrated that there is no significant effect of level of PD-L1 expression on the clinical efficacy of chemotherapy. (76, 77) These assumptions were also discussed with four UK clinical experts who validated these are reasonable and necessary in order to be able to perform an indirect treatment comparison within these subgroups.

For PD-L1 high patients, as already outlined, a MAIC will be implemented versus pembrolizumab. More details on the rationale and methodology subgroup analyses are provided in Appendix D.

NMA Scenario Analyses

Scenario analyses were conducted for the outcomes of OS and PFS, for the following networks:

- Base case network excluding PARAMOUNT study. PARAMOUNT has a different study design compared to all the other studies in the network, which might lead to bias. In PARAMOUNT, a single cohort of patients all received induction pemetrexed-based chemotherapy. Following the induction, patients who were alive and achieved a certain level of response were randomised into one of two maintenance therapy arms (pemetrexed or placebo maintenance). Only 539 of the 900 patients included in the induction phase were randomised. PFS and OS data were only reported for patients who responded to induction therapy. This is a selection of patients that have responded to induction pemetrexed-based chemotherapy, who are highly likely to be fitter and healthier and more likely to respond to any therapy, in comparison to the patients included in the other studies in the network. As such, the PARAMOUNT study population is fundamentally different from other study populations, and likely to lead to selection bias. It is important to note that PARAMOUNT was included in the base-case network to enable the comparison with pemetrexed plus platinum without pemetrexed maintenance, as this is the only study connecting pemetrexed plus platinum to the network of evidence. However, it is clear that it may lead to bias in favour of pemetrexed plus platinum with pemetrexed maintenance. As such, a sensitivity

analysis is conducted which excludes PARAMOUNT to assess its impact on the NMA results.

- Base case network excluding KEYNOTE studies. KEYNOTE-021 and KEYNOTE - 189 assessed pembrolizumab in combination with pemetrexed-based chemotherapy, which was not of interest as a comparator in our NICE evidence submission. These studies were included in the NMA in order to provide additional information on the pemetrexed-based regimens, based on their control arm. However, the KEYNOTE studies were the only studies in the network that allowed treatment crossover following progression, which might impact the OS outcome. In addition, these studies also had a shorter follow-up time (KEYNOTE-189 10.5 months, KEYNOTE-021 18.7 months) relative to the other studies, and consequently the extrapolation proved difficult and highly dependent on the model used. As such, a sensitivity analysis removing these studies is conducted.
- Base case network using an NMA model approximating proportional hazards (PH) (FP Exponential model), to assess the impact of using a model approximating PH on the NMA results

See Appendix D for more details on the rationale and methodology scenario analyses.

Methods of analysis

NMA

The outcomes of interest were analysed using Bayesian random effects (RE) and fixed effects (FE) NMA methods. Chemotherapy and immunotherapy do not share the same survival kinetics, and patients treated with chemotherapy show early antitumor effects while cancer immunotherapy shows a delayed but sustained in clinical effect. This effect has been demonstrated in IMpower150, based on the inspection of log-cumulative hazard plots (see Section B.3.3) as well as in studies of atezolizumab compared to standard chemotherapy (78, 79). As such, it was considered inappropriate to assume proportional hazards for time-to-event outcomes (OS, PFS). Fractional polynomials (FP) were therefore used to model the hazards of the different treatments, as these models do not require the assumption of proportional hazards (80, 81). In addition, sensitivity analyses were conducted that restricted the modelling space to proportional hazard models.

For the two binomial outcomes (ORR, AEs leading to discontinuation), a standard generalized linear model approach was used following NICE DSU recommendations (73). More details on the methodology used to implement the NMA can be found in Appendix D.

MAIC

The MAIC uses individual patient data (IPD) from IMpower150 for Atezo+Bev+CP, to match baseline summary statistics reported for pembrolizumab monotherapy in study KEYNOTE-024. After matching, by using an approach similar to propensity score weighting, the two treatment outcomes are compared across balanced trial populations. The MAIC, addresses the issue of no common comparator (no network connectivity) for the comparison to pembrolizumab in the PD-L1 high population.

The MAIC has been performed based on all covariates that were reported in KEYNOTE-024, therefore has used all available evidence. However, there is an unknown amount of bias in the estimates from this indirect comparison, due to unreported differences in study populations and effect modifiers that have not been included in the MAIC. In addition, an important limitation of the MAIC analysis is the lack of Kaplan-Meier data for subgroups by histology in KEYNOTE-024. Histology status can be an effect modifier, which has not been accounted for in this analysis, due to lack of data. This is likely to result in conservative estimates for Atezo+Bev+CP and is discussed in the limitations section for the MAIC. Additional details on the MAIC are reported in Appendix D.

For the comparison to pembrolizumab in binary outcomes, (ORR, Grade ≥3AEs, treatment-related AEs, AEs leading to withdrawal)), a standard generalized linear model approach was used following NICE DSU recommendations (73).

Model Selection

The process of model selection for the NMA and MAIC was sequential, and details are reported in Appendix D. The selected models for each of the analyses are listed below:

- In the NMA for OS and PFS, the fractional polynomial fixed effects model with P1=0 (Weibull) was the best statistical fit by DIC, and also in terms of visual inspection of the fitted curves and clinical plausibility of the long-term outcomes. The same NMA model specification was used for the ITT and subgroup analyses, as the underlying relationship between treatments was not expected to differ in subgroups of patients. For additional details on NMA approach to model selection, validation and assessment of heterogeneity see Appendix D.
- For the additional outcomes included in the NMA, fixed effect models were chosen. Additional details can be found in Appendix D.
- For the MAIC, the reweighted data for the OS and PFS outcomes, were extrapolated following the NICE DSU guidance (82). Based on assessment of statistical fit, visual fit and clinical plausibility, the Exponential model was selected for the extrapolation of

OS and the Log-Logistic model for PFS. More details are presented in Appendix D.

NMA results – ITT population

Results of the NMA for OS and PFS are presented (i) in forest plots of relative difference in expected survival at specific time points, as well as (ii) in terms of resulting hazard ratios (HRs) over time. Forest plots demonstrate the relative difference in expected OS and PFS in months, between Atezo+Bev+CP and the other interventions of interest over a 60 and 30 month period respectively. The expected OS and PFS were calculated as the area under the estimated survival curve over a 60 or 30-month interval. These time points are consistent with the NICE appraisal of atezolizumab in second-line NSCLC (53) and are considered appropriate in terms of robustness of the estimated survival differences for each endpoint. The forest plots represent the posterior median (dots) and 95% credible interval (solid lines) of the difference in expected survival between treatments, with a dashed line at x=0 representing no difference.

As described in the section on model selection and in Appendix D, the fixed effects 1st order P1=0 (Weibull model) was chosen as the most suitable model for both OS and PFS.

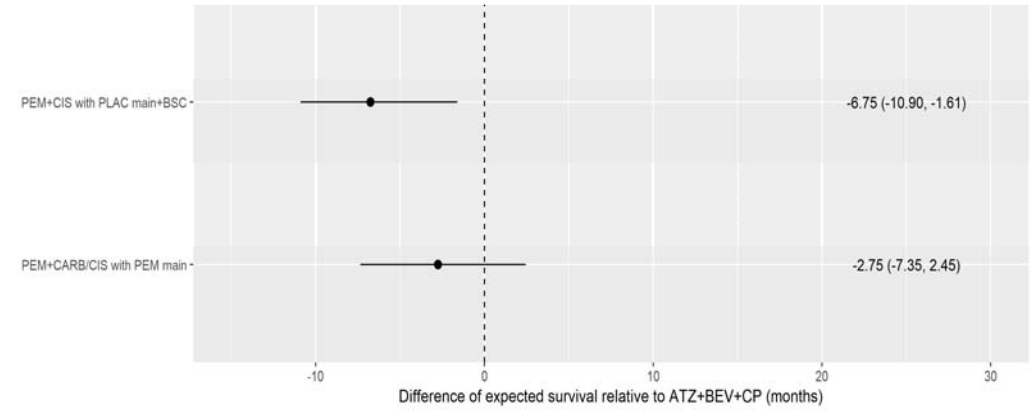
OS time-to-event analysis

The forest plot of the expected survival difference is presented in Figure 10, and the HRs in Figure 11. Atezo+Bev+CP had longer expected OS compared to pemetrexed plus carboplatin/cisplatin, [redacted].

The evidence was more uncertain relative to pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance in the base case network, [redacted] The comparison of expected OS between Atezo+Bev+CP and pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance at 60 [redacted]

It should be noted however that the base case NMA network includes PARAMOUNT, which is likely to introduce bias in favour of pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance. As such, the results vs. pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance should be interpreted with caution and in combination with the NMA scenario analysis excluding the PARAMOUNT study.

Figure 10: Forest plot of the expected mean overall survival difference relative to Atezo+Bev+CP (time horizon 60 months)



ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 11: Hazard ratios over time for overall survival compared to Atezo+Bev+CP

[redacted]

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

PFS time-to-event analysis

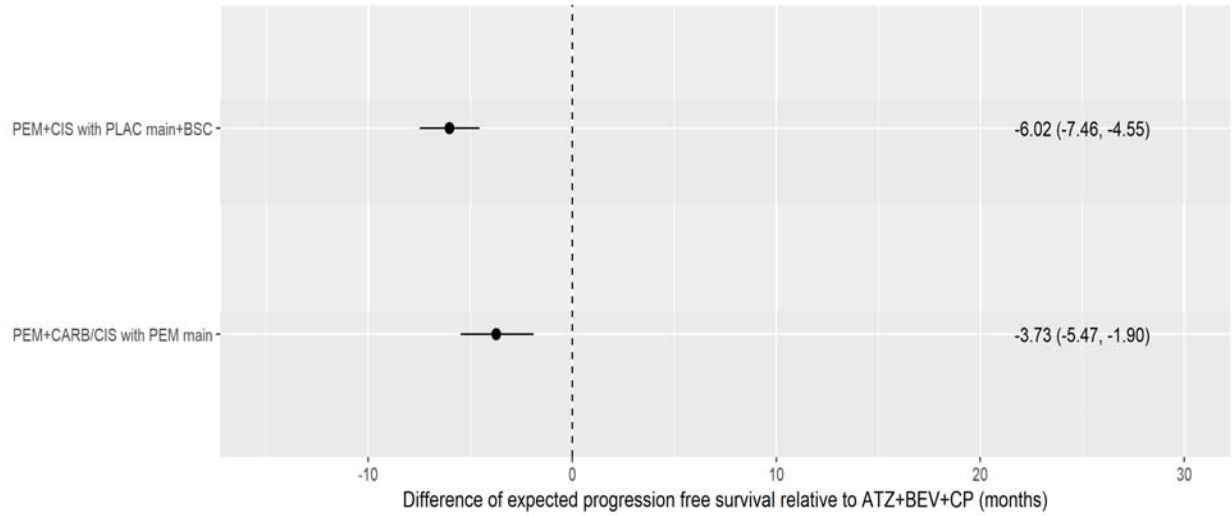
The forest plot of the expected PFS difference at 30 months is shown in When considering expected PFS at 30 months, the evidence indicated that [redacted]. For the comparison with pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance, [redacted]

Figure 12 and the relative HRs in Figure 13.

When considering expected PFS at 30 months, the evidence indicated that [redacted]. For

the comparison with pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance, [redacted]

Figure 12: Forest plot of the expected progression free survival difference relative to Atezo+Bev+CP (time horizon 30 months)



ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 13: Hazard ratio over time for progression free survival relative to Atezo+Bev+CP

[redacted]

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

NMA results – additional outcomes considered

Results from the selected (fixed effect) standard NMA models demonstrated that [redacted]. For discontinuation due to AE, the results of the NMA model provide evidence that [redacted] Additional details and forest plots are provided in Appendix D.

NMA results – subgroup analyses

The results of the NMA subgroup analyses (PD-L1 low or negative patients, patients with EGFR/ALK positive) are provided below. Additional information, as well as forest plots with expected survival difference, can be found in Appendix D.

Comparison to pemetrexed plus platinum

In the EGFR/ALK positive subgroup, [redacted] For PFS for the EGFR/ALK+ sub-group, [redacted] In terms of the estimated differences in expected OS, there is a more pronounced difference in favour of Atezo+Bev+CP in the EGFR/ALK positive subgroup compared to the ITT, but uncertainty is more evident and the confidence interval for expected OS difference crosses zero (see Appendix D).

For the PD-L1 low or negative subgroup, [redacted] The estimated differences in expected survival are consistent with the main analysis for the PD-L1 low or negative subgroup (see Appendix D).

Comparison to pemetrexed plus platinum with pemetrexed maintenance

For pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance, the results for both the EGFR/ALK+ and PD-L1 low or negative subgroups were broadly consistent with the ITT analysis for OS in terms of expected survival (see Appendix D). In terms of OS HR over time, across both subgroup analyses [redacted]

For PFS, [redacted] The difference in expected PFS is broadly consistent with

the main analysis for both subgroups (see Appendix D).

Similarly to the ITT population, for the NMA comparison to pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance, the result is likely confounded by the selection bias in favour of the pemetrexed-based intervention introduced by the PARAMOUNT study in the base case network. As such, results of the NMA network excluding PARAMOUNT should also be considered relevant for decision-making for this comparison to pemetrexed plus carboplatin/cisplatin with pemetrexed maintenance.

It should also be noted that the sub-group analyses results exhibit greater uncertainty compared to the ITT-level NMA, particularly for the EGFR/ALK+ group. This can at least partly be explained by the much smaller sample size in the IMpower150 population when subgroups of patients are analysed (see Table 16).

Table 16: IMpower150 Atezo+Bev+CP subgroup population sizes

Population, n (%)	IMpower150 Atezo+Bev+CP (ITT, Arm B, N = 400)
EGFR/ALK+	45 (11.25%)
PD-L1 low or negative	325 (81.2%5)

Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel

Figure 14: Relative hazard of OS over time; comparison of estimates using IMpower150 ITT population vs the EGFR/ALK+ subgroup of IMpower150

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 15: Relative hazard of PFS over time; comparison of estimates using IMpower150 ITT population vs the EGFR/ALK+ subgroup of IMpower150

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 16: Relative hazard of OS over time; comparison of estimates using IMpower150 ITT population with the PD-L1 low or negative subgroup of IMpower150

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 17: Relative hazard of PFS over time; comparison of estimates using IMpower150 ITT population with the PD-L1 low or negative subgroup of IMpower150

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

NMA results – scenario analyses

Scenario excluding KEYNOTE studies

The scenario analysis excluding the KEYNOTE studies demonstrated that the NMA results were not sensitive to the scenario excluding the KEYNOTE studies, for either the OS or the PFS endpoint (see Figure 18: Comparison of hazard ratios over time for overall survival for the full network and for the network excluding the PARAMOUNT study

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 19: Comparison of hazard ratios over time for progression free survival for the full network and for the network excluding the PARAMOUNT study

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 20 and Figure 21).

Scenario excluding PARAMOUNT

The scenario excluding PARAMOUNT however has a significant impact on results vs. pemetrexed plus platinum plus pemetrexed maintenance. There is a relatively large shift in the difference in expected survival for the comparison against pemetrexed plus platinum plus pemetrexed maintenance when PARAMOUNT is removed from the network (Figure 18: Comparison of hazard ratios over time for overall survival for the full network and for the network excluding the PARAMOUNT study

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 19: Comparison of hazard ratios over time for progression free survival for the full network and for the network excluding the PARAMOUNT study

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 20). PARAMOUNT has already been discussed as being different to the rest of the trials. Due to the selection of the randomised patient population (patients with better outcomes after induction therapy) this trial leads to a bias in favour of pemetrexed plus platinum plus pemetrexed maintenance. The impact of this bias can be seen in Figure 18

Therefore, it should be highlighted that including the PARAMOUNT study in the base case network for the NMA is a conservative approach, overestimating the clinical efficacy of pemetrexed plus platinum plus pemetrexed maintenance in the evidence network and subsequently in the economic model. However, PARAMOUNT was included in the base case network, to enable a comparison with pemetrexed plus platinum without pemetrexed maintenance, as this is the only study connecting pemetrexed plus platinum to the network of evidence. Nonetheless, the impact of excluding the PARAMOUNT study from the network of evidence on cost-effectiveness results is explored in a scenario analysis, the results of which should be considered relevant for decision-making for the comparison to pemetrexed plus platinum plus pemetrexed maintenance.

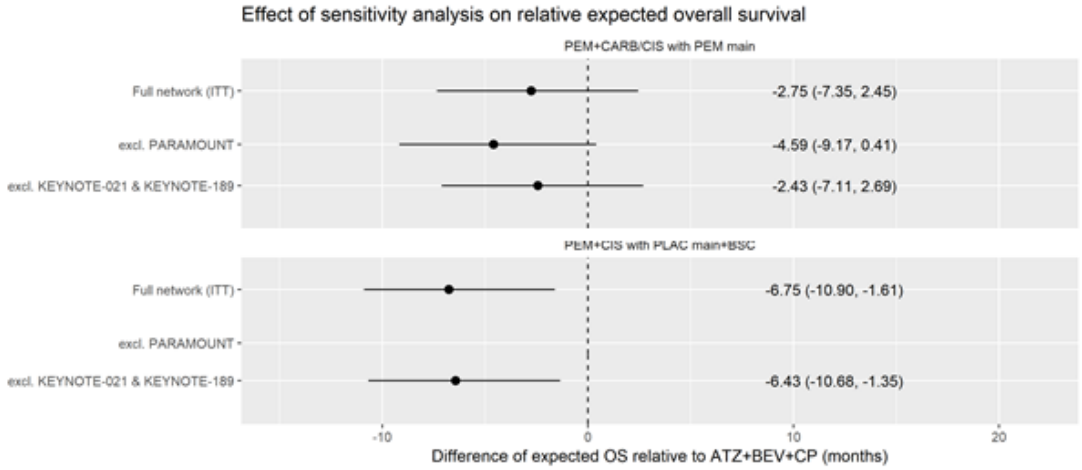
Figure 18: Comparison of hazard ratios over time for overall survival for the full network and for the network excluding the PARAMOUNT study

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 19: Comparison of hazard ratios over time for progression free survival for the full network and for the network excluding the PARAMOUNT study

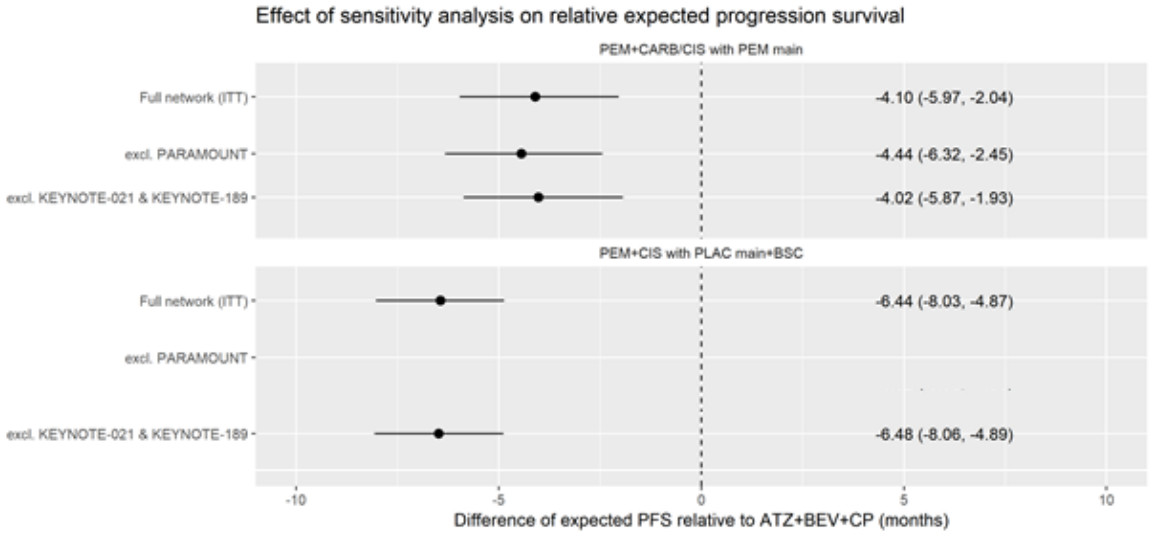
ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 20: Sensitivity analysis of the expected OS outcome (time horizon 60 months)



ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 21: Sensitivity analysis of the expected PFS outcome (time horizon 30 months)



ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

<u>Scenario using PH NMA model (Exponential FP model)</u>

The comparison of results from the base case FP NMA model versus results using a FP model approximating PH (Exponential FP model) demonstrates that the PH model results in stronger evidence in favour of Atezo+Bev+CP, for both OS and PFS. [redacted] The impact of using the PH NMA model on cost-effectiveness results is demonstrated in Section B.3.8.

Nevertheless, it should be reminded that the FP methodology was selected for the base case NMA analysis, based on its appropriateness to reflect the underlying evidence base and the presence of non-proportional hazards.

Figure 22: Impact of using an Exponential proportional hazard model on the estimated hazard ratio for the OS outcome

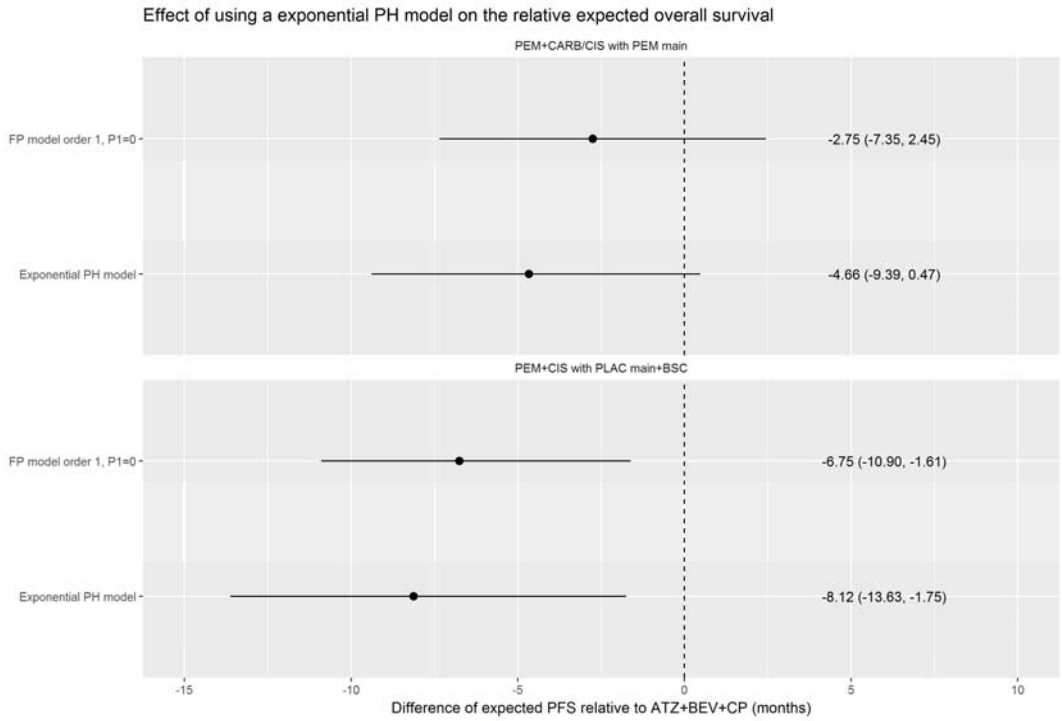
[redacted] izumab, mous 168

ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 23: Impact of using an Exponential proportional hazard model on the estimated hazard ratio of the PFS outcome

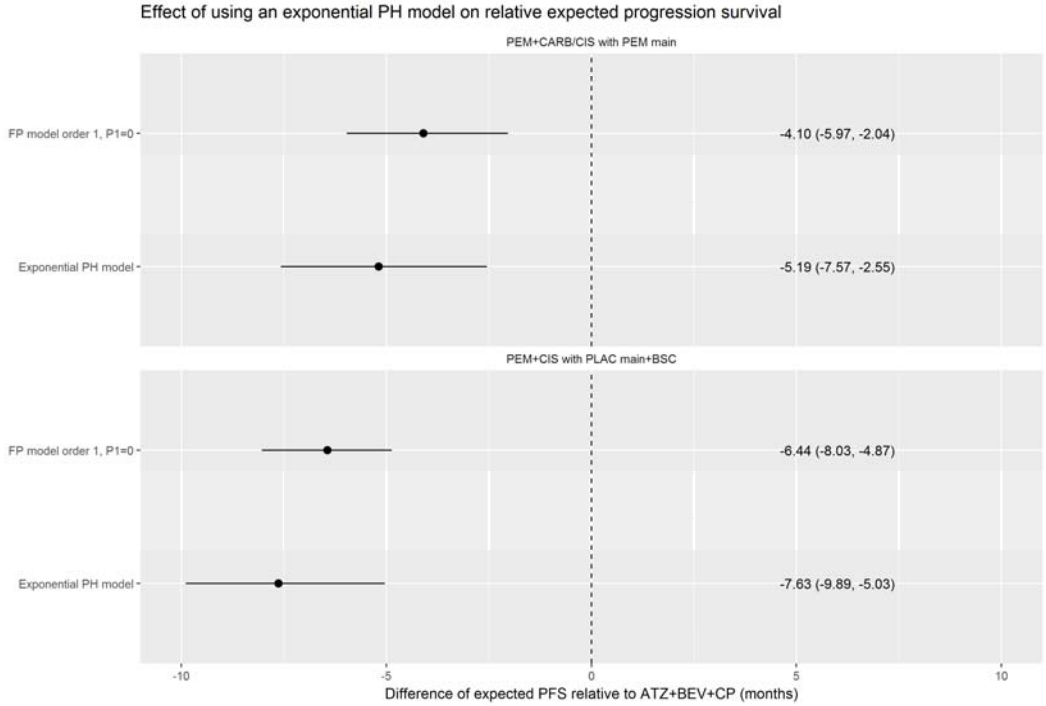
ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 24: Impact of using an Exponential proportional hazard model on the expected OS outcome (time horizon 60 months)



ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Figure 25: Impact of using an Exponential proportional hazard model on the expected PFS outcome (time horizon 30 months)



ATZ, Atezolizumab; BEV, bevacizumab; BSC, best supportive care; CARB, carboplatin; CIS, cisplatin; MAIN, maintenance; PAC, paclitaxel; PEM, pemetrexed; PEMB, pembrolizumab; PLAC, placebo

Results of the MAIC

The Kaplan-Meier curves for OS and PFS for pembrolizumab and Atezo+Bev+CP resulting from the MAIC, when using the weighted IMpower150 data, are shown in Figure 26 and

Figure 27 **respectively. The KM curves indicate that [redacted] The expected survival difference OS and PFS at 60 and 30 months respectively is shown in**

Figure 28; [redacted]

[redacted] For binary outcomes, the odds ratios and 95% confidence intervals are shown in

Figure 28 -

Figure **29**. Results demonstrate that [redacted] Therefore, it is evident from the MAIC results that [redacted].

Nonetheless, the results of the MAIC are also associated with high uncertainty and limitations; these result primarily from the differences in study populations, the fact that KEYNOTE-024 recruited less than 90% patients with non-squamous NSCLC and the fact that KM data for OS and PFS were not presented separately for squamous and non-squamous patients in KEYNOTE-024, resulting in potentially conservative MAIC estimates for Atezo+Bev+CP.

Figure 26: OS weighted KM plots Atezo+Bev+CP vs pembrolizumab (PD-L1 high expressors, MAIC)

Figure 27: PFS weighted KM plots Atezo+Bev+CP vs pembrolizumab (PD-L1 high expressors, MAIC)

Figure 28: Difference in expected OS and PFS for Atezo+Bev+CP vs pembrolizumab (PD-L1 high expressors, MAIC)

ATZ, Atezolizumab; BEV, bevacizumab; CARB, carboplatin;MAIN, maintenance; PAC, paclitaxel

Figure 29: Odds ratios and 95% confidence intervals of pembrolizumab vs. Atezo+Bev+CP (weighted), for objective response rate (ORR), adverse events (AE) leading to withdraw, treatment-related AEs, and AEs grade III or more

AE, adverse event; ORR, objective response rate.
For ORR, odds ratio <1 in favour of Atezo+Bev+CP and odds ratio >1 in favour of pembrolizumab
For AE leading to withdraw, treatment related AE, and AEs grade III or more, odds ratio <1 in favour of pembrolizumab and odds ratio >1 in favour of atezolizumab

Inconsistency and heterogeneity evaluation

For the FP NMA, because there were no loops in the network apart from that formed by the three-arm IMpower150 study, there was no possibility of conducting an inconsistency analysis. Heterogeneity was evaluated by comparing the fixed and random effects models. The small differences in DIC indicated a low level of detectable heterogeneity, given the sparse network being analysed. However, the fact that PARAMOUNT has a different study design compared to all other studies in the network has already been highlighted. This might lead to selection bias in favour of pemetrexed plus platinum plus pemetrexed maintenance. Therefore, an NMA scenario analysis excluding PARAMOUNT has been performed and should be taken into account to inform decision-making for the comparison to pemetrexed plus platinum plus pemetrexed maintenance.

Similarly, for the standard NMA methods conducted for additional outcomes, there were no loops in the network apart from that formed by the three-arm IMpower150 study, therefore no possibility of conducting an inconsistency analysis. Heterogeneity was evaluated using pairwise meta-analyses to evaluate the network links informed by more than one study. Additional details are provided in Appendix D

The MAIC analysis utilised all available evidence on covariates from IMpower150 and KEYNOTE-024 to improve the comparability of the estimated effect sizes as far as possible. However, all MAICs are limited in their ability to include all patient characteristics and effect

modifiers of the study populations in the analysis. An important limitation in terms of inconsistency for the MAIC analysis is the fact that KEYNOTE-024 recruited less than 90% patients with non-squamous NSCLC and KM data for OS and PFS were not presented separately for squamous and non-squamous patients in KEYNOTE-024, resulting in uncertain and potentially conservative MAIC estimates for Atezo+Bev+CP.

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

The section below outlines some uncertainties and limitation of the ITCs performed.

- Different levels of detail for available data. For all included studies except IMpower150, only published aggregate data were available. Patient-level data would be preferred to aggregate data, requiring fewer assumptions regarding the censoring process, and patient-level covariates being able to be used in meta-regression models.
- Extrapolation of survival curves is associated with high uncertainty. The reported time frame differed substantially between studies. The reliability of extrapolating the modelled results over a longer time horizon is uncertain. Estimated quantities such as expected OS, expected PFS and HRs over time are only presented in this Section for a restricted period of 5 years for OS (2.5 years for PFS), and should be interpreted with caution.
- Where there was uncertainty about the comparability of certain studies or interventions, scenario analyses were used to assess the impact of inclusion/exclusion. The results were broadly consistent with the main analysis, however there are concerns regarding the inclusion of the PARAMOUNT study in the base-case network. The PARAMOUNT trial is different to the rest of the trials, and may not be representative of the overall first-line NSCLC population and is potentially leading to selection bias in favour of pemetrexed plus platinum plus pemetrexed maintenance. A sensitivity analysis was therefore conducted excluding PARAMOUNT from the NMA network. The impact of this scenario was favourable for Atezo+Bev+CP in terms of expected survival difference for both OS and PFS (see Section B.2.9 and Appendix D). As such, the inclusion of the PARAMOUNT study in the base case network for the NMA should be considered a conservative approach, potentially overestimating the clinical efficacy of pemetrexed plus platinum plus pemetrexed maintenance in the base case NMA and subsequently in the economic model.
- The NMA subgroup analyses are also related with increased uncertainty. We conducted subgroup analyses for two subgroups: EGFR/ALK positive and PD-L1 low or negative patients, comparing Atezo+Bev+CP vs. pemetrexed-based regimens. Individual patient data from IMpower150 were used to inform Atezo+Bev+CP in the subgroups of interest. However, not all studies in the network had data available for these patient subgroups. As such, an assumption had to be made that PD-L1 expression and the presence of

EGFR/ALK mutations are not effect modifiers for pemetrexed-based regimens in these studies, in order for a connected network of evidence to be feasible. Published studies and UK clinicians validated this assumption.

- Also, the size of the two subgroups considered differed substantially. The EGFR/ALK positive subgroup consisted of 11.25% of patients in the Atezo+Bev+CP arm of IMpower150, whereas the PD-L1 low or negative subgroup comprised 81.25% of patients in the Atezo+Bev+CP arm of IMpower150. Therefore, results of subgroup analyses are associated with greater uncertainty.
- Mixed populations in included studies (e.g. different stages, types or histology of carcinoma) can lead to an underlying bias. For the network analysis, studies were included only if outcomes were reported separately for the population of interest or at least 90% of patients have non-squamous NSCLC at Stage IV. This was considered appropriate in order to not disregard recent and relevant evidence, whilst also ensuring comparability of the included studies.
- A MAIC was conducted vs. pembrolizumab in PD-L1 high patients, as this is a key comparison explicitly included the NICE final scope for this appraisal. However, the only published study for pembrolizumab in this indication (KEYNOTE-024) recruited less than 90% patients with non-squamous NSCLC. In addition, in KEYNOTE-024, KM data for OS and PFS were not presented separately for squamous and non-squamous patients. This could potentially lead to a bias in favour of pembrolizumab, since squamous histology in NSCLC is related to a worse prognosis compared to non-squamous NSCLC (as per the PFS HRs reported in KEYNOTE-024).

B.2.10 Adverse reactions

The safety population in the IMpower150 study included all treated patients, defined as randomised patients who received any amount of any component of study treatment. For the safety analyses, patients were grouped according to whether any amount of atezolizumab was received.

Atezo+Bev+CP treatment was well-tolerated and consistent with the known risks of each study treatment, with no new safety signals were identified. An overview of the safety profile of both treatment arms in IMpower150 is summarised below.

Table 17: Overview of the safety profile of Atezo+Bev+CP compared with Bev+CP

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
Total number of events	6419	4630
Total number of patients with at least one: Adverse event	386 (98.2)	390 (99.0)

Treatment-related AE	370 (94.1)	377 (95.7)
Grade 3–4 AE	250 (63.6)	230 (58.4)
Treatment-related Grade 3–4 AE	223 (56.7)	191 (48.5)
Grade 5 AE	24 (6.1)	21 (5.3)
Treatment-related Grade 5 AE	11 (2.8)	9 (2.3)
Serious AE	174 (44.3)	135 (34.3)
Treatment-related serious AE	103 (26.2)	78 (19.8)
AE leading to withdrawal from any treatment	133 (33.8)	98 (24.9)
AE leading to any dose modification/interruption	246 (62.6)	188 (47.7)

AE, adverse event
CCOD: 22 January 2018

Extent of exposure to study treatment

At the time of the updated analysis, the median duration of treatment with atezolizumab in the Atezo+Bev+CP arm was 8.3 months; 36.1% of patients received at least 12 months of treatment.

The median duration of treatment with bevacizumab was longer in the Atezo+Bev+CP arm (6.7 months) compared to the Bev+CP arm (5.1 months). The median dose intensity was similar in both treatment arms (96.8% vs. 97.3%). More patients in the Atezo+Bev+CP arm received at least 12 months of bevacizumab treatment (29.8% vs. 16.0%).

Table 18: Exposure to atezolizumab and bevacizumab treatment

	Bevacizumab exposure		**Atezolizumab exposure**
	Atezo+Bev+CP n=393	**Bev+CP n=394**	**Atezo+Bev+CP n=393**
Number of doses received			
n	393	393	393
Mean (SD)	12.2 (9.5)	9.6 (7.2)	14.2 (10.1)
Median (min-max)	10.0 (1–44)	8.0 (1–38)	12.0 (1–44)
Treatment duration, months			
n	393	393	393
Mean (SD)	8.4 (7.0)	6.4 (5.2)	9.7 (7.3)
Median (min-max)	6.7 (0–30)	5.1 (0–26)	8.3 (0–30)
Treatment duration, months (%)			
n	393	393	393
0 to ≤3 months	112 (28.5)	124 (31.6)	86 (21.9)
>3 months to ≤6 months	61 (15.5)	101 (25.7)	53 (13.5)
> 6 months to ≤12 months	103 (26.2)	105 (26.7)	112 (28.5)
>12 months	117 (29.8)	63 (16.0)	142 (36.1)
Dose intensity, %			
n	393	393	393
Mean (SD)	93.8 (8.2)	94.4 (7.8)	94.0 (8.3)
Median (min-max)	96.8 (51-105)	97.3 (44–105)	96.9 (51–108)
Total cumulative dose, mg			
n	393	393	393
Mean (SD)	13113.4 (10676.3)	10264.0 (8187.7)	16990.3 (12171.7)

Median (min-max)	10260.0 (560–49035)	8070.0 (585–43265)	14400.0 (1200–52800)

SD, standard deviation
CCOD: 22 January 2018

Common adverse events

At the time of the updated analysis, the majority of patients in both treatment arms (98.2% Atezo+Bev+CP and 99.0% Bev+CP) reported at least one AE (any grade). The AEs with an incidence ≥5% in the Atezo+Bev+CP arm compared with the Bev+CP arm are summarised below; these were primarily Grade 1 or 2 and are generalised symptoms and events that are consistent with those associated with the chemotherapy backbone.

Table 19: Adverse events with a difference of at least 5% between treatment arms

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
Total number of patients with at least one AE	386 (98.2)	390 (99.0)
Gastrointestinal disorders		
Nausea	154 (39.2)	125 (31.7)
Constipation	117 (29.8)	92 (23.4)
Diarrhoea	126 (32.1)	97 (24.6)
Stomatitis	51 (13.0)	25 (6.3)
General disorders and administration site conditions		
Fatigue	130 (33.1)	107 (27.2)
Pyrexia	73 (18.6)	34 (8.6)
Nervous system disorders		
Peripheral neuropathy	93 (23.7)	68 (17.3)
Skin and subcutaneous tissue disorders		
Rash	65 (16.5)	26 (6.6)
Pruritus	50 (12.7)	24 (6.1)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	66 (16.8)	87 (22.1)
Metabolism and nutrition disorders		
Decreased appetite	113 (28.8)	83 (21.1)
Hypomagnesaemia	51 (13.0)	23 (5.8)
Hypokalaemia	37 (9.4)	16 (4.1)
Endocrine disorders		
Hypothyroidism	45 (11.5)	11 (2.8)

AE, adverse event
CCOD: 22 January 2018

Treatment-related AEs

The proportion of patients experiencing AEs considered by the investigator as related to any study treatment remained comparable between treatment arms (Atezo+Bev+CP: 94.1%; Bev+CP: 95.7%).

A higher incidence (≥5% difference) of nausea (34.4% vs. 27.9%), diarrhoea (21.4% vs. 15.2%), decreased appetite (22.6% vs. 14.7%), rash (14.2% 0 vs. 5.1%), stomatitis (12.0%

vs. 5.6%), pruritus (10.7% vs. 3.3%) and peripheral neuropathy (22.4% vs. 16.8%) was reported as related to any study treatment in the Atezo+Bev+CP arm compared with the Bev+CP arm. No event was reported with a lower incidence (≥5% difference) in the Atezo+Bev+CP arm compared with the Bev+CP arm.

Investigators had the option to report events as related to more than one treatment component, including atezolizumab and/or bevacizumab. In the updated analysis, in the Atezo+Bev+CP arm, AEs related to atezolizumab treatment were reported in 72.8% of patients and AEs related to bevacizumab treatment were reported in 73.0% of patients. In the Bev+CP arm, AEs related to bevacizumab treatment were reported in 69.3% of patients.

The most common AEs related to atezolizumab treatment (at least 10% of patients) reported in the Atezo+Bev+CP included diarrhoea (16.5%), fatigue (16.3%), nausea (13.5%), rash (12.7%), arthralgia (10.4%) and decreased appetite (10.4%).

Adverse events by intensity

The proportion of patients experiencing AEs of any grade was comparable between treatment arms. A summary of the treatment-related Grade 3-4 AEs (with an incidence ≥2% in either arm) can be found below.

Table 20: Grade 3–4 treatment-related AEs (incidence ≥2 in either arm)

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
Any adverse event, grade 3–4	223 (56.7)	191 (48.5)
Gastrointestinal disorders		
Nausea	15 (3.8)	8 (2.0)
Diarrhoea	11 (2.8)	2 (0.5)
General disorders and administration site conditions		
Fatigue	13 (3.3)	10 (2.5)
Asthenia	6 (1.5)	10 (2.5)
Blood and lymphatic system disorders		
Anaemia	25 (6.4)	23 (5.8)
Neutropenia	55 (14.0)	44 (11.2)
Thrombocytopenia	17 (4.3)	17 (4.3)
Febrile neutropenia	33 (8.4)	23 (5.8)
Investigations		
Platelet count decreased	20 (5.1)	9 (2.3)
Neutrophil count decreased	34 (8.7)	25 (6.3)
White blood cell count decreased	13 (3.3)	11 (2.8)
Metabolism and nutrition disorders		
Decreased appetite	10 (2.5)	3 (0.8)
Hypokalaemia	8 (2.0)	2 (0.5)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	7 (1.8)	8 (2.0)
Vascular disorders		

Hypertension	27 (6.9)	27 (6.9)
Renal and urinary disorders		
Proteinuria	12 (3.1)	11 (2.8)

Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.
CCOD: 22 January 2018

Serious adverse events

The proportion of patients experiencing a serious AE (SAE) was higher in the Atezo+Bev+CP arm (44.3%; 174/393) compared with the Bev+CP arm (34.3%; 135/394). The proportion of patients experiencing SAEs considered by the investigator as related to any study treatment was higher in the Atezo+Bev+CP arm (25.4%) compared with the Bev+CP arm. The most common treatment-related SAE with an incidence ≥2% of patients in any treatment arm was febrile neutropenia (6.4% vs. 3.8% in the Atezo+Bev+CP and Bev+CP arms respectively). The frequency of treatment-related serious adverse events was similar to that in previously reported studies of chemotherapy combined with checkpoint inhibitors (83).

Deaths

At the time of the updated analysis, a higher proportion of patients in the Bev+CP arm (57.4%; 226/394) compared with the Atezo+Bev+CP arm (48.1%; 189/393) had died. The most common cause of death was PD in both treatment arms. Among all deaths, PD accounted for 50.0% (197/394) of deaths in the Bev+CP arm and 31.3% (123/393) of deaths in the Atezo+Bev+CP arm.

Table 21: Fatal adverse events and causes in IMpower150

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
All deaths	189 (48.1)	226 (57.4)
Adverse event	24 (6.1)	21 (5.3)
Progressive disease	153 (38.9)	197 (50.0)
Other*	12 (3.1)	8 (2.0)

*Includes fatal events that are unrelated to study treatment and occur outside the reporting period

Grade 5 adverse events

Grade 5 AEs were reported in 24 patients (6.1%) in the Atezo+Bev+CP arm and 21 patients (5.3%) in the Bev+CP arm. The most commonly (at least 3 patients) reported Grade 5 AEs were (shown for the Atezo+Bev+CP and Bev+CP arms, respectively): haemoptysis (0.8% and 0.3%), pneumonia (0% and 0.8%) and febrile neutropenia (0.8% and 0%). Grade 5 AEs related to any study treatment were comparable between treatment arms (Atezo+Bev+CP arm: 2.8%; 11/393 and Bev+CP arm: 2.3%; 9/394). Five deaths with Atezo+Bev+CP were due to pulmonary haemorrhage or haemoptysis, four of which occurred in patients with

potential high-risk features (e.g., tumour infiltration of great vessels or cavitation). These events occurred early in the study; investigators and study staff were subsequently educated to improve the early identification and care of patients with high risk features (64).

Adverse events of special interest

Adverse events of special interest (AESIs) were closely monitored as they represent identified and potential risks for atezolizumab. The majority of patients with AESIs experienced events of Grade 1 or 2 severity; 12.5% of patients in the Atezo+Bev+CP arm and 3.3% of patients in the Bev+CP arm experienced a Grade 3–4 AESI; no Grade 5 AESIs were reported.

The majority of the immune-related AEs that occurred in the Atezo+Bev+CP group were Grade 1 or 2 and none were Grade 5. The most common immune-related adverse events were rash, hepatitis, hypothyroidism, hyperthyroidism, pneumonitis, and colitis.

The AESIs that were reported with a ≥2% difference between the Atezo+Bev+CP vs. Bev+CP arms are summarised below.

Table 22: Summary of selected adverse events of special interest to atezolizumab

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
Total number of patients with at least one AESI	206 (52.4)	112 (28.4)
Total number of patients with at least one:		
Treatment-related AESI	182 (46.3)	70 (17.8)
Grade 3–4 AESI	49 (12.5)	13 (3.3)
Treatment-related Grade 3–4 AESI	42 (10.7)	8 (2.0)
Grade 5 AESI	0	0
Treatment-related Grade 5 AESI	0	0
Serious AESI	25 (6.4)	4 (1.0)
Treatment-related AESI	22 (5.6)	2 (0.5)
AESI leading to withdrawal from any treatment	26 (6.6)	3 (0.8)
AESI leading to any dose modification/interruption	51 (13.0)	16 (4.1)
Patients with at least one (incidence ≥2%)		
Immune-related rash	117 (29.8)	53 (13.5)
Immune-related hepatitis (diagnosis)	54 (13.7)	29 (7.4)
Immune-related hepatitis (laboratory abnormality)	48 (12.2)	29 (7.4)
Immune-related hypothyroidism	56 (14.2)	18 (4.6)
Infusion-related reactions	14 (3.6)	12 (3.0)
Immune-related pneumonitis	13 (3.3)	5 (1.3)
Immune-related hyperthyroidism	16 (4.1)	5 (1.3)
Immune-related colitis	11 (2.8)	2 (0.5)

AESI, adverse event of special interest;
CCOD: 22 January 2018

Adverse events leading to treatment withdrawal or dose modification/interruption

The proportion of patients experiencing AEs leading to any study treatment withdrawal was higher in the Atezo+Bev+CP arm (33.8%) compared with the Bev+CP arm (24.9%). There were no AEs leading to study treatment withdrawal that were reported with a ≥2% difference between the Atezo+Bev+CP vs. Bev+CP arms.

The proportion of patients experiencing AEs leading to atezolizumab withdrawal in the Atezo+Bev+CP arm was (15.0%); the most common AE (≥1% patients in any treatment arm) leading to atezolizumab treatment withdrawal was pneumonitis (1.8%).

The proportion of patients experiencing AEs leading to bevacizumab withdrawal was higher in the Atezo+Bev+CP arm (24.4%) compared with the Bev+CP arm (18.0%). The most common AEs (≥1% patients in any treatment arm) leading to bevacizumab withdrawal were hypertension (2.3% vs. 0.8%), proteinuria (2.8% vs. 2.0%), pulmonary embolism (1.5% vs. 1.3), haemoptysis (1.0% vs. 0), pneumonitis (1.0% vs. 0%) and cerebrovascular accident (1.0% vs. 0).

The proportion of patients experiencing AEs leading to dose modification/interruption was higher in the Atezo+Bev+CP arm (62.6%) compared with the Bev+CP arm (47.7%). AEs leading to dose modification/interruption that were reported with higher incidence (at least 2% difference) in the Atezo+Bev+CP arm vs. the Bev+CP arm were: febrile neutropenia (4.1% vs. 2.0%), platelet count decreased (7.1% vs. 5.1%), weight decreased (5.1% vs. 2.5%), pneumonia (3.1% vs. 0.5%), diarrhoea (5.1% vs. 1.0%), hypothyroidism (2.8% vs. 0%) and proteinuria (6.4% vs. 3.8%).

Overview of the safety profile of atezolizumab in IMpower150

Atezolizumab in combination with bevacizumab and carboplatin/paclitaxel chemotherapy was well tolerated and AEs reported were consistent with the known risks of each study treatment and the results seen in the interim analysis. No new safety signals were detected in IMpower150. Furthermore, the frequency of AEs observed with Atezo+Bev+CP is comparable with a pemetrexed+platinum-based chemotherapy regimen (83).

The proportion of Grade 3–4 AEs were comparable between treatment arms; however, the majority of the Grade 3–4 AEs in the Atezo+Bev+CP arm are known toxicities associated with chemotherapy. Furthermore, the incidence of Grade 5 AEs was similar between the treatment arms with the majority being known Grade 5 AEs associated with bevacizumab or chemotherapy.

The proportion of patients experiencing AEs leading to any study treatment withdrawal was higher in the Atezo+Bev+CP arm compared with the Bev+CP arm. None of the AEs leading

to atezolizumab withdrawal were reported in ≥2% of patients in the Atezo+Bev+CP arm and therefore no specific AEs were identified that were driving this discontinuation rate.

B.2.11 Ongoing studies

The IMpower150 study is currently ongoing. The final OS analysis for the primary comparison of Atezo+Bev+CP arm vs. Bev+CP arm will be conducted when there are approximately 507 OS events in the ITT-WT population in the combined Atezo+Bev+CP and Bev+CP arms. This final OS analysis is expected to occur [redacted].

B.2.12 Innovation

Despite the advances in early NSCLC identification and the availability of different options for first-line treatment, survival from lung cancer in the UK is very poor and has changed little in the last 40 years (21). For the majority of patients without high PD-L1 expression or oncogenic driver mutations (following targeted therapy), only standard of care chemotherapy is available. However, the benefit conferred by these regimens is limited, with an expected median survival of 6–14 months (35, 36, 84-86). Therefore, there remains an unmet need for an improvement of efficacy in first-line treatments for non-squamous metastatic NSCLC and further options for patients with low or negative PD-L1 expression and patients with an EGFR or ALK mutation who are ineligible for, intolerable to or have progressed on targeted therapy.

[redacted]

Since cure is not considered a realistic outcome for most patients with advanced NSCLC, multi-modality treatment combinations may be appropriate to induce a prolonged period of remission. The combination of atezolizumab with chemotherapy and an anti-angiogenic agent is an innovative option based on a strong biological rationale:

Addition of carboplatin/paclitaxel to atezolizumab

- Tumour specific mutations (neoantigens) represent ideal targets for checkpoint inhibitors to induce an anti-tumour immune response; however, immunity may also be dependent on the degree of neoantigen intratumoural heterogeneity. Analysis of a cohort of patients with NSCLC treated with a checkpoint inhibitor showed that those

deriving a durable clinical benefit had a significantly larger and more homogenous neoantigen repertoire than those patients without clinical benefit (58)

- Chemotherapy can enhance the susceptibility of subclonal neoantigen expressing tumour cells to cytotoxic T cells during cancer immunotherapy; for instance, paclitaxel increases the uptake of granzyme B, a serine protease released by cytotoxic T cells that mediates apoptosis, by non-neoantigen expressing tumour cells (59)

Addition of bevacizumab to carboplatin/paclitaxel

- Paclitaxel-based therapy has been associated with an increase in pro-angiogenic bone marrow derived circulating endothelial progenitor cells, which can be inhibited with a VEGF inhibitor (87)
- The addition of bevacizumab to paclitaxel plus carboplatin for the treatment of non-squamous NSCLC significantly improved response rate, PFS and OS compared with paclitaxel+carboplatin alone (HR for OS=0.79, 95% CI: 0.67, 0.92; p=0.003) (88)

Addition of bevacizumab to atezolizumab

- Bevacizumab inhibits VEGF-enhanced expression of PD-1 and other inhibitory checkpoints involved in cytotoxic T cell exhaustion; therefore, it could synergise with atezolizumab to enhance anti–PD-1– dependent anti-tumour effects (27)
- Bevacizumab normalises the tumour vasculature, resulting in increased infiltration of T-cells into the tumour, and by decreasing the activity of myeloid-derived suppressor cells and regulatory T-cells, enables reprogramming of the tumour microenvironment from immune-suppressive to immune-permissive (60, 61)

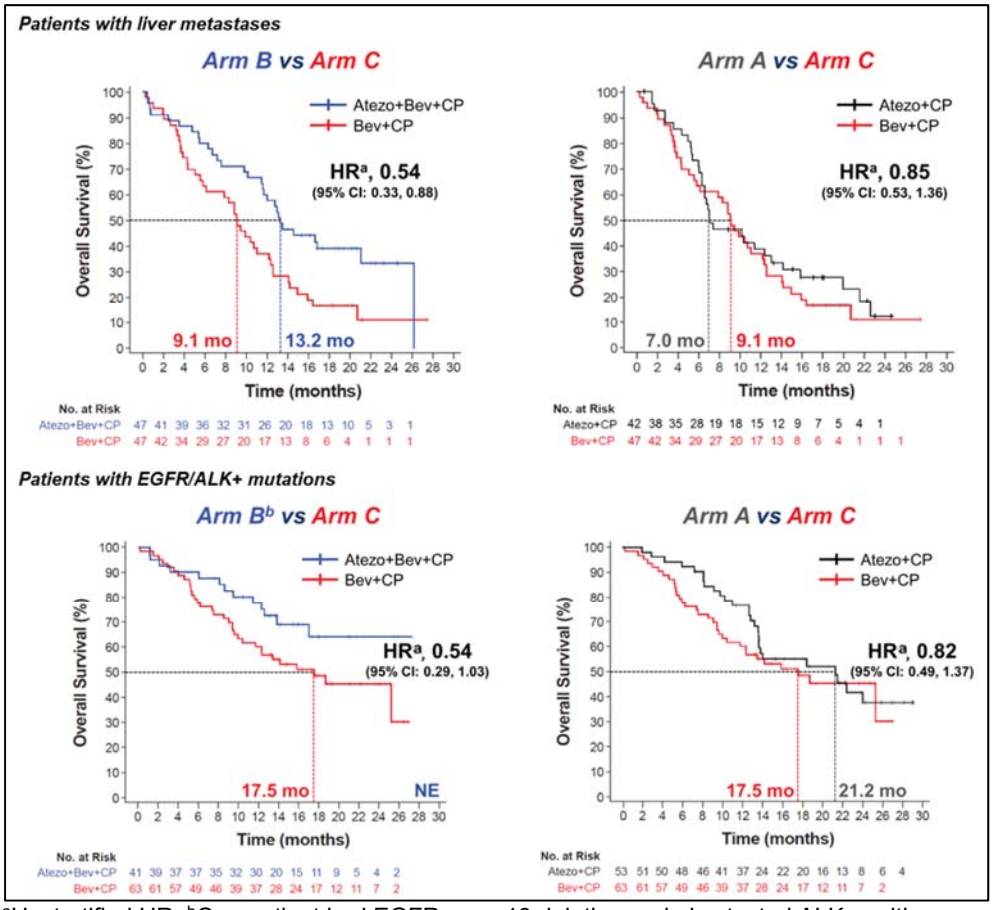
Atezolizumab is the first checkpoint inhibitor with a Phase III combination trial to demonstrate a statistically significant and clinically meaningful benefit OS and PFS in all non-squamous NSCLC patients. Furthermore, this combination improved survival in all key subgroups, including:

- **Patients with EGFR mutant and ALK-positive NSCLC** after progression on prior targeted therapy; IMpower150 is the first checkpoint inhibitor Phase III trial to read out positively for both OS and PFS in these patients. This patient population has been excluded from other checkpoint inhibitor first-line NSCLC trials such as KEYNOTE-189 and CheckMate-227 (83, 89), while other clinical trials that have investigated the use of PD-L1 or PD-1 inhibitors as monotherapy after the failure of targeted therapies have failed to show checkpoint inhibitors to be more effective than standard chemotherapy (76, 90, 91)

- **Patients with liver metastases**; tumours in these patients are characterised by immune suppressive tumour environments, and they usually demonstrate poorer outcomes (26, 27). IMpower150 is the first checkpoint inhibitor trial to prospectively measure outcomes in this population that had previously demonstrated limited therapeutic benefit with checkpoint-inhibitor monotherapy (24, 92, 93)

The impact of the atezolizumab-bevacizumab chemotherapy combination is clearly demonstrated by comparing the efficacy in these subgroups in the different treatment arms of IMpower150. Atezo+Bev+CP was shown to be effective in the setting of high VEGF levels, such as patients with oncogenic driver mutations (which lead to increased VEGF expression) and the presence of liver metastases, a hypervascular organ with high levels of VEGF) (94). The benefit in overall survival observed in these patients is not seen when bevacizumab is not combined with atezolizumab, i.e. Atezo+CP vs. Bev+CP (Arm A vs. Arm C) (Figure 30) (66), thereby supporting the biological rationale highlighted above for the inclusion of bevacizumab in a chemo-immunotherapy combination.

Figure 30: Overall survival in patients with baseline liver metastases and EGFR/ALK+ mutations: impact of bevacizumab in the treatment combination



[a]Unstratified HR; [b]One patient had EGFR exon 19 deletion and also tested ALK-positive per central lab
CCOD: 22 January 2018

Furthermore, IMpower150 is also the first Phase III trial of a checkpoint inhibitor to demonstrate a clinically meaningful benefit in PFS and OS in an all-comer patient population for the first-line treatment of metastatic NSCLC, i.e. in patients regardless of PD-L1 expression status. A numerical improvement in both PFS and OS was observed in the subgroup with low or negative PD-L1 expression. These findings in an unselected population is of relevance since the current first-line use of pembrolizumab monotherapy is limited to patients with high PD-L1 expression (TPS≥50%), whereas most patients with metastatic NSCLC have tumours with a low, negative or unknown PD-L1 status (95).

Results of an ITC versus UK standard of care therapies in first-line non-squamous metastatic NSCLC suggested that Atezo+Bev+CP has an expected OS and PFS benefit versus pemetrexed-based regimens in the ITT population (i.e. regardless of PD-L1 expression) (see Section B.2.9). This OS and PFS benefit compared to pemetrexed-based chemotherapy was consistent (i.e. similar to the ITT) in the subgroups of patients with low or negative PD-L1 expression and patients with EGFR or ALK mutations. The ITC versus pembrolizumab in PD-L1 high patients demonstrated that [redacted]. Results were however associated with limitations and high uncertainty (see Section B.2.9).

Taken together, these data suggest that the combination of Atezo+Bev+CP provides an innovative and convenient first-line treatment option that addresses the unmet need for all patients with metastatic non-squamous NSCLC, who currently do not have access to cancer immunotherapy. This includes those patients with low or negative PD-L1 expression, patients with liver metastases and patients with EGFR mutant and ALK-positive disease, after targeted therapy.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Evidence from IMpower150

IMpower150 is a Phase III, open-label, randomised study to investigate the efficacy and safety of Atezo+Bev+CP compared with Bev+CP in all chemotherapy-naïve patients with stage IV non-squamous NSCLC (64). While bevacizumab is not currently approved by NICE as a first-line treatment option for metastatic NSCLC, it is approved by the European Medicines Agency, in addition to platinum-based chemotherapy, for the first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology (13).

IMpower150 was designed to capture endpoints which are relevant to UK clinical practice and address the unmet medical need for this patient population, in particular OS and PFS, response rates and duration of response, as well as the safety and tolerability of the combination and patient-reported outcomes. Furthermore, the ITT population enrolled in IMpower150 is relevant to all first-line metastatic non-squamous NSCLC patients since it is the first Phase III trial of a chemo-immunotherapy combination regimen to recruit an unselected population, i.e. regardless of the level of PD-L1 expression and including patients with EGFR mutant and ALK-positive disease resistant (or intolerant) to targeted therapy. It is anticipated that there are [redacted] chemotherapy-naïve patients in England with stage IV metastatic non-squamous NSCLC eligible for treatment with the Atezo+Bev+CP (see Document C).

IMpower150 showed a significant improvement in PFS and OS with the addition of atezolizumab to bevacizumab and carboplatin/paclitaxel chemotherapy as first-line treatment for metastatic non-squamous NSCLC. There was no evidence of extrinsic or intrinsic confounders in IMpower, which is a well-conducted good clinical practice compliant study. Together, this suggests that the observed HRs for the co-primary endpoints are a true indication of the expected treatment effect in this population.

At the time of the interim analysis (CCOD 15 September 2017), a statistically significant and clinically meaningful reduction in the risk of disease progression or death for Atezo+Bev+CP compared with Bev+CP was observed in the ITT population (HR 0.61; 95% CI: 0.52, 0.72). At the time of the updated analysis (CCOD 22 January 2018), the stratified HR improved to 0.59 (95% CI: 0.50, 0.69). This result was consistent across all clinically relevant subgroups analysed, including patients with EGFR mutant and ALK-positive NSCLC and patients with liver metastases at baseline.

At the time of the updated analysis, the IMpower150 study demonstrated a statistically significant and clinically meaningful improvement in OS, with a 24% relative reduction in the risk of death for Atezo+Bev+CP, compared with Bev+CP in the ITT population (HR 0.76; 95% CI: 0.63, 0.93). Median OS in the Atezo+Bev+CP arm was 4.9 months longer than with Bev+CP (19.8 months [95% CI: 17.4, 24.2] vs. 14.9 months [95% CI: 13.4, 17.1]). The rates of OS were higher in the Atezo+Bev+CP arm compared with the Bev+CP arm at 1-year and 2 years (1-year: 68% vs. 61%; 2 years: 45% vs. 36%).

Improved OS was observed in the majority of clinically relevant subgroups, including patients with baseline liver metastases, a population that had previously had a limited therapeutic benefit with checkpoint-inhibitor monotherapy **(24, 92, 93)**. Median OS was longer in all PD-

L1 expression subgroups analysed, including in the PD-L1 negative subgroup (TC0 and IC0).

There was a 46% relative reduction in the risk of death among patients with EGFR mutant and ALK-positive disease (HR 0.54; 95% CI: 0.29, 1.03); median survival could not be estimated for the Atezo+Bev+CP arm and was 17.5 months (95% CI: 10.4, NE) in the Bev+CP arm. The benefit observed in these patients with Atezo+Bev+CP is notable given that monotherapy trials of PD-L1/PD-1 inhibitors in TKI therapy-resistant patients have failed to show greater efficacy over chemotherapy **(76, 90, 91)**. Furthermore, such patients have limited proven treatment options, and data are lacking from Phase III trials investigating the effectiveness of platinum-based regimens with or without PD-L1 or PD-1 inhibitors in this patient population. These data are strongly supportive of the clinical benefit of the Atezo+Bev+CP combination in the overall ITT population.

Observing some of the endpoints traditionally used in oncology trials (ORR, PFS), immunotherapy advantages over traditional chemotherapy may appear modest. However, in those patients who develop a response, these responses are demonstrating durability, with the potential for long-term survival. As demonstrated in IMpower150, the ORR was higher and the DOR was longer in the Atezo+Bev+CP compared with the Bev+CP arm in the ITT population. Of note, 39.3% of responders in the Atezo+Bev+CP arm vs. 11.4% in the Bev+CP arm had an ongoing response at the time of the updated analysis CCOD (minimum follow-up time of 13.5 months). As a class of drugs, immunotherapies have been recognised to demonstrate ongoing survival advantages to patients which have been considerably higher than historical standards with chemotherapy.

The efficacy benefit described above occurred in the context of a tolerable and manageable toxicity profile. The safety profile of Atezo+Bev+CP (at both the interim and updated analyses) was consistent with the known risks of atezolizumab, bevacizumab, carboplatin, and paclitaxel. No exacerbations in the severity of the known toxicities for each individual study treatment were observed, no new safety signals were identified, and the majority of the events were clinically manageable with the appropriate treatment. In addition, the prolonged PFS and improved OS observed with Atezo+Bev+CP compared with Bev+CP in the IMpower150 study was achieved without a detrimental effect on HRQoL and physical functioning, despite the higher treatment-related adverse event rates previously reported (2). Higher rates of AEs leading to any study treatment discontinuation and serious AEs were observed in the Atezo+Bev+CP arm; however, considering the longer duration of treatment

for patients in the Atezo+Bev+CP arm, the safety data support a positive benefit-risk profile for the treatment combination.

Evidence from indirect treatment comparison

Since UK standard of care therapies for first-line non-squamous metastatic NSCLC were not included as comparators in IMpower150, an indirect treatment comparison (ITC) had to be conducted to enable Atezo+Bev+CP to be compared to UK standard of care (pemetrexed plus platinum-based chemotherapy with or without pemetrexed maintenance for ITT population, patients PD-L1 low or negative expression and patients with EGFR/ALK mutations after targeted therapy; pembrolizumab for PD-L1 high patients). A SLR was conducted to identify relevant studies (see B.2.9 and Appendix D for further details).

A NMA feasibility assessment (Appendix D) indicated that a connected network of evidence was only feasible for the comparison with pemetrexed-based regimens. For pembrolizumab, no common treatment arm was available to enable a comparison within the NMA. As such, a MAIC was conducted in PD-L1 high patients (>50% tumour proportion score, TC/IC 3).

Comparison to pemetrexed-based interventions

For the NMA versus pemetrexed-based interventions, a fractional polynomial approach was implemented to account for the different mechanism of action between cancer immunotherapy and chemotherapies, as well as presence of non-proportional hazards between Atezo+Bev+CP and pemetrexed-based chemotherapy. The base case network of studies for the NMA was stress-tested in a series of subgroup and scenario analyses. NMA subgroup analyses were conducted for OS and PFS, for patients with low or negative PD-L1 expression, and patients with EGFR/ALK mutations, as these patient subgroups have an unmet need for cancer immunotherapy and are of particular relevance to this appraisal. The assumption that the level of PD-L1 expression and presence of EGFR or ALK mutations are not effect modifiers for pemetrexed-based regimens were necessary to enable the NMA subgroup analyses to be performed. These assumptions were validated by the literature and UK clinical experts.

Scenario analyses were also undertaken for the NMA excluding the KEYNOTE studies and excluding PARAMOUNT from the network of evidence. Importantly, PARAMOUNT has a different study design compared to all the other studies in the network, which might lead to selection bias in favour of pemetrexed plus platinum plus pemetrexed maintenance. Therefore, the NMA scenario analysis excluding PARAMOUNT is important to inform this comparison.

Results of the NMA demonstrated that there is an expected survival difference in favour of Atezo+Bev+CP vs. pemetrexed-based regimens in terms of both OS and PFS [redacted]. However, in the OS comparison with pemetrexed plus platinum chemotherapy with pemetrexed maintenance, the NMA results are likely confounded by the bias introduced by the PARAMOUNT study in the base case network. When excluding the PARAMOUNT study, the expected survival difference improves numerically in favour of Atezo+Bev+CP [redacted]. A similar impact on the OS comparison is seen when using a proportional hazards NMA model. The impact of using the NMA scenario excluding PARAMOUNT and the PH NMA model on cost-effectiveness results is presented in Section B.3.8.

Results for the subgroups of patients with low or negative PD-L1 expression or EGFR/ALK mutations are consistent with the ITT analyses, demonstrating an expected survival difference in favour of Atezo+Bev+CP vs. pemetrexed-based treatments, in terms of both PFS and OS. There is a more pronounced expected OS difference in favour of Atezo+Bev+CP in the EGFR/ALK positive subgroup compared to the ITT population; however, uncertainty is more evident. Increased uncertainty in NMA subgroup analyses can at least partly be explained by the smaller sample size in the IMpower150 population when subgroups of patients are analysed.

A standard NMA was also implemented vs. pemetrexed plus platinum chemotherapy with pemetrexed maintenance for the additional outcomes of objective response and discontinuation due to AEs. This NMA demonstrated that [redacted].

Comparison to pembrolizumab

For pembrolizumab, no common treatment arm was available to enable a comparison within the NMA. As such, a MAIC was conducted in PD-L1 high patients (>50% tumour proportion score, TC/IC 3), following the method introduced by Signorovitch et al (96) and the recommendations of NICE DSU (82). The MAIC demonstrated that [redacted]. The MAIC results are however associated with uncertainty and limitations. These are related primarily to differences in study populations, the fact that KEYNOTE-024 recruited less than 90%

patients with non-squamous NSCLC and the fact that KM data for OS and PFS were not presented separately for squamous and non-squamous patients in KEYNOTE-024, resulting in potentially conservative estimates for Atezo+Bev+CP. For additional outcomes, standard NMAs demonstrated that [redacted].

Based on [redacted], UK clinical expert opinion was sought and suggested that [redacted]. As such, a cost-effectiveness comparison with pembrolizumab is not implemented in the cost-effectiveness Section (Section B.3) and reimbursement for Atezo+Bev+CP is effectively not pursued in this subgroup of patients.

Limitations of indirect treatment comparison

The ITC analyses (NMA and MAIC) are associated with a series of uncertainties and limitations, relating primarily to the availability of evidence, the comparability of the identified studies, limitations relating to subgroup comparisons and the extrapolation of modelled outcomes. These are discussed in detail at the end of Section B.2.9.

Conclusion

The totality of the head-to-head and indirect evidence presented in our evidence submission (from study IMpower150 and the ITCs that were performed) demonstrate that the combination of Atezo+Bev+CP improves treatment outcomes for patients compared to pemetrexed-based chemotherapy, which is the UK standard of care for first-lime metastatic non-squamous NSCLC patients, who are not eligible for treatment with pembrolizumab.

Data from the ITT and subgroup populations of IMpower150, as well as from the NMAs that were implemented, show that Atezo+Bev+CP provides a consistent OS and PFS clinical benefit compared to pemetrexed-based chemotherapy for all chemotherapy-naive patients with metastatic non-squamous NSCLC. This benefit is demonstrated regardless of the level of PD-L1 expression, and in subgroups of patients with low or negative PD-L1 expression and with EGFR mutant and ALK-positive disease after targeted therapy. As such, Atezo+Bev+CP represents a significant advance in the first-line treatment of metastatic non-squamous NSCLC, compared to pemetrexed-based chemotherapy in patients that currently

have an unmet need for cancer immunotherapy i.e. patients with PD-L1 low or negative expression or EGFR/ALK positive mutation.

End-of-life criteria

The combination of Atezo+Bev+CP meets the end-of-life criteria compared to pemetrexed-based chemotherapy, in the ITT population as well as in the subgroups of patients who are PD-L1 low or negative (tumour proportion score 0-49%, TC/IC 0,1,2) or EGFR/ALK positive.

Table 23: End-of-life criteria

<table>
<tr><th>Criterion</th><th>Data available</th><th>Reference in submission (section and page number)</th></tr>
<tr><td colspan="3">Comparison to pemetrexed-based chemotherapy
[ITT population , PD-L1 low or negative, EGFR/ALK positive]</td></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>Median survival for NSCLC patients receiving standard or care chemotherapy is 6–14 months (35, 36, 84-86)
According to the PARAMOUNT trial of pemetrexed maintenance therapy in advanced non-squamous NSCLC, the median OS was 13.9 months. This value represents the maximum survival benefit for patients treated with chemotherapy in this setting. Please note that, pemetrexed-based chemotherapy is the UK standard of care for patients with non-squamous NSCLC
Median OS from economic model for pemetrexed-based regimens:
- ITT: 13.3-14.4 months
- PD-L1 low or negative: 12.0-13.8 months
- EGFR/ALK positive: 6.0-10.8 months
Please note that OS in subgroups of patients should be interpreted with caution.</td><td>B.1.3.1 – page 12

B.3.3.2 – page 102 and economic model</td></tr>
<tr><td>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</td><td>OS difference for Atezo+Bev+CP versus pemetrexed-based chemotherapy
<table>
<tr><th>Population</th><th>Incremental median OS (months)</th><th>Incremental mean OS (months)</th></tr>
<tr><td>ITT</td><td>6.0-7.1</td><td>5.1-8.9</td></tr>
<tr><td>PD-L1 low or negative</td><td>5.5–7.4</td><td>3.5-7.9</td></tr>
<tr><td>EGFR/ALK</td><td>20.9–25.8</td><td>21.5-23.6</td></tr>
</table></td><td>B.3.3.2 – page 102 and economic model</td></tr>
</table>

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify published cost-effectiveness studies in the first-line treatment of patients with non-squamous NSCLC. Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix G.

Summary of identified studies and results

Overall, a total of 137 eligible economic evaluations were identified assessing the cost-effectiveness of treatment for advanced or metastatic NSCLC in the first-line setting. Of these 137 studies, 70 were presented as full publications (of which four were foreign language publications with an English abstract), and 67 were presented as conference abstracts only.

Out of the full studies in English (n=66), ten used economic data derived from the UK. The most common type of economic evaluation was cost-utility analysis reporting an incremental cost per quality adjusted life year (QALY) for the treatment strategies considered (n=39). The remaining studies were cost-effectiveness analyses (n=19) and cost-minimisation analyses (n=8). The most commonly reported outcomes across the 19 cost-effectiveness analyses included: cost per life year gained (LYG) (n=10); cost per additional progression free survival (PFS) month (n=3); and cost per responder (n=1).

Decision analytic modelling was the most common methodological approach. Model types utilised across the studies, as reported in the publications, included: Markov model (n=25); area under the curve (AUC)/partitioned survival model (n=10); a decision analytic model (n=5); a population health model (n=2); a patient simulation model (n=1); a discrete event simulation (DES) (n=1) a decision tree (n=1); and a trial-based model (n=1). A total of 20 studies did not specify the model type. A three-state model structure was most often presented, consisting of the following health states: PFS; progressed disease (PD), and death (n=25). Other common health states included stable disease/response to treatment (n=5), consideration of adverse events (AEs) (n=2), and remission with or without dose reduction (n=1).

The payer perspective was the most commonly adopted viewpoint for the included analyses (n=54); four studies used a societal perspective, and eight did not report the perspective. Time horizon ranged from 6 months (n=2) to a lifetime (n=16) (specific lifetime horizons ranged from 5 years to 15 years). Two studies employed a 20-year time horizon, but this

was not specified as a lifetime. Model cycle length ranged from 1 week (n=7) to 1 month/28 days (n=15); however, the most commonly used cycle length was 3 weeks (n=15).

In addition, a total of 67 conference abstracts were identified for inclusion in the review, as well as the four full foreign language publications with English language abstracts that were identified. Due to limited reporting of these studies, the results are not discussed in detail; however, a summary of the approaches to modelling and base case results reported across the abstracts is provided.

Further details and results for the identified cost-effectiveness studies and abstracts can be found in Appendix G.

B.3.2 Economic analysis

The cost-effectiveness studies identified in Section B.3.1, as well as previous NICE technology appraisals, were utilised to inform the structure for the model used in the economic analysis. However, none of the identified literature appraised atezolizumab in combination with bevacizumab, carboplatin, paclitaxel (Atezo+Bev+CP) for the first-line treatment of adult patients with metastatic non-squamous NSCLC. Therefore, a de novo economic model was built to inform decision making.

B.3.2.1 Patient population

The de novo analysis assesses Atezo+Bev+CP as a first-line treatment of adult patients with metastatic non-squamous NSCLC, in comparison to pemetrexed-based chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations NSCLC should have received targeted therapy if clinically indicated prior to receiving atezolizumab. This population is consistent with the ITT population of study IMpower150, the NICE final scope for this appraisal, the decision problem and the anticipated Marketing Authorisation for Atezo+Bev+CP.

Relevant patient subgroups of the ITT population are also considered in our evidence submission:

- PD-L1 low or negative patients (with tumour proportion score of 0-49%, TC/IC 0,1,2) (72)
- EGFR or ALK-positive patients, after targeted therapy

Please note that the subgroup of patients with PD-L1 high expression (>50% tumour proportion score, TC/IC 3) (72) is not included in the cost-effectiveness Section of our submission and as such, reimbursement is effectively not pursued in this subgroup. [redacted]

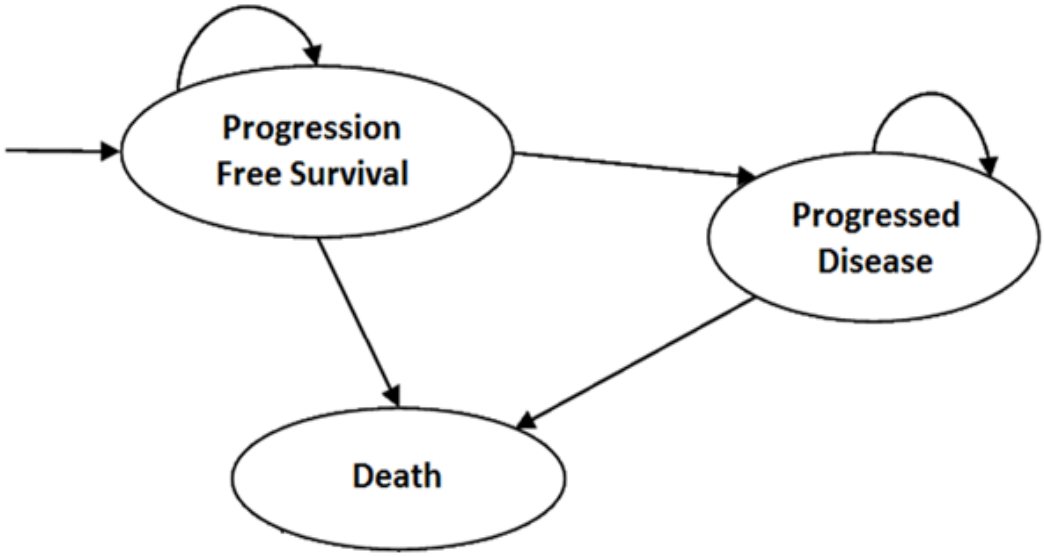
[redacted]

B.3.2.2 Model structure

The economic evaluation was developed in Microsoft Excel and is an Area-Under-the-Curve (AUC) or partitioned survival analysis model. The AUC model structure was selected, as per NICE DSU guidance (97), in order to allow for full use of the mature PFS and OS study data from IMpower150 and to be able to incorporate external evidence for additional comparators in the economic model.

The model includes three mutually exclusive health states, consistent with previous appraisals accepted by NICE for first-line NSCLC, and other metastatic oncology indications (42, 51-53, 98): “Progression-Free Survival (PFS)”, “Progressed Disease (PD)” and “Death”. The model structure can be found in Figure 31.

Figure 31: Economic model structure



The health economic model was developed to compare the cost-effectiveness of Atezo+Bev+CP vs. the UK standard of care therapies for first-line metastatic non-squamous NSCLC patients (i.e. pembrolizumab monotherapy and pemetrexed in combination with a platinum drug (carboplatin or cisplatin), with or without pemetrexed maintenance treatment), as per their licence and recommendation from NICE. More details and further justification for the comparisons to UK standard of care therapies within our submission are provided in Sections B.1.1 and B.3.2.3. However, it is reminded that the comparison with pembrolizumab monotherapy is not included in the cost-effectiveness Section of our submission. [redacted]

[redacted]

The model inputs (efficacy, safety and tolerability) are based on the results of the phase III IMpower150 trial for Atezo+Bev+CP, and on the indirect treatment comparison (FP NMA) outlined in Section B.2.9 for the relevant comparators. Model results are reported in terms of cost per life years gained (LYG) and costs per quality adjusted life years (QALY) gained. This appropriately reflects the decision problem.

Within the AUC model, health states are based on the partitioning of the proportion of patients alive into “PFS” and “PD” at discrete time points, based on the PFS and OS curves from IMpower150 and the relative treatment effects derived from the NMA. The proportion of patients in the “PD” health state is assumed to be the difference between OS and PFS. The three health states in the model represent the primary stages of disease in metastatic non-squamous NSCLC.

All patients enter the model in the PFS health state and remain in this health state until they progress. At progression, patients either transition into the PD health state or enter the absorbing health state of Death. Patients in the PD health state stay in that health state until Death. Patients cannot transition to an improved health state (back to PFS), a restriction that is consistent with previous economic modelling in oncology.

Due to the structural form of the model, patient transitions between the health states are not explicitly modelled. The proportion of patients in each health state was estimated using the partitioned survival method. Rather than transition probabilities, the proportion of patients within each health state was calculated based on the PFS and OS survival curves from IMpower150 for Atezo+Bev+CP and based on the relative treatment effects derived from the NMA, for relevant comparators. The partitioned survival approach allows for modelling of OS and PFS based on study-observed events, which is expected to accurately reflect disease progression and the long-term expected survival profile of patients treated with Atezo+Bev+CP. The primary limitations, however, of this approach are that OS and PFS are modelled as independent end points, and since transitions are not explicitly modelled, the model structure is rigid and does not allow for sensitivity or scenario analyses to be explored by altering the transition probability in specific health states only.

Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle.

The economic model uses a time horizon of 20 years, which is considered to be appropriate as a lifetime horizon for patients with first-line metastatic non-squamous NSCLC, taking into account typical age at diagnosis and advanced nature of disease. This time horizon ensures all benefits and costs accrued by patients are captured, and is consistent with the anticipated survival based on the economic model, with less than 1% of patients still alive at 20 years for Atezo+Bev+CP, and relevant comparators (pemetrexed-based interventions) in the ITT population. The 20-year time horizon is also consistent with TA 531, the recent pembrolizumab appraisal in first-line advanced or metastatic NSCLC (42).

Costs and health outcomes are discounted at 3.5 % and the perspective of the NHS and personal social services (PSS) is assumed, as per the NICE reference case (1).

The model has been designed to use a weekly cycle, with the proportion of patients in each health state calculated each week. Transition between health states can occur at any time within the cycle. To account for the over or under estimation of transitions occurring at the beginning or end of the cycle, a half-cycle correction was applied, in line with previous NICE technology appraisals in this disease area (42, 51-53, 98).

An overview of how the economic analysis for Atezo+Bev+CP compares to other NICE appraisals in first-line advanced non-squamous NSCLC is provided in Table 24.

Table 24: Features of the economic analysis

	Previous appraisals			Current appraisal	
Factor	**Pemetrexed first line NSCLC (TA181) (41)**	**Pemetrexed maintenance (TA402) (49)**	**Pembrolizumab first line NSCLC (TA531) (42)**	**Chosen values**	**Justification**
Time horizon	Lifetime (6 years)	Lifetime (equivalent to 15.99 years; range: 6-20 years)	Lifetime (20 years)	Lifetime (20 years)	NICE reference case. Time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
Cycle length	21 days (i.e. 3 weeks)	21 days (i.e. 3 weeks)	1 week	1 week	In line with the pembrolizumab recent NICE submission in 1L advanced NSCLC.
Half-cycle correction	Half-cycle correction appeared to have been	Yes	Yes	Yes	In line with previous submissions

	disabled for costs and used incorrectly for outcomes				and to mitigate bias
Were health effects measured in QALYs; if not, what was used?	Yes	Yes	Yes	Yes	NICE reference case (1) Only direct health effects related to patients were considered, and no wider societal impact or impact on carers
Discount of 3.5% for utilities and costs	No – the ERG critiqued this	Yes	Yes	Yes	NICE reference case (1)
Perspective (NHS/PSS)	Yes	NHS	Yes	Yes	NICE reference case (1)
Treatment effect stopping	Not mentioned	The committee considered comments from a clinical expert mentioning that continued benefit of pemetrexed over BSC after disease progression were difficult to explain, but not further analyses seemed to have been conducted to assess the impact of this assumption.	Considered in NICE Committee decision-making	Considered in base case and different cut-offs explored in scenario analyses	Conservative assumption. Lack of evidence that treatment effect stops after discontinuation.
Source of utilities	Nafees et al. (2008), which was a study commissioned by the manufacturer to study second-line treatment of NSCLC.	PARAMOUNT EQ-5D individual patient data.	KEYNOTE-024 EQ-5D individual patient data.	IMpower150 EQ-5D individual patient data	NICE reference case (1)
Source of costs	Patient level data from the clinical trial and resource use events from the	Resource use data from PARAMOUNT	Published literature, resource utilisation and costs accepted in previous	Published literature, resource utilisation and costs accepted in previous	Widely used and accepted sources of cost and RU data in UK HTAs

	JMDB clinical trial database		NICE submissions	NICE submissions	
Adjustment for treatment switching	No	No	No	No	Accepted assumption by ERG and NICE Appraisal committee in TA531 (42)

B.3.2.3 Intervention technology and comparators

The treatments included in the NICE final scope as relevant comparators for the Atezo+Bev+CP combination in first-line metastatic non-squamous NSCLC are outlined in Section B.1.1. However, the relevant comparators included in the economic model for Atezo+Bev+CP deviate from the NICE final scope. Please see Section B.1.1 for justification and more details.

The comparators included in the economic model, for relevant groups of the patient population, are:

- pemetrexed in combination with a platinum drug (carboplatin or cisplatin), and
- pemetrexed plus a platinum drug with pemetrexed maintenance.

The comparison with pembrolizumab in patients with high PD-L1 expression is not included in the cost-effectiveness Section of our submission. [redacted]

Pemetrexed-based chemotherapy represents the UK standard of care chemotherapy for first-line metastatic non-squamous NSCLC:

- Pemetrexed in combination with cisplatin has been recommended by NICE for locally advanced or metastatic NSCLC, only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma (i.e. non-squamous histology) (41). UK clinical expert opinion has confirmed that pemetrexed in combination with a platinum therapy (either cisplatin or carboplatin) is appropriate to be considered standard of care in the UK, for first-line metastatic non-squamous NSCLC. This is confirmed by market share data, showing that pemetrexed-based regimens account for over 80% of chemotherapy in this setting.

- Pemetrexed maintenance is recommended as an option in this population when patients have not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and their ECOG PS is 0 or 1 at the start of maintenance treatment (49). As stated in Section B.2.9, within our NMA and evidence submission pemetrexed maintenance is assumed to be administered after pemetrexed in combination with either cisplatin or carboplatin, due to the way our indirect treatment comparison was structured. This is an assumption that is consistent with the pembrolizumab appraisal in this indication (42) and was validated by four UK clinical experts.
- The comparison of Atezo+Bev+CP to pemetrexed-based regimens will be performed in the following patient populations:
    - o ITT population (i.e. regardless of the level of PD-L1 expression and including patients with EGFR or ALK mutations). This comparison aims to reflect the anticipated license for Atezo+Bev+CP and the NICE final scope, as well as the marketing authorisation and NICE reimbursement population for pemetrexed-based regimens. The ITT-level comparison also utilises the more robust relative effect estimates from the ITT NMA.
    - o PD-L1 low or negative population. Importantly, we will also perform a comparison to pemetrexed-based chemotherapy in the subgroup of patients with negative or low PD-L1 expression (tumour proportion score of 0–49%, TC/IC 0,1,2) (72), as a pragmatic approach to account for the group of patients who are not eligible for pembrolizumab monotherapy and for whom pemetrexed-based regimens are the standard of care in the UK.
    - o EGFR- or ALK-positive population: Pemetrexed in combination with a platinum drug (carboplatin or cisplatin), with or without pemetrexed maintenance, has also been validated by UK clinical experts as the appropriate chemotherapy comparator for EGFR- or ALK-positive advanced non-squamous NSCLC previously treated with (or not eligible for) targeted therapy (please see Section B.1.1 for more details).

The comparisons performed within our evidence submission are summarised below.

Table 25: Patient populations and comparators of interest considered

Patient population	Comparators of interest	Justification
ITT	- Atezo+Bev+CP - Pemetrexed plus platinum, with or without pemetrexed maintenance	- NICE final scope - Clinical guidelines - UK clinical expert opinion

		- Marketing authorisation and NICE reimbursement for pemetrexed-based regimens - Robustness of NMA estimates
PD-L1 negative or low expression (tumour proportion score >50%, TC/IC0,1,2)	- Atezo+Bev+CP - Pemetrexed plus platinum, with or without pemetrexed maintenance	Patient subgroup not eligible for pembrolizumab as a first-line therapy, for whom pemetrexed-based regimens are the UK standard of care. Validated by UK clinical expert opinion
EGFR/ALK mutation positive	- Atezo+Bev+CP - Pemetrexed plus platinum, with or without pemetrexed maintenance	In the absence of clinical guidelines for the chemotherapy that EGFR/ALK positive patients would receive after targeted therapy, UK clinical experts were consulted

ALK, anaplastic lymphoma kinase; EGFR, Epidermal growth factor receptor; IC, immune cells; ITT, intention to treat; PD-L1, Programmed death-ligand 1; TC, tumour cells

Within the economic model:

- Atezo+Bev+CP is included as per its dosing schedule in study IMpower150 and its anticipated marketing authorisation i.e. atezolizumab at a fixed dose of 1200 mg every 3 weeks (Q3W) until loss of clinical benefit or unacceptable toxicity, in combination with bevacizumab 15 mg/kg Q3W until disease progression or unacceptable toxicity, plus carboplatin 6 mg/mL/min (AUC) Q3W for four or six cycles, plus paclitaxel 15 mg/kg Q3W for four or six cycles.
- Pemetrexed plus platinum is used in the model in line with its marketing authorisation and UK clinical practice, i.e. 500 mg/m^2 Q3W up to 6 cycles. Similarly, for pemetrexed maintenance therapy the dosing for eligible patients is 500 mg/m2 Q3W as per marketing authorisation and UK clinical practice. Carboplatin is used as per its marketing authorisation and use in study IMpower150 (see above). Cisplatin is used in line with its marketing authorisation and use in UK clinical practice, i.e. 75 mg/m^2 Q3W up to 6 cycles.

B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of clinical data into the economic model

The primary data source for the Atezo+Bev+CP arm of the economic model is the data derived from the IMpower150 trial. Data from the January 2018 data cut has been used to update the clinical parameters of the cost-effectiveness model, including OS, PFS, treatment duration and safety.

PFS and OS results from IMpower150 were extrapolated to the 20-year time-horizon of the model, as life-time results are not available for patients in the IMpower150 study. Guidance from the NICE DSU was followed to identify parametric survival models for OS and PFS in the base-case of the model (82). In summary, the steps that were followed include:

1. Testing the proportional hazard (PH) assumption, to assess whether joint or separate statistical models were more appropriate for the Atezo+Bev+CP and Bev+CP treatment arms in the study. Based on the different mechanism of action between cancer immunotherapy and chemotherapies the proportional hazards assumption is not likely to hold. Visual inspection of the OS and PFS log-cumulative hazard plots for the two arms in IMpower150 confirmed that the PH assumption does not hold, as the log-cumulative hazard curves over time for Atezo+Bev+CP and Bev+CP, in the ITT population, cross (Figure 32 - Figure 33). This is true for other relevant subgroups of IMpower150 (PD-L1 low or negative, EGFR/ALK positive, see Appendix L). In addition, prior cancer immunotherapy appraisals in NSCLC (42, 51-53, 98) for atezolizumab, pembrolizumab and nivolumab have demonstrated that the proportional hazards assumption is unlikely to hold when comparing these therapies to chemotherapy for time-to-event outcomes.
2. Separate survival models therefore needed to be explored, as per recommendation from the NICE DSU (82). However, as the relevant UK relevant comparators were not included in our pivotal trial IMpower150, a network meta-analysis had to be implemented. Within our evidence submission, for the comparison with pemetrexed-based interventions we implemented a fractional polynomial NMA, to allow for non-proportional hazards to be represented by a multi-dimensional treatment effect (i.e. non-constant treatment effect) (see Section B.2.9 and Appendix D). Proportional hazards are not assumed to apply for Atezo+Bev+CP compared to pemetrexed-based interventions, due to the different mechanism of action between cancer immunotherapy and chemotherapies, as well as based on evidence of the presence of non-proportional hazards in study IMpower 150 (see point 1).
3. As such, a FP NMA was implemented for the comparison to pemetrexed-based interventions. As part of the FP NMA, the Atezo+Bev+CP KM data were parameterised, and an extrapolation was fit to the data based on best fit and clinical plausibility. Comparator curves were then constructed using the atezolizumab curve as a reference, applying the time dependent (i.e. non proportional) relative treatment effects derived from the FP method. Therefore, the FP framework removes the need for separate parameterisations for each comparator. In the base case network for all populations and all NMA comparators, the 1st order FP model with P1=0 (Weibull)

fixed effects was used, on the basis of best fit and clinically plausible tails (see Section B.2.9 and Appendix D). In the sensitivity analyses, the same model with random effects is explored as well as a NMA model approximating PH (Exponential FP model).

4. Within the various parametric survival models explored, visual inspection was used to assess the fit of the curves to the observed clinical trial data. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics were calculated to assess statistical fit. Equally important, the choice of base case parametric models was validated in terms of clinical plausibility of both short-term (visual fit to Kaplan-Meier data) and long-term extrapolations.

Figure 32: Log-cumulative hazard plot for OS in IMpower150 (Arm B vs Arm C, ITT, IMpower150)

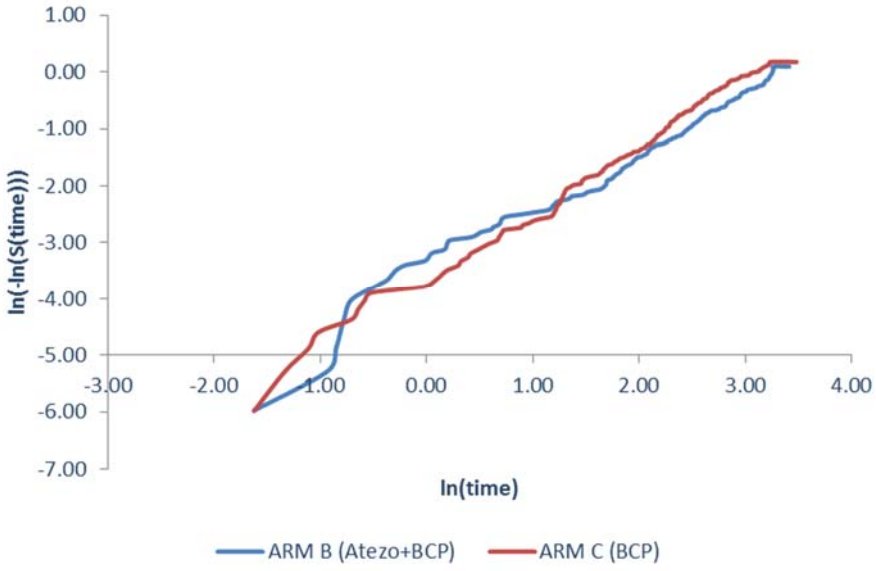
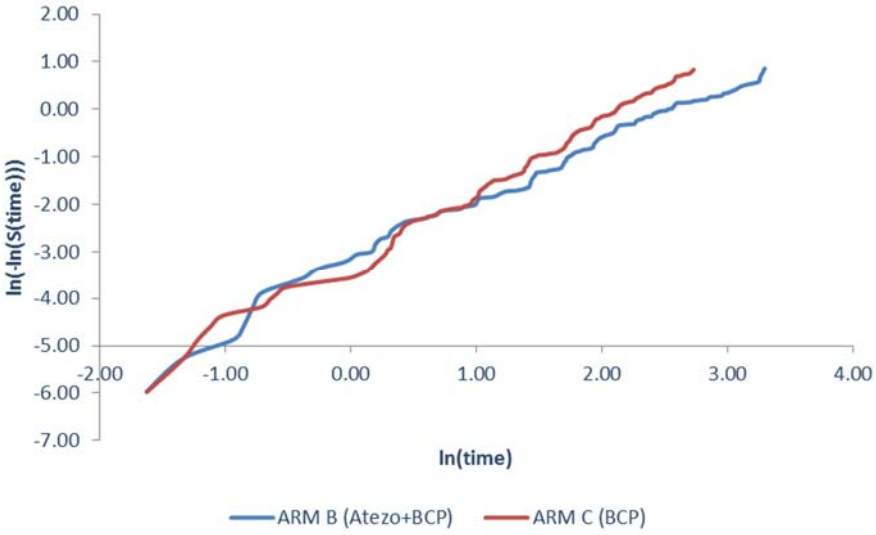


Figure 33: Log-cumulative hazard plot for PFS in IMpower150 (Arm B vs Arm C, ITT, IMpower150)



B.3.3.2 OS extrapolation

ITT population

Table 26 provides the AIC and BIC goodness of fit results for the functions used to model OS for Atezo+Bev+CP in the ITT population of IMpower150. As previously mentioned, the comparator curves were then constructed using the Atezo+Bev+CP curve as a reference, applying the time dependent relative treatment effects from the fractional polynomial NMA.

Table 26: Ranking of OS distributions for Atezo+Bev+CP based on AIC/BIC, visual fit and clinical plausibility – ITT, Atezo+Bev+CP treatment effect cap at 5 years

Parametric distribution	Atezo+Bev+CP AIC (rank)	Atezo+Bev+CP BIC (rank)	Visual fit to KM	Clinical plausibility	Ranking
Exponential	**942.3(3)**	**946.3(1)**	✓	✓	1
Weibull	941.7(2)	949.7(3)	✓	~	2
Log-logistic	947.2(5)	955.2(5)	✓	~	2
Log-normal	958.1(6)	966(6)	×	×	-
Gamma	942.8(4)	954.7(4)	~	×	-
Gompertz	940.7(1)	948.7(2)	~	×	-

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, KM, Kaplan-Meier

Based on the AIC and BIC values for Atezo+Bev+CP (jointly), the best fitting function for OS would be Weibull. However, given that parametric models with a difference in AIC / BIC less than five are considered similar, all models apart from Log-normal appear to have similar statistical fit for OS. It should be noted though that AIC and BIC tests are based only upon the relative fit of parametric models to the observed data. While these tests are useful to determine which models fit the observed data best, they cannot provide information on how suitable a parametric model is for the time period beyond the final trial follow-up. In other words, the AIC and BIC tests address only the internal validity of fitted models, but not their external validity.

A useful method for assessing the plausibility of the extrapolated portions of parametric survival models is through the use of external data and/or clinical validity. Long-term external data are available for the comparator arm only, as expected. These external data are useful for informing the extrapolation of the comparator treatment (i.e. pemetrexed based regimens).

The National Lung Cancer Audit (NLCA) (UK) data suggest that 5-year survival for patients with PS 0-1 and stage IV NSCLC is 5.0% (99). In the NICE appraisal of pembrolizumab in

first-line NSCLC (TA531), the NICE committee and ERG considered in the FAD that a 5-year survival rate of 8–11% for UK standard of care (including pemetrexed plus carboplatin/cisplatin with or without pemetrexed maintenance, or chemotherapy doublets) is reasonable for decision-making, given that cancer immunotherapies are now standard UK clinical practice as a second line treatment for advanced or metastatic NSCLC (42).

A retrospective observational cohort study using the Flatiron Health longitudinal, demographically and geographically diverse database, (100) provided 5 year OS estimates for pemetrexed-based regimens similar to the NICE committee and ERG preferred assumptions in TA531 (42). The Flatiron Health retrospective study demonstrated that the 5-year landmark OS for pemetrexed plus platinum is 8.3% and for pemetrexed plus platinum with pemetrexed maintenance it is 12.3%. Please see Appendix M for more details on the methodology and results of this retrospective observational cohort study.

For Atezo+Bev+CP, clinical expert opinion from ten UK clinicians was collected, as part of an advisory board organised by Roche. UK clinicians suggested that the 5-year OS of patients treated with Atezo+Bev+CP is anticipated to be between 12% and 27% (average of 17%) given the mechanism of action for cancer immunotherapies and the fact that a small proportion of patients are anticipated to be long-term responders and experience a long-term survival benefit. This estimated range is used to validate the long-term OS extrapolation for Atezo+Bev+CP.

Duration of treatment effect also plays a pivotal role for the extrapolation of OS for Atezo+Bev+CP. The assumption used in our base case and considered in the validation of the Atezo+Bev+CP OS extrapolation is that treatment effect is capped at 5 years. This is a conservative assumption, given the lack of evidence to support such a restriction. However, its use in our base case aims to ensure consistency with existing NICE decisions for atezolizumab in other indications (53, 98). This restriction is further discussed later in this section, whilst it will also be tested in scenario and sensitivity analyses.

Table 27 demonstrates that using the function with the best statistical fit for OS (Weibull), the 5 year survival landmark for Atezo+Bev+CP and pemetrexed plus platinum is low, and within the clinically plausible range for pemetrexed plus platinum with pemetrexed maintenance. The next best fitting function, Gompertz had even lower survival rates at 5 years for all interventions, while the Exponential model which is the third best fitting model estimated a slightly more appropriate but still conservative 5-year survival for Atezo+Bev+CP and pemetrexed plus platinum, and an estimate within the clinically plausible range for pemetrexed plus platinum with pemetrexed maintenance. Log-logistic validated well against the 5-year estimates for Atezo+Bev+CP and pemetrexed plus platinum, but produced high

estimates for pemetrexed plus platinum with pemetrexed maintenance. Log-normal provided unrealistically high estimates at the tail of the OS extrapolation for pemetrexed plus platinum with pemetrexed maintenance. Gamma provided unrealistically low estimates for all therapies.

As such, the parametric extrapolation used for OS in the ITT base case analysis is the Exponential model. It should be highlighted however that the Exponential model in our base case provides a conservative 5-year OS estimate for Atezo+Bev+CP, which is lower than the average 5-year OS that UK clinical experts suggested. Log-logistic could be an alternative plausible parametric extrapolation model for OS. Alternative plausible OS extrapolation models are explored in sensitivity analyses.

Table 27: 5 year OS for Atezo+Bev+CP and comparators based on different extrapolation models – ITT

Parametric distribution	Atezo+Bev+CP (treatment effect cap at 5 years)	Pemetrexed plus platinum	Pemetrexed plus platinum with pemetrexed maint.	Clinical plausibility
Exponential	**13%**	**2%**	**12%**	✓
Weibull	10%	1%	9%	~
Log-logistic	20%	5%	18%	~
Log-normal	24%	7%	21%	×
Gamma	4%	0%	5%	×
Gompertz	3%	0%	4%	×

For the comparison with pemetrexed plus platinum, Figure 34 shows the resulting long-term OS curves for both therapies, including the treatment effect cap at 5 years for Atezo+Bev+CP, to reflect our base-case analysis. Figure 35 demonstrates the impact of excluding such a restriction i.e. assuming no treatment effect cap for Atezo+Bev+CP. It is evident that the long term OS extrapolation (after 5 years) for Atezo+Bev+CP in the latter figure is more in line with the long-term expectation for cancer immunotherapies, as well as consistent with previous NICE appraisals for cancer immunotherapies, (42, 51, 53) where a small proportion of patients is anticipated to be long-term responders and experience a long-term survival benefit. As stated already, the treatment effect cap at 5 years for Atezo+Bev+CP aims to ensure consistency with existing NICE recommendations for atezolizumab in other indications (53, 98). The impact of excluding this treatment effect cap on cost-effectiveness results is explored in scenario analyses.

Figure 34: OS extrapolation curves – Atezo+Bev+CP vs. pemetrexed plus platinum – Exponential function - ITT, Atezo+Bev+CP treatment effect cap at 5 years

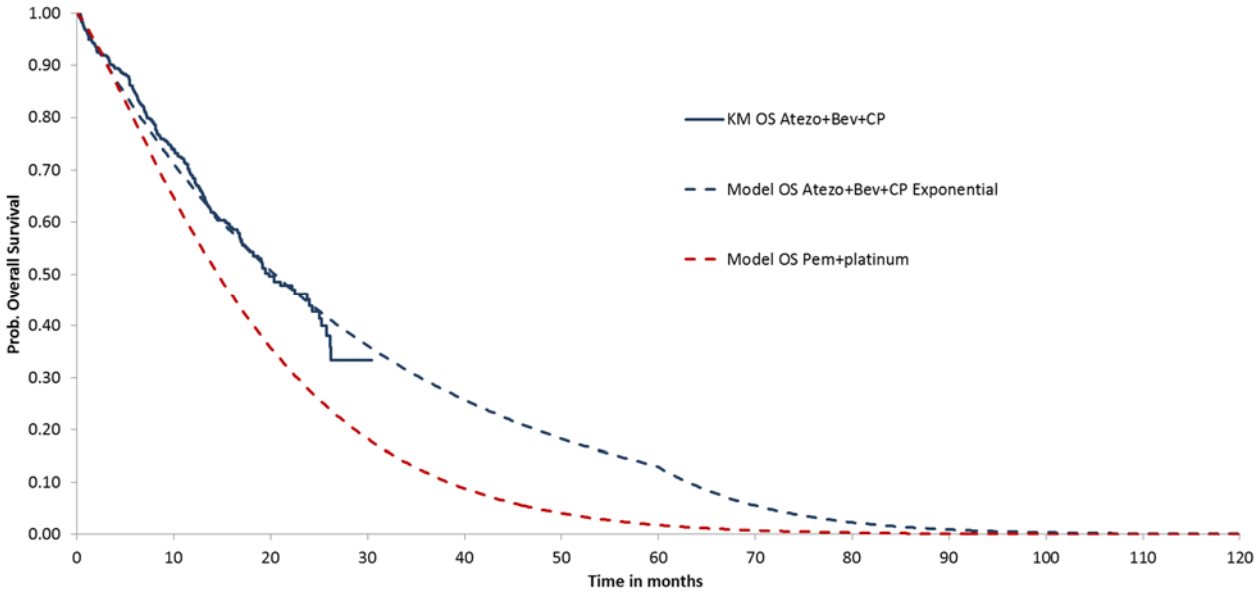
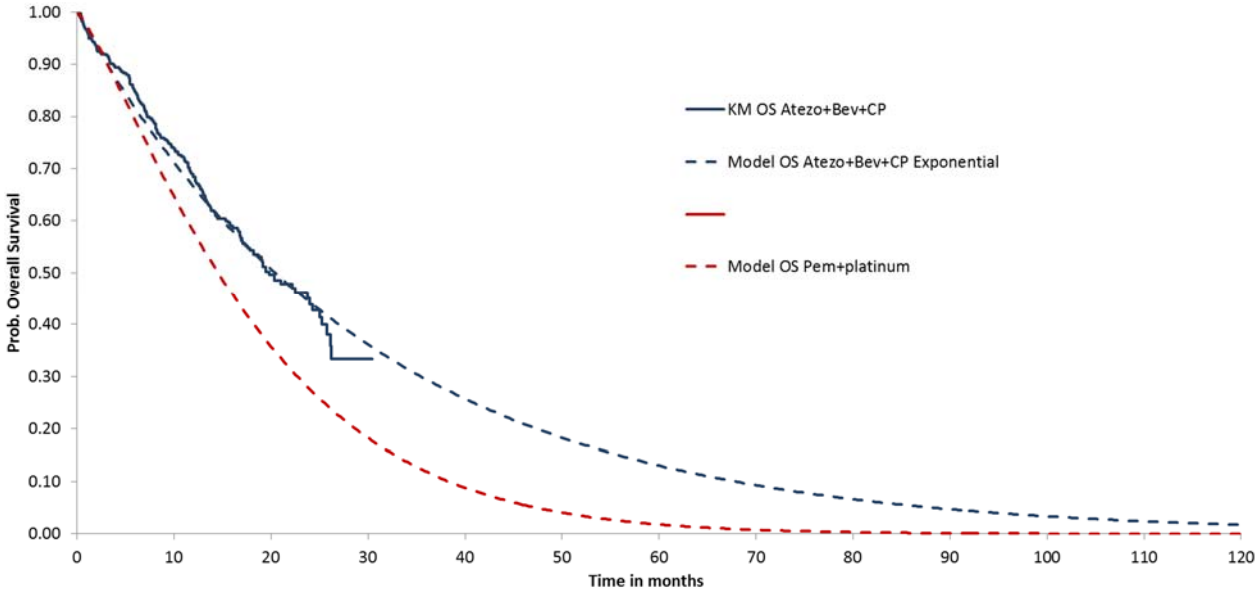


Figure 35: OS extrapolation curves – Atezo+Bev+CP vs. pemetrexed plus platinum – Exponential function - ITT, no treatment effect cap for Atezo+Bev+CP



For the comparison with pemetrexed plus platinum plus pemetrexed maintenance, Figure 36 shows the resulting long-term OS curves vs. pemetrexed plus platinum plus pemetrexed maintenance including the treatment effect cap at 5 years for Atezo+Bev+CP and when the base case NMA network is used, i.e. including the PARAMOUNT study. The treatment effect cap at 5 years implies that after this point, the survival rate from the comparator arm is applied to Atezo+Bev+CP, which is equivalent to assuming a HR of one between the two interventions. When the treatment effect cap is excluded, the long-term OS curves for Atezo+Bev+CP and pemetrexed plus platinum plus pemetrexed maintenance cross, with the

extrapolated OS showing a survival benefit in favour of the pemetrexed-based intervention (Figure 37). This result lacks clinical validity, given the different mechanism of action and the anticipated long-term OS outcomes for cancer immunotherapy versus chemotherapy treatments, whilst it is also inconsistent with previous NICE appraisals for cancer immunotherapy. (42, 53)

This clinically implausible OS for pemetrexed plus platinum plus pemetrexed maintenance in Figure 37 is likely a result of the inclusion of the PARAMOUNT study in the base case NMA network, which introduces selection bias in favour of pemetrexed plus platinum plus pemetrexed maintenance (see Section B.2.9). PARAMOUNT was included in the base case network, to enable a comparison with pemetrexed plus platinum without pemetrexed maintenance, as this is the only study connecting pemetrexed plus platinum to the network of evidence.

Figure 38 demonstrates the impact of excluding PARAMOUNT from the NMA network of studies, with a lifetime treatment effect assumed for Atezo+Bev+CP. The extrapolated long-term OS outcome in Figure 38 is aligned with the clinical expectation for a long-term benefit from cancer immunotherapies over chemotherapy and has external validity and consistency with previous NICE appraisals for cancer immunotherapy. (42, 53) As such, we believe that these results are more appropriate as a basis for decision making for this comparison. However, the NMA network including PARAMOUNT was used in order to enable a comparison against both pemetrexed-based interventions in our evidence submission.

Figure 36: OS extrapolation curves – Atezo+Bev+CP vs. pemetrexed plus platinum plus pemetrexed maintenance – NMA including PARAMOUNT, Exponential function - ITT, Atezo+Bev+CP treatment effect cap at 5 years

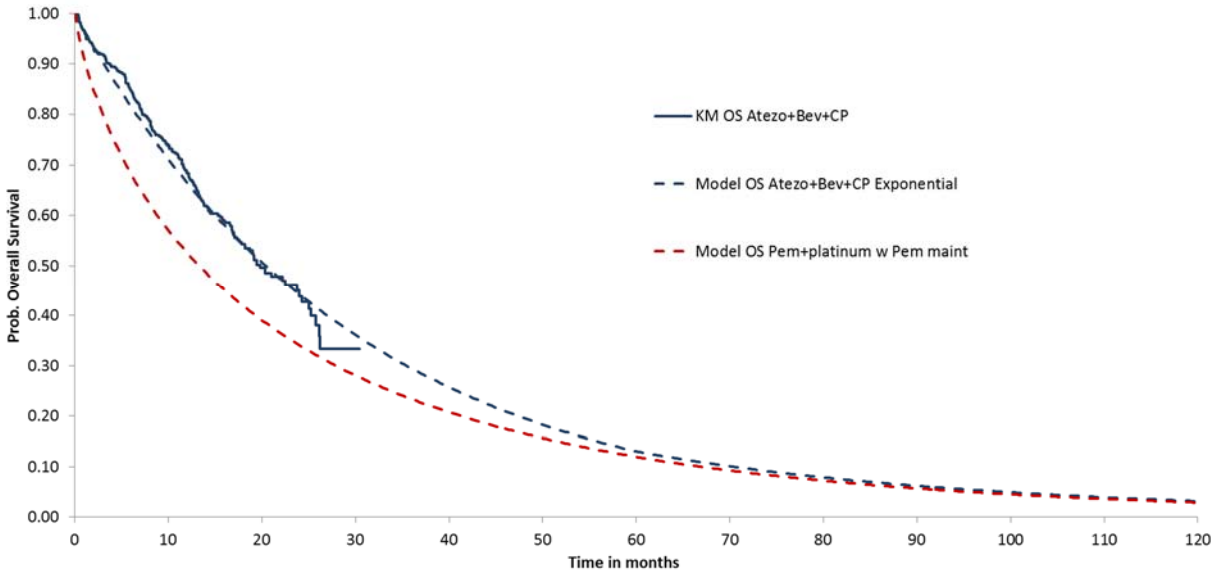


Figure 37: OS extrapolation curves – Atezo+Bev+CP vs. pemetrexed plus platinum plus pemetrexed maintenance – NMA including PARAMOUNT, Exponential function - ITT, no treatment effect cap for Atezo+Bev+CP

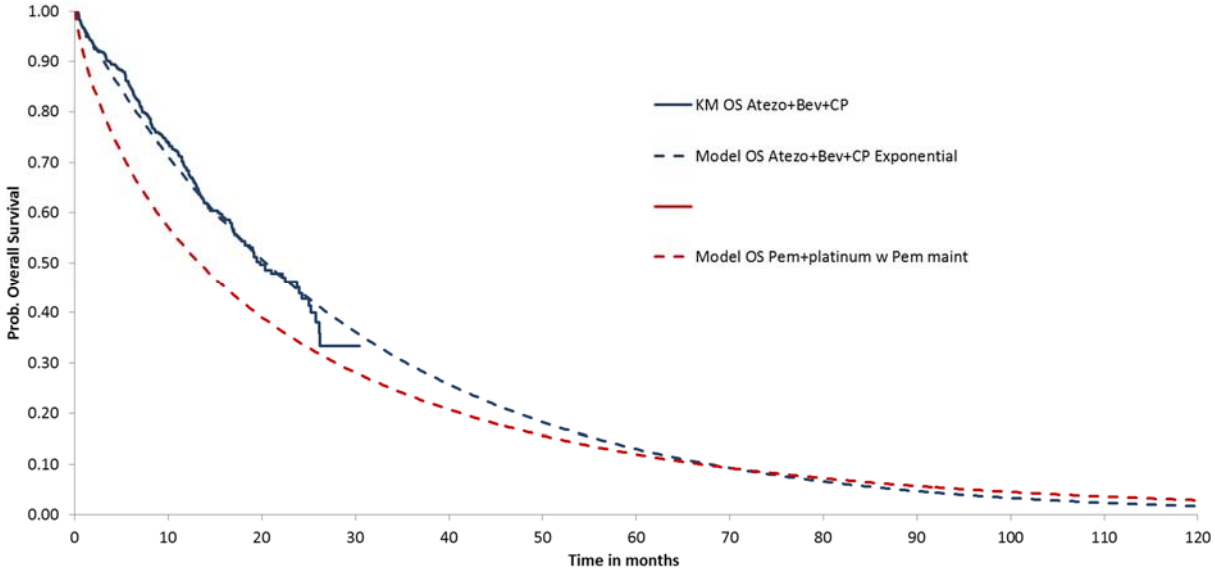
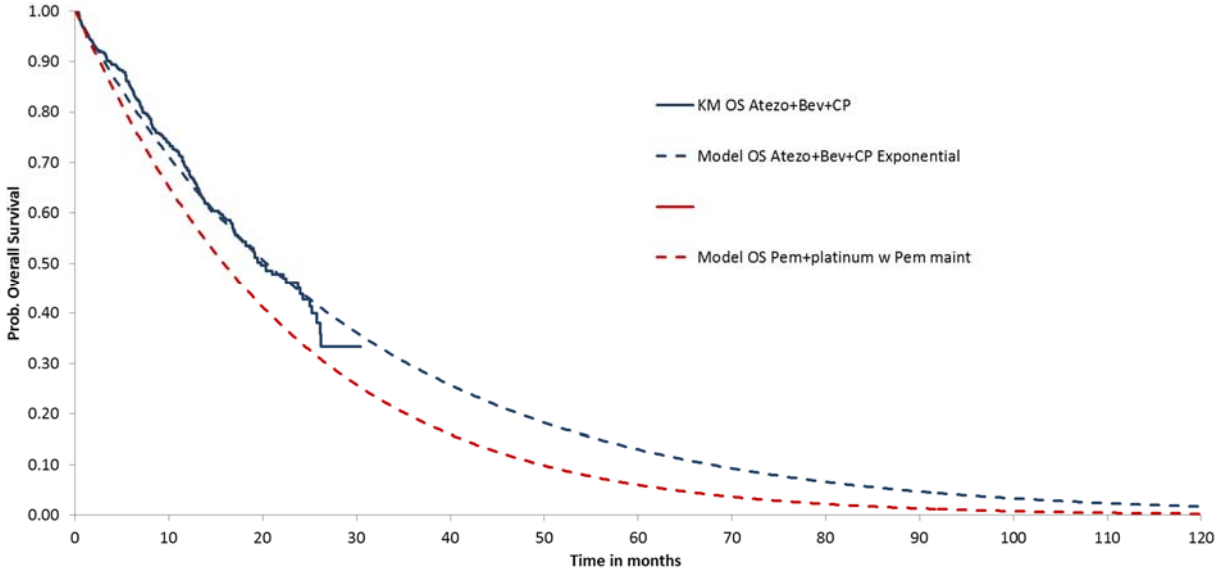


Figure 38: OS extrapolation curves – Atezo+Bev+CP vs. pemetrexed plus platinum plus pemetrexed maintenance – NMA excluding PARAMOUNT, Exponential function - ITT, no treatment effect cap for Atezo+Bev+CP



Subgroups

A similar approach was taken for the extrapolation of OS in relevant subgroups of interest (EGFR/ALK positive, PD-L1 negative or low). Based on the assessment of statistical and visual fit, as well as long-term validity of the extrapolated OS, the selected extrapolation models for the relevant subgroups of interest are:

- PD-L1 low or negative (TC/IC 0,1,2): Exponential

- EGFR/ALK positive: Exponential

Other plausible OS extrapolation models for these subgroups are explored in scenario analyses. Further details are provided in Appendix N.

Treatment effect duration and treatment stopping rule

As mentioned already in this section, in previous appraisals for atezolizumab (51, 98) different assumptions for the duration of treatment effect of atezolizumab on OS and PFS were considered relevant for decision-making by the NICE appraisal committee: lifetime treatment effect, and treatment effect capped at either 3 or 5 years following treatment discontinuation at 2 years. Whilst there is uncertainty around the long-term treatment benefit for atezolizumab, the committee-preferred scenario for the duration of treatment effect for atezolizumab was 5 years (i.e. treatment effect continues for 3 years following treatment discontinuation at 2 years). We consider that this is a conservative assumption, given the lack of evidence to support such a restriction. However, in order to ensure consistency across the NICE committee decisions for atezolizumab, we have included in our base case (in the ITT and all relevant subgroups) a treatment stopping rule at 2 years for Atezo+Bev+CP and have set the treatment effect to be capped at 3 years after treatment discontinuation (i.e. at 5 years from model entry). After that cut-off point, the survival rate from the comparator arm is applied to the Atezo+Bev+CP, which is equivalent to assuming a hazard ratio of one between the two interventions.

B.3.3.3 PFS extrapolation

ITT population

Table 28 provides the AIC and BIC goodness of fit results for the functions used to model PFS for Atezo+Bev+CP in the ITT population. Similarly to the approach for OS, the comparator curves were constructed using the Atezo+Bev+CP curve as a reference, applying the time dependent relative treatment effects from the fractional polynomial NMA.

Table 28: Ranking of PFS distributions for Atezo+Bev+CP based on AIC/BIC, visual fit and clinical plausibility – ITT

Parametric distribution	Atezo+Bev+CP AIC (rank)	Atezo+Bev+CP BIC (rank)	Visual fit to KM	Clinical plausibility
Exponential	1099.4(5)	1103.3(4)	✓	×
Weibull	1093.1(3)	1101.1(2)	~	×
Log-logistic	**1086.2(1)**	**1094.1(1)**	✓	✓
Log-normal	1096.5(4)	1104.5(5)	✓	✓
Gamma	1089.2(2)	1101.2(3)	✓	~
Gompertz	1100.1(6)	1108.1(6)	~	×

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, KM, Kaplan-Meier.

Based on the AIC and BIC values for Atezo+Bev+CP (jointly), the best fitted function for PFS is Log-Logistic. For the PFS curve, most of the events in IMpower150 had already been observed at the time of the January 2018 data cut off (73% for the Atezo+Bev+CP). Hence, there is less uncertainty in the extrapolation of the survival curves beyond the observed period. As such, the AIC/BIC values and the visual fit to the observed data should be a good indicator of the best choice for extrapolation. Clinical plausibility however was also considered; model predictions for 5-year landmark PFS for Atezo+Bev+CP were compared against clinical expert opinion from ten UK clinicians, indicating a PFS of 2%-5% at 5 years. According to all these criteria, the Log-logistic was determined to be the most appropriate function and is used in the base case.

Given that the PFS data for Atezo+Bev+CP in IMpower150 are relatively complete, it was deemed appropriate to use the PFS KM curve followed by the Log-logistic distribution, as this was the parametric model showing the best visual fit to the observed PFS data. The cut-off point for switching from KM to parametric extrapolation is when 20% of patients remain at risk (101), to ensure robustness in terms of patient numbers whilst the KM data being utilised. Alternative PFS extrapolations are explored in sensitivity analyses.

Also, in order to ensure consistency in the way the treatment effect cap for Atezo+Bev+CP is implemented across the different endpoints, the restriction on the duration of treatment effect for Atezo+Bev+CP is applied to both OS and PFS.

Figure 39: PFS extrapolation curves – Atezo+Bev+CP vs. pemetrexed plus platinum – KM+Log-logistic function - ITT

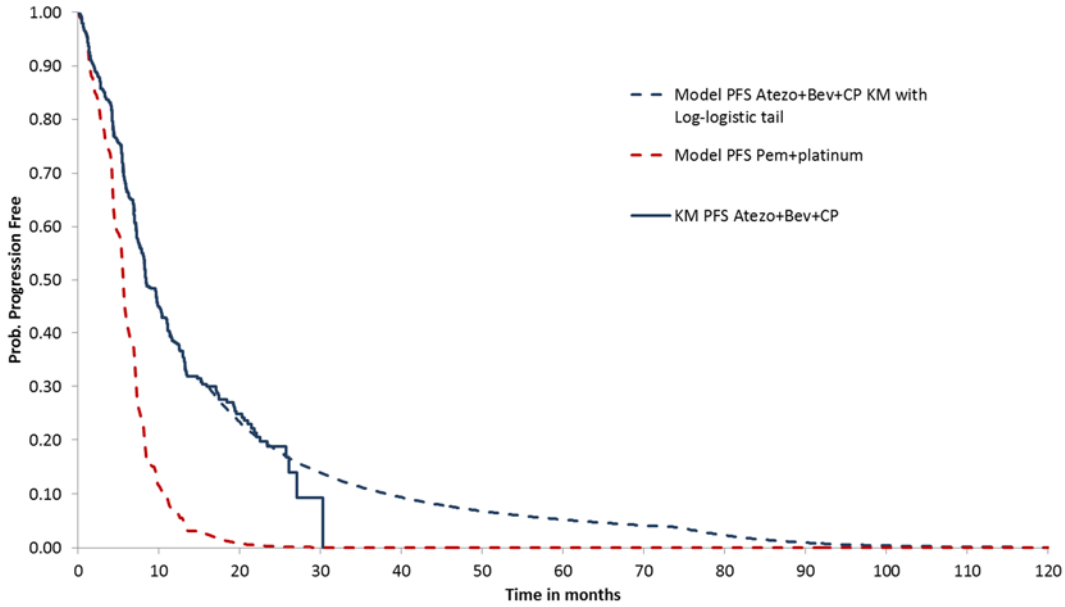
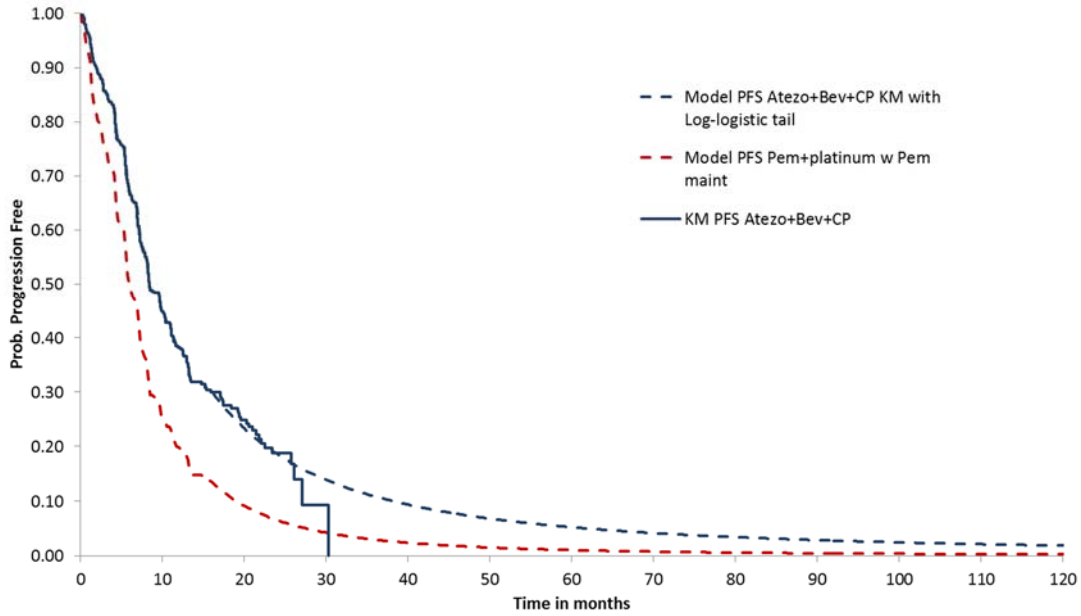


Figure 40: PFS extrapolation curves – Atezo+Bev+CP vs. pemetrexed plus platinum plus pemetrexed maintenance – KM+Log-logistic function - ITT



Subgroups

A similar approach was taken for the extrapolation of PFS in relevant subgroups of interest (EGFR/ALK positive, PD-L1 negative or low). For PFS, as data are relatively complete in study IMpower150, the AIC/BIC values and the visual fit to the observed data should be a good indicator of the best choice for extrapolation. According to these, the base case PFS extrapolations for each of the relevant patient subgroups are shown below.

- PD-L1 low or negative (TC/IC 0,1,2): KM+Log-logistic
- EGFR/ALK positive: Log-normal (fully parametric due to lower patient numbers)

Further details are provided in Appendix O.

B.3.3.4 Treatment duration extrapolation

Atezolizumab is used until loss of clinical benefit or unmanageable toxicity in study IMpower150, in line with its anticipated license for this indication. Results from the IMpower150 study, and clinical trial evidence from other indications for atezolizumab, suggest that patients continue to receive treatment with atezolizumab beyond disease progression. As such, PFS is not a good surrogate for the treatment duration of atezolizumab as it is likely to underestimate the true treatment duration expected in clinical practice, and subsequently, treatment cost.

Data on time to treatment discontinuation (TTD) are available for Atezo+Bev+CP in IMpower150. As such, TTD data directly from the IMpower150 study were used to inform treatment duration for atezolizumab in the economic model. For bevacizumab, whilst it is administered until disease progression or unacceptable toxicity, we still consider that TTD data from the study are more accurate to estimate treatment duration, compared to PFS.

Not all patients had discontinued treatment in IMpower150; approximately 20% and 10% of patients were still on treatment with atezolizumab and bevacizumab respectively at the time of the IMpower150 data cut (January 2018). As such, it was necessary to extrapolate the study results so that treatment duration could be estimated beyond the trial period. Parametric distributions were fitted to the TTD Kaplan–Meier curves and assessed for their goodness of fit to the data using the AIC/BIC statistics, visual assessment and clinical plausibility of each of the extrapolations.

The chemotherapy combination partners (carboplatin and paclitaxel) are given for a fixed number of cycles in the model as per the study protocol. The proportion of patients on chemotherapy treatment during the first 6 cycles is taken from the atezolizumab TTD curve for simplicity (i.e. assuming that the same proportion of patients who are on atezolizumab will also receive chemotherapy for the first 6 cycles).

Table 29 provides the AIC and BIC goodness of fit results for the functions used to model TTD. According to AIC/BIC only, the best function to model TTD would be the Gamma; however, the resulting extrapolated curves do not seem to visually fit the observed data at the beginning of the curve for both atezolizumab and bevacizumab. The next best fitting models, Weibull, Log-Normal and Log-Logistic provided poor fit to the observed data and

very long unrealistic tails. Gompertz did not converge. Therefore, the Exponential parametric distribution is used in the base case for the extrapolation of TTD, because whilst it does not provide the best statistical fit, it does demonstrate the best visual fit out of all potential distributions, as well as clinical validity. Alternative plausible distributions are explored in sensitivity analyses.

Table 29: Ranking of TTD distributions for Atezo and Bev in Atezo+Bev+CP based on AIC/BIC, visual fit and clinical plausibility – ITT

Parametric distribution	Atezo in Atezo+Bev+CP AIC (rank)	Bev in Atezo+Bev+CP AIC (rank)	Atezo in Atezo+Bev+CP BIC (rank)	Bev in Atezo+Bev+CP BIC (rank)	Visual fit to KM	Clinical plausibility
Exponential	**1584.3(4)**	**1669.2(4)**	**1588.3(4)**	**1673.1(4)**	✓	✓
Weibull	1499(2)	1570(2)	1507(2)	1577.9(2)	×	×
Log-logistic	1559.1(3)	1651.3(3)	1567.1(3)	1659.3(3)	×	×
Log-normal	1642.9(6)	1730.5(6)	1650.8(6)	1738.4(6)	×	×
Gamma	1462.5(1)	1519(1)	1474.4(1)	1530.9(1)	~	~
Gompertz	1586.3(5)	1671.2(5)	1594.2(5)	1679.1(5)	×	×

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, KM, Kaplan-Meier

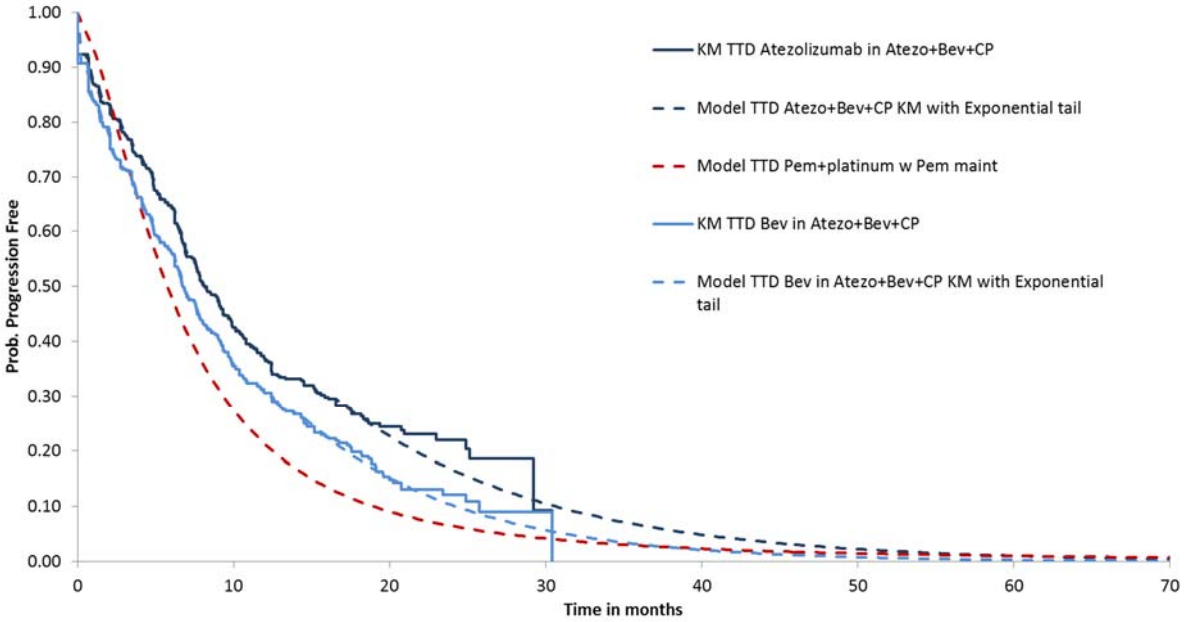
Given that the observed TTD data for Atezo+Bev+CP in IMpower150 are relatively complete, it was deemed appropriate to use the TTD KM curve followed by the Exponential distribution, as this was the parametric model showing the best visual fit to the observed data, for both atezolizumab and bevacizumab. The cut-off point for switching from KM to parametric extrapolation is when 20% of patients remain at risk (101), to ensure robustness in terms of patient numbers whilst the KM data being utilised. The resulting extrapolations in the base case analysis are displayed in Figure 41 below.

Treatment stopping rule

As mentioned already, a stopping rule at 2 years is applied to treatment with Atezo+Bev+CP, in line with previous In line with previous NICE appraisals for atezolizumab, in which the NICE committee preferred scenario included this restriction (51, 98). We consider that there is lack of evidence on whether a stopping rule should be applied to treatment with atezolizumab and whether two years is the appropriate time point for such a restriction. However, we have included this treatment stopping rule at 2 years for Atezo+Bev+CP in our base case, to ensure consistency with previous NICE committee decisions for atezolizumab. The treatment stopping rule at 2 years is applied in the economic model by assuming that drug acquisition and drug administration costs for Atezo+Bev+CP are zero after 2 years.

Please note that whilst the curves in Figure 41 and Appendix P show that a proportion of patients are still on Atezo+Bev+CP treatment after 2 years, the treatment stopping rule at 2 years is still applied in the economic model by assuming that treatment-related costs for Atezo+Bev+CP are zero after 2 years. The impact of excluding this restriction is explored in scenario analyses.

Figure 41: TTD extrapolation curves – Atezo+Bev+CP – Kaplan-Meier plus Exponential parametric extrapolation - ITT



Subgroups

A similar approach was taken for the extrapolation of TTD in relevant subgroups of interest (EGFR/ALK positive, PD-L1 negative or low). As in the ITT population, the observed TTD data in IMpower150 in PD-L1 low or negative patients are relatively complete, and the TTD KM curve followed by the Exponential distribution is used in this subgroup. For the EGFR/ALK positive population, due to the small number of patients a fully parametric Exponential model is used to extrapolate TTD. Further details are provided in Appendix P.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Health-related quality of life (HRQoL) data were collected in the IMpower150 study directly from first line metastatic non squamous NSCLC patients via the EQ-5D-3L questionnaire. Measurement and valuation of HRQoL using EQ-5D-3L directly from patients is consistent

with the NICE reference case (1), hence HRQoL from IMpower150 is used in our base case analysis.

EQ-5D-3L data were collected in IMpower150 at each scheduled study visit prior to administration of study drug and prior to any other study assessment(s). During survival follow-up the EQ-5D-3L was completed at 3 and 6 months following disease progression (or loss of clinical benefit for atezolizumab-treated patients). In total 96% of the patients completed the EQ-5D-3L at least once. The EQ-5D-3L index scores were calculated using UK tariffs (102).

We considered two different approaches for the calculation of utility values from IMpower150: (i) the proximity to death approach and (iii) the pre- and post-progression approach. This section provides further detail on both approaches. However, the proximity to death approach was used in the base case analysis, as it reflects the known decline in cancer patients' quality of life during the terminal phase of the disease, while it is also consistent with recent NICE appraisals in NSCLC (49, 51, 98).

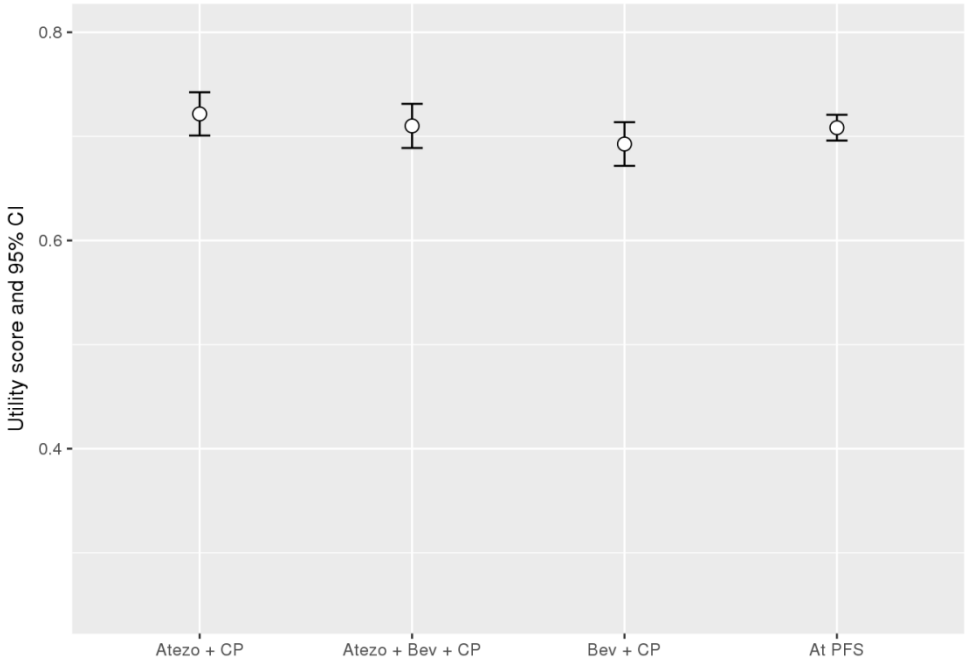
To estimate the mean utility scores we used repeated measurement models initially assuming an unstructured correlation between observations coming from the same subject. Where convergence issues were observed, an exchangeable correlation structure was assumed.

Pre- and post-progression approach

We fit two models one for the pre-progression period and one for the post-progression period.

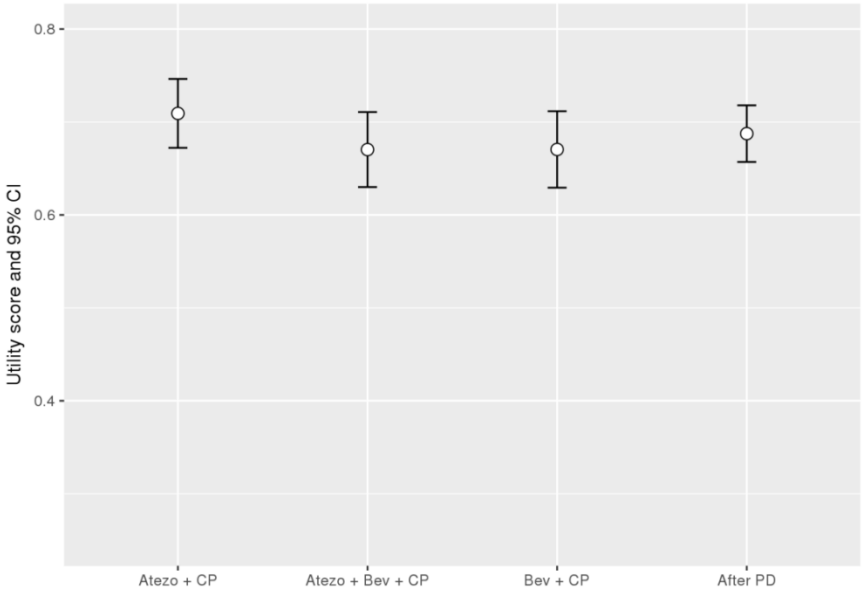
For utilities during the pre-progression period, a fixed effects model was used, including day of assessment, treatment arm and an indicator variable taking a value of one if a patient had a treatment related adverse event Grade ≥3 during pre-progression and zero otherwise, with an exchangeable working correlation. Since we did not observe a significant difference between mean utilities by treatment arm, and the confidence intervals overlapped, for the economic model we used a pooled pre-progression mean utility, regardless of treatment arm.

Figure 42: Pre-progression utility values from IMpower150



For the post-progression period, a fixed effects model was used, including day of assessment and treatment arm as covariates, with an exchangeable working correlation. Since there are fewer observations during the post-progression period, we observed larger variability of the means and broader confidence intervals. As such, we also used a pooled post-progression mean utility in the economic model, regardless of treatment arm.

Figure 43: Post-progression utility values from IMpower150



Proximity to death approach

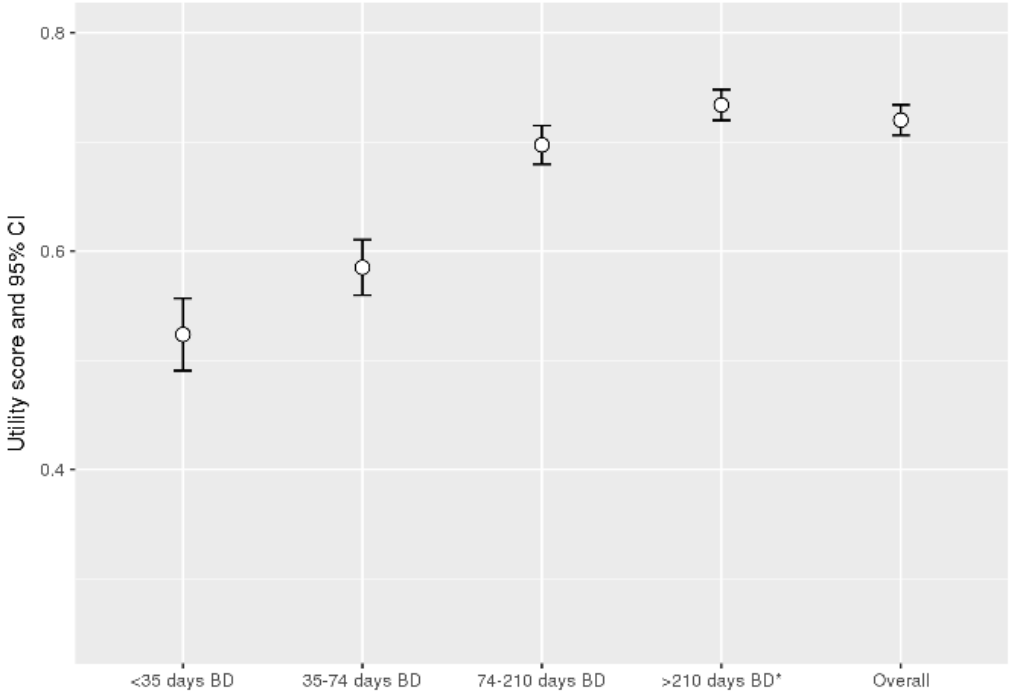
As already stated, the proximity to death approach was considered as more relevant, since it reflects the known decline in cancer patients' quality of life during the terminal phase of the disease, while it is also consistent with recent cancer immunotherapy NICE appraisals in NSCLC (51, 98). The proximity to death utilities were analysed for patients who were both on treatment and patients who had discontinued treatment. We considered four intervals for the proximity to death approach, in line with the atezolizumab NICE submission for second-line NSCLC (53):

- Group 1: less than 35 days before death (BD)
- Group 2: more than 34 and less than 75 days BD
- Group 3: more than 74 and less than 210 days BD
- Group 4: more than 211 days BD

At time of clinical cut-off 47.8% of patients were still alive; these patients provided almost ten thousand of HRQoL observations. In principle, the proximity to death approach would not include utilities for patients who are alive. However, following this approach would result in discarding 68.5% of the utility observations available from the study. Therefore, in Group 4 we included utilities for patients still alive and with more than 211 days follow up.

We fitted a model including time before death group, assessment time and treatment arm as covariates and we assumed an exchangeable working correlation. Initially we considered two separate models according to the treatment status: on and off treatment. However, results for off-treatment utilities produced broad confidence intervals which would overlap. This would produce unrealistic results in the probabilistic sensitivity analysis (PSA) of the economic model where patients closer to death would have higher utility than those further away from death. Therefore, we decided to fit and to report only utilities by time before death group according to the proximity to death as it is shown in the following figure.

Figure 44: Proximity to death utility values from IMpower150



The utility values from IMpower150 considered in our evidence submission are summarised in Table 30.

B.3.4.2 Mapping

HRQoL was collected using the EQ-5D-3L questionnaire in the IMpower150 study, consistent with the NICE reference case (1). As such, no mapping techniques were required.

B.3.4.3 Health-related quality-of-life studies

A SLR was conducted to identify HRQoL evidence in the first-line treatment of patients with non-squamous NSCLC. Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix H.

Summary of identified studies and results

Overall, the review identified a total of 43 publications reporting health state utility values associated with advanced or metastatic NSCLC being treated in the first-line setting. Of these, a total of five reported utilities in graph format only and were tagged. The remaining 38 studies reported unique, original HSUV data for the population of interest and form the basis of the results section of the current report. Of these 38 studies, 17 were presented as full publications, and 21 were presented as conference abstracts only. Utilities were reported for a range of health states for the population of interest, including intervention-specific utilities, progression status (progression free/progressive disease/stable disease), treatment

line, disease stage, and patient characteristics such as age, gender, time since diagnosis, presence or absence of metastatic disease, and recurrence status.

With regard to utility relevance for NICE, of the full publications identified, the majority utilised the EQ-5D to derive utilities in line with the NICE reference case. However, only five studies fully met the NICE requirements; that is, utilities were derived directly from patients using the preferred EQ-5D and health states were valued using UK societal preference elicited using the direct TTO method (103-107). From these five studies, an assessment of suitability was conducted to determine which publications would be more appropriate for use in the economic model. The two studies selected to be included in the model were studies by Nafees et al. (28) and Chouaid et al. (103). In addition, those two studies were found to have been used in most of the economic evaluations published in NSCLC (see the SLR on published cost-effectiveness studies, Section B.3.1). The utility values from these studies are implemented as scenario analyses

Similarly, among the conference abstracts identified, the EQ-5D was the most commonly used instrument for measuring patient HRQOL; however, only four abstracts specified the method of valuation for health states, of which only two utilised the UK tariff (including the EQ-5D-5L UK crosswalk value set) in line with NICE requirements. A summary of the studies and conference abstracts relevant to NICE identified in the systematic review summary and the reported utility data are presented in Appendix H.

B.3.4.4 Adverse reactions

Two approaches could be taken regarding the inclusion of the impact of AEs on HRQoL:

1. The assumption that any disutility has already been incorporated in to the base case health state utilities through the trial derived EQ-5D utilities, and incorporating an additional disutility could be considered double counting;
2. The assumption that averaged trial-derived utilities underestimate disutilities associated with adverse events, and therefore an additional disutility must be applied.

Consistent with previous appraisals in this indication the base case analysis takes the former assumption and does not include any disutility for AEs (42, 51, 53). However, for completeness, a scenario analysis is included exploring quality of life decrements of AEs. Detailed information on how disutilities were implemented in this scenario analysis are provided in Appendix Q.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Table 30: 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 study. Methodology as per NICE reference case
> 5 & ≤ 15 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 study.
Post-progression	0.69	0.66 - 0.72		
Pembrolizumab utilities - Proximity to death approach – US publication (108) - 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*			

*calculated based on reported regression coefficients; CI: confidence interval

Consistency of literature utility values with values derived from IMpower150

Progression free utility estimates from the literature are broadly in line with the pre-progression utility values from IMpower150, as well as with the two intervals less close to death, in the proximity to death approach from IMpower150. In terms of progressed disease

utility values from the literature, these are not consistent between the two identified published studies. It should be noted that progressed utilities from the Nafees et al study have been criticised in previous appraisals as unrealistically low. Nonetheless, the utility values from IMpower150 - either for the post-progression period or for the two intervals closer to death in the proximity to death approach - are within the range defined by the progressed disease utility values in the two published studies (see Table 30).

In addition, in NICE TA531 a proximity to death utility approach was followed for pembrolizumab in first line NSCLC (42); the utility values were however redacted in the company submission. Within the publicly available committee papers for NICE TA531, the range of utility values was reported, which was 0.48-0.808 across the four intervals before death being assumed. The ERG and NICE committee critiqued that the higher end of this range (utility for interval >360 days to death) is implausibly high and in the NICE preferred analysis this utility was capped to match the UK population norm. In the utility values used in our evidence submission from IMpower150 (proximity to death approach), there is no concern around the plausibility of the derived utility values and how they compare to the UK population norm. Since the utility values from NICE TA531 are not publicly available, we have implemented a scenario analysis in our evidence submission using the proximity to death utilities from the published cost-effectiveness analysis of pembrolizumab as a first-line treatment for metastatic NSCLC in the United States. (108)

The impact of using different utility values from IMpower150 or from the literature (see Table 30) is explored in scenario analyses.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

A SLR was conducted to identify recent studies (published in the last five years) presenting novel cost and resource use data associated with non-squamous advanced or metastatic non-small-cell lung cancer (NSCLC), irrespective of treatment line, relevant to the economic model of atezolizumab as a first-line treatment of patients with non-squamous metastatic NSCLC.

Summary of identified studies and results

A total of 9 records, representing 7 unique studies, ultimately met the inclusion criteria of the SLR. Detailed descriptions of the search strategy, search terms and extraction methods, as well as details of the included studies, are provided in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs for the treatments being considered in the model are presented in Table 31. Where available, the unit cost for the drugs included in the model were taken from the electronic market information tool (eMIT) which provides prices for generic drugs based on the average price paid by the NHS (16). For drug costs were not available from eMIT, the costs from the British national Formulary (BNF) were used (15). It is also useful to note that pembrolizumab and pemetrexed maintenance, are associated with confidential discounts.

The dosing for each of the drugs considered in the model is outlined below:

- Atezolizumab: as per anticipated marketing authorisation for Atezo+Bev+CP and dosing schedule in study IMpower150 i.e. atezolizumab at a fixed dose of 1200 mg Q3W until loss of clinical benefit or unacceptable toxicity.
- Bevacizumab: as per dosing schedule in study IMpower150 and anticipated marketing authorisation for Atezo+Bev+CP i.e.15 mg/kg Q3W until disease progression or unacceptable toxicity.
- Carboplatin: as per dosing schedule in study IMpower150 within Atezo+Bev+CP i.e. 6 mg/mL/min (AUC) for four or six cycles Q3W
- Paclitaxel: as per dosing schedule in study IMpower150 within Atezo+Bev+CP i.e. 15 mg/kg for four or six cycles Q3W
- Pemetrexed: in line with its marketing authorisation and use in UK clinical practice, i.e. 500mg/m^2 Q3W up to 6 cycles
- Cisplatin: in line with its marketing authorisation and use in UK clinical practice, i.e. 75mg/m^2 Q3W up to 6 cycles

The average weight (71.9kg) and BSA (1.81m^2 using the Dubois formula) from the IMpower150 study (Arms B and C) were utilised to estimate the average cost per dose per patient for the treatments with dosing according to weight or BSA. The drug costs of the combination therapies were assumed to be equal to the sum of individual drug's costs included in a combination therapy (e.g., the drug costs for the combination pemetrexed/cisplatin therapy per administration is the sum of drug costs for pemetrexed per administration plus the drug costs for cisplatin per administration).

As a conservative assumption, the base case of the economic model assumes full vial sharing (i.e., no wastage) for the administration of all weight-based drugs in the model. For completeness, a scenario analysis is provided assuming drug wastage of weight-based drugs.

Table 31: Drug acquisition costs

Drug	Vial/pack concentration	Vial/pack volume	Dose per vial/pack	Cost per vial/pack	Cost per mg	Source
Atezolizumab	60 mg/ml	20 ml	1200 mg	£3807.69	£3.17	BNF
Bevacizumab	25 mg/ml	4 ml	100 mg	£242.66	£2.43	BNF
Bevacizumab	25 mg/ml	16 ml	400 mg	£924.40	£2.31	BNF
Pemetrexed	100 mg powder			£160	£1.60	BNF
Pemetrexed	500 mg powder			£800	£1.60	BNF
Carboplatin	10 mg/ml	15 ml	150 mg	£6.35	£0.04	eMIT
Cisplatin	1 mg/ml	100 ml	100 mg	£10.13	£0.10	eMIT
Paclitaxel	6 mg/ml	16.7 ml	100 mg	£9.85	£0.10	eMIT

eMIT: 12 month period until end June 2017

Table 32: Dosing schedule and dose per administration

Drug	Dosing per administration	Frequency of administration	Total dose	Reference for dosing
Atezolizumab	1200 mg fixed	Q3W	1200 mg	SmPC (2), IMpower150
Bevacizumab	15 mg/kg	Q3W	1079 mg	IMpower150
Pemetrexed	500 mg/m²	Q3W	905 mg	SmPC (109)
Carboplatin	6 mg/mL/min (AUC)	Q4W	692 mg	SmPC, (110),IMpower150
Cisplatin	75 mg/m²	Q3W	136 mg	SmPC (111)
Paclitaxel	200 mg/m²	Q3W	362 mg	SmPC, (112), IMpower150
Docetaxel	75 mg/m²	Q3W	136 mg	SmPC (113)
Nivolumab	3mg/kg	Q2W	216 mg	SmPC (114)

Q3W, every three weeks; Q4W, every four weeks; AUC, area under the curve

Table 33: Drug cost per treatment cycle for interventions used in the cost-effectiveness model

Comparator	Method and frequency of administration	Total drug cost per cycle (with vial sharing)	Drug cost per combination partner per cycle
Atezo+Bev+CP	IV, Q3W	£6.445.89	Atezo: £3,807.69 Bev: £2,573.73 C: £29.31* P: £35.71*
Pemetrexed plus cisplatin/carboplatin	IV, Q3W	£1,471.61	Pemetrexed: £1,450.07 Carboplatin: £29.31 Cisplatin: £13.77

IV: intravenous; Q3W: every three weeks

*Carboplatin and paclitaxel only administered for 4 or 6 cycles

Subsequent therapies

The costs of subsequent lines of therapy are included in the progressed disease health state of the model. Although data on the treatment and type duration of subsequent lines of therapy, after discontinuation from Atezo+Bev+CP were collected IMpower150 study, these are not fully representative of UK clinical practice, as a proportion of patients treated with Atezo+Bev+CP in IMpower 150 receive subsequent cancer immunotherapy, bevacizumab or pemetrexed-based chemotherapy.

In order to account for this in the model base case, an adjustment was made with respect to subsequent therapies. This approach is in line with UK clinical practice and was accepted by the NICE committee and the ERG in the recent NICE appraisal of pembrolizumab in first-line NSCLC (TA531) (42). As such, in the model base-case, all patients treated with Atezo+Bev+CP are assumed to receive docetaxel second-line. This is reflective of UK clinical practice and in line with the second-line marketing authorisation of cancer immunotherapies. For patients treated with pemetrexed-based chemotherapy in the model, 15% are assumed to receive docetaxel as a second-line therapy, based on the current market share of docetaxel in second-line metastatic non-squamous NSCLC (Roche assumption, based on market share data). The remaining proportion of patients is assumed to receive a cancer immunotherapy as a second-line treatment (see **Error! Not a valid bookmark self-reference.**). Our base-case approach to subsequent therapies is outlined in **Error! Not a valid bookmark self-reference.**. Drug acquisition costs and dosing schedule for subsequent therapies are presented in Table 35 - Table 36.

Table 34: 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%	18.00	Docetaxel SmPC (113)
Nivolumab	0%	34%	26.52	NICE TA484 (52)
Pembrolizumab *	0%	34%	21.59	NICE TA428 (51)
Atezolizumab	0%	17%	35.80	NICE TA520 (53)

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

Table 35: Drug acquisition costs – subsequent therapies

Drug	Vial/pack concentration	Vial/pack volume	Dose per vial/pack	Cost per vial/pack	Cost per mg	Source
Atezolizumab	60 mg/ml	20 ml	1200 mg	£3807.69	£3.17	BNF
Pembrolizumab	25 mg/ml	4 ml	100 mg	£2630.00	£26.30	BNF
Pembrolizumab	Powder for concentrate for IV solution		50 mg	£1315.00	£26.30	BNF
Docetaxel	20 mg/ml	7 ml	140 mg	£20.62	£0.19	eMIT
Docetaxel	20 mg/ml	1 ml	20 mg	£3.85	£0.15	eMIT
Nivolumab	10 mg/ml	4 ml	40 mg	£439.00	£10.98	BNF

eMIT: 12 month period until end June 2017

Table 36: Dosing schedule and dose per administration – subsequent therapies

Drug	Dosing per administration	Frequency of administration	Total dose	Reference for dosing
Atezolizumab	1200 mg fixed	Q3W	1200 mg	SmPC (2), IMpower150
Pembrolizumab	2 mg/kg	Q3W	144mg	SmPC (115)
Docetaxel	75 mg/m²	Q3W	136 mg	SmPC (113)
Nivolumab	3mg/kg	Q2W	216 mg	SmPC (114)

Q3W, every three weeks; Q4W, every four weeks; AUC, area under the curve

In the scenario utilising data from IMpower 150, post-discontinuation therapies were included based on a 2% occurrence threshold in the study, i.e. if at least 2% of patients had received the therapy in IMpower150. In the IMpower150 dataset, lines of treatment were not distinguished; hence subsequent therapies represent second or further-line therapies. It was

also not possible to distinguish combination therapies in the database, i.e. treatments were coded separately and not as combinations. Therefore, it was assumed that pemetrexed is always given with a platinum chemotherapy, for which a 50/50 split was assumed. For the rest of the treatments included (e.g. cancer immunotherapy and docetaxel), it was considered appropriate to assume that they were given as monotherapies, as per their marketing authorisations in second line NSCLC. The duration of treatment on these therapies was sourced from the literature or based on assumptions. Treatment duration could not be accurately obtained by the study, given the short follow up after discontinuation.

Data on subsequent therapies after Atezo+Bev+CP in IMpower150 are presented in Table 37. These data include type of treatment, proportion of patients receiving each treatment and duration of post-discontinuation therapy. It is evident from Table 37 that a proportion of patients received a cancer immunotherapy (nivolumab) after discontinuation from Atezo+Bev+CP. In addition, a proportion of patients in the study also received bevacizumab and pemetrexed-based chemotherapy as a subsequent therapy. This is not fully aligned with UK clinical practice and as such, an adjustment was made with respect to subsequent therapies in our base case analysis.

Table 37: Subsequent therapies after discontinuation from Atezo+Bev+CP in IMpower150 – used in scenario analysis

Post-disc therapy	Proportion of use after Atezo+Bev+CP	Duration of therapy (weeks)	Source for duration of therapy
Pemetrexed plus platinum	63%	18.00	Pemetrexed SmPC (109)
Docetaxel	17%	18.00	Docetaxel SmPC (113)
Nivolumab	11%	26.52	NICE TA484 (52)
Bevacizumab	9%	11.62	IMpower150

Drug administration costs

The costs of administration used in the economic model for Atezo+Bev+CP and comparators are shown in Table 38. The administration cost for Atezo+Bev+CP is assumed to be that of a complex chemotherapy with prolonged infusion treatment as a day case (as described in the NHS reference costs 2016-17 (116)), to account for the prolonged infusion time and administration burden, given the inclusion of four different combination partners for the intervention. The administration costs for comparator therapies are sourced primarily from published NICE technology appraisals for these drugs (41, 42, 49).

Table 38: Drug administration costs

Drug	Type of administration		NHS reference code	Cost per administration	Source
Atezo+Bev+CP	Deliver complex chemotherapy, including prolonged infusion treatment, at first attendance	Day case	SB14Z (day case)	£385.99	NHS reference costs 2016-17
Pemetrexed plus cisplatin/carboplatin	Deliver complex chemotherapy, including prolonged infusion treatment, at first attendance	Outpatient setting or Day case (depending on combination partner)	SB14Z (average of outpatient and day case)	£327.92	NICE TA531, NICE TA181, NICE TA NHS reference costs 2016-17
Pemetrexed maintenance	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z (outpatient)	£173.99	NICE TA531,NICE TA402, NHS reference costs 2016-17

Subsequent therapies

The administration costs of subsequent therapies for Atezo+Bev+CP and comparators are shown below.

Table 39: Drug administration costs – subsequent therapies

Drug	Type of administration		NHS reference code	Cost per administration	Source
Atezolizumab	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z (outpatient)	£173.99	NICE TA520(53)(53)(53)(53)(53)(53), NHS reference costs 2016-17
Pembrolizumab	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z (outpatient)	£173.99	NICE TA531, NHS reference costs 2016-17
Nivolumab	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z (outpatient)	£173.99	NICE TA531, NHS reference costs 2016-17

Docetaxel	Deliver simple parenteral chemotherapy at first attendance	Outpatient setting	SB12Z (outpatient)	£173.99	NICE TA531, NHS reference costs 2016-17

B.3.5.2 Health-state unit costs and resource use

Supportive care costs are applied for both PFS, and PD health states. The types of resource and frequency of use are derived from previous NICE technology appraisals, published sources, the SLR and input from UK clinicians. Unit costs were derived from NHS reference costs (116) and PSSRU published costs (117). Table 40 details the resource use for the PFS and PD health state and Table 41 presents the unit cost for each element of resource use.

Table 40: Resource use for PFS and PD health state

Resource	PFS	PD	Unit	Source
Outpatient visit	9.61	7.91	per annum	NICE TA531 (42)
Chest Radiography	6.79	6.5	per annum	NICE TA531 (42)
CT scan (chest)	0.62	0.24	per annum	NICE TA531 (42)
CT scan (other)	0.36	0.42	per annum	NICE TA531 (42)
ECG	1.04	0.88	per annum	NICE TA531(42)
Community nurse visit	8.7	8.7	visits (20 minutes) per patient	Appendix 1 of NICE Guideline CG121 (40) Marie Curie report (118)
Clinical nurse specialist	12	12	hours contact time per patient	Appendix 1 of NICE Guideline CG121 (40)
GP surgery	12	0	consultations per patient	Appendix 1 of NICE Guideline CG121(40)
GP home visit	0	26.09	per annum (fortnightly)	Marie Curie report (118)
Therapist visit	0	26.09	per annum (fortnightly)	Appendix 1 of NICE Guideline CG121 (40)

PFS, progression free state; PD, progressed disease state; GP, general practitioner; CT, computerised tomography; ECG, electrocardiogram; NICE, The National Institute for Health and Care Excellence; CG, clinical guidance

Table 41: Unit costs (PFS and PD health states)

Resource	Unit cost	Unit	Source
Outpatient follow-up visit	£136.43	per visit	NHS Reference Costs 2016-2017(116), Outpatient attendance data, Consultant Led, Service code 800, Clinical Oncology
Chest Radiography	£27.78	per case	NICE technology appraisal TA199 (119); (£24.04 in 2009 - inflated to 2016/17 using the PSSRU HCHS index)
CT scan (chest)	£112.07	per case	NHS Reference Costs 2016-2017 (116), Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)
CT scan (other)	£112.07	per case	NHS Reference Costs 2016-2017 (116), Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)
ECG	£224.99	per case	NHS Reference Costs 2016–2017 (116), Complex ECG, HRG code EY50Z
Community nurse visit	£62.00	per hour	PSSRU 2017 (120) p.159: Cost per hour Band 8a
Clinical nurse specialist	£62.00	per contact hour	PSSRU 2017 (120) p.207: Cost per hour Band 8a
GP surgery visit	£38.00	per visit	PSSRU 2017 (120), p.162: Cost per patient contact lasting 9.22 minutes, including direct care staff costs, including qualifications
GP home visit	£94.82	per visit	PSSRU 2016 (117), p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel - inflated to 2016/17 using the PSSRU HCHS index
Therapist visit	£45.00	per visit	PSSRU 2017 (120), p.177: Cost per hour for community occupational therapist, including training

GP, general practitioner; CT, computerised tomography; ECG, electrocardiogram; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; NICE, The National Institute for Health and Care Excellence; HRG, Healthcare Resource Groups; HCHS, hospital and community health services

The resulting health state costs for PFS and PD are a product of the resource use (Table 40) multiplied by the unit costs (Table 41). For the total supportive care cost per week in PD, the distribution of subsequent therapies and the associated costs are also taken into account. The total cost per week in the PFS health state is £61.8 and for the PD state £117.0.

Cost of terminal care

An end of life / terminal care cost is applied to patients who enter the death state as a one off cost, in line with previous appraisals in NSCLC (42, 52, 53, 55, 121) and a published NIHR HTA study by Brown et al. (122). The terminal care cost reflects the resource consumption in various care settings, and is weighted by the proportion of patients treated in each setting. This cost is assumed equal for all treatments in the economic model. Resource use and costs are shown in Table 42. The total cost of end of life is £4,456.13.

Table 42: Resource use and unit costs for terminal care/end of life

Resource	Unit cost	Number of consumption	% of patients in each setting	Assumptions / Source
Community nurse visit	£62.00 per hour	28.00 hours	27%	PSSRU 2017 (120), p.159: Cost per hour Band 8a
GP Home visit	£94.82 per visit	7.00 visits	27%	PSSRU 2016 (117), p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel - inflated to 2016/17 using the PSSRU HCHS index
Macmillan nurse	£41.35 per hour	50.00 hours	27%	Assumed to be 66.7% of community nurse cost
Drugs and equipment	£574.57 per patient	Average drug and equipment usage	27%	Value from Brown et al study (2013) (122)- inflated to 2016/17 using the PSSRU HCHS index (120)
Terminal care in hospital	£4,003.46 per episode	1 episode (9.66 days)	56%	NICE TA531(42), inflated to 2016/17 using the PSSRU

				HCHS index (120)
Terminal care in hospice	£5,004.33 per episode	1 episode (9.66 days)	17%	NICE TA531(42), assumed 25% increase on hospital inpatient care
Total cost	£4,456.13 per episode			

B.3.5.3 Adverse reaction unit costs and resource use

Adverse event data used in the model for Atezo+Bev+CP were taken directly from the IMpower150 study. Previous appraisals within this therapy area have utilised all Grade ≥3 treatment related AEs with an incidence of ≥2% - ≥5% in either treatment arm in to the economic model (42, 51, 53). In order to ensure a more robust assessment of the safety profile of the treatment regimens being compared all Grade ≥3 treatment-related AEs with an incidence of ≥2% in the Atezo + Bev + CP arm of the IMpower150 trial are included in the base case analysis. The respective Grade ≥3 treatment-related AEs with an incidence of ≥2% for the comparator therapies were sourced from the SLR outlined in Section B.2.9 and Appendix D.

The approach outlined above for AE inclusion was followed both for the ITT population, as well as for the patient subgroups of interest (EGFR/ALK positive, PD-L1 negative or low). The resulting adverse events included in the economic model are shown in Table 43 for the ITT population. For PD-L1 low or negative and EGFR/ALK positive patients, the AE occurrence from the ITT population for Atezo+Bev+CP is also assumed (see Table 43). This aims to ensure that a conservative approach is taken, as the AE occurrence for pemetrexed-based regimens is taken from the ITT population in the respective studies, since no PD-L1 or EGFR/ALK subgroup results were reported in the pemetrexed-based studies.

Please note that there may be a difference in the number of AEs included in the economic model, compared to the AEs reported in the adverse reactions section (Section B.2.10). The reason for this is that in the economic model, we have to account for multiple occurrences of an AE per patient in order to be able to calculate the probability of occurrence for each AE, whilst in the reporting of the clinical study, multiple occurrences of the same AE in an individual are counted once at the highest grade for this patient, as per standard reporting of safety results from clinical studies.

Table 43: Adverse events included in the economic model (Grade ≥3 treatment related AEs, with incidence ≥2% in the Atezo+Bev+CP arm of IMpower150) – ITT population

Events, n	Atezo+Bev+CP	Pemetrexed plus platinum	Pemetrexed plus platinum plus pemetrexed maintenance
Anaemia	27	16	34
Decreased appetite	10	0	0
Dehydration	9	0	0
Diarrhoea	12	0	0
Fatigue	13	15	0
Febrile neutropenia	41	0	0
Hypertension	30	0	0
Hypokalaemia	8	0	0
Leukopenia	8	0	0
Nausea	16	1	0
Neutropenia	66	13	42
Neutrophil count decreased	59	0	0
Platelet count decreased	23	0	0
Proteinuria	12	0	0
Thrombocytopenia	19	4	41
White blood cell count decreased	17	0	0

The unit costs related to the management of AEs were mainly derived from previous NICE STA submissions (42, 51-53, 98) and from the Brown et al NIHR HTA study (122). When unit costs were not available an assumption was applied, and when AE management costs were trivial they were assumed to be zero. All unit costs were inflated to 2016/17 prices using the hospital and community health services (HCHS) index published by PSSRU for 2017 (120). Table 44 below presents the unit costs per AE for which costing was applied in the cost-effectiveness model.

Table 44: Unit cost per AE used in the economic model

Adverse Event	Unit cost	Reference
Anaemia	£2,748.57	NICE TA531 - inflated to 2016/17 using the PSSRU HCHS index
Asthenia	£2,914.59	Assumed same as fatigue
Decreased appetite	£0.00	Assumption
Dehydration	£176.24	Consultant led visit - Medical oncology. Service code 370 2016-17 costs
Diarrhoea	£0.00	NICE TA531 - inflated to 2016/17 using the PSSRU HCHS index, Brown 2013
Fatigue	£2,914.59	Brown 2013 (inflated to 2016-17 using PSSRU inflation indices)
Febrile neutropenia	£7,097.41	NICE TA531 - inflated to 2016/17 using the PSSRU HCHS index
Hypertension	£176.24	Consultant led follow up visit - Medical oncology. Service code 370 2016-17 costs
Hypokalaemia	£176.24	Consultant led follow up visit - Medical oncology. Service code 370 2016-17 costs
Leukopenia	£376.80	NICE TA531 - inflated to 2016/17 using the PSSRU HCHS index
Nausea	£1019.12	Brown 2013 (inflated to 2016-17 using PSSRU inflation indices)
Neutropenia	£601.23	Brown 2013 (inflated to 2016-17 using PSSRU inflation indices)
Neutrophil count decreased	£0.00	NICE TA428
Platelet count decreased	£0.00	Assumed same as neutrophil count decreased
Proteinuria	£176.24	Consultant led follow up visit - Medical oncology. Service code 370 2016/17 costs
Pulmonary embolism	£1,432.27	Weighted average of pulmonary embolus HRG codes (DZ09J-DZ09Q). NHS Reference Costs 2016-17 costs
Thrombocytopenia	£123.51	NICE TA484, NICE TA520, NICE TA525
White blood cell count decreased	£449.34	NICE TA484, NICE TA520, NICE TA525

B.3.5.4 Miscellaneous unit costs and resource use

All elements of resource use and cost have been outlined in previous sections.

UK clinical experts have confirmed that PD-L1 testing is now considered standard clinical practice in the UK. As such, it is excluded from the analysis.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A table summarising the full list of variables applied in the economic model is presented in Appendix R.

B.3.6.2 Assumptions

Table 45: Key assumptions used in the economic model (base case)

Area	Assumption	Justification
Time horizon	20 years	The average age of patients in the model is 63. The 20 year model horizon is in line with NICE reference case (1), and also long enough to reflect the difference in costs and outcomes between the interventions being compared in this submission. Also consistent with previous NICE appraisals in this indication (41, 42, 53).
Treatment pathway	Once first-line NSCLC patients treated with chemotherapy progress, they receive subsequent cancer immunotherapies	In line with UK clinical practice, the licence of second-line cancer immunotherapies, UK clinical expert opinion and previous NICE preferred assumptions in the appraisal for pembrolizumab (42).
PD-L1 testing cost	Not included in base case	UK clinical experts have confirmed that PD-L1 testing in first-line NSCLC is now standard clinical practice in the UK. As such, since including PD-L1 testing cost would not have a differential impact on the comparators being considered, it was excluded from the analysis.
Comparators considered in the economic model	ITT population, EGFR/ALK+ patients, PLD1 low or negative: Pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed maintenance treatment	See Section B.1.1 The comparison with pembrolizumab monotherapy in PD-L1 high patients is not considered in the cost-effectiveness section of our submission, [redacted]

Atezo+Bev+CP: clinical efficacy and safety	IMpower150 study data were used for Atezo+Bev+CP. Efficacy and safety results from IMpower150 are transferable to the UK population	Advice from UK clinical experts suggested that the outcomes seen from the study are expected in UK patients given the similarity of patient characteristics between the trial and patients in the UK.
Comparators: clinical efficacy and safety (relative treatment effect)	Lack of head-to-head trials versus UK standard of care comparators. As such, a fractional polynomial NMA was conducted vs. pemetrexed-based interventions, to account for the absence of proportional hazards.	As per NICE guide to the methods of technology appraisal (1), and based on availability and limitations of published evidence for relevant comparators.
Extrapolation of time-to-event endpoints	Best fit according to combined data on AIC / BIC, visual fit to observed data and long-term clinical plausibility. In order to validate long-term OS for pemetrexed based comparators, UK published estimates, precedent from NICE committee-preferred assumptions and the Flatiron Health database were used. For Atezo+Bev+CP, UK clinical expert opinion was used to validate long-term OS estimates	Based on NICE DSU recommendation (82)
Treatment stopping rule Atezo+Bev+CP	Treatment stopping at 2 years for Atezo+Bev+CP	Conservative assumption, to ensure consistency with previous NICE decisions for atezolizumab (51, 98)
Duration of treatment effect Atezo+Bev+CP	Treatment effect for Atezo+Bev+CP stopping at 5 years (i.e. 3 years after treatment discontinuation)	Conservative assumption, to ensure consistency with previous NICE decisions for atezolizumab (51, 98)
HRQoL	Based on EQ-5D data collected in IMpower150.Proximity to death utility approach used in the base-case analysis.	In line with NICE reference case (1), consistent with previous appraisals (42, 53) and validated by UK clinical experts
Safety	Grade ≥3 treatment related adverse events experienced by ≥2% of patients in the Atezo+Bev+CP arm of IMpower150 were included. Same AEs were considered for comparators, with occurrence	The threshold of 2% for AE inclusion is conservative as an approach. No disutility from AEs in base-case analysis to avoid double-counting; disutility associated with AEs was assumed to have been captured in the EQ-5D responses in IMpower150.

	informed by the clinical SLR. No disutility from AEs considered in base-case analysis.	

AE, adverse event; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DSU, Decision Support Unit; KM, Kaplan-Meier; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TA, technology appraisal

B.3.7 Base-case results

Key information and limitations for economic results sections

- Two sets of cost-effectiveness results for the comparisons versus pemetrexed-based chemotherapy are presented in our evidence submission within each population of interest, as per the NICE user guide for company evidence submissions (Sections B.3.7 - B.3.8 and Appendices S and T):
  i. model results with all interventions at list price
  ii. model results with confidential PAS for atezolizumab and bevacizumab, and all comparators at list price
- A limitation of the with-PAS analysis, however, is that confidential discounts are in place for pemetrexed maintenance therapy and other therapies in the treatment pathway, which Roche is unable to account for
- Due to the implementation of the treatment effect cap for OS and PFS for Atezo+Bev+CP, only pairwise ICERs are provided and not a fully incremental set of results. For the same reason, the cost effectiveness acceptability curves can only be run for pairwise comparisons and as such do not reflect the entire decision problem. Further details are provided in Sections B.3.7.1 and B.3.8.1
- It is reminded that the comparison to pembrolizumab in patients with PD-L1 high expression is not included in the cost-effectiveness Section of our submission, due to the reasons outlined in Section B.3.2
- At list price for all comparators and therapies included in the treatment pathway, [redacted].
- At PAS price for atezolizumab and bevacizumab and list price for all comparators (and therapies in the treatment pathway) Atezo+Bev+CP either dominates the pemetrexed-based interventions or has an ICER of £7,014 to £20,163, in the ITT population and across the patient subgroups with low or negative PD-L1 expression and EGFR or ALK mutation. These ICERs are well below the cost-effectiveness threshold for end-of-life

therapies, and therefore at PAS price, Atezo+Bev+CP demonstrates a clinically- and cost-effective treatment option for the NHS.

- Extensive sensitivity and scenario analyses were conducted in the economic model to demonstrate the uncertainty around the parameters used, assess the plausibility of different scenarios and approaches, and help understand what key variables and assumptions potentially have a major impact on cost-effectiveness results.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Base-case results of the economic model based on the list price for atezolizumab, bevacizumab and all comparators are presented in Table 46 - Table 51.

It should be noted that the way the treatment effect duration cap for OS and PFS is applied to Atezo+Bev+CP in the model base case, has an impact on model results. After the cut-off point for treatment effect, the survival rate from the comparator arm is applied to Atezo+Bev+CP; this is equivalent to assuming a hazard ratio of one between the two interventions. This results in the long-term outcomes (after 5 years) for Atezo+Bev+CP being different, depending on the intervention used for each pairwise comparison. As such, only pairwise ICERs can be provided and not a fully incremental set of results, since the long-term outcomes of Atezo+Bev+CP within each population are not identical versus each comparator. The pairwise ICERs at list price are presented below.

For each of the populations of interest, we consider that a weighted ICER between the two pemetrexed-based interventions more appropriately reflects the cost-effectiveness of Atezo+Bev+CP and its actual impact to the NHS, and as such is a more appropriate basis for decision-making. This is consistent to the approach taken in TA531 (42) where a comparison versus the standard of care (i.e. the control arm of study KEYNOTE-024 including a selection of chemotherapy regimens) was considered appropriate for decision making. The relative market shares of pemetrexed-based interventions in first-line metastatic non-squamous NSCLC were used for the weighting, as well as information from the pemetrexed maintenance NICE appraisal (TA402): [redacted] for pemetrexed plus platinum and [redacted] for pemetrexed plus platinum with pemetrexed maintenance

Table 46: Base-case results ITT population vs. pemetrexed plus platinum – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat	[redacted]	[redacted]	[redacted]				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years;; Pem+plat, pemetrexed plus platinum

Table 47: Base-case results ITT population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]				

Table 48: Base-case results PD-L1 negative/low population vs. pemetrexed plus platinum – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat	[redacted]	[redacted]	[redacted]				

Table 49: Base-case results PD-L1 negative/low population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]				

Table 50: Base-case results EGFR and ALK positive population vs. pemetrexed plus platinum – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat	[redacted]	[redacted]	[redacted]				

Table 51: Base-case results EGFR and ALK positive population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]				

In the ITT population (Table 46-Table 47) and at list price for Atezo+Bev+CP and all comparators:

- Comparison to pemetrexed plus platinum: Atezo+Bev+CP provided a QALY gain of 1.50, and life-year gain of 2.13, at a total overall cost of [redacted]. The pemetrexed plus platinum comparator provided a gain of 1.01 QALYs and 1.46 life years, at total costs of [redacted]. The resulting ICER for Atezo+Bev+CP compared to pemetrexed plus platinum is [redacted] per QALY.
- Comparison to pemetrexed plus platinum plus pemetrexed maintenance: Atezo+Bev+CP provided a QALY gain of 1.68, and life-year gain of 2.37, at a total drug overall cost of [redacted]. The pemetrexed plus platinum plus pemetrexed maintenance comparator provided a gain of 1.39 QALYs and 1.98 life years, at total costs of [redacted]. The resulting ICER for Atezo+Bev+CP compared to pemetrexed plus platinum plus pemetrexed maintenance is [redacted] per QALY
- Weighted ICER versus pemetrexed-based interventions: [redacted] per QALY

For PD-L1 low or negative patients (tumour proportion score of 0-49%, TC/IC 0,1,2) (Table 48-Table 49), at list price for Atezo+Bev+CP and all comparators:

- Comparison to pemetrexed plus platinum: Atezo+Bev+CP provided a QALY gain of 1.46, and life-year gain of 2.07, at a total overall cost of [redacted]. The pemetrexed plus platinum comparator provided a gain of 1.02 QALYs and 1.48 life years, at total costs of [redacted]. The resulting ICER for Atezo+Bev+CP compared to pemetrexed plus platinum is [redacted] per QALY
- Comparison to pemetrexed plus platinum plus pemetrexed maintenance: Atezo+Bev+CP provided a QALY gain of 1.64, and life-year gain of 2.32, at a total overall cost of [redacted]. The pemetrexed plus platinum plus pemetrexed maintenance comparator provided a gain of 1.43 QALYs and 2.03 life years, at total costs of [redacted]. The resulting ICER for Atezo+Bev+CP compared to pemetrexed plus platinum is [redacted] per QALY

- Weighted ICER versus pemetrexed-based interventions: [redacted] per QALY

For EGFR and ALK positive patients (Table 50-Table 51), at list price for Atezo+Bev+CP and all comparators:

- Comparison to pemetrexed plus platinum: Atezo+Bev+CP provided a QALY gain of 2.43, and life-year gain of 3.39, at a total overall cost of [redacted]. The pemetrexed plus platinum comparator provided a gain of 1.29 QALYs and 1.84 life years, at total costs of [redacted]. The resulting ICER for Atezo+Bev+CP compared to pemetrexed plus platinum is [redacted] per QALY.
- Comparison to pemetrexed plus platinum plus pemetrexed maintenance: Atezo+Bev+CP provided a QALY gain of 3.04, and life-year gain of 4.21, at a total overall cost of [redacted]. The pemetrexed plus platinum plus pemetrexed maintenance comparator provided a gain of 1.83 QALYs and 2.56 life years, at total costs of [redacted]. The resulting ICER for Atezo+Bev+CP compared to pemetrexed plus platinum is [redacted] per QALY
- Weighted ICER versus pemetrexed-based interventions: [redacted] per QALY

As such, at list price for Atezo+Bev+CP and all comparators and therapies in the treatment pathway, Atezo+Bev+CP is [redacted].

The equivalent ICERs when incorporating the existing PAS for atezolizumab and the submitted PAS for bevacizumab are presented in Table 53 - Table 58. The discounts considered in these analyses are outlined in Table 52 below. In these comparisons, all comparators (and therapies included in the treatment pathway) are at list price.

Table 52: Level of confidential discount considered in the with PAS model results

Technology	Level of confidential discount	Justification
Atezolizumab	[redacted]	Current level of confidential discount
Bevacizumab	[redacted]	Submitted PAS for this appraisal
Atezolizumab – second line treatment	[redacted]	Current level of confidential discount

Table 53: Base-case results ITT population versus pemetrexed plus platinum (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
Pem+plat	[redacted]	[redacted]	[redacted]				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; Pem+plat, pemetrexed plus platinum

Table 54: Base-case results ITT population versus pemetrexed plus platinum plus pemetrexed maintenance (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

Table 55: Base-case results PD-L1 negative/low population versus pemetrexed plus platinum (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,956
Pem+plat	[redacted]	[redacted]	[redacted]				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; Pem+plat, pemetrexed plus platinum

Table 56: Base-case results PD-L1 negative/low population versus pemetrexed plus platinum plus pemetrexed maintenance (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

Table 57: Base-case results EGFR and ALK positive population versus pemetrexed plus platinum (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,220
Pem+plat	[redacted]	[redacted]	[redacted]				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; Pem+plat, pemetrexed plus platinum

Table 58: Base-case results EGFR and ALK positive population versus pemetrexed plus platinum plus pemetrexed maintenance (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

Results of the with-PAS analysis show that Atezo+Bev+CP either dominates the pemetrexed-based interventions or has an ICER of £7,014 to £20,163, well below the cost-effectiveness threshold for end-of-life therapies vs. pemetrexed-based interventions, across the ITT, PD-L1 low or negative and EGFR/ALK positive populations. Results of the comparisons with pemetrexed-based chemotherapy in the subgroups of patients with PD-L1 low or negative expression or EGFR/ALK positive mutation are very relevant for decision-making, since these patients are not eligible for treatment with pembrolizumab and as such, pemetrexed-based chemotherapy is the UK standard of care for these subgroups. There is therefore unmet need for cancer immunotherapies in these subgroups of patients, in which atezolizumab Atezo+Bev+CP demonstrates a clinically significant OS and PFS benefit.

As such, at PAS price for atezolizumab and bevacizumab and list price for all comparators (and therapies included in the treatment pathway) Atezo+Bev+CP is cost-effective versus pemetrexed-based chemotherapy and good value for money to the NHS, across all patient populations considered in our evidence submission.

However, we acknowledge that our with-PAS analysis does not account for confidential discounts that are in place for pemetrexed maintenance therapy, as well as for pembrolizumab (in first and second-line NSCLC) and nivolumab (in second-line NSCLC). An exploratory set of results for each of the populations of interest (ITT and relevant subgroups)

is provided in Appendix S, incorporating the PAS price for atezolizumab and bevacizumab as well as an estimate for the level of confidential discount for relevant comparators.

In addition, in Appendix J the clinical outcomes from the model are presented as well as the disaggregated results of the base-case cost effectiveness analysis.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means, and sources used to estimate the parameters are detailed in Appendix R. Results of the PSA compared to deterministic results at list price are presented in Table 59. The with-PAS equivalent comparison is presented in Table 60. Deterministic and probabilistic results are similar, in the ITT population as well as in the patient subgroups considered, therefore not indicating any signs of non-linearity in the model.

The cost-effectiveness planes in Figure 45 - Figure 46 show the PSA iterations for the comparisons to pemetrexed-based interventions in the ITT population at list price, and the cost effectiveness acceptability curves for the ITT population at list price are shown in Figure 47 -

Figure 48. The equivalent plots for subgroups of interest (PD-L1 low or negative patients, EGFR/ALK positive patients) are presented in Appendix T. Cost effectiveness planes and cost effectiveness acceptability curves incorporating the PAS for atezolizumab and bevacizumab can be found in the confidential PAS Appendix (Appendix S).

As mentioned in Section B.3.7.1, the treatment effect duration cap for Atezo+Bev+CP at 5 years in our base-case, results in long-term outcomes for Atezo+Bev+CP being different depending on the intervention used for each pairwise comparison. As such, the cost effectiveness acceptability curves versus pemetrexed-based chemotherapy can only be run for pairwise comparisons, and therefore do not reflect the entire decision problem.

Table 59: PSA results compared to base-case (without PAS)

	Costs		QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
ITT population						
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]		
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]		
PD-L1 low or negative						
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]		
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]		
EGFR / ALK positive						
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]		
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]		

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; Pem+plat, pemetrexed plus platinum; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

Table 60: PSA results compared to base-case (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

	Costs		QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
ITT population						
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	£20,163	£20,826
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]		
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]		
PD-L1 low or negative						
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	£15,956	£16,658
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]		
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]		
EGFR / ALK positive						
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	£18,220	£17,961
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]		
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	£7,014	£5,501
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]		

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; Pem+plat, pemetrexed plus platinum; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

Figure 45: Cost-Effectiveness Plane – ITT population vs. pemetrexed plus platinum – list price

Figure 46: Cost-Effectiveness Plane – ITT population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

Figure 47: Cost-Effectiveness Acceptability Curve – ITT population vs. pemetrexed plus platinum – list price

Figure 48: Cost-Effectiveness Acceptability Curve – ITT population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

B.3.8.2 Deterministic sensitivity analysis

The choice of parameters to include in univariate analysis was considered a-priori, with focus on the parameters having the greatest impact on the resulting ICER. The parameter values used in the analyses which had the greatest impact on the results can be found in Table 61 below. The base case value of most parameters was varied using the 5% and 95% confidence intervals for the variables, with the exception of discount rates which varied from 1.5%-6.0%. Key remaining model parameters were tested in scenario analyses.

Deterministic sensitivity analyses results for the ITT population using Atezo+Bev+CP at list price are displayed in

- Figure 50. Results versus pemetrexed-based interventions for subgroups of interest (PD-L1 low or negative, EGFR/ALK positive patients) are provided in Appendix T. For the with-PAS results of the deterministic sensitivity analysis versus pemetrexed plus platinum in the ITT population please see Figure 51. The with-PAS tornado plot versus pemetrexed plus platinum plus pemetrexed maintenance is not meaningful to present, as Atezo+Bev+CP dominates the pemetrexed-based intervention. For the with-PAS results in subgroups of patients please see the confidential PAS Appendix (Appendix R).

Based on the deterministic sensitivity analyses at list and PAS price, and in both the ITT population and subgroups of interest, the most influential parameters appear to be the discount rates for costs and for health outcomes, the administration cost for Atezo+Bev+CP, the utility value for the interval of >30 weeks before death and the weekly AE costs for Atezo+Bev+CP.

Table 61: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value	Justification
Discount costs	3.50%	1.5%	6.0%	Assumption
Discount effects	3.50%	1.5%	6.0%	Assumption
Supportive care cost: PFS	61.78	60.08	63.59	95% CI
Supportive care cost: PD	116.97	113.49	120.39	95% CI
Weekly AE cost: Atezo+Bev+CP	526.34	971.38	1,703.91	95% CI
Weekly AE cost: Pem+platinum	272.54	207.68	375.03	95% CI
Cost of administration: Atezo+Bev+CP	385.99	370.55	402.24	95% CI
Cost of administration: Pem+platinum	327.92	318.59	337.67	95% CI
Utility values: <≤5 weeks BD	0.52	0.49	0.54	95% CI
Utility values : (5,10] weeks BD	0.59	0.56	0.60	95% CI
Utility values : (10,30] weeks BD	0.70	0.68	0.71	95% CI
Utility values: >30 weeks BD	0.73	0.72	0.74	95% CI

AE, adverse event; PD, progressive disease; PFS, progression-free survival; PPS, post-progression survival, Pem+plat, pemetrexed plus platinum; CI, confidence interval

Figure 49: Tornado diagram – ITT population vs. pemetrexed plus platinum – list price

Figure 50: Tornado diagram – ITT population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

Figure 51: Tornado diagram – ITT population vs. pemetrexed plus platinum – PAS price

B.3.8.3 Scenario analysis

Scenario analyses were conducted to assess uncertainty around remaining parameter inputs and structural assumptions of the model. Scenarios demonstrating changes in the following parameters were explored:

- Alternative plausible OS Extrapolations (see B.3.3.4)
- Alternative plausible PFS Extrapolations (see B.3.3.5)
- Alternative plausible TTD Extrapolations (see B.2.9)
- Alternative NMA networks and models (see B.3.3.5)
- No treatment stopping rule for atezolizumab and bevacizumab (see B.3.3.4)
- Alternative time points for cap of treatment effect duration (see B.3.3.4)
- Alternative wastage assumptions (see B.3.2.3)
- Alternative utility values (see B.3.4.5)
- Alternative subsequent therapy approach (see B.3.5.1)
- Disutility for AEs (see B.3.5.3)

Scenario analyses results for the ITT population are presented below, both at list price and with PAS. Results for subgroups of interest (PD-L1 low or negative, EGFR/ALK positive patients) are provided in Appendix T (list price) and Appendix S (PAS price).

It should be highlighted that not all scenario analyses are appropriate to consider for decision-making. The appropriateness and plausibility of the different scenario analyses is discussed right after the Tables with the scenario analyses results, in the “Summary of sensitivity analyses results” Section.

Table 62: Scenario analyses results – ITT population vs. pemetrexed plus platinum – list price

	Description	Atezo+Bev+CP			Pem+platinum			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
PFS distribution	KM - Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution	KM- Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
Alternative NMA network	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ITT exclude Keynote	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ITT exclude Paramount	Comparison not feasible - no connected network						
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NMA - Fract Poly (RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

Table 63: Scenario analyses results – ITT population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

	Description	Atezo+Bev+CP			Pem+platinum w Pem maint			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]						
	Weibull	[redacted]						
	Log-normal	[redacted]						
	Gen Gamma	[redacted]						
	Log-logistic	[redacted]						
	Gompertz	[redacted]						
PFS distribution	KM - Log-logistic tail (base case)	[redacted]						
	Exponential	[redacted]						
	Weibull	[redacted]						

	Log-normal	[redacted]						
	Gen Gamma	[redacted]						
	Log-logistic	[redacted]						
	Gompertz	[redacted]						
TTD distribution	KM - Exponential tail (base case)	[redacted]						
	Exponential	[redacted]						
	Weibull	[redacted]						
	Log-normal	[redacted]						
	Gen Gamma	[redacted]						
	Log-logistic	[redacted]						
	Gompertz	Does not converge						
Alternative NMA network	ITT (base case)	[redacted]						
	ITT exclude Keynote	[redacted]						
	ITT exclude Paramount	[redacted]						
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]						
	NMA – PH	[redacted]						
	NMA - Fract Poly (RE)	[redacted]						
Treatment stopping rule	At 2 years (base case)	[redacted]						
	No treatment stopping rule	[redacted]						
Treatment effect duration	5 years (base case)	[redacted]						
	105 months	[redacted]						
	150 months	[redacted]						
	195 months	[redacted]						
	240 months (lifetime)	[redacted]						
Wastage	With vial sharing (base case)	[redacted]						
	No vial sharing	[redacted]						
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]						
	IMpower150 (Pre/Post progression)	[redacted]						
	Pembrolizumab utilities (US publication)	[redacted]						
	Chouaid et al. 2013	[redacted]						

	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IMpower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

Table 64: Scenario analyses results – ITT population vs. pemetrexed plus platinum – PAS price for atezolizumab and bevacizumab

	Description	Atezo+Bev+CP			Pem+platinum			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,416
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,763
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,412
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,381
	Gompertz	Does not converge						
PFS distribution	KM - Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,128
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,784
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,367
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,193
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,155
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,271
TTD distribution	KM - Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,687
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,095
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,589
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,614
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,277
	Gompertz	Does not converge						
	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163

Alternative NMA network	ITT exclude Keynote	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,627
	ITT exclude Paramount	Comparison not feasible - no connected network					
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
	NMA – PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,717
	NMA - Fract Poly (RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,360
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,096
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,105
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,691
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,610
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,595
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,174
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,875
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,373
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,628
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,463
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
	IMpower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,659
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,163
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,302

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

Table 65: Scenario analyses results – ITT population vs. pemetrexed plus platinum plus pemetrexed maintenance – PAS price for atezolizumab and bevacizumab

	Description	Atezo+Bev+CP			Pem+platinum w Pem maint			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
PFS distribution	KM - Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£130
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£612
TTD distribution	KM - Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£546
	Gompertz	Does not converge						
Alternative NMA network	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ITT exclude Keynote	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ITT exclude Paramount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	NMA – PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	NMA - Fract Poly (RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Treatment stopping rule	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,234
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IMpower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,201
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

B.3.8.4 Summary of sensitivity analyses results

As demonstrated in the PSA and across the scenario analyses, Atezo+Bev+CP is associated with a QALY gain over pemetrexed-based comparators across all populations considered (ITT, PD-L1 negative or low, EGFR/ALK positive). This was tested and confirmed in a series of scenario analyses including the use of different NMA models, alternative NMA networks, different extrapolation models for time-to-event endpoints and different durations of treatment effect for Atezo+Bev+CP.

Regarding the NMA against pemetrexed-based interventions, it should be noted that the use of a FP FE NMA model in our base case produces conservative results compared to the use of a proportional hazards NMA model. However, the FP model was selected on the basis of its appropriateness to reflect the underlying data and the presence of non-proportional hazards.

Equally important, our base-case NMA network includes the PARAMOUNT study, in order to enable an indirect comparison of Atezo+Bev+CP versus both pemetrexed-based interventions i.e. including pemetrexed plus platinum. However, PARAMOUNT has a different study design compared to all other studies in the network, which might lead to selection bias in favour of pemetrexed plus platinum with pemetrexed maintenance (see Section B.2.9). This results in conservative cost-effectiveness results versus pemetrexed plus platinum with pemetrexed maintenance when the base case NMA network is used. This is more pronounced in scenarios that include longer treatment effect duration for Atezo+Bev+CP, in which Atezo+Bev+CP is associated with a lower QALY gain over the model time horizon compared to the base case that includes a conservative treatment effect restriction. This lacks external clinical validity and is inconsistent with previous cancer immunotherapy NICE appraisals. This implausible outcome is likely to be a result of the bias introduced by PARAMOUNT in the base case NMA network. As such, we consider that the NMA scenario analysis excluding PARAMOUNT is important to inform the comparison versus pemetrexed plus platinum with pemetrexed maintenance.

For the comparisons with pemetrexed plus platinum, all scenario analyses assuming a longer duration of treatment effect for Atezo+Bev+CP provide more plausible and expected results, i.e. more favourable for Atezo+Bev+CP compared to the base case.

In terms of scenarios with different models to extrapolate the time-to-event endpoints, the scenario analyses varying OS appear to have a greater impact on results, However, caution must be exercised when analysing the scenario results with different distributions for extrapolating OS, as the base-case distribution was chosen on the basis of fit to the

observed data (statistical, visual fit) as well as validity of long-term outcomes. As such, only a subset of the alternative OS distributions can be considered to provide potentially plausible long-term OS (Log-Logistic, Weibull). The Exponential model used in our base case provides a conservative estimate of the long-term clinical benefit of Atezo+Bev+CP. Log-Logistic is an alternative clinically plausible and appropriate OS extrapolation model, which results in long-term OS for Atezo+Bev+CP in line with clinical expectations for cancer immunotherapies and consistent with previous NICE appraisals for cancer immunotherapy. (42, 53) The remaining OS distributions provide implausible results due to either lack of statistical and visual fit to the observed data, or lack of validity and clinical plausibility for long-term outcomes, or both.

[redacted]

At PAS price for Atezo+Bev+CP, Atezo+Bev+CP consistently dominates or is cost-effective versus pemetrexed-based interventions across all the scenarios considered and across all populations of interest (ITT, PD-L1 low or negative and EGFR/ALK positive), when taking into account the cost-effectiveness threshold for technologies meeting the end-of-life criteria.

B.3.9 Subgroup analysis

For the subgroups of patients considered (patients with low or negative PD-L1 expression, and patients with EGFR/ALK mutation) results are presented in Section B.3.7 and B.3.8 (deterministic and probabilistic results respectively). Additional results at list price for these subgroups (cost effectiveness planes, cost-effectiveness acceptability curves, tornado diagrams and scenario analyses) are presented in Appendix T, whilst the equivalent subgroup results including PAS are in Appendix S.

It should be highlighted that results of subgroup analyses comparisons of Atezo+Bev+CP with pemetrexed-based chemotherapy in patients with PD-L1 low or negative expression or EGFR/ALK positive mutation are very relevant for decision-making, since these patients are not eligible for treatment with pembrolizumab and as such pemetrexed-based chemotherapy is the UK standard of care for them. There is therefore unmet need for cancer immunotherapies in these subgroups of patients, in which atezolizumab Atezo+Bev+CP demonstrates a treatment option with clinically significant incremental OS and PFS benefit over the treatment options currently administered.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Selection of the appropriate distributions for time-to-event endpoints was driven by statistical fit to the data, visual fit to the KM and, importantly, clinical plausibility of the outcomes. All outcomes of the economic model have been extensively compared to and validated against all available evidence, as well as clinical expert opinion, to assess the accuracy of the modelled survival (See Section B.3.3 and Appendices M-P).

The economic model was developed specifically from the UK NHS and PSS perspective. The structure is consistent with other cancer immunotherapy models and previous NSCLC submissions to NICE and all costs are sourced from UK published sources. In addition, the model approach and inputs were validated by a number of UK clinical experts to ensure the model is reflective of clinical practice. This includes, but is not limited to: health state inclusion, relevant comparators, resource use, OS and PFS projections and extrapolation techniques.

Internal quality control and validation of the model was conducted by an external consultancy. Cell by cell validation was conducted which included formula checking, cell references and all aspects of model functionality. A number of pressure tests were also conducted, often using extreme values. The results of the model using these values were then compared to expected outputs to assess functionally accuracy.

B.3.11 Interpretation and conclusions of economic evidence

Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of Atezo+Bev+CP as a first-line treatment of adult patients with metastatic non-squamous NSCLC; patients with EGFR activating mutations or ALK-positive tumour mutations NSCLC should have received targeted therapy if clinically indicated prior to receiving atezolizumab.

No study assessing the cost-effectiveness of Atezo+Bev+CP for the target population outlined above was identified from the SLR. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation is consistent with the population in our pivotal study IMpower150 and our anticipated licence. As mentioned previously (see section B.3.3), efficacy and safety data from IMpower150 were used for Atezo+Bev+CP, and results

of the indirect treatment comparison (NMA or MAIC) outlined in Section B.2.9 were used to inform relative efficacy and safety for relevant comparators.

However, it is reminded that the comparison with pembrolizumab monotherapy in patients with high PD-L1 expression is not included in the cost-effectiveness analysis in our submission. [redacted] Therefore, the economic evaluation is relevant to all patients – apart from patients with high PD-L1 expression receiving pembrolizumab - who could potentially use from Atezo+Bev+CP as a first line therapy for non-squamous metastatic NSCLC.

Importantly, for the comparison to pemetrexed-based regiments, the economic evaluation in this submission focuses not only in the ITT population but also in relevant subgroups of first line metastatic non-squamous NSCLC patients currently receiving pemetrexed-based chemotherapy, who could potentially benefit from use of Atezo+Bev+CP. Therefore, although pemetrexed-based regimens have a licence and reimbursement from NICE for all patients with first-line non-squamous metastatic NSCLC, this is not reflective of current clinical practice. Patients with high PD-L1 expression now have access to treatment with pembrolizumab; as such, it is the subgroup of patients with PD-L1 low or negative expression for whom pemetrexed-based chemotherapy is standard of care in the UK. This is something we have accounted for in our evidence submission, by comparing Atezo+Bev+CP with pemetrexed-based regimens in the subgroup of patients with low or negative PD-L1 expression. In addition, we have conducted a subgroup analysis versus pemetrexed-based chemotherapy for patients with EGFR or ALK mutation, following targeted therapy. Both of these are patient subgroups with an unmet need for cancer immunotherapies, in which atezolizumab Atezo+Bev+CP has demonstrated a clinically significant OS and PFS benefit in study IMpower 150 and in the ITC versus pemetrexed-based chemotherapy.

Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in IMpower150 and the de novo economic evaluation are reflective of first-line patients with metastatic non-squamous NSCLC in the UK. Advice from UK clinical experts suggested that - despite the fact that IMpower150 did not include any UK sites – the patient population in IMpower 150 is broadly consistent with UK patients treated in clinical practice. Therefore, the outcomes seen from the study are expected in UK patients given the similarity of patient characteristics between the trial and patients in the UK.

- The economic model structure is consistent with other oncology models and previous NICE submissions in NSCLC.
- The resource utilisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs, PSSRU and previous NICE submissions, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of Atezo+Bev+CP.
- Given that UK standard of care therapies were not included as comparators in study IMpower150, an indirect treatment comparison (ITC) was conducted to enable Atezo+Bev+CP to be compared to UK standard of care therapies in first-line non-squamous NSCLC, making use of all available evidence and the appropriate methodologies.
- The base case network for ITC analyses were stress-tested in a series of subgroup and scenario analyses to account for different subgroups of patients relevant to this appraisal (patients with low or negative PD-L1 expression and patients with EGFR/ALK mutations) as well as to exclude studies that might introduce bias to ITC results.
- Extensive scenario and sensitivity analyses were conducted in the economic model, considering alternative approaches to the extrapolation of time-to-event endpoints, different NMA networks and NMA models, alternative parameter inputs and data sources.
- The 5-year landmark OS projections from the model were validated against all available UK sources and UK clinical expert opinion to ensure the clinical plausibility of the model and its applicability to UK clinical practice.

Strengths and weaknesses of the evaluation

The key strengths associated with the cost-effectiveness analysis are related to the use of the best available evidence and methods to inform the model:

- Efficacy and safety data from IMpower150 were used to model OS, PFS and TTD for Atezo+Bev+CP.
- Utility values were obtained directly from EQ-5D IMpower150 data. The proximity to death approach was used in our model base-case (four intervals before death were considered). The proximity to death approach reflects the known decline in cancer patients' quality of life during the terminal phase of the disease, while it is also consistent with recent NICE appraisals in NSCLC (42, 51, 98).
- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from UK published sources and previous NICE

appraisals, accounting for the feedback provided by NICE and ERGs in the most recent submissions.

- A conservative assumption was used for Atezo+Bev+CP, by including a treatment stopping rule at 2 years and a treatment effect cap for OS and PFS at 5 years. Whilst we consider that this is a conservative assumption, given the lack of evidence to support such restrictions, we have included this in our model base-case to ensure consistency with previous NICE committee decisions for atezolizumab (51, 98).
- The ITCs implemented, enabled a comparison between Atezo+Bev+CP and UK standard of care therapies, by applying appropriate methodology and making use of all available evidence.
- Extensive sensitivity and scenario analyses were conducted in the economic model to inform the uncertainty around the parameters used and help understand what key variables and assumptions potentially have a major impact on cost-effectiveness results.

Nevertheless, the economic analysis is also associated with limitations:

- The UK standard of care therapies were not included as comparator arms in IMpower150 and as such we had to implement an ITC to enable a comparison between Atezo+Bev+CP and UK standard of care therapies. The base case network for the NMA versus pemetrexed-based interventions is associated with limitations, primarily resulting from the bias in favour of pemetrexed plus platinum plus pemetrexed maintenance introduced from the inclusion of the PARAMOUNT study (see Section B.2.9). This bias is reflected in the cost-effectiveness results and the implausible long-term outcomes versus this comparator when using the base-case NMA network and without applying a treatment effect cap for Atezo+Bev+CP. An NMA network excluding the PARAMOUNT study is explored in scenario analyses to address this limitation.
- Limitations of the NMA also include low patient numbers and assumptions that had to be made in order to enable indirect comparisons within subgroups of patients (see Section B.2.9).
- All these ITC limitations have an impact on the economic model results. We have however implemented extensive sensitivity and scenario analyses to inform the long-term plausibility and appropriateness of alternative NMA networks, approaches and methodology
- Extrapolation of time-to-event endpoints is also subject to uncertainty. Nevertheless, by following a robust and comprehensive approach for the survival extrapolation, the best efforts have been taken to ensure the methods were statistically sound, clinically plausible, and reflective of real-world clinical practice. Extensive sensitivity and scenario

analyses were conducted to inform the impact of alternative extrapolation models and assess the long-term plausibility and appropriateness of each scenario

- Only pairwise ICERs and pairwise cost effectiveness acceptability curves could be provided, because of the impact of the Atezo+Bev+CP treatment effect duration cap on long-term OS outcomes for the Atezo+Bev+CP intervention. As such, cost effectiveness acceptability curves also do not reflect the entire decision problem in the comparisons versus pemetrexed-based interventions.

Since the majority of the key approaches and assumptions in the base-case analysis of our economic evaluation are conservative, we believe that the cost-effectiveness results are appropriate for decision-making. The model results support the conclusion that, within the context of innovative end-of-life therapies, and at PAS price atezolizumab and bevacizumab and list price for all comparators, Atezo+Bev+CP is a cost-effective treatment option versus pemetrexed-based interventions in first line patients with metastatic non-squamous NSCLC, regardless of level of PD-L1 expression and including patients with EGFR or ALK mutations after targeted therapy. In addition, results in subgroups of patients with PD-L1 low or negative expression or EGFR/ALK positive mutation explicitly demonstrate that Atezo+Bev+CP is also cost-effective versus pemetrexed-based chemotherapy in these populations. These subgroup results are very relevant for decision-making, since these patients are not eligible for treatment with pembrolizumab and as such, pemetrexed-based chemotherapy is the UK standard of care for them. There is therefore unmet need for cancer immunotherapies in these subgroups of patients, in which atezolizumab Atezo+Bev+CP demonstrates a clinically significant OS and PFS benefit and a cost-effective treatment option.

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B.5 Appendices

Appendices are provided as a separate document.

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Single technology appraisal

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

Dear Roche Products,

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have looked at the submission received on 6 September 2018 from Roche Products. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **12th October 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Lucy Beggs, Technical Lead (Lucy.Beggs@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

General issues

A1. Table 2 in the company submission states "Paclitaxel: IV infusion, 15 mg/kg q3w until disease progression or unacceptable toxicity" but the paper by Socinski et al. (2018) included in the references states "paclitaxel at a dose of 200 mg per square meter of body-surface area (175 mg per square meter for Asian patients)". Please confirm the dosing for paclitaxel, and whether there was a different dosing of paclitaxel for Asian patients.

A2. Table 2 in the company submission states that atezolizumab is given until loss of clinical benefit. How is loss of clinical benefit defined?

IMPower150 trial

A3. **Priority question**: please provide the baseline characteristics for each trial arm in the intention-to-treat wild-type genotype (ITT-WT) subgroup, and in the EGFR-positive/ALK-positive subgroup.

A4. **Priority question**: Please provide the Independent Review Facility (IRF) progression-free survival results for the ITT, ITT-WT populations and subgroup analyses.

A5. **Priority question:** Page 114 of the company submission states that 'health-related quality of life (HRQoL) data were collected in the IMpower150 study directly from first line metastatic non squamous NSCLC patients via the EQ-5D-3L questionnaire' and the Clinical Study Report states '[redacted]' Please provide full results for the EQ-5D results collected in the IMPower150 trial (e.g. UK index values (n, mean and standard errors/95% CI) at all time points for respective trial arms).

A6. The clinical effectiveness evidence quality assessment for IMpower150 presented in Table 8 of the company submission uses the NICE suggested criteria. Some of the questions and answers in this table differ from the detailed risk of bias assessment in Appendix D Table 32. Please confirm the correct answers for Table 8 (and update the row for the IMpower150 trial in Appendix D Table 32 if necessary).

A7. The numbers and percentages reported in Table 11 of the company submission do not appear to be consistent. For example, the number of responders reported in the atezolizumab with bevacizumab, paclitaxel and carboplatin (Atezo+Bev+CP) arm

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(n=28) is 7% of the total number of patients in the arm (397), not 68.3% as reported. Please confirm the definition of 'responders' and provide the correct data for this row of Table 11 of the company submission.

A8. Hazard ratios comparing the treatment effect between the treatment arms in the primary analysis were estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test. Were any unstratified analyses performed in the primary analysis? If so, please provide these analyses.

A9. Please provide a copy of the Statistical Analysis Plan for the trial.

A10. Please provide the full censoring criteria used for assessing progression-free survival in the trial. What was the rationale for the choice of these criteria? (e.g. study investigators' choice, or FDA/EMA/regulator requirement?). Please provide the results of any sensitivity analysis of these criteria.

A11. Were any interaction tests were performed in the subgroup analyses? Was any adjustment made for multiple testing among the subgroup analyses? If so, please provide details.

Systematic literature review

A12. **Priority question.** Appendix D states that after screening records identified by the search 14 trials were identified that meet the inclusion criteria of the systematic review. Of these, seven were relevant to the UK network and a further seven to the global network. What were the inclusion and exclusion criteria for the UK network?

A13. **Priority question.** Please clarify why no trials comparing pemetrexed with other chemotherapy based regimens (i.e. docetaxel, gemcitabine, paclitaxel, or vinorelbine) were included in the network meta-analysis. In particular, it is not clear why trials included in NICE TA181 (pemetrexed for the first-line treatment of non-small-cell lung cancer) were excluded from the current network. Inclusion of these trials would have permitted indirect comparisons between atezolizumab and gemcitabine (plus cisplatin), and docetaxel (plus cisplatin) (see also clarification question B1).

A14. **Priority question:** The reference pack does not appear to contain all the references cited in the Appendices. In particular the key publications for some of the trials in the network meta analysis (NMA) as listed in Appendix D Table 11 are missing: Galetta et al. (ERACLE), Langer et al. (KEYNOTE-021), Reck 2016 (KEYNOTE-024) and Zinner et al (PRONOUNCE). Please provide electronic copies of these missing references.

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A15. Appendix D states that 7 trials were included in the UK network. These are IMpower150, ERACLE, KEYNOTE-021, KEYNOTE-0.24, KEYNOTE-189, PARAMOUNT and PRONOUNCE. Appendix D Table 32 provides the detailed risk of bias assessment for trials included in the clinical systematic literature review and in the NMA feasibility assessment but in this table KEYNOTE-024 is absent and a different trial, BEYOND, is present. BEYOND appears to be a trial that was excluded from both the UK and Global networks (Appendix D Table 12, reference Zhou et al 2013). Please provide the detailed risk of bias assessment for the KEYNOTE-024 study.

A16. Please provide details about how references identified by the literature search were screened at the title and abstract, and full paper screening stages. For example, please outline the number of reviewers (i.e. single or multiple reviewers) and the procedures used (i.e. single or duplicate (independent) screening).

Network meta-analysis – fractional polynomial model

A17. **Priority question**. Please clarify the interval used for dividing the follow-up period in the fractional polynomial model (e.g. monthly). Please confirm how this was determined and whether it was explored in sensitivity analysis. Please also supply the tabulated hazard ratios and 95% credible intervals for each tested fractional polynomial model for each interval time point for the overall and progression-free survival outcomes.

A18. Please provide the hazard ratio plots for all the fractional polynomial models tested (i.e. first and second order, with exponents) for the overall survival, progression-free survival and treatment duration outcomes.

A19. Please provide the DIC values for the random effects models.

A20. **Priority question**. Please provide the results of the random effects fractional polynomial models for OS and PFS (i.e. hazard ratio plots for all models). This will allow comparison with the fixed effect models.

A21. **Priority question**. Although aggregate overall and progression-free survival data are reported in Appendix D Tables 20 and 21, data generated from individual patient data/Kaplan-Meier used in the fractional polynomial model does not appear to have been provided. Please provide WinBUGS/JAGS code for the fractional polynomial models together with the overall/progression-free survival data and priors as formatted in the models.

A22. Please provide the overall and progression-free survival data (analogous to the data in Appendix D Tables 20 and 21) for the EGFR/ALK-positive and PD-L1 low/negative subgroup in the network-meta analyses.

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a. It is our understanding that for the PD-L1 low/negative subgroup analyses, PD-L1 low/-ve subgroup data were used for IMPower150 and KEYNOTE-189, and the ITT population data of the remaining three chemotherapy trials were used. Please confirm whether this is the case.

b. It is our understanding that for the EGFR/ALK-positive sub-group analyses, EGFR/ALK sub-group data from IMPower150 used, compared with ITT population data from the remaining 3 pemetrexed trials. Please confirm whether this is the case.

A23. Please clarify which fractional polynomial model was used for the EFGR/ALK-positive and the PD-L1 low/negative subgroup analyses (for example, whether it was the same 'best fitting' model used in the base case). Please report the model fitting details for these subgroups.

A24. Page 56 of the company submission states the KEYNOTE-021 and KEYNOTE-189 studies were included in the NMA "to provide additional information on the pemetrexed-based regimens, based on their control arm". Please provide more information about what this means and how these data were used. The relative treatment effects comparing the pembrolizumab regimen to pemetrexed with carboplatin/cisplatin and pemetrexed maintenance should not impact the rest of the network unless the pemetrexed with carboplatin/cisplatin and pemetrexed maintenance single-arm results were pooled to be used in the fractional polynomial model in some way. Please clarify whether this was the case.

A25. Differences in expected overall and progression-free survival for treatments compared to atezolizumab with bevacizumab, paclitaxel and carboplatin (Atex+Bev+CP) are provided in Figures 10 and 12 of the company submission. Please provide absolute overall and progression-free survival for Atez+Bev+CP.

A26. Some of the text and hazard plots referred to on pages 58-61 of the company submission appear to have the wrong labels, for example

a. Under the heading OS time-to-event analysis, the sentence "[redacted]…" relates to Figure 11 (right side plot). However, this refers to pemetrexed and cisplatin with placebo maintenance and best supportive care.
b. Under the heading PFS time-to-event analysis, the sentence "[redacted]…" relates to Figure 13 (right side plot). However, this refers to pemetrexed and cisplatin with placebo maintenance and best supportive care.
c. Under the heading Comparison to pemetrexed plus platinum, we believe that Figure 15 should read Figure 14, and Figure 16 should read Figure 15. Figure 22 is also incorrectly referenced.

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Please check these sections for any errors/typos and ensure clarity in the descriptions of the comparisons since there is potential for ambiguity in the naming of the regimens.

A27. We note that median overall survival is reported as 'not reached' for some of the trials in the NMA (Appendix D Table 20). Please comment on the maturity status of the overall and progression-free survival data from the comparator trials included in the NMA.

A28. Page 115 of Appendix D says that some studies in the NMA reported progression based on investigator assessment while others reported progression according to blinded central review. Please indicate the type of assessment (i.e. independent/investigator) for each trial.

Matched adjusted indirect comparison

A29. Please explain the rationale for the choice of matched adjusted indirect comparison (MAIC) for matching patient characteristics rather than Simulated Treatment Comparison (STC).

A30. Please give details of whether a review of prognostic variables was conducted to inform the populating matching exercise. If so, please indicate if any important prognostic factors omitted from the matching exercise.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** We note that the decision problem does not include all the comparator treatments listed in the NICE scope (Table 1 of the company submission).. Please provide the full clinical effectiveness and cost effectiveness results for the other comparators stated in the NICE scope:

a. For untreated advanced, non-squamous NSCLC: Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) with or without pemetrexed maintenance treatment.
b. For EGFR-or ALK-positive advanced, non-squamous NSCLC previously treated with targeted therapy: Docetaxel, Pembrolizumab.

B2. **Priority question:** We note that the company is not seeking reimbursement for the comparison of atezolizumab (in combination with carboplatin plus paclitaxel with bevacizumab) and pembrolizumab in people whose tumours express PD-L1 with at least a 50% tumour proportion score. A cost-effectiveness comparison is therefore not presented. Please can you confirm this is the case?

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B3. **Priority question**: The submission provides limited information about the repeated measures analyses of IMpower150 EQ-5D data (pages 114 to 118 of the company submission). In particular, no evidence is provided to justify the robustness of the proximity to death model used in the base case analysis, or the exclusion of treatment indicator variables. Please provide full results and diagnostics, including sample sizes (patients and observations), coefficient estimates (mean and 95% confidence intervals) and measures of model fit for the pre/post progression and proximity to death models including treatment indicators**.**

B4. **Priority question**: The submission does not present a fully incremental analysis comparing the three included comparators. Page 137 of the company submission suggests that this is due to the way the treatment effect duration cap has been implemented in the model. However, this results in different absolute cost and QALY estimates for Atezo+Bev+CP depending on the comparator, which is illogical. Please consider alternative ways of modelling the relative effects of the three comparators on OS and PFS after the treatment effect duration cap.

- setting the hazard ratio for both pemetrexed comparators vs. the atezolizumab combination equal to 1 at the specified time point
- setting the effect HR for the combination with pemetrexed maintenance vs. atezolizumab combination equal to 1, while maintaining a relative treatment benefit for both of these relative to pemetrexed without maintenance.

B5. Page 103 of the company submission states that 'based on the AIC and BIC values for Atezo+Bev+CP (jointly), the best fitting OS would be Weibull'. However, this does not appear to be consistent with the statistics presented in Table 26 on the same page: Gompertz has the lowest AIC and exponential has the lowest BIC. Please explain the ranking of the distributions.

B6. Please provide denominators for the adverse event frequencies in Table 43 of the company submission (page 132).

B7. We note that a unit cost for pulmonary embolism is included in Table 44 of the company submission (page 133) but not in Table 43. Please confirm whether pulmonary embolism met the criteria for including adverse events in the model, and if so, please provide the event rates in Table 43.

B8. Please clarify why the stated average weight used in the model is 71.9 kg (page 122 of the company submission), whereas the average weight calculated in the Dosing worksheet (cell E29) of the economic model is 70.8 Kg.

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B9. It is unclear from the information given in Table 41 of the company submission, exactly which NHS reference cost codes have been used for outpatient follow-up and ECG. Please provide the unit cost codes for these resources.

Section C: Textual clarifications and additional points

C1. Appendix D Table 10 states the inclusion criteria for the population in the systematic review and indicates that patients "have not received prior CT treatment for Stage IV NSCLC". The CS abbreviations list shows CT is computed tomography, and therefore seems to be an error. Please state what type(s) of prior treatment patients should not have received in order to be included in the systematic review.

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

Roche Responses to ERG clarification questions

Please find Roche's responses to the ERG's clarification questions below.

In addition to the responses, Roche would also like to highlight that since the company evidence submission to NICE in September 2018, the IMpower150 regimen, i.e. Atezolizumab plus bevacizumab, carboplatin and paclitaxel has been included in the updated 2018 ESMO guidelines for metastatic NSCLC as a first-line therapeutic option for patients with EGFR/ALK negative disease, regardless of PD-L1 status, and as an additional treatment option for patients with EGFR or ALK positive disease, after targeted therapies (1).

Section A: Clarification on effectiveness data

General issues

A1. Table 2 in the company submission states "Paclitaxel: IV infusion, 15 mg/kg q3w until disease progression or unacceptable toxicity" but the paper by Socinski et al. (2018) included in the references states "paclitaxel at a dose of 200 mg per square meter of body-surface area (175 mg per square meter for Asian patients)". Please confirm the dosing for paclitaxel, and whether there was a different dosing of paclitaxel for Asian patients.

This is a factual inaccuracy in the company submission. Paclitaxel is administered in the economic model in line with its licence and the paper by Socinski et al. (2), i.e. at a dose of 200 mg per square meter of body-surface area. Body surface area was calculated in the economic model based on patient characteristics from the IMpower 150 study (Arms B and C), using the Dubois formula. No differential dosing of paclitaxel was considered (e.g. for Asian patients).

A2. Table 2 in the company submission states that atezolizumab is given until loss of clinical benefit. How is loss of clinical benefit defined?

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Due to the potential for pseudoprogression/tumour-immune infiltration, study IMPower150 will allow patients randomised to atezolizumab treatment arms to remain on atezolizumab after apparent radiographic progression, provided the benefit-risk ratio is judged to be favourable. Patients were discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

Patients were permitted to continue treatment with atezolizumab after RECIST v1.1 criteria for progressive disease were met, if they meet all of 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 could be 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 provide written consent to acknowledge deferring other treatment options in favour of continuing atezolizumab at the time of initial progression.

Patients treated with atezolizumab in whom radiographic disease progression was confirmed at a subsequent tumour assessment were considered for continued study treatment at the discretion of the investigator if they continued to meet the criteria above. A tumor biopsy sample collection was mandated at the time of first radiographic progression on atezolizumab treatment, in order to distinguish pseudoprogression/tumour immune infiltration from true disease progression.

IMpower150 trial

A3. **Priority question**: please provide the baseline characteristics for each trial arm in the intention-to-treat wild-type genotype (ITT-WT) subgroup, and in the EGFR-positive/ALK-positive subgroup.

Table 1: Demographics and baseline characteristics in the ITT-WT population

	Atezo+Bev+CP n=359	Bev+CP n=337
Mean age, years (SD) Median age, (range)	63.4 (9.3) 63.0 (31–89)	63.4 (9.0) 63.0 (41–87)
Male, n (%)	219 (61.0)	208 (61.7)
Race, n (%) American Indian or Alaska native Asian Black or African American White Multiple Unknown	 3 (0.8) 43 (12.0) 3 (0.8) 296 (82.5) 2 (0.6) 12 (3.3)	 1 (0.3) 23 (6.8) 11 (3.3) 297 (88.1) 0 5 (1.5)
ECOG PS, n (%) 0 1	 140 (39.3) 216 (60.7)	 143 (42.8) 191 (57.2)
Smoking status, n (%) Never Current Previous	 59 (16.4) 83 (23.1) 217 (60.4)	 50 (14.8) 84 (24.9) 203 (60.2)

Non-squamous histology detail, n (%)		
Adenocarcinoma	338 (94.2)	316 (93.8)
Adenocarcinoma with neuroendocrine features	3 (0.8)	2 (0.6)
Adenosquamous	1 (0.3)	2 (0.6)
Bronchioloalveolar carcinoma	1 (0.3)	4 (1.2)
Large cell	5 (1.4)	4 (1.2)
Sarcamatoid	1 (0.3)	0
Undifferentiated	7 (1.9)	3 (0.9)
NA	1 (0.3)	1 (0.3)
Unknown	2 (0.6)	5 (1.5)
EGFR mutation status, n (%)		
Negative	347 (96.7)	329 (97.6)
Unknown	12 (3.3)	8 (2.4)
EML4-ALK rearrangement status, n (%)		
Negative	357 (99.4)	335 (99.4)
Unknown	2 (0.6)	2 (0.6)
KRAS mutation status, n (%)		
Positive	44 (12.3)	36 (10.7)
Negative	56 (15.6)	70 (20.8)
Unknown	259 (72.1)	231 (68.5)
Liver metastases at enrolment from IxRS, n (%)		
Yes	47 (13.1)	47 (13.9)
No	312 (86.9)	290 (86.1)
PD-L1 IHC stratification factor from IxRS, n (%)		
TC0/1/2 and IC0/1	264 (73.5)	252 (74.8)
TC0/1/2 and IC2/3	50 (13.9)	39 (11.6)
TC3 and any IC	45 (12.5)	46 (13.6)

CCOD:22 January 2018

Table 2: Demographics and baseline characteristics in the EGFR/ALK+ population

	Atezo+Bev+CP n=41	Bev+CP n=63
Mean age, years (SD)	59.9 (10.8)	61.4 (10.7)
Median age, (range)	63.0 (35–76)	61.0 (31–90)
Male, n (%)	21 (51.2)	31 (49.2)
Race, n (%)		
Asian	13 (31.7)	23 (36.5)
Black or African American	0	1 (1.6)
White	26 (63.4)	38 (60.3)
Multiple	1 (2.4)	0
Unknown	1 (2.4)	1 (1.6)
ECOG PS, n (%)		
0	20 (45.5)	36 (56.3)
1	24 (54.5)	28 (43.8)

Smoking status, n (%)		
Never	23 (56.1)	27 (42.9)
Current	7 (17.1)	8 (12.7)
Previous	11 (26.8)	28 (44.4)
Non-squamous histology detail, n (%)		
Adenocarcinoma	40 (97.6)	61 (96.8)
Adenosquamous	0	1 (1.6)
Bronchioloalveolar carcinoma	1 (2.4)	1 (1.6)
EGFR mutation status, n (%)		
Positive	34 (82.9)	45 (71.4)
Negative	6 (14.6)	16 (25.4)
Unknown	1 (2.4)	2 (3.2)
EML4-ALK rearrangement status, n (%)		
Positive	11 (26.8)	20 (31.7)
Negative	29 (70.7)	41 (65.1)
Unknown	1 (2.4)	2 (3.2)
KRAS mutation status, n (%)		
Positive	2 (4.9)	2 (3.2)
Negative	4 (9.8)	7 (11.1)
Unknown	35 (85.4)	54 (85.7)
Liver metastases at enrolment from IxRS, n (%)		
Yes	5 (12.2)	10 (15.9)
No	36 (87.8)	53 (84.1)
PD-L1 IHC stratification factor from IxRS, n (%)		
TC0/1/2 and IC0/1	35 (85.4)	49 (77.8)
TC0/1/2 and IC2/3	3 (7.3)	11 (17.5)
TC3 and any IC	3 (7.3)	3 (4.8)

CCOD:22 January 2018

A4. **Priority question**: Please provide the Independent Review Facility (IRF) progression-free survival results for the ITT, ITT-WT populations and subgroup analyses.

Table 3: IRF-assessed progression-free survival in IMpower150

	ITT		ITT-WT		EGFR/ALK+	
	Atezo+Bev+CP n=400	Bev+CP n=400	Atezo+Bev+CP n=356	Bev+CP n=336	Atezo+Bev+CP n=44	Bev+CP n=64
Pts with event, n (%)	269 (67.3)	296 (74.0)	245 (68.8)	246 (73.2)	24 (54.5)	50 (78.1)
Median PFS, mo (95% CI)	8.5 (8.1, 9.7)	7.0 (6.1, 7.8)	8.5 (7.7, 9.7)	7.0 (6.3, 8.0)	9.6 (6.8, 17.0)	5.7 (5.1, 8.3)
Stratified HR (95% CI) p value	0.67 (0.56, 0.79) p<0.0001		0.71 (0.59, 0.85) p=0.0002		0.47 (0.28, 0.81) p=0.0052	

HR, hazard ratio; mo, months; PFS, progression-free survival
CCOD: 15 September 2017 – the IRF was disbanded after the primary endpoint for PFS was met therefore only IRF data for the earlier data cut is available.

A5. **Priority question:** Page 114 of the company submission states that 'health-related quality of life (HRQoL) data were collected in the IMpower150 study directly from first

line metastatic non squamous NSCLC patients via the EQ-5D-3L questionnaire' and the Clinical Study Report states [redacted] Please provide full results for the EQ-5D results collected in the IMPower150 trial (e.g. UK index values (n, mean and standard errors/95% CI) at all time points for respective trial arms).

Full results of the EQ-5D health status data collected in the IMpower150 trial (UK index values [n, mean and standard errors/95% CI] at all time points for respective trial arms) for the ITT population, are provide as a separate file named "ID1210_IMPower150_EQ-5D utility values_UK tariff_ACIC.xlsx"

A6. The clinical effectiveness evidence quality assessment for IMpower150 presented in Table 8 of the company submission uses the NICE suggested criteria. Some of the questions and answers in this table differ from the detailed risk of bias assessment in Appendix D Table 32. Please confirm the correct answers for Table 8 (and update the row for the IMpower150 trial in Appendix D Table 32 if necessary).

Please see below revised versions of Table 8 of the company submission and of the detailed risk of bias assessment (Appendix D, Table 32).

Table 4: Clinical effectiveness evidence quality assessment

Study question	IMpower150 (NCT02366143)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A (open label study)
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Table 5: Detailed risk of bias assessment for trials included in the clinical SLR, and in the NMA feasibility assessment

Author / trial ID	Was the allocation sequence adequately generated?	Was the concealment of treatment allocation adequate?	Was knowledge of the allocated interventions adequately prevented from participants and personnel	Was knowledge of the allocated interventions adequately prevented from outcome assessors	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?
IMpower 150	Randomisation via interactive voice/Web response system. Permuted block randomization was applied to ensure a balanced assignment to each treatment arm and was stratified by: - Sex, presence of liver metastases, PD-L1 expression	For patients who were eligible for enrolment, the study site obtained the patient's randomization number and treatment assignment from the IxRS.	Open-label study. The Sponsor was blinded to treatment arm allocation and patient-level data on PD-L1 expression and Teff gene signature until the database had been locked for analysis.	For independently -reviewed endpoints (IRF PFS), all primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints.	For efficacy data, patients who were not reported as having an event were censored. Patients who did not have post-baseline information were censored at the date of randomisation plus 1 day. The study had predefined methods for handling missing data and censoring rules.	All of the study's pre-specified outcomes have been reported in the CSR	Yes
	Yes	Yes	N/A (open label study)	Yes	Yes	Yes	Yes

A7. The numbers and percentages reported in Table 11 of the company submission do not appear to be consistent. For example, the number of responders reported in the atezolizumab with bevacizumab, paclitaxel and carboplatin (Atezo+Bev+CP) arm (n=28) is 7% of the total number of patients in the arm (397), not 68.3% as reported. Please confirm the definition of 'responders' and provide the correct data for this row of Table 11 of the company submission.

There was an error in Table 11 in the original submission. Please see the updated table with correct values below.

Table 6: Summary of ORR in the ITT population of IMpower150 (updated analysis)

	Atezo+Bev+CP n=397	Bev+CP n=393
Responders, n (%)	224 (56.4)	158 (40.2)
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 (%)	111 (28.0)	160 (40.7)

(95% CI)	(23.6, 32.7)	(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)

CCOD: 22 January 2018

A8. Hazard ratios comparing the treatment effect between the treatment arms in the primary analysis were estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test. Were any unstratified analyses performed in the primary analysis? If so, please provide these analyses.

Table 7: Unstratified analyses of investigator-assessed progression-free survival in IMpower150 (updated analysis)

	ITT		ITT-WT		EGFR/ALK+	
	Atezo+Bev+CP n=400	Bev+CP n=400	Atezo+Bev+CP n=359	Bev+CP n=337	Atezo+Bev+CP n=41	Bev+CP n=63
Pts with event, n (%)	291 (72.8)	355 (88.8)	263 (73.3)	298 (88.4)	28 (63.3)	57 (90.5)
Median PFS, mo (95% CI)	8.4 (8.0, 9.9)	6.8 (6.0, 7.0)	8.3 (7.7, 9.8)	6.8 (6.0, 7.1)	10.0 (7.9, 15.2)	6.1 (5.6, 8.4)
Unstratified HR (95% CI) p value	0.58 (0.50, 0.68) p<0.0001		0.59 (0.50, 0.70) p<0.0001		0.55 (0.35, 0.87) p=0.0101	

HR, hazard ratio; mo, months; PFS, progression-free survival
CCOD: 22 January 2018

Table 8: Unstratified analyses of overall survival in IMpower150 (updated analysis)

	ITT		ITT-WT		EGFR/ALK+	
	Atezo+Bev+CP n=400	Bev+CP n=400	Atezo+Bev+CP n=359	Bev+CP n=337	Atezo+Bev+CP n=41	Bev+CP n=63
Pts with event, n (%)	192 (48.0)	230 (57.5)	179 (49.9)	197 (58.5)	13 (31.7)	33 (52.4)
Median OS, mo (95% CI)	19.8 (17.4, 24.2)	14.9 (13.4, 17.1)	19.2 (17.0, 23.8)	14.7 (13.3, 16.9)	NE (17.0, NE)	17.5 (10.4, NE)
Unstratified HR (95% CI) p value	0.77 (0.63, 0.93) p=0.0064		0.78 (0.64, 0.96) p=0.017		0.54 (0.29, 1.03) p=0.0578	

HR, hazard ratio; mo, months; OS, overall survival
CCOD: 22 January 2018

A9. Please provide a copy of the Statistical Analysis Plan for the trial.

The Statistical Analysis Plan has been provided along with this response document.

A10. Please provide the full censoring criteria used for assessing progression-free survival in the trial. What was the rationale for the choice of these criteria? (e.g. study investigators' choice, or FDA/EMA/regulator requirement?). Please provide the results of any sensitivity analysis of these criteria.

PFS was defined as the time from randomisation to the first documented disease progression (PD) as determined by the investigator with the use of RECIST v1.1 or death from any cause, whichever occurred first. As per FDA guidance (3), data for patients who were alive and who did not experience PD at the time of analysis were censored at the date of the last tumour assessment. Data for patients with no post-baseline tumour assessment were censored at the date of randomization plus 1 day.

The impact of missing scheduled tumour assessments on PFS was assessed depending on the number of patients who missed assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or the data cut-off.

Results for the sensitivity analysis for patients who missed two or more scheduled assessments immediately prior to the date of disease progression per RECIST v1.1 or the data cut-off and were censored at the last tumour assessment prior to the missed visits is shown below.

Table 9: Time-to-event summary for PFS censoring for missing tumour assessments (ITT-WT Population)

	Atezo+Bev+CP n=356	Bev+CP n=336
Pts with event, n (%)	227 (63.8)	264 (78.6)
Median PFS, months (95% CI)	8.3 (7.7, 9.8)	6.8 (6.0, 7.1)
Stratified HR (95% CI) p value	0.62 (0.52, 0.74) p<0.0001	

HR, hazard ratio; PFS, progression-free survival
CCOD: 15 September 2017

A11. Were any interaction tests were performed in the subgroup analyses? Was any adjustment made for multiple testing among the subgroup analyses? If so, please provide details.

No interaction tests or multiplicity adjustment were performed in the subgroup analyses.

Systematic literature review

A12. **Priority question.** Appendix D states that after screening records identified by the search 14 trials were identified that meet the inclusion criteria of the systematic review. Of these, seven were relevant to the UK network and a further seven to the global network. What were the inclusion and exclusion criteria for the UK network?

The full list of eligibility criteria for the systematic review is presented in Table 10 (page 14) of the Appendices to the company evidence submission. The only two differences between the UK and Global network, in terms of eligibility criteria, are:

- The set of interventions considered as relevant comparators; the Global network included a wider set relevant comparators.
- The eligibility criteria in terms of the proportion of patients within each study with Stage IV non-squamous NSCLC; this differed between the UK and Global network. In the

Global network this criterion was relaxed (80% vs 90% in the UK network) to enable a connected network for the wider set of relevant interventions being considered.

A13. **Priority question.** Please clarify why no trials comparing pemetrexed with other chemotherapy based regimens (i.e. docetaxel, gemcitabine, paclitaxel, or vinorelbine) were included in the network meta-analysis. In particular, it is not clear why trials included in NICE TA181 (pemetrexed for the first-line treatment of non-small-cell lung cancer) were excluded from the current network. Inclusion of these trials would have permitted indirect comparisons between atezolizumab and gemcitabine (plus cisplatin), and docetaxel (plus cisplatin) (see also clarification question B1).

Please see response to question B1.

A14. **Priority question:** The reference pack does not appear to contain all the references cited in the Appendices. In particular the key publications for some of the trials in the network meta analysis (NMA) as listed in Appendix D Table 11 are missing: Galetta et al. (ERACLE), Langer et al. (KEYNOTE-021), Reck 2016 (KEYNOTE-024) and Zinner et al (PRONOUNCE). Please provide electronic copies of these missing references.

These references have been provided along with this response document.

A15. Appendix D states that 7 trials were included in the UK network. These are IMpower150, ERACLE, KEYNOTE-021, KEYNOTE-0.24, KEYNOTE-189, PARAMOUNT and PRONOUNCE. Appendix D Table 32 provides the detailed risk of bias assessment for trials included in the clinical systematic literature review and in the NMA feasibility assessment but in this table KEYNOTE-024 is absent and a different trial, BEYOND, is present. BEYOND appears to be a trial that was excluded from both the UK and Global networks (Appendix D Table 12, reference Zhou et al 2013). Please provide the detailed risk of bias assessment for the KEYNOTE-024 study.

Table 10: Detailed risk of bias assessment for the KEYNOTE-024 study

Author / trial ID	Was the allocation sequence adequately generated?	Was the concealment of treatment allocation adequate?	Was knowledge of the allocated interventions adequately prevented from participants and personnel	Was knowledge of the allocated interventions adequately prevented from outcome assessors	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?
KEYNOTE-024	Sequence was generated by a proprietary Clinical Schedule Generation system.	Interactive voice-response system.	Not blinded (open-label)	Radiological assessments were made by centralised, blinded reviewers	ITT analysis for safety. Efficacy data censored at time of last follow up if missing.	No evidence of selective reporting	No evidence of other sources of bias
	Yes	Yes	N/A (open label study)	Yes	Yes	Yes	Yes

A16. Please provide details about how references identified by the literature search were screened at the title and abstract, and full paper screening stages. For example, please outline the number of reviewers (i.e. single or multiple reviewers) and the procedures used (i.e. single or duplicate (independent) screening).

Study selection

The search results were rapidly assessed according to their relevance in providing information in relation to the review and obviously irrelevant records were excluded. The types of studies excluded at this stage were animal studies, commentaries, news items, and records on issues unrelated to the topic of interest. Two reviewers independently undertook the record selection, with a third reviewer adjudicating any disagreements.

We obtained and assessed full texts of potentially relevant studies in detail for relevance to the review's eligibility criteria. This produced a list of eligible and ineligible studies. Where results for one study were reported in more than one paper, all related papers were identified and grouped together to ensure that participants in individual studies were only included once.

Table 12 in Appendices to company submission (pages 19-81) provides a list of studies excluded after assessment of the full document, along with the reasons for exclusion.

Data extraction

A data extraction sheet was developed as an Excel spreadsheet and reviewers piloted the form on a number of studies before progressing to full data extraction. Two reviewers independently extracted data from eligible publications. A third reviewer adjudicated any disagreements. For each outcome, data were collected at all time points reported.

Network meta-analysis – fractional polynomial model

A17. **Priority question**. Please clarify the interval used for dividing the follow-up period in the fractional polynomial model (e.g. monthly). Please confirm how this was determined and whether it was explored in sensitivity analysis. Please also supply the tabulated hazard ratios and 95% credible intervals for each tested fractional polynomial model for each interval time point for the overall and progression-free survival outcomes.

In the fractional polynomial model, the follow-up period and the data was discretised into monthly intervals. Monthly intervals were chosen, on the basis that using a smaller interval would add noise without adding meaningful precision to the analysis. No formal sensitivity analysis was conducted on this. Tabulated hazard ratios with credible intervals can be found in Appendix A.

A18. Please provide the hazard ratio plots for all the fractional polynomial models tested (i.e. first and second order, with exponents) for the overall survival, progression-free survival and treatment duration outcomes.

Hazard ratio plots for all fractional polynomial models tested are provided below. Treatment duration was not included as an outcome in the fractional polynomial NMA as this was not reported in most trials, resulting in a disconnected network.

The two matrix plots below show the hazard ratio on the odds ratio scale relative to ATZ+BEV+CP for the five fixed effects fractional polynomial models tested and the 1st order random effect fractional polynomial model with P1=0. Figure 1 shows the hazard ratios for the overall survival outcome; Figure 2 shows the hazard ratios for the progression free survival outcome. The light grey shaded regions indicate the 95% posterior credible intervals. The OS outcome is extrapolated up to 60 months, while the PFS outcome is extrapolated up to 30 months. The Y-axis is log-transformed; each point on the Y-axis indicates a change by a factor of two of the odds ratio.

Figure 1: OS hazard ratios over time for each tested first and second order fractional polynomial model relative to Atezo+Bev+CP (time horizon 60 months); HR > 1 favours Atezo+Bev+CP; shaded region indicates 95% credible interval

Figure 2: PFS hazard ratios over time for each tested first and second order fractional polynomial model relative to Atezo+Bev+CP (time horizon 30 months); HR > 1 favours Atezo+Bev+CP; shaded region indicates 95% credible interval

DIC values for all models that were fitted (i.e. five fixed effects fractional polynomial models and the 1st order random effect fractional polynomial model with P1=0) are provided below.

Table 11: Deviance information criteria for all fitted models

Model	Notes	P1	P2	OS	PFS
Exponential	Proportional Hazard	0	-	1512.455	2151.955
FP order 1	Weibull	0	-	1406.577*	1917.61†
FP order 1	Gombertz	1	-	1461.521	2083.962
FP order 2		0	0	1377.799	1632.611
FP order 2		1	0	1367.564	1656.748
FP order 2		1	1	1364.96	1731.708

* OS Random effects DIC: 1407.12
† PFS Random effects DIC: 1920.256

A20. **Priority question**. Please provide the results of the random effects fractional polynomial models for OS and PFS (i.e. hazard ratio plots for all models). This will allow comparison with the fixed effect models.

Hazard ratio plots for the random effects models have been provided in response to question A18, included as part of the two matrix plots of all model hazard ratios.

We only fitted a random effects version of the selected fractional polynomial (order 1, P1=0 model) for OS and PFS, that was chosen as part of the model selection process. We can therefore only report results for these models. Hazard ratio tables and plots for these models are provided as part of the responses to questions A17 and A18, showing the hazard ratios for all fitted models. The random effect models give very similar results to the fixed effect versions of the same models, with almost identical point estimates and only slightly wider confidence intervals.

A21. **Priority question**. Although aggregate overall and progression-free survival data are reported in Appendix D Tables 20 and 21, data generated from individual patient data/Kaplan-Meier used in the fractional polynomial model does not appear to have been provided. Please provide WinBUGS/JAGS code for the fractional polynomial models together with the overall/progression-free survival data and priors as formatted in the models.

The WinBUGS/JAGS code for the fractional polynomial models, the OS and PFS data and prior values are provided in Appendix B.

A22. Please provide the overall and progression-free survival data (analogous to the data in Appendix D Tables 20 and 21) for the EGFR/ALK-positive and PD-L1 low/negative subgroup in the network-meta analyses.

Table 12: Overall survival summary statistics for the IMpower150 PD-L1 low/no and EGFR/ALK+ sub-groups, and the KEYNOTE-189 PD-L1 low/no subgroup

Trial identifier	Intervention	Definition of outcome	Number analysed	Overall survival			12 months Overall Survival
				Median [months] (95% CI)	HR (95% CI)	KM	% (95% CI)
IMpower150 PD-L1 low/no	ATZ+PAC+CARB	Time from randomization to death from any cause	334	19.2 (15.1-21.4)	0.861 (0.701-1.057), p=0.152 vs. BEV+PAC+CARB	YES	65.19 (60.23-70.56)
	ATZ+BEV+PAC+ CARB		325	19.1 (16.8-23.8)	0.800 (0.648-0.988), p=0.038 vs. BEV+PAC+CARB		66.89 (61.90-72.28)
	BEV+PAC+CARB		327	14.9 (13.5-17.1)			62.42 (57.32-67.97)
KEYNOTE-189 PD-L1 low/no	PEMB+CIS/CARB+PEM then PEM maintenance	Time from randomization to death from any cause	255	NR (NR-NR)	0.570 (0.411-0.790), p=0.001	YES[1]	67.52 (61.54-74.08)
	PEM+CIS/CARB+PLAC then PEM maintenance		121	12.0 (8.7-NR)			51.08 (42.64-61.19)
IMpower150 EGFR/ALK+	ATZ+PAC+CARB	Time from randomization to death from any cause	53	21.2 (13.6-NR)	0.833 (0.500, 1.387), p=0.482 vs. BEV+PAC+CARB	Yes	76.63 (65.88-89.13)
	ATZ+BEV+PAC+CARB		41	NR (17.0-NR)	0.544 (0.286-1.034), p=0.063 vs. BEV+PAC+CARB		77.69 (65.83-91.68)
	BEV+PAC+CARB		63	17.5 (11.7-NR)			60.10 (49.10-73.55)

ATZ – Atezolizumab; BEV – bevacizumab; CARB – carboplatin; CI – confidence interval; CIS – cisplatin; HR – hazard ratio; ITT – intention to treat; KM – Kaplan-Meier; NR – not reached; PAC – paclitaxel; PEM – pemetrexed; PEMB – pembrolizumab; PLAC – placebo
IMPower 150 CCOD:22 January 2018

1 Kaplan-Meier (KM) data were reported separately by PD-L1 subgroup (<1%, 1-49%, ≥50%) for KEYNOTE-189. The reconstructed individual patient data (Guyot, 2012) from the digitised <1% and 1-49% KM curves were combined to provide estimates for the no/low expression sub-group (i.e. PD-L1 expression <50%).

Table 13: Progression free survival summary statistics for IMpower150 PD-L1 low/no and EGFR/ALK+ sub-groups

Trial identifier	Intervention	Definition of outcome	Number analysed	Progression free survival		
				Median [months] (95% CI)	HR (95% CI)	KM
IMpower150 PD-L1 low/no	ATZ+PAC+CARB	Time from randomization to the first documented disease progression or death from any cause, whichever occurred first	334	6.0 (5.6-6.9)	0.945 (0.801-1.114) p=0.498 vs. BEV+PAC+CARB	YES
	ATZ+BEV+PAC+ CARB		325	8.2 (7.2-8.8)	0.681 (0.575-0.807) p<0.001 vs. BEV+PAC+CARB	
	BEV+PAC+CARB		327	6.8 (5.9-7.1)		
KEYNOTE-189 PD-L1 low/no	PEMB+CIS/CARB+PEM then PEM maintenance	Time from randomization to disease progression Assessed according to RECIST criteria by blinded, independent central radiologic review, or death from any cause, whichever occurred first	255	7.5 (6.7-8.9)	0.648 (0.503-0.836) p=0.001	YES[2]
	PEM+CIS/CARB+PLAC then PEM maintenance		121	4.9 (4.8-6.8)		
IMpower150 EGFR/ALK+	ATZ+PAC+CARB	Time from randomization to the first documented disease progression or death from any cause, whichever occurred first	53	6.9 (5.7-8.1)	1.120 (0.760-1.653) p=0.566 vs. BEV+PAC+CARB	Yes
	ATZ+BEV+PAC+CARB		41	10.0 (7.9-17.1)	0.544 (0.345-0.859) p=0.009 vs. BEV+PAC+CARB	
	BEV+PAC+CARB		63	6.1 (5.7-8.5)		

ATZ – Atezolizumab; BEV – bevacizumab; CARB – carboplatin; CI – confidence interval; CIS – cisplatin; HR – hazard ratio; ITT – intention to treat; KM – Kaplan-Meier; NR – not reached; PAC – paclitaxel; PEM – pemetrexed; PEMB – pembrolizumab; PLAC - placebo

IMPower 150 CCOD:22 January 2018

2 Kaplan-Meier (KM) data were reported separately by PD-L1 subgroup (<1%, 1-49%, ≥50%) for KEYNOTE-189. The reconstructed individual patient data (Guyot, 2012) from the digitised <1% and 1-49% KM curves were combined to provide estimates for the no/low expression sub-group (i.e. PD-L1 expression <50%).

a. It is our understanding that for the PD-L1 low/negative subgroup analyses, PD-L1 low/-ve subgroup data were used for IMPower150 and KEYNOTE-189, and the ITT population data of the remaining three chemotherapy trials were used. Please confirm whether this is the case.

This is correct.

b. It is our understanding that for the EGFR/ALK-positive sub-group analyses, EGFR/ALK sub-group data from IMPower150 used, compared with ITT population data from the remaining 3 pemetrexed trials. Please confirm whether this is the case.

This is correct. The EGFR/ALK subgroup data from IMPower150 were compared against the ITT populations of the pemetrexed-based arms of ERACLE, PRONOUNCE, and PARAMOUNT.

A23. Please clarify which fractional polynomial model was used for the EFGR/ALK-positive and the PD-L1 low/negative subgroup analyses (for example, whether it was the same 'best fitting' model used in the base case). Please report the model fitting details for these subgroups.

The same FP NMA model specification (fractional polynomial order 1, P1=0) was used for the ITT and the EFGR/ALK positive and the PD-L1 low/negative subgroup analyses, on the basis that the underlying relationship between treatments was not expected to differ in subgroups of patients. Choice of the same NMA model would also allow comparison of the subgroup analyses with the main results. There are no additional model fitting details to report.

A24. Page 56 of the company submission states the KEYNOTE-021 and KEYNOTE-189 studies were included in the NMA "to provide additional information on the pemetrexed-based regimens, based on their control arm". Please provide more information about what this means and how these data were used. The relative treatment effects comparing the pembrolizumab regimen to pemetrexed with carboplatin/cisplatin and pemetrexed maintenance should not impact the rest of the network unless the pemetrexed with carboplatin/cisplatin and pemetrexed maintenance single-arm results were pooled to be used in the fractional polynomial model in some way. Please clarify whether this was the case.

Studies KEYNOTE-021 and KEYNOTE-189 were included in the NMA network as the pemetrexed-based intervention in their control arm, is a relevant comparator for the UK NMA. No pooling of the pemetrexed-based interventions single-arm results was however conducted in the fractional polynomial model. The KEYNOTE-021 and KEYNOTE-189 studies have a minor effect on the results of the rest of the NMA network, since including an additional study will only

have a very small effect on the shape, but not the location, of the modelled hazard over time for the pemetrexed-based interventions in the fractional polynomial models.

A sensitivity analysis was conducted that excluded the two KEYNOTE studies from the NMA (see pages 65-67 of company submission). This analysis demonstrated that the two KEYNOTE studies have a small impact on the NMA results and their exclusion does not alter any of the conclusions of the main NMA analysis. In addition, the NMA results excluding the KEYNOTE studies were incorporated as a scenario analysis in the economic model, and the impact on results was also minimal (see pages 151-157 of company submission).

A25. Differences in expected overall and progression-free survival for treatments compared to atezolizumab with bevacizumab, paclitaxel and carboplatin (Atex+Bev+CP) are provided in Figures 10 and 12 of the company submission. Please provide absolute overall and progression-free survival for Atez+Bev+CP.

The following two tables show the absolute expected survival results (OS, and PFS) for Atezo+Bev+CP that result from fitting the NMA results from each fractional polynomial model to the ITT population. These data were used as baseline for the other comparators when reporting the differences in expected survival, which were presented in the company submission.

Table 14: Expected OS (in months) for all models

Model	Type	Expected Overall Survival	95% CrI
Exponential PH model	Fixed effects	25.58	[23.09, 28.15]
FP order 1, P1=0	Fixed effects	23.03	[20.89, 25.37]
FP order 1, P1=0	Random Effects	23.01	[20.84, 25.48]
FP order 1, P1=1	Fixed effects	21.75	[19.74, 24.1]
FP order 2, P1=0,P2=0	Fixed effects	24.13	[21.7, 26.93]
FP order 2, P1=1,P2=0	Fixed effects	25.13	[22.18, 28.3]
FP order 2, P1=1,P2=1	Fixed effects	26.61	[23.36, 29.87]

Table 15: Expected PFS (in months) for all models

Model	Type	Expected Progression Free Survival	95% CrI
Exponential PH model	Fixed effects	11.95	[10.93, 13]
FP order 1, P1=0	Fixed effects	11.86	[10.97, 12.79]
FP order 1, P1=0	Random Effects	11.86	[10.98, 12.8]
FP order 1, P1=1	Fixed effects	11.83	[10.86, 12.8]
FP order 2, P1=0,P2=0	Fixed effects	12.04	[11.11, 13.06]
FP order 2, P1=1,P2=0	Fixed effects	12.07	[11.12, 13.09]
FP order 2, P1=1,P2=1	Fixed effects	12.08	[11.11, 13.09]

The Figures below present the same information as the previous two Tables, in Figure format.

Figure 3: Estimated Expected OS (in months) for Atezo+Bev+CP, as estimated in the main ITT population with 95% posterior Credible Interval, for all fitted fractional polynomial models. Dots indicate the posterior median, and lines indicate the range of the 95% CrI. Time is censored at 60 months for the OS outcome.

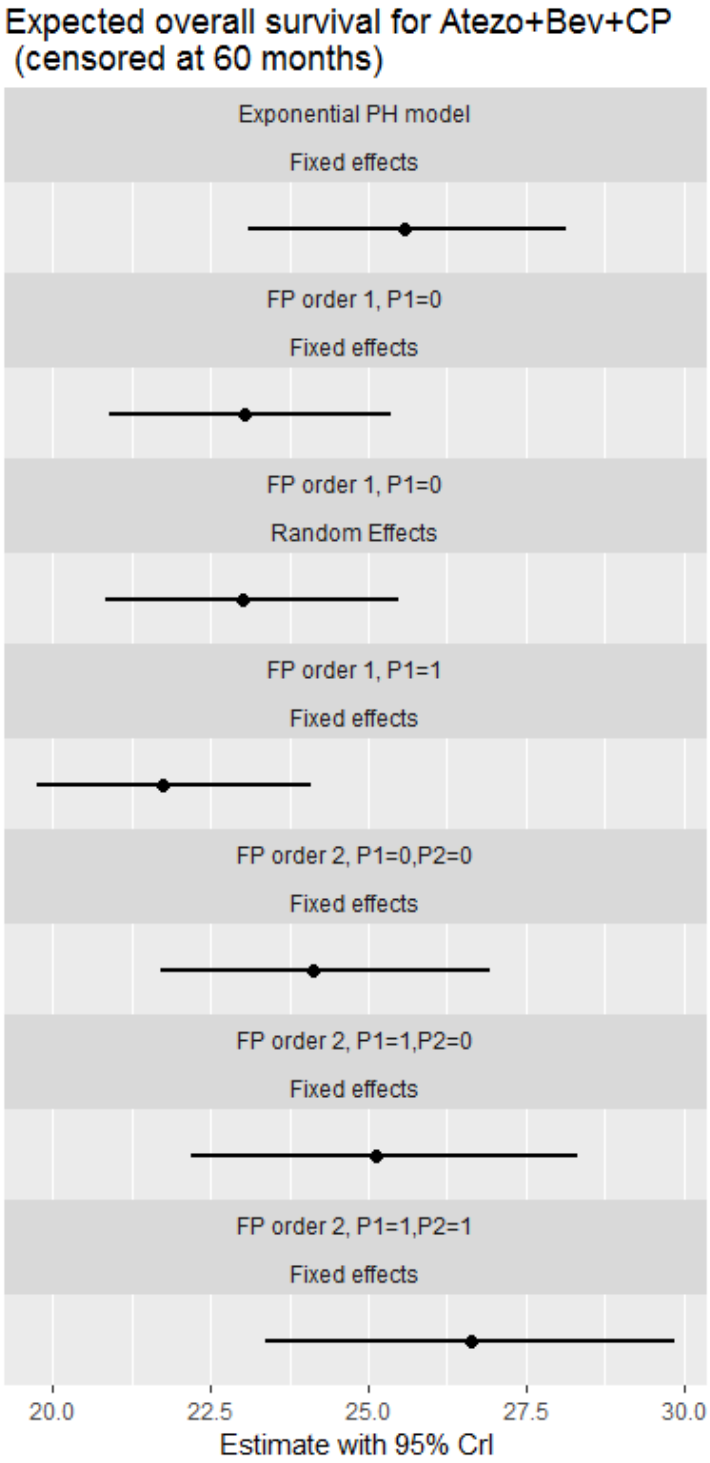
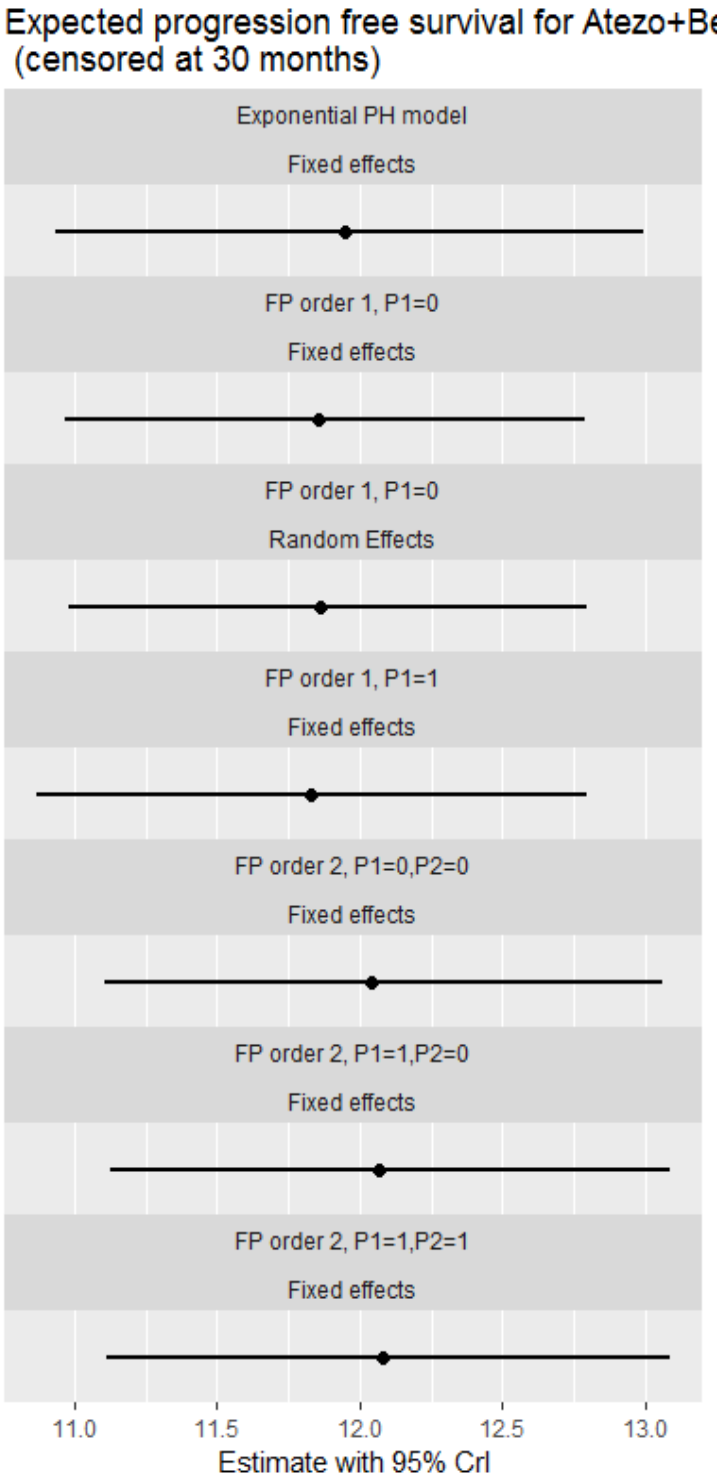


Figure 4: Expected PFS (in months) for Atezo+Bev+CP, as estimated in the main ITT population with 95% posterior Credible Interval, for all fitted fractional polynomial models. Dots indicate the posterior median, and line indicate the range of and line indicate the range of the 95% CrI. Time is censored at 30 months for the PFS outcome.



A26. Some of the text and hazard plots referred to on pages 58-61 of the company submission appear to have the wrong labels, for example

a. Under the heading OS time-to-event analysis, the sentence [redacted] relates to Figure 11 (right side plot). However, this refers to pemetrexed and cisplatin with placebo maintenance and best supportive care.
b. Under the heading PFS time-to-event analysis, the sentence [redacted] relates to Figure 13 (right side plot). However, this refers to pemetrexed and cisplatin with placebo maintenance and best supportive care.
c. Under the heading Comparison to pemetrexed plus platinum, we believe that Figure 15 should read Figure 14, and Figure 16 should read Figure 15. Figure 22 is also incorrectly referenced.

Please check these sections for any errors/typos and ensure clarity in the descriptions of the comparisons since there is potential for ambiguity in the naming of the regimens.

Please note that this is a result of slightly different labelling of interventions and abbreviations in Figures of the NMA section, compared to other sections of the company submission. For points (a) and (b) the text matches the figures that it refers to, but the ERG is correct in saying that the labelling of the pemetrexed-based treatments differs between the text and the Figures. This is due to the fact that whilst pemetrexed plus platinum (either carboplatin or cisplatin) was considered as one intervention in the SLR and NMA, this is not reflected in the labelling of Figure 11 - Figure 25.

Regarding point (c), the ERG is correct – this is a factual inaccuracy for Figures 14 – 16. Figure 22 appears to also be mistakenly referenced in section “NMA results – subgroup analyses; Comparison to pemetrexed plus platinum” (page 61) where it should read Figure 14. Figure 22 however in page 67 is appropriately referenced.

A27. We note that median overall survival is reported as ‘not reached’ for some of the trials in the NMA (Appendix D Table 20). Please comment on the maturity status of the overall and progression-free survival data from the comparator trials included in the NMA.

A summary of the maturity status of the OS and PFS data from the comparator trials included in the NMA is provided in the Table below.

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Table 16: Summary of maturity status of OS and PFS data from trials in the NMA

					OS			PFS		
Study	Follow-up, median (months)	Follow-up, maximum[1] (months)	Arm	N	Events[2]	Maturity (Events/N)	Median (months)	Events[2]	Maturity (Events/N)	Median (months)
IMpower150 ITT	20	32	ATZ+PAC+CARB	402	206	51%	19.5	330	82%	6.7
			ATZ+BEV+PAC+ CARB	400	192	48%	19.8	290	73%	8.4
			BEV+PAC+CARB	400	230	58%	14.9	355	89%	6.8
ERACLE	27	30	CIS+PEM then PEM main	60	43	72%	14.0	50	83%	8.1
			CARB+PAC+BEV then BEV main	58	41	71%	14.4	51	88%	8.3
KEYNOTE-021	18.7	25	PEMB+CARB+ PEM then PEMB then PEM main	60	20	33%	NE	26	43%	19.0
			PEM+CARB then PEM maintenance	63	31	49%	20.9	40	63%	8.9
KEYNOTE-189	10.5	20	PEMB+CIS/CARB+PEM then PEM maintenance	410	125	30%	NE	237	58%	8.8
			PEM+CIS/CARB+PLAC then PEM maintenance	206	106	51%	11.3	161	78%	4.9
PARAMOUNT	24.3	35	CIS+PEM then PEM main	359	198	55%	13.9	321	89%	4.4
			CIS+PEM then PLAC+BSC maintenance	180	106	59%	11.0	157	87%	2.8
PRONOUNCE	NR	30	CARB+PEM then PEM maintenance	182	126	69%	10.5	138	76%	4.4
			CARB+PAC+BEV then BEV main	179	120	67%	11.7	121	68%	5.5

[1] From last observation time on the KM curve; [2] Derived from digitised KM curves, where applicable; NE, not estimated; NR, not reported

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For OS, the data maturity (percentage of randomised patients experiencing the event) ranged from 33% in KEYNOTE-021 to 72% in ERACLE. The median follow-up ranged from 10.5 months in KEYNOTE-189 to 27 months in ERACLE. Comparing this to the observed median survivals, which are typically 11 to 21 months, the duration of follow-up and maturity in some trials was insufficient for the median OS to be reached – this will be exacerbated for more effective treatments where events happen more slowly. Therefore, the median OS was not reached for the pembrolizumab arms of the two KEYNOTE trials, where the follow-up was the shortest, but the treatment was one of the more effective.

For PFS, data were reasonably mature (over 50%) in all studies except for KEYNOTE-021. Within KEYNOTE-021, 63% of patients had events in the PEM+CARB arm but only 43% had events in the PEMB+PEM+CARB arm. Although the median PFS was reached for this arm, it was 19.0 months which is over twice as long as the median PFS in any other study, including the similar treatment arm in KEYNOTE-189. The upper limit of the 95% CI was not reached. With the exception of this study, median PFS ranged from 3 to 9 months, therefore the duration of follow-up and maturity was sufficient for the median PFS to be reached.

The impact of lower maturity is to increase uncertainty around the extrapolated tails of any fitted survival curves. Therefore, in the presentation of the NMA results the time horizon for calculating expected survival (PFS and OS) was restricted to reduce the influence of the extrapolated portion. This is in line with the previous NICE appraisal of atezolizumab in second-line NSCLC (4) where a fractional polynomial NMA was also implemented.

It should be noted that the two KEYNOTE studies with the least mature data have a minor impact on the NMA comparison of atezolizumab to the relevant comparators for the UK. A NMA scenario analysis was nonetheless performed excluding the KEYNOTE studies, one of the reasons being due to shorter follow-up time in these studies. Results of this scenario analysis demonstrated a minimal impact on NMA results. Please see response to question A24 for additional details.

A28. Page 115 of Appendix D says that some studies in the NMA reported progression based on investigator assessment while others reported progression according to blinded central review. Please indicate the type of assessment (i.e. independent/investigator) for each trial.

For IMpower150, data from latest data cut-off (January 2018) were used consistently for all outcomes. For this data cut, only PFS by investigator assessment is available. PFS assessment based on both methods (by independent review committee and investigator assessed) was only conducted for the previous data cut (September 2017) and, as per protocol, PFS assessment by independent review committee was not repeated for the later data cut.

Most of the studies included in the NMA used the RECIST criteria to determine progression, assessed by independent review committee (see Table below). The PARAMOUNT trial used

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investigator-assessed PFS, whilst the PRONOUCE trial did not provide details on the PFS assessment method.

Table 17: PFS assessment method in studies included in the NMA

Trial identifier	Interventions	PFS criteria information
IMpower150	ATZ+CP	RECIST v1.1 by investigator (January 2018 data cut)
	ATZ+BEV+CP	
	BEV+CP	
	CARB+PAC+BEV then BEV main	
KEYNOTE-021	PEMB+CARB+ PEM then PEMB then PEM main	RECIST v1.1 criteria by IRC
	PEM+CARB then PEM maintenance	
KEYNOTE-024	PEBM	RECIST 1.1 criteria by IRC
	Standard chemotherapy	
KEYNOTE-189	PEMB+CIS/CARB+PEM then PEM maintenance	RECIST v1.1 criteria by IRC
	PEM+CIS/CARB+PLAC then PEM maintenance	
PARAMOUNT	CIS+PEM then PEM maintenance	RECIST 1.0 investigator assessed
	CIS+PEM then PLAC+BSC maintenance	
PRONOUNCE	CARB+PEM then PEM maintenance	No details
	CARB+PAC+BEV then BEV maintenance	
	PAC + CARB	

Matched adjusted indirect comparison

A29. Please explain the rationale for the choice of matched adjusted indirect comparison (MAIC) for matching patient characteristics rather than Simulated Treatment Comparison (STC).

For the purpose of an unanchored comparison, such as the comparison versus pembrolizumab in patients with high PD-L1 expression in our company submission, both MAIC and STC make the strong assumption that the absolute treatment effect can be predicted from the included variables, and therefore require that both effect modifiers and prognostic variables be included in the analysis (5). From this perspective, there is therefore little reason to prefer one method over the other. However, the STC approach requires predicting the outcome in the new model. Since the main outcome of interest was overall survival, it was considered that conducting a covariate-adjusted survival analysis would introduce more technical uncertainties than the combination of logistic regression followed

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by a weighted analysis that is required by MAIC. In addition, MAIC has been used more extensively in the published literature, and thus seems more widely accepted (5).

A30. Please give details of whether a review of prognostic variables was conducted to inform the populating matching exercise. If so, please indicate if any important prognostic factors omitted from the matching exercise.

A targeted literature search was conducted to identify prognostic and predictive factors (effect modifiers) in first-line NSCLC (Roche data on file).

The following covariates that were included and reported in KEYNOTE-024 were also available for IMpower150, and therefore could be matched: age, sex, smoking status, previous systemic neoadjuvant therapy, previous systemic adjuvant therapy, histology, region, brain metastases, and ECOG performance.

Please note that the covariate distribution in KEYNOTE-024 was only reported for the overall study population (i.e. regardless of histology), while the target population for the comparison to Atezo+Bev+CP is the non-squamous subgroup. We therefore had to assume that the covariate distribution in study KEYNOTE-024 is the same for the non-squamous subgroup as for the whole study.

Populations in KEYNOTE-024 and in IMpower150 (PD-L1 high subgroup) were similar with respect to negative EGFR/ALK mutation status and high level of PD-L1 expression. Information about other prognostic factors, i.e. mutations (e.g. ROS1, excision repair cross-complementation group 1 (ERCC1), blood-based tumour mutational burden (bTMB)) was not available.

There was only one covariate that was available in both studies but not used – brain metastases. Brain metastasis was not present in any patient in the Atezo+Bev+CP arm of IMpower150 and therefore patients could not be weighted based on this characteristic.

Some covariates that are available for IMpower150 and possibly prognostic had to be omitted as they were not reported for KEYNOTE-024 (e.g. ethnicity, performance status, liver metastases, time since diagnosis).

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** We note that the decision problem does not include all the comparator treatments listed in the NICE scope (Table 1 of the company submission).. Please provide the full clinical effectiveness and cost effectiveness results for the other comparators stated in the NICE scope:

a. For untreated advanced, non-squamous NSCLC: Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) with or without pemetrexed maintenance treatment.
b. For EGFR-or ALK-positive advanced, non-squamous NSCLC previously treated with targeted therapy: Docetaxel, Pembrolizumab.

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No clinical effectiveness or cost effectiveness comparison was performed versus the comparators listed in the ERG question. Within our company submission we describe in detail the rationale for the deviation from the NICE final scope, in terms of the relevant comparators included in the economic model (please see Section B.1.1 and Section B.3.2.3).

The aim of the NICE final scope is to include all interventions that are licensed and reimbursed in the indication being appraised, since these can potentially be relevant comparators. However, the economic model in our company submission only includes a comparison versus the UK standard of care therapies in first-line metastatic non-squamous NSCLC, as this comparison is representative of clinical practice and an appropriate basis for decision-making.

The comparators included in the economic model (on the basis of UK clinical expert opinion and UK market share data) are:

- Pemetrexed in combination with a platinum drug (carboplatin or cisplatin), and
- Pemetrexed plus a platinum drug with pemetrexed maintenance

It is reminded that the comparison with pembrolizumab in patients with high PD-L1 expression is excluded from the cost-effectiveness section of our submission.

The justification for pemetrexed-based chemotherapy representing the UK standard of care chemotherapy for first-line metastatic non-squamous NSCLC is outlined below:

- In order to ensure that the appropriate chemotherapy comparators are used in the indirect treatment comparison and in the economic model of our submission, Roche sought opinion from ten UK clinical experts in 2018 through different advisory board platforms[3]. All UK clinical experts agreed that pemetrexed in combination with a platinum therapy (either cisplatin or carboplatin), with or without pemetrexed maintenance, is appropriate to be considered standard of care in the UK.
- UK clinical experts also advised that the vast majority (approximately >95%) of first-line metastatic non-squamous NSCLC patients receive pemetrexed plus platinum, provided that they are fit for chemotherapy. This was confirmed by UK market share data, showing that pemetrexed-based regimens account for over 83% of the chemotherapy used in first-line metastatic non-squamous NSCLC patients with no active EGFR or ALK mutation (Kantar Health tracker, Q1 2016-Q2 2019, Roche data on file).

[3] Advisory Board members who provided permission for their names to be provided in the submission to support this information included: Dr Sanjay Popat (Royal Marsden, London), Dr Riyaz Shah (Maidstone and Tunbridge Well NHS Trust, Kent), Dr Nicola Steele (Beaston Institution for Cancer Research, Glasgow), Dr Martin Forster (UCLH, London), Dr Alastair Greystoke (Freeman Hospital, Newcastle upon Tyne)

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- For non-squamous NSCLC patients with an EGFR or ALK mutation, no clinical guidance is available for which chemotherapy they receive after targeted therapy. Again, clinical expert opinion was sought (from six UK clinical experts) and suggested that again the vast majority (almost all) receive pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed maintenance, is the appropriate UK chemotherapy comparator in this setting (i.e. EGFR/ALK positive advanced, non-squamous NSCLC after targeted therapy)

In addition, it should be noted that that the comparators listed in the NICE final scope for EGFR/ALK non-squamous NSCLC patients previously treated with targeted therapy are not appropriate (the NICE final scope includes docetaxel and pembrolizumab as comparators). These therapies however are licensed and reimbursed for EGFR/ALK positive patients after targeted therapy and after treatment with chemotherapy (i.e. effectively second-line after targeted therapy). Therefore, these therapies represent a later line of therapy compared to the scope of this appraisal for EGFR/ALK positive patients following targeted therapy, and are not appropriate to be considered as relevant comparators.

B2. **Priority question:** We note that the company is not seeking reimbursement for the comparison of atezolizumab (in combination with carboplatin plus paclitaxel with bevacizumab) and pembrolizumab in people whose tumours express PD-L1 with at least a 50% tumour proportion score. A cost-effectiveness comparison is therefore not presented. Please can you confirm this is the case?

This is correct. We do not seek reimbursement as a treatment alternative to pembrolizumab, which is licensed and recommended for patients with high PD-L1 expression (>50% tumour proportion score, TC/IC 3), excluding patients with EGFR or ALK mutations.

Our company evidence submission focuses on the comparison to pemetrexed-based chemotherapy and seeks reimbursement for Atezo+Bev+CP as a treatment alternative to pemetrexed-based regimens. This comparison is conducted firstly in the ITT population, as this reflects the marketing authorisation and NICE reimbursement for pemetrexed-based interventions, and provides a more robust evidence base for the indirect treatment comparison. However, the following subgroup analyses are provided and reimbursement is effectively pursued for Atezo+Bev+CP in the subgroups of patients with:

1. low or negative PD-L1 expression and
2. EGFR or ALK tumour mutations (regardless of PD-L1 expression)

These are the subgroups of patients who are not eligible for treatment with pembrolizumab as a first-line NSCLC therapy and as such, have an unmet need for a cancer immunotherapy treatment option.

B3. **Priority question**: The submission provides limited information about the repeated measures analyses of IMpower150 EQ-5D data (pages 114 to 118 of the company

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submission). In particular, no evidence is provided to justify the robustness of the proximity to death model used in the base case analysis, or the exclusion of treatment indicator variables. Please provide full results and diagnostics, including sample sizes (patients and observations), coefficient estimates (mean and 95% confidence intervals) and measures of model fit for the pre/post progression and proximity to death models including treatment indicators.

A separate report with full details on the models used to estimate utility values from the EQ-5D data collected in IMpower150 is provided in Appendix C. Please note that the utility values used in our economic model are the resulting overall mean utility values, i.e. mean utility values regardless of treatment arm, on the basis that we did not observe a significant difference between mean utilities by treatment arm in any of the models considered, and the confidence intervals overlapped.

B4. **Priority question**: The submission does not present a fully incremental analysis comparing the three included comparators. Page 137 of the company submission suggests that this is due to the way the treatment effect duration cap has been implemented in the model. However, this results in different absolute cost and QALY estimates for Atezo+Bev+CP depending on the comparator, which is illogical. Please consider alternative ways of modelling the relative effects of the three comparators on OS and PFS after the treatment effect duration cap.

- setting the hazard ratio for both pemetrexed comparators vs. the atezolizumab combination equal to 1 at the specified time point
- setting the effect HR for the combination with pemetrexed maintenance vs. atezolizumab combination equal to 1, while maintaining a relative treatment benefit for both of these relative to pemetrexed without maintenance.

The originally submitted model used the active comparator in each pair-wise comparison as the source for transition probabilities for Atezo+Bev+CP after the treatment effect duration cap, meaning that the risk of having an event would be the same for patients treated with Atezo+Bev+CP and the active comparator after the treatment effect cut-off. This approach resulted in in the long-term outcomes (after 5 years) for Atezo+Bev+CP being different, depending on the intervention used for each pairwise comparison. As such, only pairwise ICERs could be provided in our company submission and not a fully incremental set of results.

The first ERG suggestion as a way to model the relative effects of the three comparators i.e. setting the hazard ratio for both pemetrexed comparators versus the atezolizumab combination equal to 1 at the specified time point is exactly the approach we followed in our company submission and leads to different long-term outcomes for Atezo+Bev+CP (after 5 years) depending on the intervention in each pairwise comparison.

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We therefore updated the economic model based on the ERG's second suggestion. The current model uses pemetrexed plus platinum plus pemetrexed maintenance as the source for transition probabilities for Atezo+Bev+CP after the treatment effect cut-off, irrespective of which comparator is used in the pair-wise analyses. The result is that the number of QALYs and costs accrued in the Atezo+Bev+CP arm does not change depending on the active comparator. The model now allows for a fully incremental analysis comparing all three interventions included in the model to be conducted, both deterministic and probabilistic.

A full set of updated model results is provided in Appendix D. The updated economic model is provided as a separate file (named ID1210_Atezolizumab 1L non-squamous NSCLC_Economic model_06092018_ACIC_update 12102018.xlsx)

B5. Page 103 of the company submission states that 'based on the AIC and BIC values for Atezo+Bev+CP (jointly), the best fitting OS would be Weibull'. However, this does not appear to be consistent with the statistics presented in Table 26 on the same page: Gompertz has the lowest AIC and exponential has the lowest BIC. Please explain the ranking of the distributions.

Whilst Gompertz appeared to be the best-fitting distribution in terms of AIC and BIC for Atezo+Bev+CP, it did not converge for the comparison to pemetrexed plus platinum. Therefore, Gompertz could not be considered as an appropriate option for the extrapolation of OS in the economic model.

B6. Please provide denominators for the adverse event frequencies in Table 43 of the company submission (page 132).

The adverse event frequencies in Table 43 of the company submission were divided by the total duration of follow-up for adverse events (i.e. number of patients multiplied by adverse event follow up in weeks), to derive the probability per week for each adverse event occurring. This serves as an input in the economic model to calculate adverse event costs.

For Atezo+Bev+CP the adverse event follow up was informed by the IMPower150 study. For pemetrexed-based chemotherapy comparators the following assumptions had to be made:

- Pemetrexed plus platinum adverse event follow up: 6 months (maximum treatment duration as per license)
- Pemetrexed plus platinum plus pemetrexed maintenance adverse event follow up: mean PFS as in economic model (from fractional polynomial NMA) 8.06 months

B7. We note that a unit cost for pulmonary embolism is included in Table 44 of the company submission (page 133) but not in Table 43. Please confirm whether pulmonary embolism met the criteria for including adverse events in the model, and if so, please provide the event rates in Table 43.

Pulmonary embolism did not meet the adverse event inclusion criteria for the economic model. As such, the pulmonary embolism unit cost reported in Table 44 (page 133) is not

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used in the model. Please note that Table 43 appropriately reflects the adverse events included in the economic model.

B8. Please clarify why the stated average weight used in the model is 71.9 kg (page 122 of the company submission), whereas the average weight calculated in the Dosing worksheet (cell E29) of the economic model is 70.8 Kg.

The base case of the economic model uses average weight of 71.9kg ("Model inputs" worksheet, cell F35) to calculate the actual dose for weight-based regimens, as stated in our company submission. The 70.8kg average weight ("Dosing" worksheet, cell E29) is only used when the individual patient dosing is considered in scenario analyses varying dosing assumptions. This is demonstrated to have a minimal impact on model results (see company submission, pages 150–157)

The reason for the discrepancy is that missing values from some individual baseline characteristics in the dosing array ("Dosing" worksheet, cells E30:E829) were copied across as zero values and thus were counted in the calculation of the mean. When the zeros are removed, the two mean values for patient weight match. Again, we would like to note that the average weight of 70.8kg has an insignificant impact on model results and is used only in specific scenario analyses (and not in the model base-case)

B9. It is unclear from the information given in Table 41 of the company submission, exactly which NHS reference cost codes have been used for outpatient follow-up and ECG. Please provide the unit cost codes for these resources.

- Outpatient follow-up visit – location in NHS Reference Costs 2016-2017: File name "2016-17_National_schedule_of_reference_costs_-_main_schedule.xls", worksheet "Total Outpatient Attendances" , Service code 800, Clinical Oncology, Consultant Led, (cell G143)

- ECG – location in NHS Reference Costs 2016-2017: File name "2016-17_National_schedule_of_reference_costs_-_main_schedule.xls", worksheet "Total HRGs" , HRG code EY50Z (cell D724)

Section C: Textual clarifications and additional points

C1. Appendix D Table 10 states the inclusion criteria for the population in the systematic review and indicates that patients "have not received prior CT treatment for Stage IV NSCLC". The CS abbreviations list shows CT is computed tomography, and therefore seems to be an error. Please state what type(s) of prior treatment patients should not have received in order to be included in the systematic review.

CT stands for chemotherapy in Appendix D Table 10. Apologies for the inconsistency.

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APPENDIX A – Tabulated hazard ratios and 95% credible intervals for each tested fractional polynomial model

The Tables below present the hazard ratios of pemetrexed-based interventions compared to Atezo+Bev+CP, with 95% credible intervals, for all time points and from all evaluated fractional polynomial models. The second results column reports the estimates from the 1st order fractional polynomial model with P1=0 (i.e. the selected model) with random effects.

Treatment duration was not included as an outcome in the fractional polynomial NMA, as this was not reported in most trials, resulting in a disconnected network.

Table 18: OS estimated hazard ratios (95% CrI) for PEM+CARB/CIS with PEM main relative to Atezo+Bev+CP for all first and second order FP models; months 1-60; HR > 1 favour Atezo+Bev+CP

Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
1	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
17	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
31	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
37	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
38	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
39	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
41	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
43	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
44	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
46	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
47	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
49	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
51	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
53	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
54	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
56	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
57	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
58	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
59	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 19: OS estimated hazard ratios (95% CrI) for PEM+CIS with PLAC main+BSC relative to Atezo+Bev+CP for all first and second order FP models; months 1-60; HR > 1 favour Atezo+Bev+CP

Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
1	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
4	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
30	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
31	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
32	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
34	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
37	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
38	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
39	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
41	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
43	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
44	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
46	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
47	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
49	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
51	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
53	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
54	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
56	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
57	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
58	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
59	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 20: PFS estimated hazard ratios (95% CrI) for PEM+CARB/CIS with PEM main relative to favour Atezo+Bev+CP for all first and second order FP models; months 1-30; HR > 1 favour favour Atezo+Bev+CP

Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
1	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
18	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	PEM+CARB/CIS with PEM main	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 21: PFS estimated hazard ratios (95% CrI) for PEM+CIS with PLAC main+BSC relative to Atezo+Bev+CP for all first and second order FP models; months 1-30; HR > 1 favour Atezo+Bev+CP.

Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
1	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Months	Treatment	FP order 1, P1=0	FP order 1, P1=0 (random)	FP order 1, P1=1	FP order 2, P1=0,P2=0	FP order 2, P1=1,P2=0	FP order 2, P1=1,P2=1
9	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	PEM+CIS with PLAC main+BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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APPENDIX B – WinBUGS/JAGS code for the fractional polynomial models, OS and PFS data and prior values

Please see below the JAGS code used to fit the 1st and 2nd order fixed effects fractional polynomial models and the 1st order random effects fractional polynomial models.

JAGS code for the 1st order fractional polynomial fixed effects model

```
#
# 1st order fractional polynomial model
#

# Data inputs
# P1: controls for of fractional polynomial model
# NS: number of studies
# dt: time interval (set to 4 weeks in this case)
# maxt: maximum time to predict results for
# trt: a vector identifying the treatment for each study
# dataframe with columns:
#  time[i] s[i] r[i] n[i]

# Estimated parameters


# Data outputs


model{

  # Set up models for data from comparator arms ------------
  for (i in 1:nobs){
    # Time (transformations 1 and 2)
    time_t1[i]<- equals(P1,0)*log(time[i]) + (1-equals(P1,0))*pow(time[i],
P1)

    # likelihood (for available data)
    r[i]~ dbin(p[i],n[i])
    p[i]<-1-exp(-h[i]*dt)  # cumulative hazard over interval [t,t+dt] expr
essed as deaths per person-week

    #Random effects model
    #Beta[study,arm,coef]
    log(h[i])<- Beta[s[i],arm[i],1]+Beta[s[i],arm[i],2]*time_t1[i]

   # Deviance contribution
   # rhat[i] <- p[i]*n[i]
   # dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i])) + (n[i]-r[i]) * (log(n
[i]-r[i]) - log(n[i]-rhat[i])))
```

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```
  }

  for (i in 1:NS){

    for (j in 1:nArms[i]){
      # Beta[study,arm,x]
      Beta[i,j,1]<-mu1[i] + d[trt[i,j],1]-d[trt[i,1],1]
      Beta[i,j,2]<-mu2 + d[trt[i,j],2]-d[trt[i,1],2]
    }

  }

  #priors
  for (k in 1:NS){
    mu1[k] ~ dnorm(0,.0001)
  }
  mu2 ~ dnorm(0,.0001)

  d[1,1]<-0
  d[1,2]<-0
  for (k in 2:NT){
    for (j in 1:2){
      d_tmp[k-1,j] ~ dnorm(0,.0001)
      d[k,j]<-d_tmp[k-1,j]
    }
  }

#Output
 for (m in 1:maxt){
    time1[m]<-(equals(P1,0)*log(m) + (1-equals(P1,0))*pow(m,P1)    )
 }

  for (nn in 2:NT){
    for (m in 1:maxt){
      log(HR1[1,nn,m])<-(d[nn,1]-d[1,1])+(d[nn,2]-d[1,2])*time1[m]
   }
  }
}
```

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JAGS code for the 2nd order fractional polynomial fixed effects model

```
#
# 2nd order fractional polynomial model
#

# Data inputs
# P1: controls for of fractional polynomial model
# NS: number of studies
# dt: time interval (set to 4 weeks in this case)
# maxt: maximum time to predict results for
# trt: a vector identifying the treatment for each study
# dataframe with columns:
#  time[i] s[i] r[i] n[i]

# Estimated parameters


# Data outputs

model{

  # Set up models for data from comparator arms ------------
  for (i in 1:nobs){
    # Time (transformations 1 and 2)
    time_t1[i]<- equals(P1,0)*log(time[i]) + (1-equals(P1,0))*pow(time[i],
P1)
    time_t2[i]<- (1-equals(P2,P1))*(equals(P2,0)*log(time[i]) + (1-equals(
P2,0))*pow(time[i],P2)) +
                    equals(P2,P1)*(equals(P2,0)*log(time[i])*log(time[i])
+
                    (1-equals(P2,0))*pow(time[i],P2)*log(time[i]))


    # likelihood (for available data)
    r[i]~ dbin(p[i],n[i])
    p[i]<-1-exp(-h[i]*dt)  # cumulative hazard over interval [t,t+dt] expr
essed as deaths per person-week

    #Random effects model
    #Beta[study,arm,coef]
    log(h[i])<- Beta[s[i],arm[i],1]+Beta[s[i],arm[i],2]*time_t1[i]+Beta[s[
i],arm[i],3]*time_t2[i]

    # Deviance contribution #GR: Double-check this!
   # rhat[i] <- p[i]*n[i]
   # dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i])) + (n[i]-r[i]) * (log(n
[i]-r[i]) - log(n[i]-rhat[i])))

  }
```

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```
  for (i in 1:NS){

    for (j in 1:nArms[i]){
      # Beta[study,arm,x]
      Beta[i,j,1]<-mu1[i] + d[trt[i,j],1]-d[trt[i,1],1]
      Beta[i,j,2]<-mu2 + d[trt[i,j],2]-d[trt[i,1],2]
      Beta[i,j,3]<-mu3 + d[trt[i,j],3]-d[trt[i,1],3]
    }

  }

  #priors
  for (k in 1:NS){
    mu1[k] ~ dnorm(0,.0001)
  }
  mu2 ~ dnorm(0,.0001)
  mu3 ~ dnorm(0,.0001)
  d[1,1]<-0
  d[1,2]<-0
  d[1,3]<-0

  for (k in 2:NT){
    for (j in 1:3){
      d_tmp[(k-1),j] ~ dnorm(0,.0001)
      d[k,j] <- d_tmp[(k-1),j]

    }
  }

#Output
 for (m in 1:maxt){
    time1[m]<-(equals(P1,0)*log(m) + (1-equals(P1,0))*pow(m,P1)    )
 }

  for (nn in 2:NT){
    for (m in 1:maxt){
      log(HR1[1,nn,m])<-(d[nn,1]-d[1,1])+(d[nn,2]-d[1,2])*time1[m]
   }
  }
}
```

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JAGS code for the 1st order fractional polynomial random effects model

```
#
# 1st order Random effects Fractional polynomial model
#
#

# Data inputs
# P1: controls for of fractional polynomial model
# NS: number of studies
# NPred: number of predicted nivolumab results = number of studies * numbe
r of timepoints per study
# dt: time interval (set to 4 weeks in this case)
# maxt: maximum time to predict results for
# trt: a vector identifying the treatment for each study
# dataframe with columns:
#  time[i] s[i] log.h.adj[i] prec.log.h.adj[i] r[i] n[i]

# Estimated parameters


# Data outputs

model{


  # Set up models for data from comparator arms ------------
  for (i in 1:nobs){

    # Time (transformations 1 and 2)
    time_t1[i]<- equals(P1,0)*log(time[i]) + (1-equals(P1,0))*pow(time[i],
P1)

    # likelihood (for available data)
    r[i]~ dbin(p[i],n[i])
    p[i]<-1-exp(-h[i]*dt)  # cumulative hazard over interval [t,t+dt] expr
essed as deaths per person-week

    #Random effects model
    #Beta[study,arm,coef]
    log(h[i])<-  Beta[s[i],arm[i],1]+Beta[s[i],arm[i],2]*time_t1[i]

  }

  for (i in 1:NS){
    w[i, 1] <- 0
    delta[i,1]<-0

    for (j in 1:nArms[i]){
      # Beta[study,arm,x]
```

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```
      Beta[i,j,1]<-mu1[i] + delta[i,j]
      Beta[i,j,2]<-mu2 + d[trt[i,j],2]-d[trt[i,1],2]

    }
    for (j in 2:nArms[i]){

    delta[i, j] ~ dnorm(md[i, j], taud[i, j])
    md[i, j] <- d[trt[i, j], 1] - d[trt[i, 1], 1] + sw[i, j]
    w[i, j] <- (delta[i, j] - d[trt[i, j], 1] + d[trt[i, 1], 1])
    sw[i, j] <- sum(w[i, 1:(j - 1)]) / (j - 1)
    taud[i, j] <- tau * 2 * (j - 1) / j

  }
}
  #priors
  for (k in 1:NS){
    mu1[k] ~ dnorm(0,.0001)
  }
  mu2 ~ dnorm(0,.0001)

  d[1,1]<-0
  d[1,2]<-0
  for (k in 2:NT){
    for (j in 1:2){
      d[k,j] ~ dnorm(0,.0001)
    }
  }

  priorStudyPrec<-priorStudySD^(-2)
  variance~dlnorm(priorStudyMean,priorStudyPrec)
  tau <- 1/variance
  sd <- variance^(1/2)

}
```

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OS Data for fixed-effects Fractional Polynomial models order 1 and 2

This data is provided by the use of the "dump()" function in R, on the list object that was provided to JAGS. To read in, simply copy/paste or source the below text in an R session.

```
nma.data <-
structure(list(s = c(1L, 1L, 2L, 2L, 3L, 3L, 4L, 4L, 5L, 5L,
5L, 6L, 6L, 1L, 1L, 2L, 2L, 3L, 3L, 4L, 4L, 5L, 5L, 5L, 6L, 6L,
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2L, 3L, 3L, 4L, 4L, 5L, 5L, 5L, 6L, 6L, 1L, 1L, 2L, 2L, 3L, 3L,
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2L), time = c(1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 2, 2, 2,
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31, 31, 32, 32, 32, 32, 33, 33, 33, 34, 34, 34, 35, 35, 35, 36,
37, 38, 39), r = c(1, 0, 5, 7, 0, 1, 5, 9, 14, 8, 9, 1, 1, 2,
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0, 0, 1, 1, 1, 2, 0, 0, 0, 1, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0,
0, 0, 0, 0, 0, 0, 0, 0), n = c(58, 60, 179, 182, 359, 180, 206,
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365, 351, 357, 344, 57, 56, 49, 57, 127, 136, 300, 146, 158,
353, 347, 343, 335, 57, 56, 49, 54, 121, 125, 268, 131, 148,
345, 333, 332, 317, 57, 55, 48, 51, 111, 115, 258, 121, 131,
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241, 44, 48, 33, 34, 73, 71, 194, 78, 59, 163, 265, 258, 233,
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53, 42, 151, 54, 19, 52, 162, 153, 139, 36, 41, 23, 26, 45, 36,
141, 51, 14, 36, 147, 136, 123, 33, 39, 20, 24, 38, 33, 135,
49, 8, 18, 130, 120, 104, 29, 36, 18, 23, 34, 30, 122, 41, 12,
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26, 12, 18, 28, 20, 105, 35, 73, 76, 68, 17, 22, 12, 16, 22,
16, 95, 31, 62, 59, 51, 14, 18, 10, 14, 14, 13, 87, 26, 45, 44,
41, 11, 11, 9, 13, 10, 11, 77, 23, 38, 31, 36, 9, 7, 9, 12, 8,
11, 67, 18, 32, 25, 27, 8, 12, 6, 11, 52, 14, 18, 15, 15, 7,
11, 3, 11, 43, 11, 10, 10, 6, 7, 11, 3, 10, 34, 10, 2, 7, 3,
6, 11, 2, 8, 23, 9, 2, 1, 5, 15, 7, 1, 5, 10, 6, 1, 5, 6, 4,
5, 2, 3, 5, 2, 2, 5, 5, 5, 5), trt = structure(c(2L, 2L, 3L,
```

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```
3L, 1L, 3L, 3L, 3L, 4L, 5L, 6L, 5L, NA, NA, NA, NA, 2L, NA), .Dim = c(6L,
3L)), arm = c(1, 2, 1, 2, 1, 2, 1, 2, 1, 2, 3, 1, 2, 1, 2, 1,
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1, 2, 1, 2, 1, 3, 2, 1, 2, 3, 2, 1, 2, 3, 2, 1, 2, 2, 1, 2, 2,
1, 2, 2, 2, 2, 2), NS = 6L, NT = 6L, nArms = c(2L, 2L, 2L, 2L,
3L, 2L), nobs = 379L, dt = 1, P1 = 0, maxt = 65), .Names = c("s",
"time", "r", "n", "trt", "arm", "NS", "NT", "nArms", "nobs",
"dt", "P1", "maxt"))
```

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PFS Data for fixed-effects Fractional Polynomial models order 1 and 2

This data is provided by the use of the "dump()" function in R, on the list object that was provided to JAGS. To read in, simply copy/paste or source the below text in an R session.

```
nma.data <-
structure(list(s = c(1L, 1L, 2L, 2L, 3L, 3L, 4L, 4L, 5L, 5L,
5L, 6L, 6L, 1L, 1L, 2L, 2L, 3L, 3L, 4L, 4L, 5L, 5L, 5L, 6L, 6L,
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3L, 5L, 3L, 3L, 3L, 3L, 3L), time = c(1, 1, 1, 1, 1, 1, 1, 1,
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    2, 1, 2, 1, 1, 2, 1, 1, 1, 1, 1, 1, 1), NS = 6L, NT = 6L,
    nArms = c(2L, 2L, 2L, 2L, 3L, 2L), nobs = 337L, dt = 1, P1 = 1,
    maxt = 65), .Names = c("s", "time", "r", "n", "trt", "arm",
"NS", "NT", "nArms", "nobs", "dt", "P1", "maxt"))
```

Priors for random effects models

In order to add the priors for OS to the above data, run the below two lines in R.

```
##Priors from Turner 2015 for all-cause mortality, pharma vs pharma.
nma.data$priorStudyMean<- -4.18
nma.data$priorStudySD<- 1.41
```

In order to add priors for PFS, instead run the following lines:

```
Priors from Turner 2015 for external structure, pharma vs pharma
nma.data$priorStudyMean<- -2.94
nma.data$priorStudySD<- 1.79
```

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APPENDIX C – Models to estimate utility values from the EQ-5D data collected in IMpower150

Model of utilities based on proximity to death approach

Proximity to death approach utilities were demonstrated as more relevant as they reflect the known decline in cancer patients' quality of life during the terminal phase of the disease. The proximity to death utilities were analysed for patients who were on treatment and patients who discontinued treatment.

We consider four intervals for time to death approach, following the atezolizumab NICE submission for second-line NSCLC (4):

- Group 1: less than 35 days before death (BD)
- Group 2: more than 34 and less than 75 days BD
- Group 3: more than 74 and less than 210 days BD
- Group 4: more than 211 days BD

At time of clinical cut-off 47.8% of patients were still alive; these patients provided almost ten thousand of HRQoL observations. In principle, the proximity to death approach would not include utilities for patients who are alive. However, following this approach would result in discarding 68.5% of the utility observations available from the study. Therefore, in Group 4 we included utilities for patients still alive and with more than 211 days follow up.

Table 22 presents number of patients per treatment arm and number of observations included in the model.

Table 22: Number of patients and observations per treatment arm included in proximity to death model

Treatment arm	Number of patients	Number of observations
Atezo+CP	371	3310
Atezo+Bev+CP	363	3831
Bev+CP	340	2606

Figure 5 shows utilities before treatment with a trend for the three arms of IMPower150 based on smoothing splines. In the last ten months of life the trends by treatment basically overlap.

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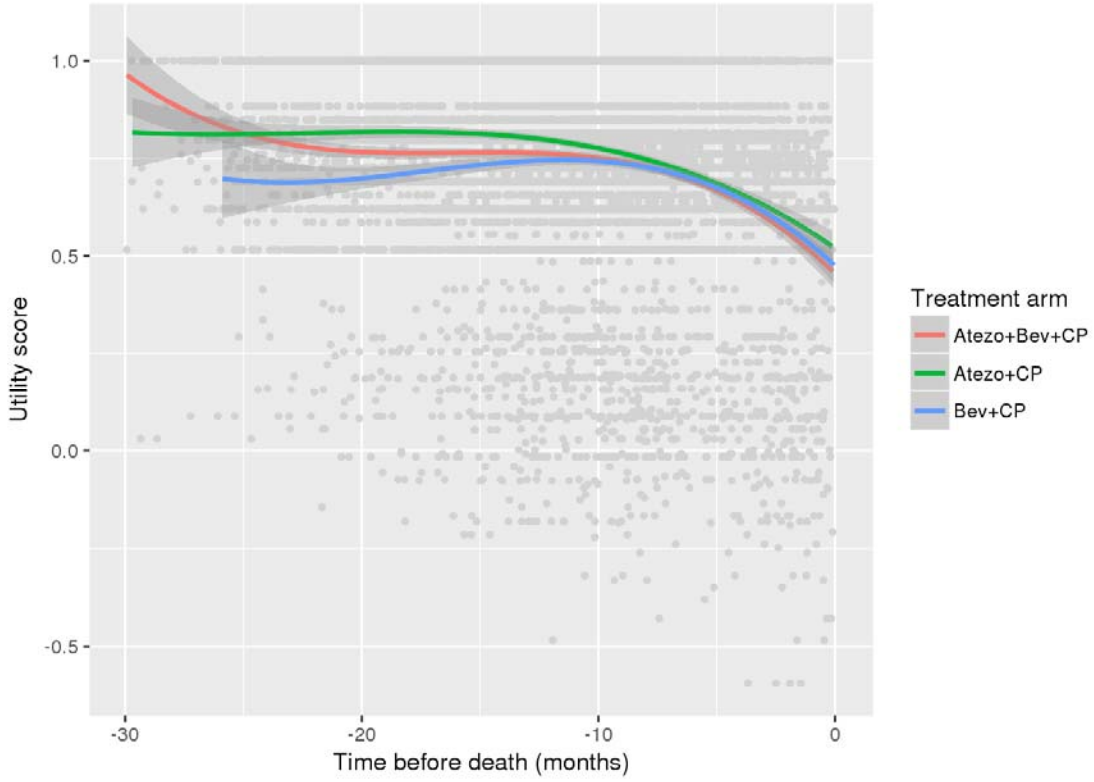
Figure 5: Utilities for time to death with smoothing trend by treatment arm



We fitted a repeated measurements model including time before death group, assessment time and treatment arm as covariates and we assumed an exchangeable working correlation.

Convergence criteria for the model were met, and overall likelihood ratio test indicated that at least one of the covariates in the model is significant. Information criteria were AIC: -5440 and BIC -5430.

Type III tests results indicated that treatment arm is not significant (F p-value: 0.1438), the same holds by and time of assessment (F p-value: 0.1471). Covariance parameter estimate is equal to 0.038 and the residual variance is equal to 0.0255

Fixed effects model coefficients are shown in Table 23

Table 23: Fixed effect coefficients in the proximity to death model

Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
Intercept	0.7239	0.0118	0.70070	0.74700
Atezo+CP	0.0276	0.0158	-0.00329	0.05854
Atezo+Bev+CP	0.0024	0.0158	-0.02860	0.03344
Bev+CP	0			
1:<35 days BD	-0.2103	0.0161	-0.24190	-0.1786

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Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
2: 35-74 days BD	-0.1489	0.0117	-0.17180	-0.1259
3: 75-210 days BD	-0.0366	0.0067	-0.04977	-0.0235
4: > 210 days BD	0			
Assessment time (days)	-0.00002	0.000015	-0.00005	0.000007415

Treatment arm and time of assessment are not statistically significant as indicated by type III tests. However they are kept in the model because they are considered clinically relevant to explain variability of utilities.

IMpower150 utilities based on proximity to death approach correspond to model-based estimates for four intervals are presented in Table 24 and in Figure 6. Here, we also present overall model-based estimate of utilities.

Table 24: Model-based estimates proximity to death model

Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
Atezo + CP	0.7128	0.0093	0.6945	0.7311
Atezo + Bev + CP	0.6975	0.0094	0.6790	0.7160
Bev + CP	0.6917	0.0097	0.6727	0.7108
Overall	0.7200	0.0071	0.7061	0.7340
1:<35 days BD	0.5236	0.0168	0.4905	0.5567
2: 35-74 days BD	0.5850	0.0130	0.5596	0.6105
3: 75-210 days BD	0.6972	0.0090	0.6795	0.7149
4: > 210 days BD	0.7339	0.0072	0.7198	0.7479

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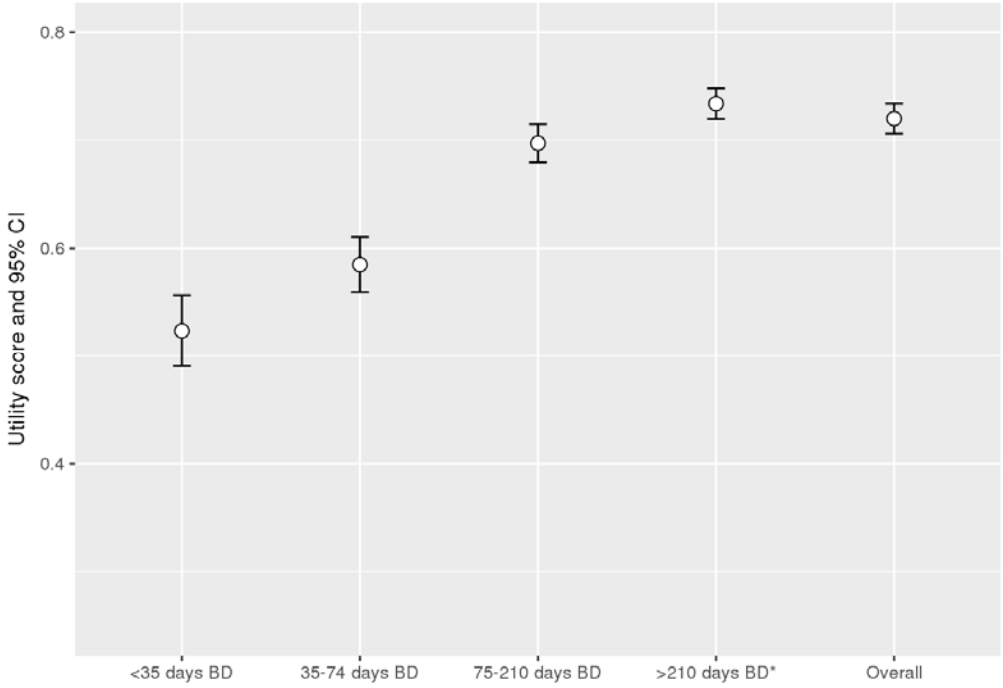
Figure 6: Model-based utilities following proximity to death approach



Model of utilities before progression

Number of patients per treatment arm and number of observations included in the model are presented in Table 25.

Table 25: Number of patients and observations per treatment arm included in before progression model

Treatment arm	Number of patients	Number of observations
Atezo+CP	392	4019
Atezo+Bev+CP	376	4754
Bev+CP	382	3551

Figure 7 shows utilities before progression with a trend for three arms based on smoothing splines. We note the decline in the utilities in the Bevacizumab arm after 20 months is driven by very few observations. Similarly in the Atezolizumab + Bevacizumab arm we observed an increase after 25 months but again it is driven by very few observations.

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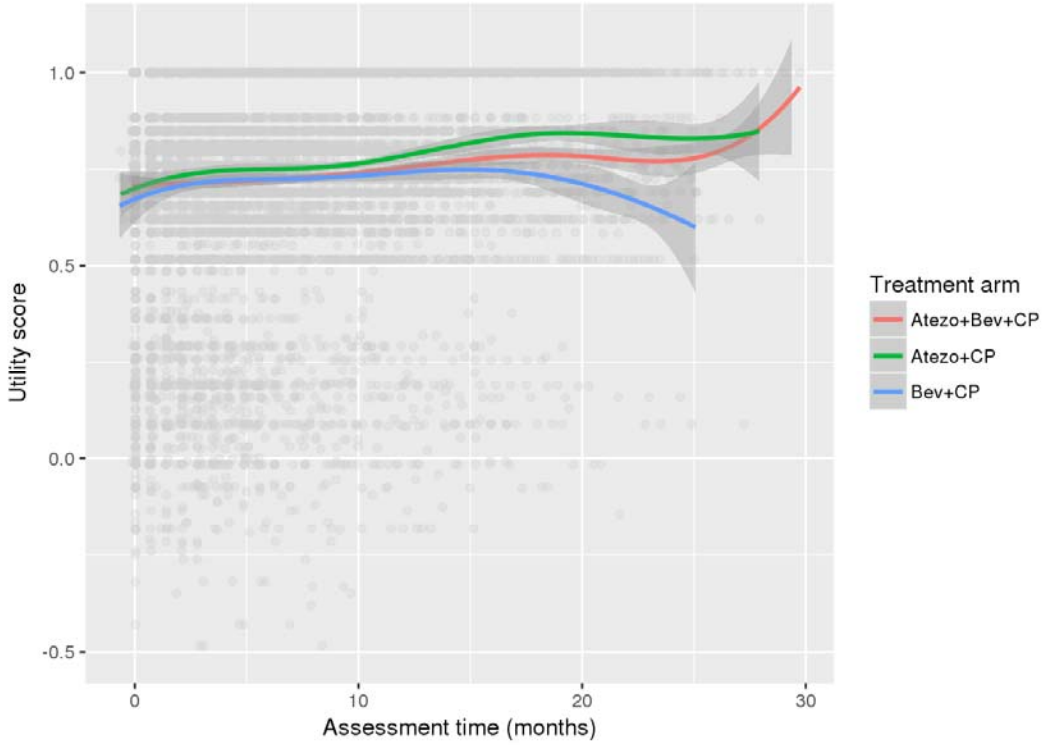
Figure 7: Utilities before progression with smoothing trend by treatment arm



A repeated measurements model was fitted including as covariates: assessment time (in days), treatment arm and a dummy variable for adverse events (Yes if a patient had a related adverse event grade 3 or more during PFS stage and No if a patient did not have it) and we assumed an exchangeable working correlation.

Convergence criteria for the model were met, overall likelihood ratio test indicates that at least one of the covariates in the model is significant. Information criteria were AIC: -7478.5 and BIC -7468.4.

Type III tests results indicate that treatment arm is not significant (F p-value: 0.1509), whereas p-value for time of assessment is borderline (F p-value: 0.0825) and incidence of adverse event during PFS is highly significant (F p-value: 0.0003).Covariance parameter estimate is equal to 0.038 and the residual variance is equal to 0.025

Fixed effects model coefficients are shown in Table 26

Table 26: Fixed effect coefficients in the before progression model

Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
Intercept	0.6701	0.0124	0.6457	0.6944
Atezo+CP	0.0289	0.0150	-0.0004	0.0583
Atezo+Bev+CP	0.0174	0.0151	-0.0122	0.0470
Bev+CP	0			

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AE during PFS: No	0.0452	0.0123	0.0210	0.0694
AE during PFS: Yes	0			
Assessment time (days)	0.00002	0.00001	0.00000	0.00004

Treatment arm is not statistically significant as indicated by type III tests. However it is are kept in the model because it is considered clinically relevant to explain variability of utilities.

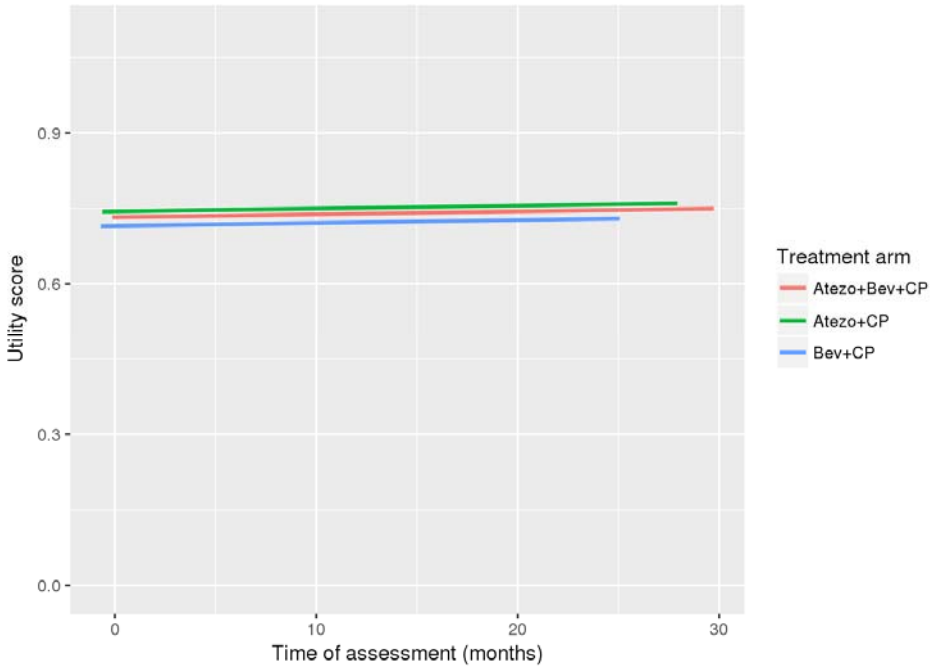
IMpower150 utilities based on before progression correspond to model based estimates for four intervals are presented in Table 27.

Table 27: Model based estimates for before progression

Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
Atezo + CP	0.7216	0.0106	0.7008	0.7424
Atezo + Bev + CP	0.7100	0.0108	0.6888	0.7312
Bev + CP	0.6927	0.0107	0.6717	0.7136
Before progression or death	0.7083	0.0063	0.6960	0.7207
Before progression without AE 3+	0.7317	0.0088	0.7144	0.7490
Before progression with AE 3+	0.6858	0.0088	0.6686	0.7030

Figure 8 shows the model-based utilities by arm for patients without an adverse event.

Figure 8: Model-based utilities before progression by arm for patients without AE



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Model of utilities after progression

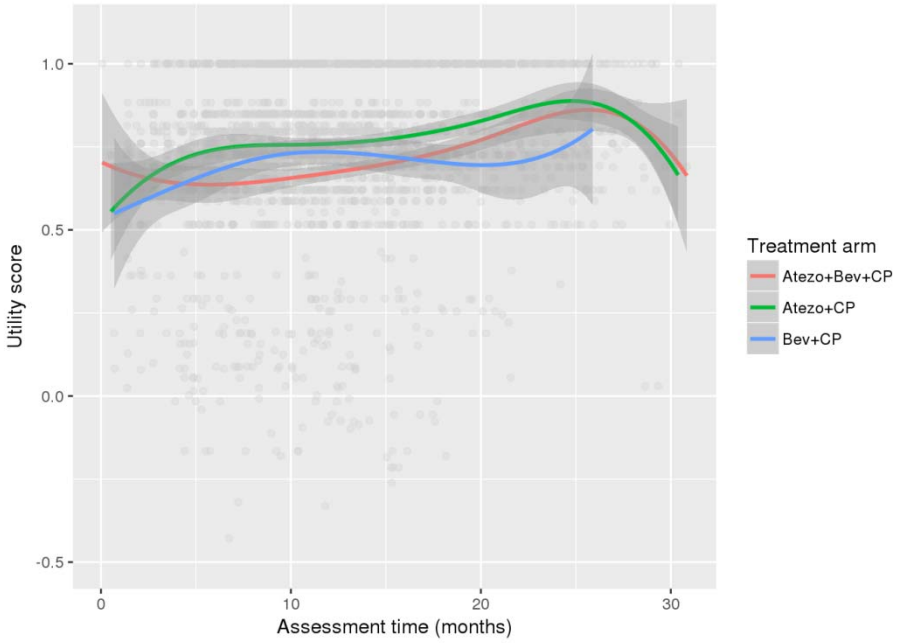
Number of patients per treatment arm and number of observations included in the model are presented in Table 28.

Table 28: Number of patients and observations per treatment arm included in after progression model

Treatment arm	Number of patients	Number of observations
Atezo+CP	256	967
Atezo+Bev+CP	237	876
Bev+CP	186	380

Figure 9 shows utilities after progression with a trend for three arms based on smoothing splines.

Figure 9: Utilities after progression with smoothing trend by treatment arm



A repeated measurement model was fitted including assessment time and treatment arm as covariates and we assumed an exchangeable working correlation.

Convergence criteria for the model were met; overall likelihood ratio test indicates that at least one of the covariates in the model is significant. Information criteria were AIC: -877.9 and BIC -868.8. Type III tests results indicate that treatment arm is not significant (F p-value: 0.1188), the same holds by and time of assessment (F p-value: 0.047). Covariance parameter estimate is equals to 0.0456 and the residual variance is equal to 0.0224

Fixed effects model coefficients are shown in Table 29.

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Table 29: Fixed effect coefficients in the after progression model

Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
Intercept	0.6704	0.02095	0.6293	0.7116
Atezo+CP	0.0388	0.0232	-0.0068	0.0844
Atezo+Bev+CP	-0.0001	0.0237	-0.0467	0.0465
Bev+CP	0			
Assessment time (days)	0.000066	0.000033	8.794E-07	0.000131

Treatment arm variables are not statistically significant as indicated by type III tests. However they are kept in the model because they are considered clinically relevant to explain variability of utilities.

IMpower150 utilities post-progression correspond to model based estimates presented in Table 30 and in Figure 10.

Table 30: Model based estimates by before death group

Effect	Estimate	Standard Error	Lower limit 95% CI	Upper limit 95% CI
Atezo+CP	0.7092	0.01889	0.6721	0.7463
Atezo+Bev+CP	0.6703	0.02055	0.6300	0.7107
Bev+CP	0.6704	0.02095	0.6293	0.7116
After progression	0.6875	0.01551	0.6570	0.7179

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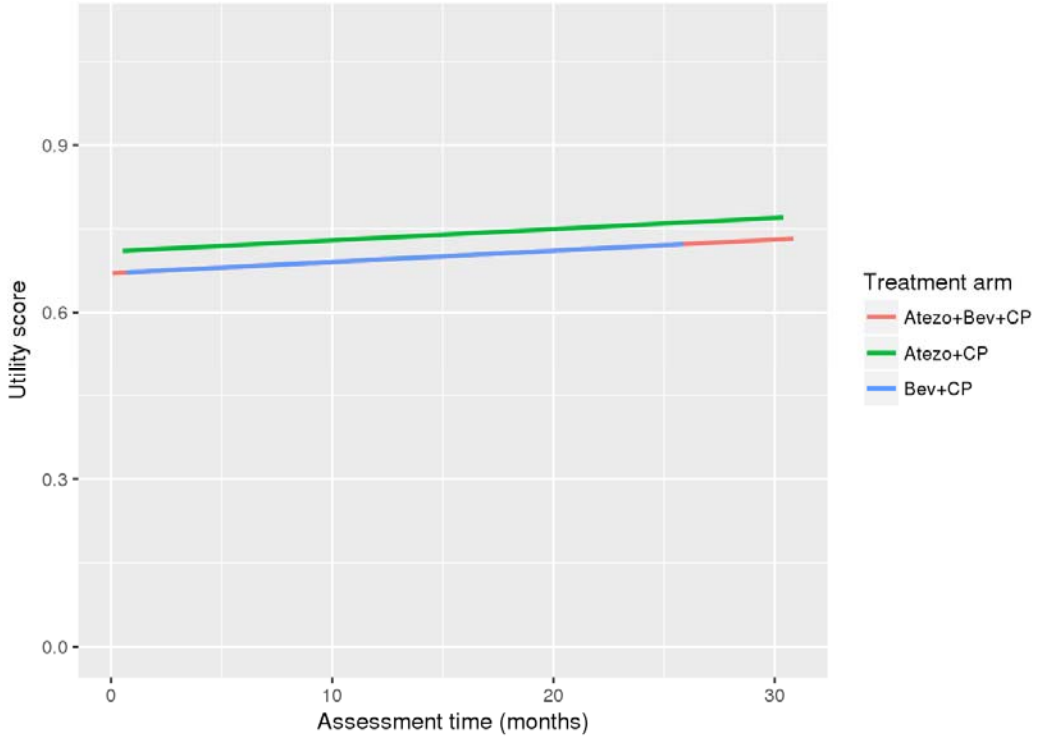
Figure 10: Model-based utilities after progression by arm



Complementary graphs

Figure 11: Bar plots - Model based utilities before progression

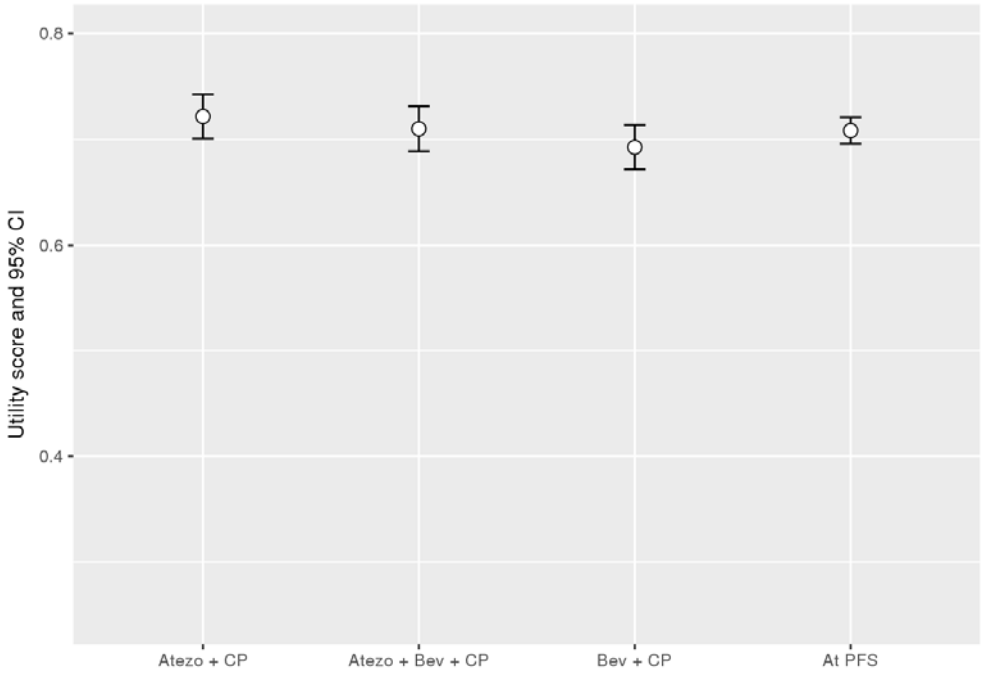


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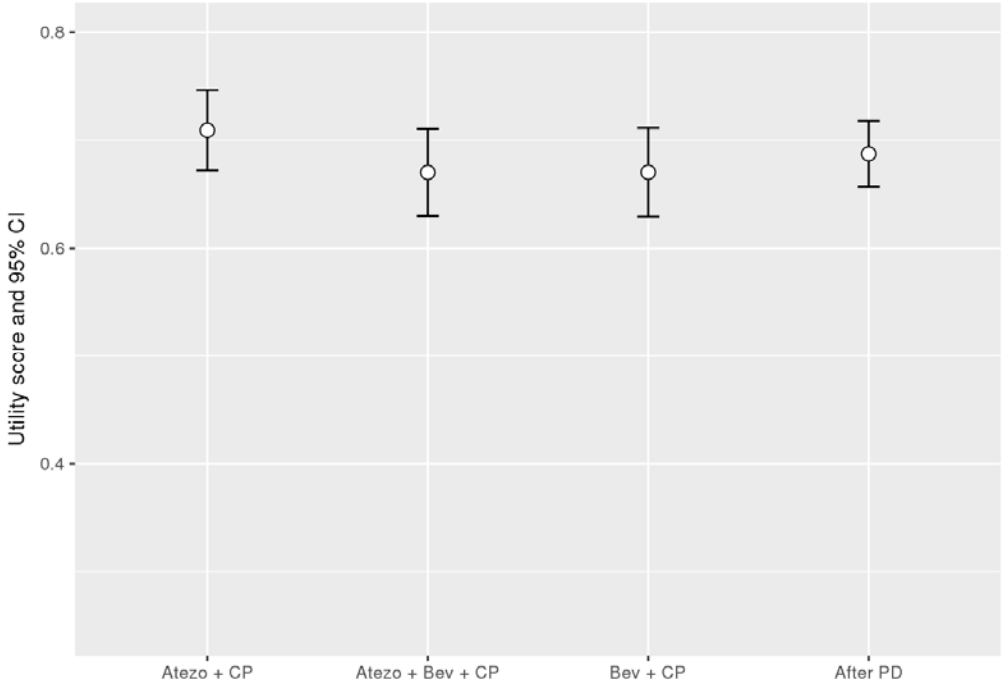
Figure 12: Bar plots - Model based utilities after progression



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APPENDIX D – Updated economic results

Base-case incremental cost-effectiveness analysis results

Fully incremental results of the base-case of the economic model, based on the list price for atezolizumab, bevacizumab and all comparators, are presented in the Tables below. Interventions are ranked in ascending order in terms of clinical outcomes. In the second to last column of the Tables fully incremental ICERs are presented. In addition, the last column provides pair-wise ICERs for Atezo+Bev+CP versus each relevant pemetrexed-based comparator.

Table 31: Base-case results ITT population – list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
Pem+plat	[redacted]	[redacted]	-	-		[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Pem+plat, pemetrexed plus platinum; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

Table 32: Base-case results PD-L1 negative/low population – list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
Pem+plat	[redacted]	[redacted]	-	-		[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Pem+plat, pemetrexed plus platinum; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

Table 33: Base-case results EGFR and ALK positive population – list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
Pem+plat	[redacted]	[redacted]	-	-		[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Pem+plat, pemetrexed plus platinum; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

As seen from the fully incremental analysis and the pair-wise ICERs above, at list price for Atezo+Bev+CP and all comparators and therapies in the treatment pathway, Atezo+Bev+CP is [redacted].

The equivalent ICERs when incorporating the existing PAS for atezolizumab and the submitted PAS for bevacizumab are presented in the Tables below. The discounts considered in these analyses are outlined in Table 34. In these comparisons, all comparators (and therapies included in the treatment pathway) are at list price.

Table 34: Level of confidential discount considered in the with PAS model results

Technology	Level of confidential discount	Justification
Atezolizumab	[redacted]	Current level of confidential discount
Bevacizumab	[redacted]	Submitted PAS for this appraisal
Atezolizumab – second line treatment	[redacted]	Current level of confidential discount

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Table 35: Base-case results ITT population (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
Pem+plat	[redacted]	[redacted]	-	-		£16,419
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	£35,985	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Pem+plat, pemetrexed plus platinum; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

Table 36: Base-case results PD-L1 negative/low population (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
Pem+plat	[redacted]	[redacted]	-	-		£13,424
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	£38,943	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Pem+plat, pemetrexed plus platinum; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

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Table 37: Base-case results EGFR and ALK positive population (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
Pem+plat	[redacted]	[redacted]	-	-		£14,552
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	£31,523	£7,014
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	£7,014	-

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Pem+plat, pemetrexed plus platinum; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

Results of the with-PAS fully incremental analysis show that Atezo+Bev+CP is the most cost-effective intervention, either by dominating pemetrexed plus platinum plus pemetrexed maintenance (in the ITT and -L1 negative/low population) or by having an ICER well below the cost-effectiveness threshold for end-of-life therapies versus pemetrexed plus platinum plus pemetrexed maintenance in the EGFR/ALK population (£7,014).

As such, at PAS price for atezolizumab and bevacizumab and list price for all comparators (and therapies included in the treatment pathway) Atezo+Bev+CP is cost-effective versus pemetrexed-based interventions and good value for money to the NHS, across all patient populations considered in our evidence submission.

However, we acknowledge that our with-PAS analysis does not account for confidential discounts that are in place for pemetrexed maintenance therapy, as well as for pembrolizumab (in first and second-line NSCLC) and nivolumab (in second-line NSCLC).

Sensitivity analyses

Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. Results of the PSA pair-wise ICERs compared to deterministic results at list price are

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presented in Table 38. The with-PAS equivalent comparison is presented in Table 39. Deterministic and probabilistic results are similar, in the ITT population as well as in the patient subgroups considered, therefore not indicating any signs of non-linearity in the model.

Cost-effectiveness planes and the cost effectiveness acceptability curves are also presented in Figures below for all populations of interest. The updated model allows for a fully incremental analysis comparing all three interventions to be conducted, and as such, the cost effectiveness acceptability curves versus pemetrexed-based chemotherapy interventions reflect the entire decision problem.

Table 38: PSA results compared to base-case (without PAS)

	Costs		QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
ITT population						
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	-	-
PD-L1 low or negative						
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	-	-
EGFR / ALK positive						
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	-	-

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; Pem+plat, pemetrexed plus platinum; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

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Table 39: PSA results compared to base-case (with PAS for atezolizumab and bevacizumab and list price for relevant comparators)

	Costs		QALYs		ICERs	
	Deterministic base case	PSA	Deterministic base case	PSA	Deterministic base case	PSA
ITT population						
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]	£16,419	£16,658
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	-	-
PD-L1 low or negative						
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]	£13,424	£13,730
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	-	-
EGFR / ALK positive						
Pem+plat	[redacted]	[redacted]	[redacted]	[redacted]	£14,552	£15,203
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]	£7,014	5,400
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	[redacted]	-	-

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; Pem+plat, pemetrexed plus platinum; Pem+plat+pem maint, pemetrexed plus platinum plus pemetrexed maintenance

Figure 13: Cost-Effectiveness Plane – ITT population – list price

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Figure 14: Cost-Effectiveness Acceptability Curve – ITT population – list price

[redacted]

Figure 15: Cost-Effectiveness Plane – ITT population – PAS price

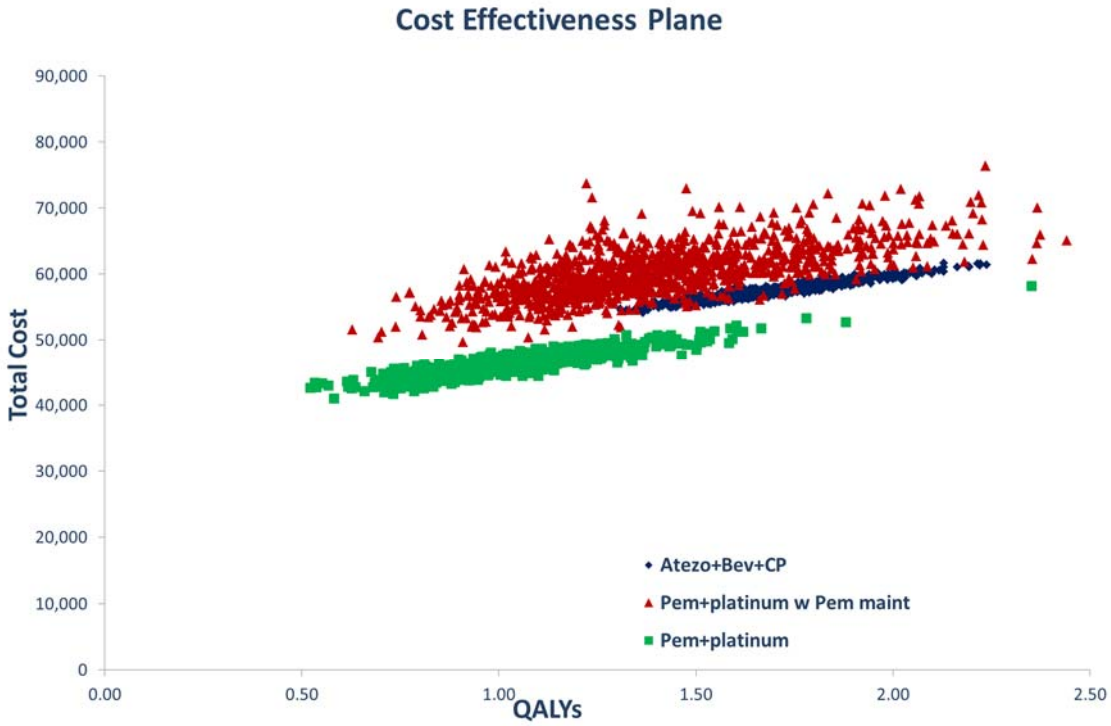

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Figure 16: Cost-Effectiveness Acceptability Curve – ITT population – PAS price

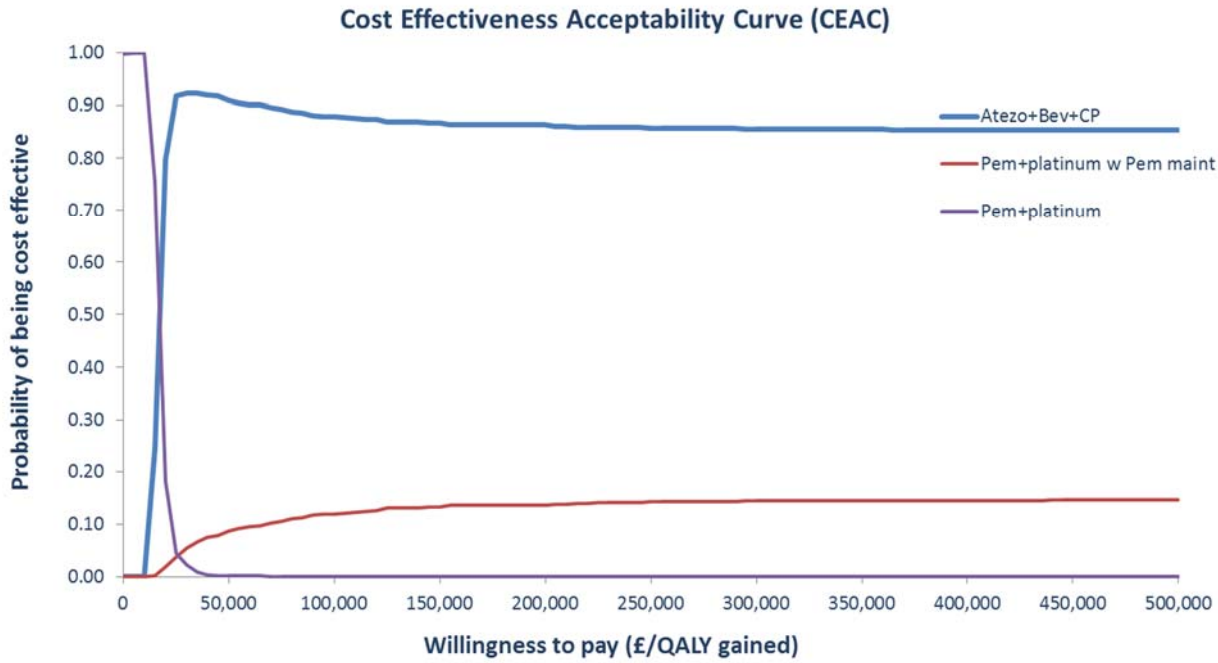

Figure 17: Cost-Effectiveness Acceptability Curve – PD-L1 negative/low population – list price

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Figure 18: Cost-Effectiveness Plane – PD-L1 negative/low population – list price

Figure 19: Cost-Effectiveness Plane – PD-L1 negative/low population – PAS price

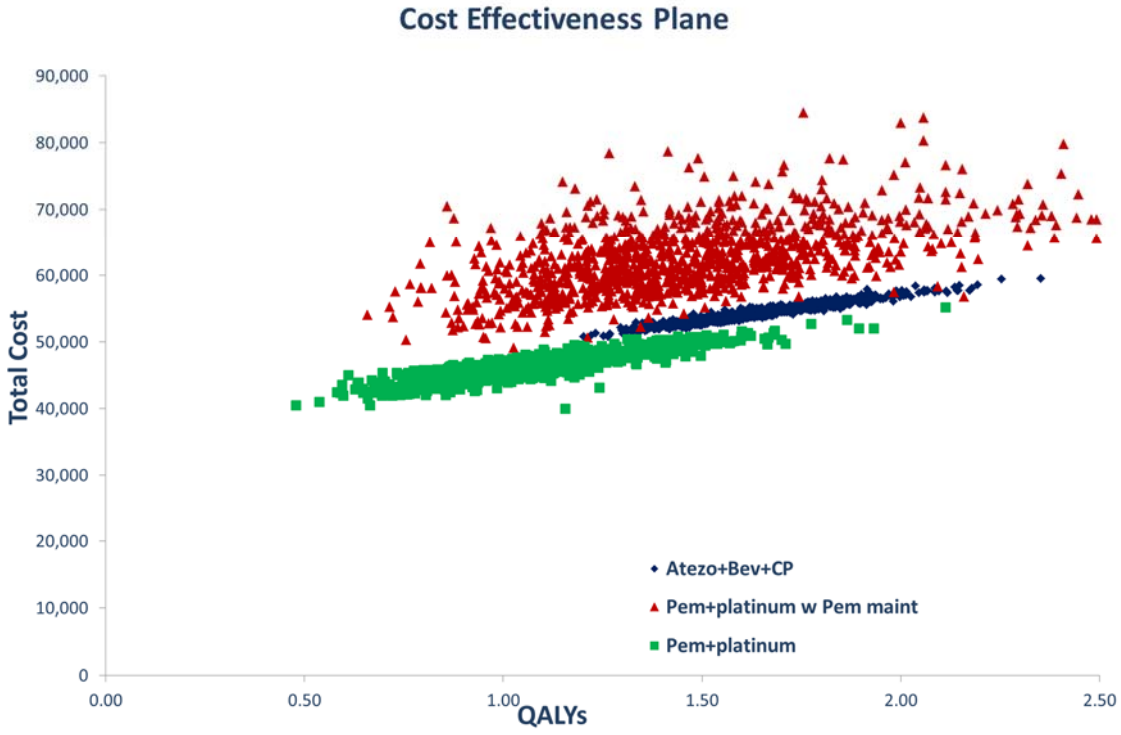

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Figure 20: Cost-Effectiveness Acceptability Curve – PD-L1 negative/low population – PAS price

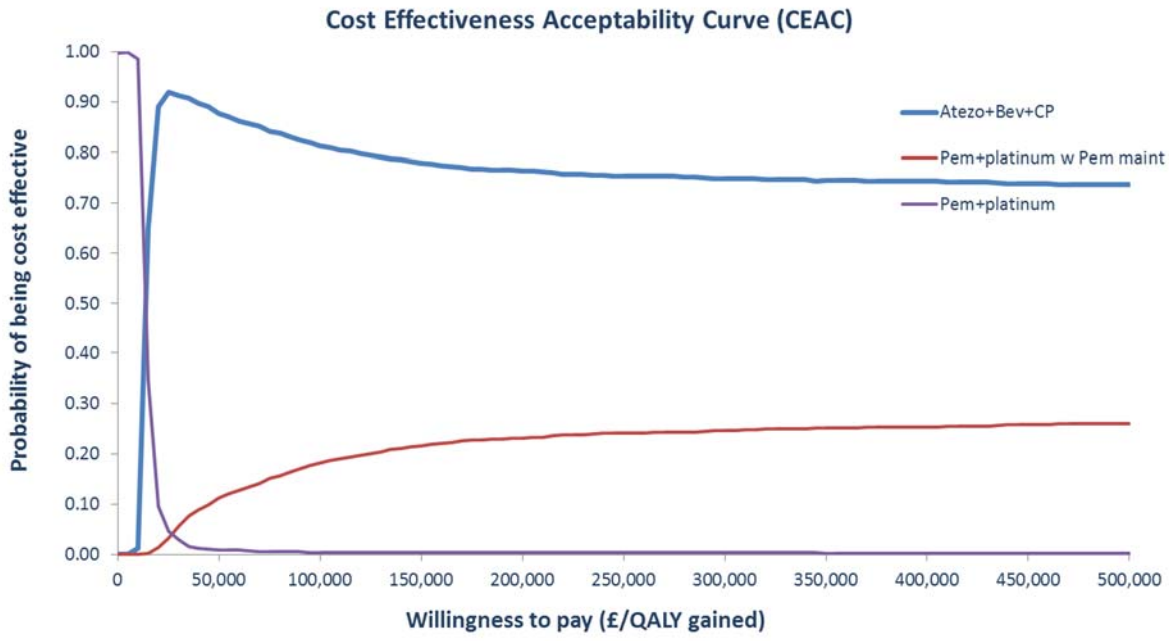

Figure 21: Cost-Effectiveness Plane – EGFR and ALK positive population – list price

[redacted]

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Figure 22: Cost-Effectiveness Acceptability Curve – EGFR and ALK positive population – list price

[redacted]

Figure 23: Cost-Effectiveness Plane – EGFR and ALK positive population – PAS price

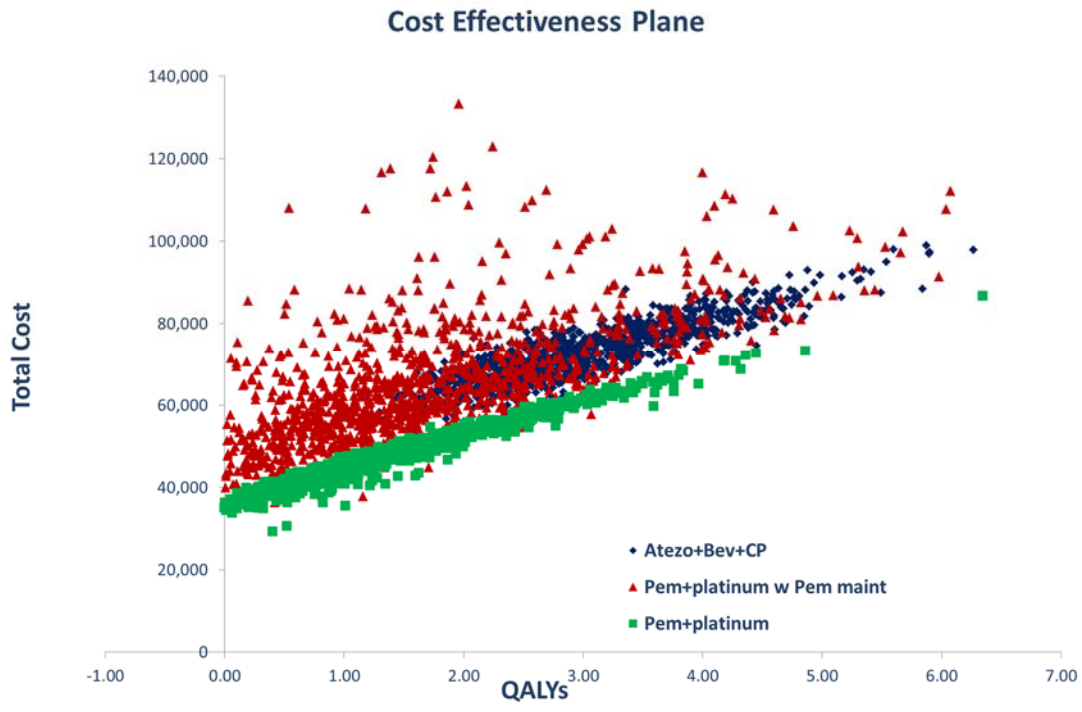

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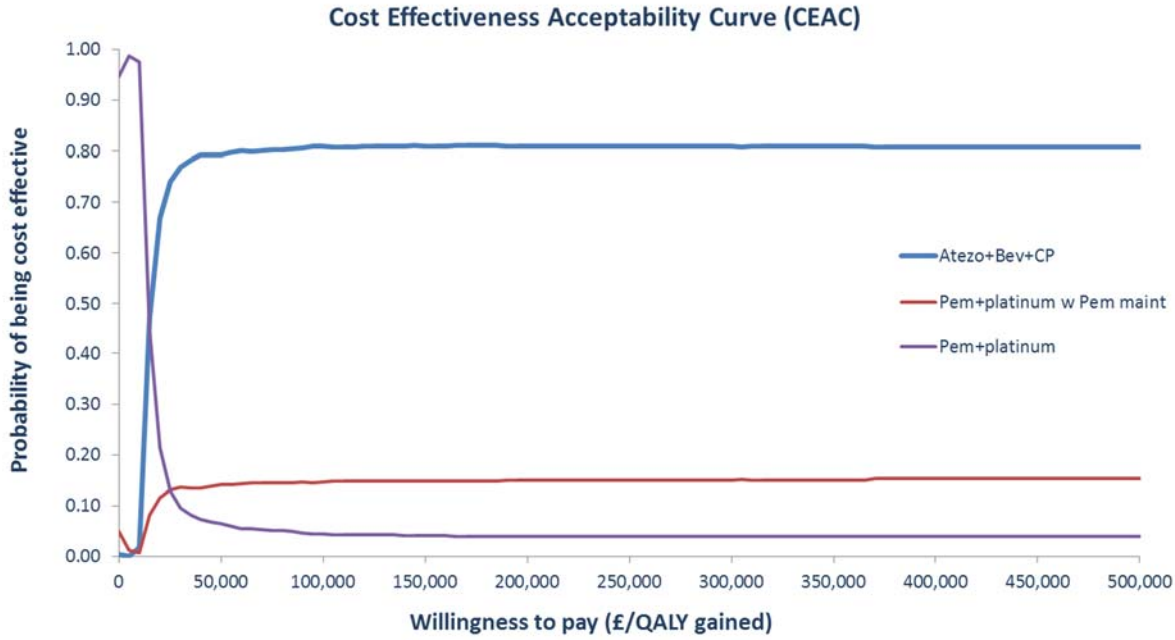
Figure 24: Cost-Effectiveness Acceptability Curve – EGFR and ALK positive population – PAS price



Deterministic sensitivity analyses

Based on the deterministic sensitivity analyses at list and PAS price, and in both the ITT population and subgroups of interest, the most influential parameters appear to be the discount rates for costs and for health outcomes, the administration cost for Atezo+Bev+CP, the utility value for the interval of >30 weeks before death and the weekly AE costs for Atezo+Bev+CP.

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Table 40: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value	Justification
Discount costs	3.50%	1.5%	6.0%	Assumption
Discount effects	3.50%	1.5%	6.0%	Assumption
Supportive care cost: PFS	61.78	60.08	63.59	95% CI
Supportive care cost: PD	116.97	113.49	120.39	95% CI
Weekly AE cost: Atezo+Bev+CP	526.34	971.38	1,703.91	95% CI
Weekly AE cost: Pem+platinum	272.54	207.68	375.03	95% CI
Cost of administration: Atezo+Bev+CP	385.99	370.55	402.24	95% CI
Cost of administration: Pem+platinum	327.92	318.59	337.67	95% CI
Utility values: <≤5 weeks BD	0.52	0.49	0.54	95% CI
Utility values : (5,10] weeks BD	0.59	0.56	0.60	95% CI
Utility values : (10,30] weeks BD	0.70	0.68	0.71	95% CI
Utility values: >30 weeks BD	0.73	0.72	0.74	95% CI

AE, adverse event; PD, progressive disease; PFS, progression-free survival; PPS, post-progression survival, Pem+plat, pemetrexed plus platinum; CI, confidence interval

Figure 25: Tornado diagram – ITT population vs. pemetrexed plus platinum – list price

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Figure 26: Tornado diagram – ITT population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

[redacted]

Figure 27: Tornado diagram – ITT population vs. pemetrexed plus platinum – PAS price

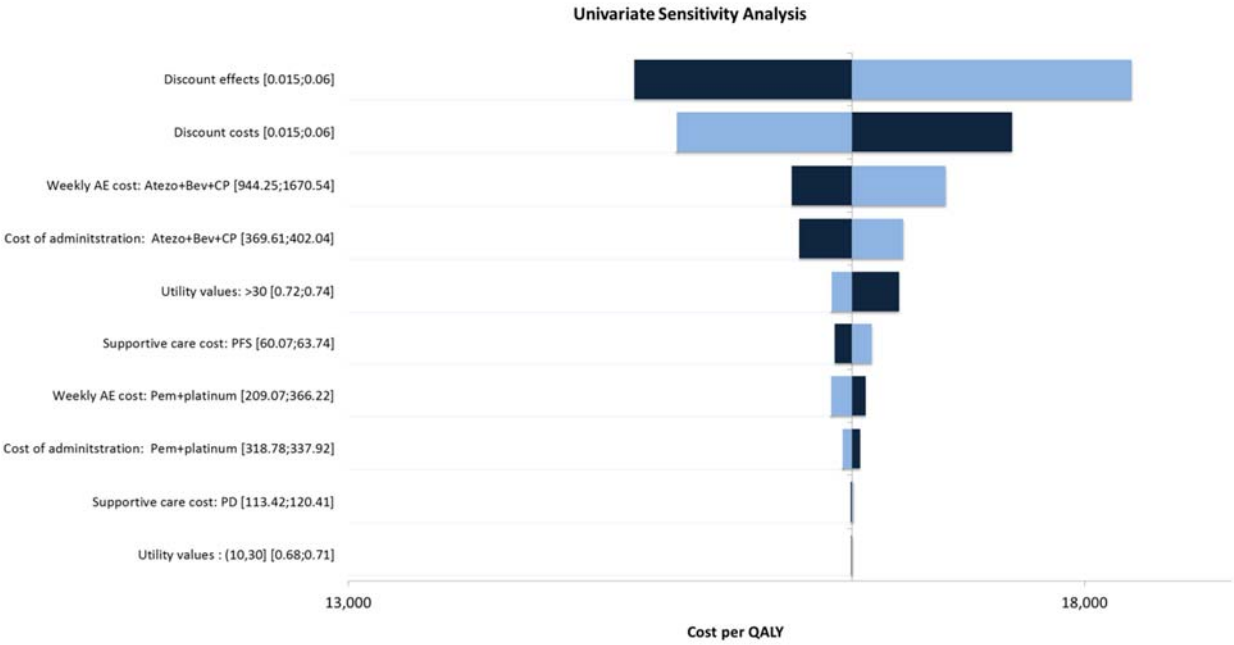

Figure 28: Tornado diagram – PD-L1 negative/low population vs. pemetrexed plus platinum – list price

[redacted]

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Figure 29: Tornado diagram – PD-L1 negative/low population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

Figure 30: Tornado diagram – PD-L1 negative/low population vs. pemetrexed plus platinum – PAS price

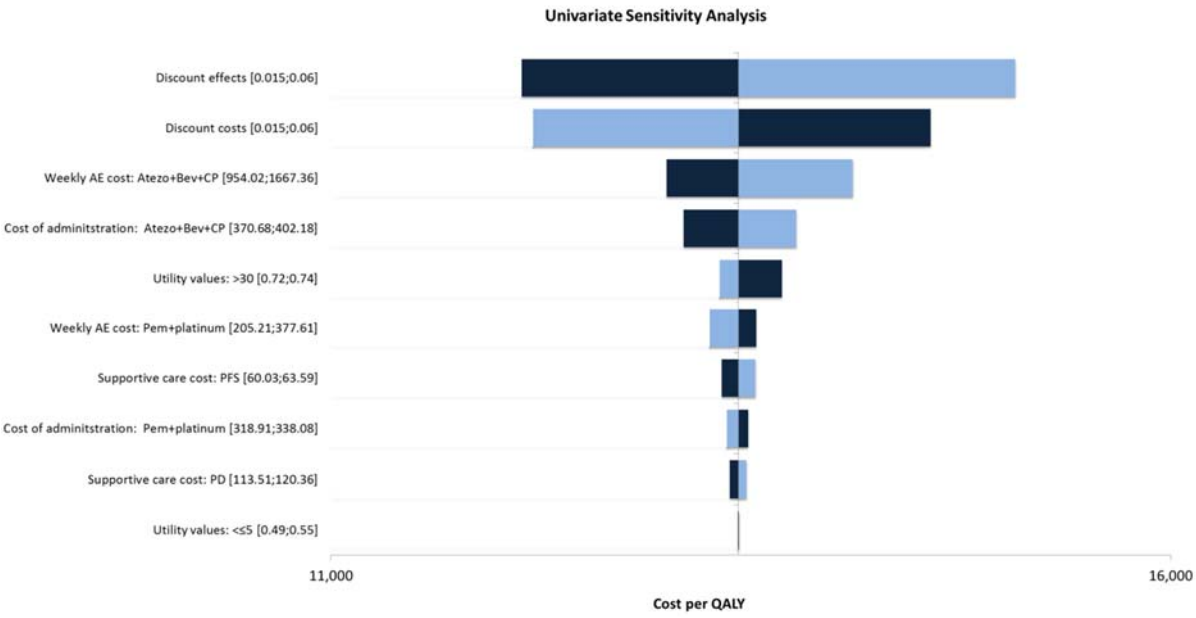

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Figure 31: Tornado diagram – EGFR/ALK positive population vs. pemetrexed plus platinum – list price

Figure 32: Tornado diagram – EGFR/ALK positive population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

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Figure 33: Tornado diagram – EGFR/ALK positive population vs. pemetrexed plus platinum – PAS price

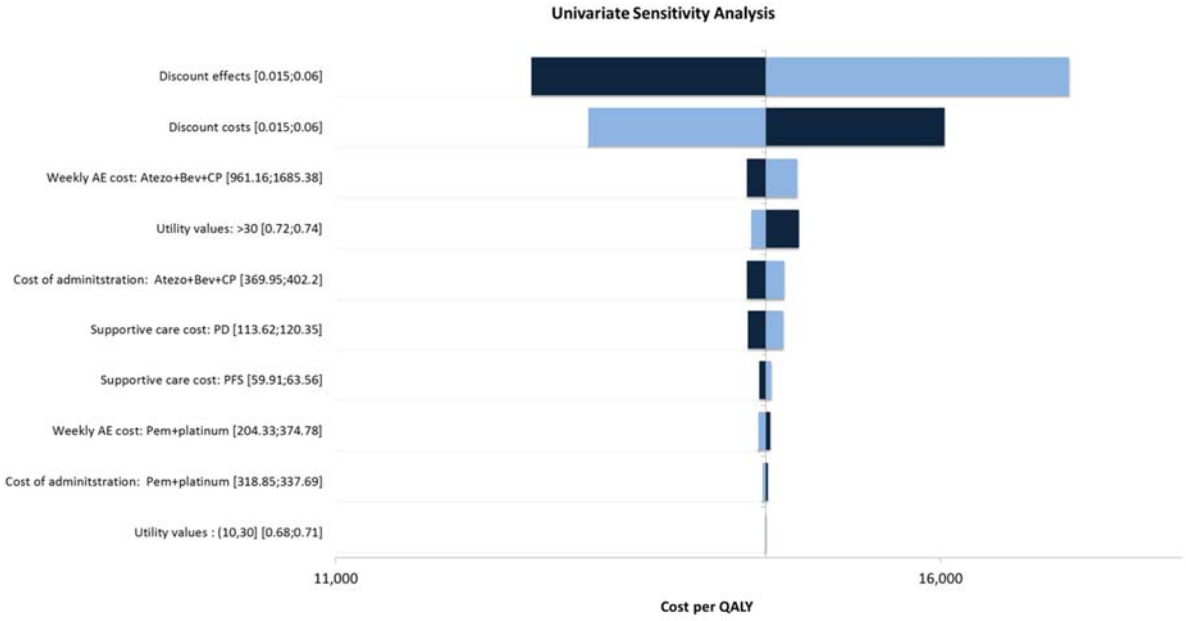
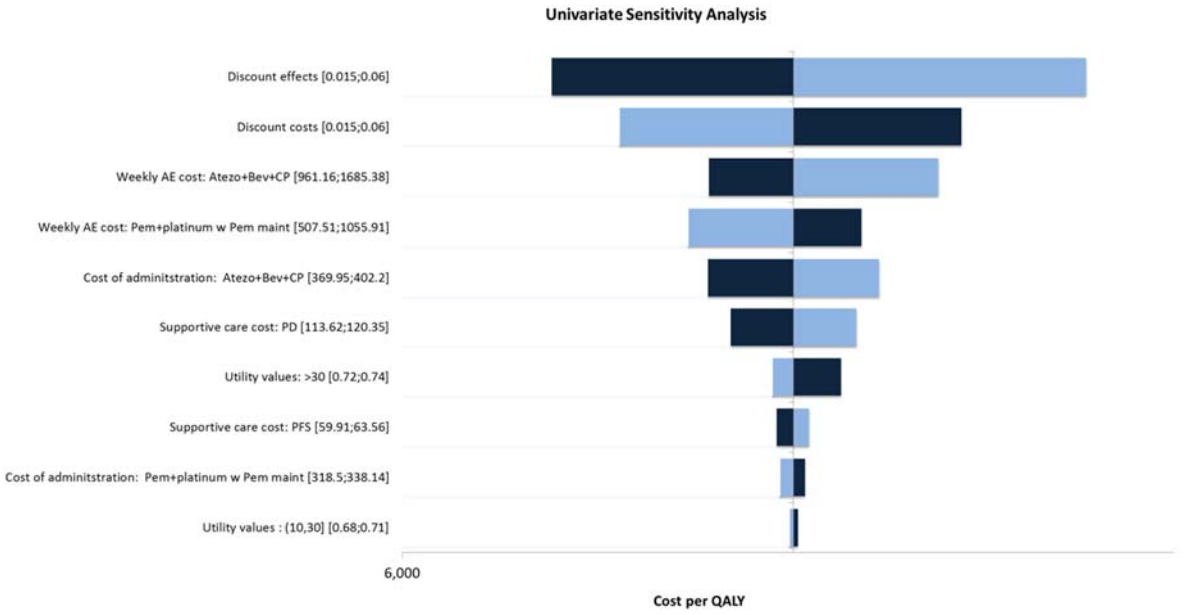


Figure 34: Tornado diagram – EGFR/ALK positive population vs. pemetrexed plus platinum plus pemetrexed maintenance – PAS price



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Scenario analyses

Scenario analyses were conducted to assess uncertainty around remaining parameter inputs and structural assumptions of the model. Scenarios demonstrating changes in the following parameters were explored:

- Alternative plausible OS Extrapolations
- Alternative plausible PFS Extrapolations
- Alternative plausible TTD Extrapolations
- Alternative NMA networks and models
- No treatment stopping rule for atezolizumab and bevacizumab
- Alternative time points for cap of treatment effect duration
- Alternative wastage assumptions
- Alternative utility values
- Alternative subsequent therapy approach
- Disutility for AEs

Scenario analyses results for pairwise ICERs are presented below, both at list price and with PAS.

It should be highlighted that not all scenario analyses are appropriate to consider for decision-making. The appropriateness and plausibility of the different scenario analyses is discussed right after the Tables with the scenario analyses results.

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Table 41: Scenario analyses results – ITT population vs. pemetrexed plus platinum – list price

	Description	Atezo+Bev+CP			Pem+platinum			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
PFS distribution	KM - Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution	KM- Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
Alternative NMA network	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ITT exclude Keynote	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	ITT exclude Paramount	Comparison not feasible - no connected network						
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]						
	NMA - PH	[redacted]						
	NMA - Fract Poly (RE)	[redacted]						
Treatment stopping rule	At 2 years (base case)	[redacted]						
	No treatment stopping rule	[redacted]						
Treatment effect duration	5 years (base case)	[redacted]						
	105 months	[redacted]						
	150 months	[redacted]						
	195 months	[redacted]						
	240 months (lifetime)	[redacted]						
Wastage	With vial sharing (base case)	[redacted]						
	No vial sharing	[redacted]						
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]						
	IMpower150 (Pre/Post progression)	[redacted]						
	Pembrolizumab utilities (US publication)	[redacted]						
	Chouaid et al. 2013	[redacted]						
	Nafees et al. 2008	[redacted]						
Subsequent treatments	Base case	[redacted]						
	IMpower 150	[redacted]						
AE disutility	No (base case)	[redacted]						
	Yes	[redacted]						

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

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Table 42: Scenario analyses results – ITT population vs. pemetrexed plus platinum plus pemetrexed maintenance – list price

	Description	Atezo+Bev+CP			Pem+platinum w Pem maint			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS distribution	KM - Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution	KM - Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
Alternative NMA network	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ITT exclude Keynote	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	ITT exclude Paramount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NMA – PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NMA - Fract Poly (RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IMpower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

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Table 43: Scenario analyses results – ITT population vs. pemetrexed plus platinum – PAS price for atezolizumab and bevacizumab

	Description	Atezo+Bev+CP			Pem+platinum			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,470
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,840
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,304
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,376
	Gompertz	Does not converge						
PFS distribution	KM - Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,324
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,073
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,738
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,637
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,418
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,428
TTD distribution	KM - Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,533
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,639
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,191
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,558
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,885
	Gompertz	Does not converge						
Alternative NMA network	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	ITT exclude Keynote	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,501

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	ITT exclude Paramount	Comparison not feasible - no connected network					
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	NMA – PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,028
	NMA - Fract Poly (RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,523
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,865
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,223
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,522
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,586
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,595
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,427
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,090
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,960
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,974
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,438
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	IMpower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,866
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,419
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,502

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

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Table 44: Scenario analyses results – ITT population vs. pemetrexed plus platinum plus pemetrexed maintenance – PAS price for atezolizumab and bevacizumab

	Description	Atezo+Bev+CP			Pem+platinum w Pem maint			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
PFS distribution	KM - Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£130
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£612
TTD distribution	KM - Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£546
	Gompertz	Does not converge						
	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

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Alternative NMA network	ITT exclude Keynote	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	ITT exclude Paramount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	NMA – PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	NMA - Fract Poly (RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,234
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IMpower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,201
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

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Table 45: Scenario analyses results – PD-L1 low or negative population versus pemetrexed plus platinum – list price

	Description	Atezo+Bev+CP			Pem+platinum			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
PFS distribution	KM with Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution	KM with Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Gompertz	Does not converge						
Alternative NMA model *	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Impower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

* Scenario analyses with a restricted NMA network (i.e. excluding KEYNOTE studies or excluding PARAMOUNT) or with a RE NMA model have not been implemented in subgroups of patients

Table 46: Scenario analyses results – PD-L1 low or negative population versus pemetrexed plus platinum plus pemetrexed maintenance – list price

	Description	Atezo+Bev+CP			Pem+platinum w Pem maint			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS distribution	KM with Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution	KM with Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
Alternative NMA model *	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Impower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

* Scenario analyses with a restricted NMA network (i.e. excluding KEYNOTE studies or excluding PARAMOUNT) or with a RE NMA model have not been implemented in subgroups of patients

Table 47: Scenario analyses results – PD-L1 low or negative population versus pemetrexed plus platinum – PAS price

	Description	Atezo+Bev+CP			Pem+platinum			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,424
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,375
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,459
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,316
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,847
	Gompertz	Does not converge						

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PFS distribution	KM with Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,424
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,810
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,809
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,761
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,509
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,320
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,666
TTD distribution	KM with Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,424
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,959
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,870
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,844
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,009
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,845
	Gompertz	Does not converge						
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,424
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,496
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,424
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,866
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,424
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,344
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,646
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,717
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,726

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Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,424
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,432
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,424
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,027
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,239
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,995
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,821
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,424
	Impower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,256
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,424
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,481

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

* Scenario analyses with a restricted NMA network (i.e. excluding KEYNOTE studies or excluding PARAMOUNT) or with a RE NMA model have not been implemented in subgroups of patients

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Table 48: Scenario analyses results – PD-L1 low or negative population versus pemetrexed plus platinum plus pemetrexed maintenance – PAS price

	Description	Atezo+Bev+CP			Pem+platinum w Pem maint			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
PFS distribution	KM with Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
TTD distribution	KM with Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

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	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Gompertz	Does not converge						
Alternative NMA model *	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Impower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

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* Scenario analyses with a restricted NMA network (i.e. excluding KEYNOTE studies or excluding PARAMOUNT) or with a RE NMA model have not been implemented in subgroups of patients

Table 49: Scenario analyses results – EGFR/ALK positive population versus pemetrexed plus platinum – list price

	Description	Atezo+Bev+CP			Pem+platinum			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS distribution	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
Alternative NMA model *	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Impower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

* Scenario analyses with a restricted NMA network (i.e. excluding KEYNOTE studies or excluding PARAMOUNT) or with a RE NMA model have not been implemented in subgroups of patients

Table 50: Scenario analyses results – EGFR/ALK positive population versus pemetrexed plus platinum plus pemetrexed maintenance – list price

	Description	Atezo+Bev+CP			Pem+platinum w Pem maint			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS distribution	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
Alternative NMA model *	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Impower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

* Scenario analyses with a restricted NMA network (i.e. excluding KEYNOTE studies or excluding PARAMOUNT) or with a RE NMA model have not been implemented in subgroups of patients

Table 51: Scenario analyses results – EGFR/ALK positive population versus pemetrexed plus platinum – PAS price

	Description	Atezo+Bev+CP			Pem+platinum			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,715
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,488
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,292
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,965
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552
PFS distribution	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,652
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,172
	Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,531
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,438
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,650
TTD distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,796
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,547

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	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,344
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,557
	Gompertz	Does not converge						
Alternative NMA model *	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,738
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,947
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,748
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,914
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,282
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,351
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,555
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,368
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,166
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,509
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,566
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552
	Impower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,302
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,552

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	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,594

ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

* Scenario analyses with a restricted NMA network (i.e. excluding KEYNOTE studies or excluding PARAMOUNT) or with a RE NMA model have not been implemented in subgroups of patients

Table 52: Scenario analyses results – EGFR/ALK positive population versus pemetrexed plus platinum plus pemetrexed maintenance – PAS price

	Description	Atezo+Bev+CP			Pem+platinum w Pem maint			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,918
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,692
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,708
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,963
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
PFS distribution	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,636
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,364
	Log-normal (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,869
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,038
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,994
TTD distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,922
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,007

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	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,269
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,466
	Gompertz	Does not converge						
Alternative NMA model *	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
Treatment stopping rule	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
	No treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,805
Treatment effect duration	5 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
	105 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,582
	150 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,338
	195 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,283
	240 months (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,293
Wastage	With vial sharing (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
	No vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,019
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
	IMpower150 (Pre/Post progression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,359
	Pembrolizumab utilities (US publication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,419
	Chouaid et al. 2013	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,440
	Nafees et al. 2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,562
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014
	Impower 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,710
AE disutility	No (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,014

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ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; Atezo+Bev+CP, atezolizumab in combination with bevacizumab, carboplatin, paclitaxel; KM, Kaplan Meier; NMA, network meta-analysis; FP, fractional polynomial; FE, fixed effects; RE, random effects; PH, proportional hazards; AE, adverse events

* Scenario analyses with a restricted NMA network (i.e. excluding KEYNOTE studies or excluding PARAMOUNT) or with a RE NMA model have not been implemented in subgroups of patients

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The scenario analyses demonstrate that Atezo+Bev+CP is associated with a QALY gain over pemetrexed-based comparators across all populations considered (ITT, PD-L1 negative or low, EGFR/ALK positive). This was tested and confirmed in a series of scenario analyses including the use of different NMA models, alternative NMA networks, different extrapolation models for time-to-event endpoints and different durations of treatment effect for Atezo+Bev+CP.

Regarding the NMA against pemetrexed-based interventions, it should be noted that the use of a FP FE NMA model in our base case produces conservative results compared to the use of a proportional hazards NMA model. However, the FP model was selected on the basis of its appropriateness to reflect the underlying data and the presence of non-proportional hazards.

In terms of scenarios with different models to extrapolate the time-to-event endpoints, the scenario analyses varying OS appear to have a greater impact on results, However, caution must be exercised when analysing the scenario results with different distributions for extrapolating OS, as the base-case distribution was chosen on the basis of fit to the observed data (statistical, visual fit) as well as validity of long-term outcomes. As such, only a subset of the alternative OS distributions can be considered to provide potentially plausible long-term OS (Log-Logistic, Weibull). The Exponential model used in our base case provides a conservative estimate of the long-term clinical benefit of Atezo+Bev+CP. Log-Logistic is an alternative clinically plausible and appropriate OS extrapolation model, which results in long-term OS for Atezo+Bev+CP in line with clinical expectations for cancer immunotherapies and consistent with previous NICE appraisals for cancer immunotherapy. The remaining OS distributions provide implausible results due to either lack of statistical and visual fit to the observed data, or lack of validity and clinical plausibility for long-term outcomes, or both.

[redacted]

At PAS price for Atezo+Bev+CP and list price for comparators, Atezo+Bev+CP consistently dominates or is cost-effective versus pemetrexed-based interventions across all the scenarios considered and across all populations of interest (ITT, PD-L1 low or negative and EGFR/ALK positive), when taking into account the cost-effectiveness threshold for technologies meeting the end-of-life criteria.

Question 1: Companion diagnostic

A1. We note from the IMpower150 first interim CSR and updated CSR that the SP142 assay was used in the clinical trial to measure PD-L1 expression. Do you intend for this companion diagnostic to be used in clinical practice to establish the PD-L1 tumour proportion score (TPS) <50% population that could be treated with atezolizumab in combination with bevacizumab, carboplatin and paclitaxel?

No, we do not intend to make the SP142 assay the companion diagnostic for IMpower150 use. A post-hoc analysis presented at AACR in 2018 by Socinski M et al showed that PD-L1 prevalence in IMpower150 using SP142 and 22C3 IHC assays was similar and substantial overlaps in PD-L1 populations was observed.[1]

Nevertheless, our company evidence submission seeks reimbursement for the atezolizumab combination for the subgroups of patients who do not currently have access to pembrolizumab monotherapy (as assessed through 22C3). Therefore, it would be a potentially unnecessary use of resources to test samples twice to determine eligibility for pembrolizumab monotherapy (using 22C3) and IMpower150 (SP142).

A2. We note from the company submission for this appraisal that no PD-L1 testing costs were included (page 134, company submission). The rationale for not including this cost was that PD-L1 testing in first-line NSCLC is now clinical practice in the UK. However, we understand from a clinical expert that the 22C3 assay is used in clinical practice as a companion diagnostic for pembrolizumab. Have the costs for PD-L1 testing been omitted from the company submission because the intention is for the 22C3 assay to be used, thus incurring no additional costs.

We consider that the use of the 22C3 assay to determine PD-L1 status is appropriate for all patients, both as per current clinical practice and following the introduction of the atezolizumab combination. Patients who do not have highPD-L1 expression (as per 22C3) would be eligible for IMpower150 and a second test with SP142 would not be required, as it would be a potentially unnecessary use of resources.

A3. If a different assay to the 22C3 assay is intended to be used (i.e. the SP142 assay), what are the costs involved in setting this up and running costs, for example, laboratories will need to buy new platforms. Can the company please provide an analysis that includes these costs.

Roche are comfortable with the current standard of care PD-L1 testing using 22C3 to continue for lung cancer patients, as post-hoc analyses have

shown there substantial overlap between the PD-L1 populations identified by the two tests. Therefore there is no need for a different assay to be used.

A4. Does a TPS < 50% using the 22C3 assay correspond to a similar cut off using the SP142 assay, or any other assay that Roche intend to use?

The post-hoc analysis (N=503) from Kowanetz et al showed similar and substantial overlap between the two tests. The SP142 assay showed a 20% PD-L1 high rate (N=101) and the SP263 assay showed a 25% PD-L1 high rate (N=126). The hazard ratios were remarkably similar; 0.49 and 0.50 respectively for these two PD-L1 groups by different assays. Similar analysis has been done for the OAK trial in second-line NSCLC with similar results.

References:

1. Kowanetz M et al. IMpower150: Efficacy of atezolizumab (atezo) plus bevacizumab (bev) and chemotherapy (chemo) in 1L metastatic nonsquamous NSCLC (mNSCLC) across key subgroups. AACR Annual Meeting 2018; April 14-18, 2018; Chicago, IL (Oral Presentation and Abstract CT076)

2. Gadgeel S et al. Clinical Efficacy of Atezolizumab (Atezo) in PD-L1 Selected Subgroups Defined by SP142 and 22C3 IHC Assays in 2L+ NSCLC: Results From the Randomized OAK Trial. ESMO Annual Meeting 2017; March 09-12, 2017; Madrid, Spain Oral Presentation and Abstract 1296O)

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Professional organisation submission

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College Of Pathologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	**X** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Royal College of Pathologists represents pathologists in the UK and provides guidance for reporting lung cancer pathological specimens**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To stop progression of lung cancer and prolong life

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Not applicable for a pathologist to answer
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Not applicable for a pathologist to answer
• Are any clinical guidelines used in the treatment of the	NICE guidelines for treatment of lung cancer, RCPath Minimum Data set on handling tissue.

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes
• What impact would the technology have on the current pathway of care?	Not applicable for a pathologist to answer
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Pathologists already test for PD-L1 status using immunohistochemistry, in order to identify those eligible for first line or second line therapy, though it is with a specific companion diagnostic (223C for pembrolizumab). What RCPath need to know is what companion diagnostic are pathologists expected to use if this is approved. It will be problematic if alternative antibodies and scoring systems are required to be put in place.
• How does healthcare resource use differ between the technology and current care?	Potentially a different testing strategy
• In what clinical setting should the technology be	Not applicable for a pathologist to answer

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This will depend on what testing strategy is expected of pathologists and whether it differs from current practice.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Not applicable for a pathologist to answer
• Do you expect the technology to increase length of life more than current care?	Not applicable for a pathologist to answer
• Do you expect the technology to increase health-related quality of life more than current care?	Not applicable for a pathologist to answer

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The scoping document states those with >50% staining with a biological marker
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This depends on what biological marker is being proposed.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not applicable for a pathologist to answer
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not applicable for a pathologist to answer
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Not applicable for a pathologist to answer

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Not applicable for a pathologist to answer
• Does the use of the technology address any particular unmet need of the patient population?	Not applicable for a pathologist to answer
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not applicable for a pathologist to answer
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Not applicable for a pathologist to answer

• If not, how could the results be extrapolated to the UK setting?	Not applicable for a pathologist to answer
• What, in your view, are the most important outcomes, and were they measured in the trials?	Not applicable for a pathologist to answer
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable for a pathologist to answer
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not applicable for a pathologist to answer
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not applicable for a pathologist to answer

21. How do data on real-world experience compare with the trial data?	Not applicable for a pathologist to answer
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • is the biological marker that identifies patient subsets different to those in current use? • if not, what training will be given and how will the costs for implementation be met? • If so, will costs be met in similar fashion to current practice? •	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**ROYAL COLLEGE OF PATHOLOGISTS**

NICE National Institute for Health and Care Excellence

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): pathologist who deals with testing for those who might receive the drug
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

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The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce disease and slow progression
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Not for pathologist
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Not for pathologist
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Not for pathologist
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Not for pathologist
• Do you expect the technology to increase length of life more than current care?	

• Do you expect the technology to increase health-related quality of life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	**The main issue for pathologists in relation to treatment with this kind of drug is the probable need for an associated diagnostic test that may decide whether the patient is eligible for treatment.** **Data suggest that those with greater immunostaining of the tumour for PD-L1 have a better response.** **If this is the case, pathologists will have to be trained in interpretation and systems for validation will need to be put in place, as well as the cost of the test (and possible rebiopsy) taken into account.** **Impact on biomedical scientists workloads/staff will also need to be taken into account.**
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	This depends on whether there will be a companion diagnostic and if so, which one.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not for pathologist
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not for pathologist
17. Do you consider the technology to be innovative in its potential to make a	Not for pathologist

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not for pathologist
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Not for pathologist
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not for pathologist
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. Is pemetrexed in combination with cisplatin/carboplatin, with or	

without pemetrexed, maintenance the appropriate UK chemotherapy in this setting?	
24. Is it reasonable to include a two year stopping rule to treatment with atezolizumab plus bevacizumab, paclitaxel and carboplatin? Is this representative of clinical practice in the UK?	Not for pathologist
Key messages	

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25. In up to 5 bullet points, please summarise the key messages of your statement.

- Impact on the RCPath community will depend on whether there is a companion diagnostic and, if so, which one the company want the pathologist to use
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Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

X Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Samreen Ahmed**
2. Name of organisation	**BTOG/NCRI**

3. Job title or position	
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Treatment of non-squamous NSCLC. Stop progression and improve survival
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	PFS and OS differences between drugs being tested and SOC
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	NSCLC still is unmet need as median survival still in the region of 12months for advanced disease
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Carb/cis pem, pem maintenance Carb/pem/pembrolizumab Keynote 189 NICE TA557
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	PDL1 >50%: Pembrolizumab PDL1 1-29%: Carb/pem/pembro or carb/pem followed by 2nd line pembro/nivo/atezo
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined and currently and rapidly evolving treatment paradigm. All patients at some point in their pathway will receive immunotherapy either in combination or single agent
• What impact would the technology have on the current pathway of care?	IMPOWER 150 is showing OS of 19.8m in Atezo/bev/CP arm compared to 14.9 months in Bev/CP. Bev/CP is licensed combination in this disease however is not SOC in UK. Much of US and Europe still use is this combination as SOC
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	New combination and will require more monitoring but all drugs are frequently used separately in oncology

• How does healthcare resource use differ between the technology and current care?	Longer time to deliver 4 drugs
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist chemotherapy suites only
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Longer treatment time
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Data suggests longer PFS and OS in all but in particular liver met patients, low/neg PDL1 and post EGFR/ALK TKI treatment
• Do you expect the technology to increase length of life more than current care?	Yes as significant difference in PFS and OS in all groups including ITT group

• Do you expect the technology to increase health-related quality of life more than current care?	HRQOL does not appear to be impaired with 4 drugs. PS0 and 1 MUST be stipulated in guidance so that 30 mortality is not increased with poor PS patients being given complex regimen
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	PDL1 low/neg. Post TKI patients
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Longer treatment time in chemotherapy suite

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Usual radiology and PS better than 2 to continue
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	None
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	NO all drugs currently used but not in combination
• Does the use of the technology address any particular unmet need of the patient population?	Breaks the ceiling of median OS of 12months
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Bev CP is NOT SOC in UK
• If not, how could the results be extrapolated to the UK setting?	In comparison to the paramount study of carb/cisp/pem
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS/OS/QOL All assessed
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None
20. Are you aware of any relevant evidence that might	None

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Very fit patients recruited so important to emphasise when real life use employed
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Is it reasonable to include a two year stopping rule to treatment with atezolizumab	Yes and patients are accepting of this if expectations managed proactively

plus bevacizumab, paclitaxel and carboplatin? Is this representative of clinical practice in the UK?	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Complex 4 drug regimen taking longer to give
- PFS/OS both superior to any other regimens in this group of non-sq NSCLC
- PS0/1 must be reiterated when adopted to real life practice
- New SOC for post EGFR/ALK TKI patients: Many of these patienst progress with brain mets and therefore maynot be fit enough to receive this
- Attrition to second line treatment remains high so use best up front should be mantra
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Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**NLCFN representation by Carol A Davies**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ ✓ National lung cancer forum for nurses
3. Name of your nominating organisation	NLCFN
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ ✓ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ ✓ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ ✓I have other relevant personal experience. Please specify what other experience: I work as Macmillan Lung Cancer Nurse Specialist working with patients with lung cancer supporting them throughout their lung cancer journey (investigations, diagnosis, treatment, discharge at 5 years, progression and end of life) I do not have personal experience of this drug regime ☐
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patients often struggle with side effects of lung cancer; many are breathless & fatigued Carers often feel helpless

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers always looking for new effective treatments which do not affect their quality of life.
10. Is there an unmet need for patients with this condition?	Yes
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	I have very limited personal experience with this technology, as such unable to answer this question
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I have very limited personal experience with this technology, as such unable to answer this question
Patient population	
13. Are there any groups of patients who might benefit	Performance status 0-1. Individuals with poor performance status likely to struggle with side effects.

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Not to my knowledge**
Other issues	
15. Are there any other issues that you would like the committee to consider?	Not to my knowledge
Topic-specific questions	
16. Would patients experience disutility from adverse events	Not to my knowledge

that is not captured by the EQ-5D questionnaire?	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

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National Institute for Health and Care Excellence

Cancer Drugs Fund Clinical Lead statement

Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel for the 1st line treatment of metastatic non squamous non small cell lung cancer [ID1210]

Background

1. The treatment pathway for non small cell lung cancer (NSCLC) and for the non squamous (NS) variety (the main histological type) is currently changing rapidly and has the potential to change even more in the near future as immunotherapy both moves to earlier lines of treatment in the treatment pathway and is combined with other treatments.

2. For those patients with NS NSCLC and either EGFR activated or ALK mutations, the treatment pathway is also subject to potential imminent change with new targeted agents and combinations of immunotherapy and targeted drugs.

3. The marketing authorisation (MA) for atezolizumab in combination with bevacizumab, carboplatin and paclitaxel is likely to be [redacted]

4. Atezolizumab monotherapy is NICE-recommended for routine commissioning in NSCLC in patients with locally advanced/metastatic disease who have had previous platinum-based chemotherapy (and targeted treatment if they have EGFR-

or ALK-positive disease). There is a 2 year stopping rule in operation for atezolizumab in this indication and this NICE recommendation applies regardless of PD-L1 expression.

5. Bevacizumab is not used for NSCLC in NHS England as its two planned NICE appraisals were terminated on account of a failure by Roche to make submissions to NICE. The combination of bevacizumab, carboplatin and paclitaxel is therefore not commissioned by NHS England.

6. The combination of carboplatin and paclitaxel has very little use as 1st line therapy for locally advanced/metastatic NSCLC in NHS England. Although this combination was recommended as an option for treatment by NICE in 2001, it has been superseded by more efficacious treatment in NS NSCLC: platinum-based chemotherapy in combination with pemetrexed and then followed by maintenance pemetrexed in appropriate patients.

Treatment pathway and comparators

7. Roche has elected to narrow the population of patients for which it seeks a NICE recommendation for treatment using the combination of atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP). For patients without EGFR or ALK mutations, the population to be appraised is metastatic NS NSCLC patients who have a tumour proportion score (TPS) for PD-L1 of 0-49% and embarking on 1st line therapy. The other NS NSCLC population for which NICE recommendation is sought is the one in which patients have EGFR or ALK mutations and have already received appropriate treatment with targeted therapy or therapies but have not yet received cytotoxic chemotherapy.

Metastatic NS NSCLC without EGFR/ALK mutations with a TPS 0-49%

8. The two 1st line NICE routinely recommended treatments for metastatic NS NSCLC without EGFR or ALK mutations are i) in patients with a TPS of 0-100% a platinum-based combination therapy with pemetrexed with maintenance pemetrexed and ii) pembrolizumab monotherapy in those patients with a TPS of 50-100%. The combination of pembrolizumab with platinum-based chemotherapy with pemetrexed and then pembrolizumab maintenance for patients with a TPS of 0-100% is in the CDF. The correct comparator for ABCP in the 1st line metastatic NS NSCLC TPS 0-49% population is thus platinum-based chemotherapy in combination with pemetrexed plus maintenance pemetrexed (NB most patients proceed to maintenance pemetrexed as only those who progress on induction chemotherapy are ineligible for maintenance pemetrexed). The CDF pembrolizumab combination with platinum-based chemotherapy with pemetrexed is not a comparator as it is not routinely recommended.

9. There is little clinical interest in the use of ABCP in this non-EGFR/ALK mutation 1st line population for a number of reasons. The first is that the chemotherapy spine (carboplatin plus paclitaxel, CP) in ABCP is not the most efficacious chemotherapy in NS NSCLC. The second is that clinicians are unfamiliar with the use of CP in this population of patients and would be especially unfamiliar with CP as part of a 4 drug combination. The third is that a relatively high dose of carboplatin (AUC 6) was used in the IMpower150 trial and this will make clinicians wary of using this higher dose. The fourth is that carboplatin plus paclitaxel results in hair loss whereas a platinum-based combination with pemetrexed does not. The fifth is that clinicians are unfamiliar with the use of bevacizumab in this populations of patients and especially so as part of a 4 drug combination. The sixth is that severe pulmonary haemorrhage is a rare but serious potential adverse event associated with bevacizumab therapy in NSCLC. The seventh is

that patients and clinicians have access to the best chemotherapy spine in NS NSCLC in combination with immunotherapy as they have access via the CDF to pembrolizumab in combination with platinum-based combination chemotherapy with pemetrexed. For these (and another reason which will be described in paragraphs 16 and 17), NHS England does not envisage much use of ABCP in the 1st line setting in the NS NSCLC population without EGFR/ALK mutations.

10. NHS England therefore does not regard the non-EGFR/ALK mutation group as being very relevant to this appraisal of ABCP in view of the above issues. It has no concern that a comparison has not been done between ABCP and other induction chemotherapies approved by NICE (docetaxel/paclitaxel/gemcitabine/vinorelbine in combination with carboplatin/cisplatin) ± maintenance pemetrexed as these induction therapies are rarely used in the stage IIIB/IV NS NSCLC population in NHS England.

Metastatic NS NSCLC with EGFR/ALK mutations

11. The metastatic NS NSCLC population with EGFR or ALK mutations are currently treated with targeted treatment whether as 1st line therapy (and where appropriate as 2nd line therapy). NHS England regards appropriate targeted treatment for EGFR activated mutation NS NSCLC to be the first line options of erlotinib or gefitinib or afatinib and where appropriate as 2nd line treatment the CDF option of osimertinib. NHS England regards appropriate targeted treatment for ALK positive NS NSCLC to be 1st line alectinib or 1st line ceritinib or 1st line crizotinib followed by 2nd line ceritinib. The only sequence of targeted therapies commissioned by NHS England for ALK-positive disease is crizotinib and then ceritinib. As a point of correction for the Roche

submission therefore, NHS England does not commission the use of crizotinib after previous ceritinib (or alectinib).

12. The next line of treatment following failure of targeted therapy is cytotoxic chemotherapy in the form of a platinum-based combination with pemetrexed and maintenance pemetrexed as appropriate. The next routinely recommended line of treatment after cytotoxic chemotherapy is with immunotherapy monotherapy: atezolizumab for a TPS of 0-100% or pembrolizumab for a TPS of 1-100%. Nivolumab for a TPS of 1-100% is available via the CDF. The correct comparator for ABCP in this EGFR/ALK mutation population previously only treated with targeted therapy is therefore platinum-based chemotherapy in combination with pemetrexed followed by maintenance pemetrexed.

13. There is much more interest amongst clinicians for the use of ABCP in patients failing targeted therapies in the EGFR/ALK mutation NS NSCLC groups. The main reason for this is that ABCP advances the inclusion of immunotherapy to an earlier line in the treatment pathway. As there is always considerable attrition of lung cancer patient numbers from one line of systemic therapy to the next, clinicians assess that the benefits of ABCP in fit patients with EGFR/ALK mutations outweigh the benefits of the option of sequential chemotherapy and then immunotherapy.

14. NHS England regards the EGFR/ALK mutation group as being of high relevance to this appraisal of ABCP.

Platinum-based induction combination chemotherapy with pemetrexed

15. NICE specifically recommended cisplatin plus pemetrexed as induction chemotherapy in 1st line palliation of NS NSCLC in TA 181. The administration of cisplatin requires considerable chair time for hydration and cisplatin has more side-effects than

carboplatin, a drug that can be given much more quickly. NHS England has formally only previously commissioned pemetrexed in combination with cisplatin although the majority of use of pemetrexed is in combination with carboplatin. The recent NICE recommendation to the CDF for pembrolizumab in combination with cisplatin- or carboplatin-based chemotherapy with pemetrexed as 1st line treatment in NS NSCLC has resulted in NHS England now formally commissioning the use of carboplatin in combination with pemetrexed as long as a standard dose of carboplatin is used (AUC 5).

Commissioning issues

16. In terms of assessment versus the correct comparator for ABCP in this appraisal, the use of ABCP will result in a significantly increased use of chair time for patients in most chemotherapy units. There is more use of carboplatin rather than cisplatin as the platinum agent when combined with pemetrexed and this trend continues to increase. Atezolizumab if well tolerated adds an infusion time of 30 minutes. Bevacizumab if well tolerated adds a 30 minute infusion time. Paclitaxel is infused over 3 hours and requires patients to receive premedication in advance so as to reduce allergic reactions. This paclitaxel infusion time is in contrast to pemetrexed which is given over 10 minutes. Carboplatin infusion times would be similar whether given with pemetrexed or as part of ABCP. Once the cytotoxic chemotherapy phase has been completed, the infusion times of atezolizumab plus bevacizumab will be for 1 hour in contrast to a figure of 10 minutes for pemetrexed.

17. In terms of the competition between the CDF platinum-based pemetrexed pembrolizumab combination, a similar argument

would apply to increased chair time for most centres although the disparity after the completion of the chemotherapy phase reduces.

Comment on clinical trial data

18. Because of the Roche submission which is aimed at two subgroups of the IMpower150 trial, the statistical power of these subgroup analyses is weakened, particularly in the EGFR/ALK mutation subgroup. NHS England notes that the benefit of ABCP in the two subgroups is consistent with that seen in the intention to treat population. NHS England notes with concern the small number of patients in the EGFR/ALK mutation group (only 104 patients) and the substantial imbalance between the two arms in terms of patients analysed: 41 patients in the ABCP arm and 63 patients in the BCP arm.

19. The IMpower150 trial did not use the optimal chemotherapy regimen (platinum-based chemotherapy in combination with pemetrexed with the use of maintenance pemetrexed) as the backbone on which to test the addition of atezolizumab and bevacizumab. This is disappointing from the clinical relevance and applicability points of view. It also results in the need for an indirect treatment comparison with all the resultant issues as regards heterogeneity and the need for comparison with trials performed a long time ago when the lung cancer treatment pathway was very different.

20. NHS England notes that the Roche submission has made an error in stating the dose of paclitaxel in the ABCP regimen. The dose in the trial was 200mg/m² but the Roche submission states that the dose of paclitaxel is 15mg/kg. This is a very big difference and NHS England presumes that Roche has confused the dose of paclitaxel with that of bevacizumab. The ERG has not made this mistake.

21. The IMpower150 trial had 3 arms, arm A being ACP which contained atezolizumab but not bevacizumab. NHS England notes with interest that there was no difference in overall survival between ACP and BCP HR 0.88 (95% CI 0.72-1.08). NHS England is surprised that the atezolizumab addition to chemotherapy did not improve survival. This gives credence to the view that immunotherapy drugs may not be interchangeable at least when combined with chemotherapy in NS NSCLC. It is known already that chemotherapy regimens are not interchangeable in this setting.

22. NHS England notes that the IMpower trial was stratified by the presence of liver metastases. Although Roche may claim particular efficacy of ABCP in patients with liver metastases, NHS England is unimpressed by this analysis as it does not see a biologically plausible reason for this claimed superiority in efficacy and regards the observation as hypothesis-generating at best.

23. The median duration of follow-up was 13.5 months which therefore represents a relatively immature dataset. Few patients are at risk in the survival analysis after 22 months. The number of events in the survival analysis for the EGFR/ALK mutation group was only 46. NHS England notes that the final trial analysis is due in [redacted] ie in the near future.

24. NHS England notes the increase in toxicity in the ABCP arm versus BCP with increased serious adverse events (44% vs 34%), febrile neutropenia (6.4% vs 3.8%), grade 3-4 treatment emergent adverse events (57% vs 49%), adverse events leading to withdrawal (34% vs 25%) and adverse events leading to dose modification (63% vs 48%). This comparison is against BCP, a combination that is neither used nor commissioned in England.

Specific issues for this technology appraisal

25. The indirect treatment comparison of ABCP versus chemotherapy must be with the clinically relevant comparator ie with induction platinum-based chemotherapy plus pemetrexed **and** maintenance pemetrexed.

26. The IMpower150 trial allowed 4 or 6 cycles of chemotherapy with carboplatin and paclitaxel. Standard practice in England in NSCLC is to give 4 cycles of platinum-based chemotherapy with pemetrexed ± maintenance pemetrexed. NHS England notes that no English patients were recruited into this trial. If NICE recommends ABCP, then NHS England would wish to commission only 4 cycles of induction cytotoxic chemotherapy.

27. The IMpower150 trial did not cap the duration of treatment to 2 years and hence the efficacy of ABCP with a 2 year treatment cap is not known. Roche has capped the treatment duration and cost of atezolizumab and bevacizumab at 2 years in the economic model and this makes a substantial difference to the ICER. If NICE recommends ABCP then NHS England is confident that it can commission a 2 year stopping rule in practice.

28. NHS England notes that Roche has assumed that there is full vial sharing in the preparation of bevacizumab. NHS England considers that this is unlikely as there is currently only modest use of bevacizumab in oncology pharmacies in England and thus the opportunity for vial sharing will be variable and limited. Nevertheless, NHS England notes that there is little effect of vial sharing on the ICER.

29. NHS England notes that the level of discount for pembrolizumab in the ERG's confidential economic analysis is incorrect. NHS England also observes that nivolumab should not figure in the benefit and costing of treatments in the patient treatment pathway at all as nivolumab is in the CDF (and not in routine

commissioning) and thus should not be considered in the economic analysis. NHS England also observes that there is only very modest use of docetaxel plus nintedanib in practice.

Commissioning perspective

30. NHS England is aware that immunotherapy drugs as monotherapy or in combination with chemotherapy are recommended by NICE as 1st line therapy and as monotherapies after chemotherapy (pembrolizumab and atezolizumab are routinely commissioned; nivolumab is in the CDF). NHS England confirms that it does not commission the sequential use of any immunotherapy drugs in the NSCLC pathways. This is because of the lack of evidence of any sequential use and the biological plausibility argument of greatly reduced efficacy of a second immunotherapy drug after failure of a first immunotherapy drug.

31. The patent expiry for bevacizumab is in 2020 and a biosimilar bevacizumab has already received a positive CHMP opinion. More companies are expected to bring biosimilar bevacizumab to market and thus the cost of the drug is likely to reduce in the not too distant future.

Generalisability to NHS practice

32. As has been dealt with above, there is a substantial narrowing from the marketing authorisation and also from the clinical trial by Roche in terms of the two patients groups for which it seeks a NICE recommendation.

33. NHS England notes that the marketing authorisation states that use of ABCP should be in patients with metastatic NS NSCLC. The IMpower150trial included patients with recurrent NS NSCLC which will have included patients with locally recurrent but not distantly metastatic disease. The use of platinum-based

chemotherapy in combination with pemetrexed is used in patients with distantly metastatic (stage IV) and locally advanced stage IIIB disease. NHS England would wish to commission the use of ABCP in patients with locally advanced or metastatic disease.

34. The IMpower150 trial only allowed entry of patients with an ECOG performance score of 0 or 1. 43% of patients were of PS 0 which represents an impressive level of fitness for lung cancer patients. Restricting entry of just PS 0 or 1 patients into a clinical trial is reasonable given that both atezolizumab and bevacizumab are being added to chemotherapy, one drug of which is being given at a higher dose than usual (carboplatin at a dose of AUC 6). NHS England would wish to commission use of ABCP in patients with a performance status of 0 or 1 (as it does for the 3 drug combination of pembrolizumab and a platinum-based combination with pemetrexed).

35. As has been mentioned already, NHS England will continue to commission the standard duration of cytotoxic chemotherapy for NS NSCLC ie the maximal duration of treatment will be for 4 cycles of carboplatin and paclitaxel

Implementing a positive NICE recommendation

NICE recognises that in the event of a positive recommendation, more prescriptive clinical commissioning criteria for treatments commissioned via Specialised Services will be implemented by NHS England to ensure appropriate use within the NHS.

NHS England is responsible for ensuring that the final clinical commissioning criteria are aligned with final guidance (section 1 – recommendation and section 3 – committee discussion).

Draft commissioning criteria

36. If ABCP for treating advanced/metastatic NS NSCLC is recommended for use within its marketing authorisation, NHS England proposes to use the following commissioning criteria:

- The patient must have histologically- or cytologically-confirmed NS NSCLC which is locally advanced (stage IIIB) or distantly metastatic (stage IV) disease.
- The patient must have had testing for PD-L1, activated EGFR and ALK mutations and it is expected that ROS1 testing has also been done as well
- The patient must **either** have previously untreated locally advanced/metastatic disease which is at least EGFR and ALK mutation negative and also has a PD-L1 TPS of 0-49% **or** have advanced disease which is positive for EGFR or ALK or ROS1 mutations and also been treated with at least one appropriate targeted tyrosine kinase inhibitor (unless contra-indicated)
- The patient must not have received cytotoxic chemotherapy for his/her stage IIIB or stage IV disease. Patients who have received adjuvant chemotherapy, neoadjuvant chemotherapy or chemotherapy concurrent with radiotherapy for earlier stage disease are eligible for ABCP as long as there has been a treatment-free interval of at least 6 months from the last dose of chemotherapy
- The patient must have an ECOG performance score of 0 or 1
- The patient must commence cytotoxic chemotherapy at a dose of carboplatin calculated as being AUC 6 by the Calvert formula and paclitaxel at a dose of 200mg/m²
- The patient should receive a maximum of 4 cycles of carboplatin plus paclitaxel
- The patient does not have a contra-indication to bevacizumab

- The patient should not have received any previous PD-1, PD-L1, PD-L2, anti CD137 agent or any checkpoint inhibitor
- The patient must not have any symptomatically active brain metastases or leptomeningeal disease

If this technology is recommended for routine commissioning in a subpopulation or with certain specifications (for example, a treatment continuation rule), the final commissioning criteria will reflect these conditions.

37. If ABCP for treating advanced/metastatic NS NSCLC is recommended for use in the Cancer Drugs Fund, the final commissioning criteria will reflect the patient eligibility criteria in the managed access agreement

Issues for discussion

38. All relevant issues for discussion have been raised above.

Issues for decision

39. All relevant issues for decision-making have been raised above.

Equality

40. IMpower150 did not knowingly include/exclude patients with ROS1 mutations. NHS England regards it as being consistent with the NSCLC treatment pathway for ROS1 patients to be treated in the same way as patients with EGFR or ALK mutations.

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
Atezo	Atezolizumab
AUC	Area under the curve
Bev	Bevacizumab
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSC	Best supportive care
CARB	Carboplatin
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIS	Cisplatin
CP	Carboplatin and paclitaxel
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DIC	Deviance Information Criteria
DOR	Duration of response
DSU	Decision Support Unit
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC	The European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5-Dimension
ERG	Evidence Review Group
FDA	Food and Drug Administration
FE	Fixed effect
FP	Fractional polynomials
HR	Hazard ratio
HRQoL	Health related quality of life

ICER	Incremental cost effectiveness ratio
IRF	Independent review facility
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intent-to-treat population
IV	Intravenous
KM	Kaplan-Meier
LYG	Life years gained
MAIC	Matching adjusted indirect comparisons
MRI	Magnetic resonance imaging
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NLCA	National Lung Cancer Audit
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAC	Paclitaxel
PAS	Patient access scheme
PD	Progressive disease
PEM	Pemetrexed
PEMB	Pembrolizumab
PF	Progression free
PFS	Progression-free survival
PH	Proportional hazards
PLAC	Placebo
PR	Partial response
PRO	Patient-reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year

QLQ	Quality of life questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TA	Technology appraisal
TEAE	Treatment emergent adverse events
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation
TTO	Time trade-off
WT	Wild-type

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 ineligible for, intolerant to or who have progressed on targeted therapy 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,

gemcitabine, paclitaxel or vinorelbine in combination with carboplatin), followed by maintenance treatment with pemetrexed. This treatment regimen is not included in the CS.

Summary of submitted clinical effectiveness evidence

The company conducted a systematic review to identify and select clinical effectiveness evidence. The ERG considers that the literature searches are of good quality and are fit for purpose. The searches and inclusion criteria were designed to identify relevant randomised controlled trials (RCTs) of atezolizumab and comparator treatments for potential inclusion in a network meta-analysis (NMA).

The systematic review identified one RCT of atezolizumab, the IMpower150 RCT. This trial evaluated atezolizumab in combination with carboplatin plus paclitaxel with or without bevacizumab. A further six RCTs of comparator treatments were identified for possible inclusion in the NMA.

IMpower150 is a Phase III, open-label RCT which enrolled adult chemotherapy-naive patients with stage IV non-squamous NSCLC. Eligible patients were randomised in a 1:1:1 ratio to one of three treatment arms:

- Arm A (n=402): Atezolizumab + carboplatin + paclitaxel (Atezo+CP) induction (four or six 21-day cycles) followed by atezolizumab maintenance (21-day cycles)
- Arm B (n=400): Atezolizumab + bevacizumab + carboplatin + paclitaxel (Atezo+Bev+CP) induction (four or six 21-day cycles) followed by atezolizumab + bevacizumab maintenance (21-day cycles)
- Arm C (n=400): Bevacizumab + carboplatin + paclitaxel (Bev+CP) induction (four or six 21-day cycles) followed by bevacizumab maintenance (21-day cycles).

The marketing authorisation applied for covers Atezo+Bev+CP (Arm B) only and therefore data for Atezo+CP (Arm A) were not included in the CS. The Atezo+CP regimen was included in the NICE scope but as it is not included in the marketing authorisation NICE will not be able to include it in its guidance.

Trial results are available for two data cuts: 15th September 2017 (final progression free survival (PFS), interim overall survival (OS)), and 22nd January 2018 (updated PFS; second interim OS). The most recent data from the second interim OS results are based on 422 deaths across the two treatment arms relevant to this appraisal, with a median follow-up of approximately 20 months. Median OS has been reached in both treatment arms, however, final OS data is expected in [redacted].

The sample size calculation for the trial was performed for the co-primary endpoints of OS and PFS in two trial subgroups, the intention to treat wild type (ITT-WT) patient population (that is, all patients except those with EGFR / ALK mutations) (for the outcomes of OS and PFS) and the Teff-high WT population (for the outcome of PFS only). The latter refers to patients who had a specific T-effector (Teff) gene signature, excluding patients with an activating EGFR mutation or ALK translocation. The CS reports that, since the Atezo+Bev+CP combination demonstrated a clinically meaningful improvement in outcomes regardless of Teff gene signature status, this biomarker was not deemed to be clinically relevant and therefore these data did not impact the anticipated marketing authorisation. This population is not reported in detail in the CS, and is not mentioned in the NICE scope. Therefore, it is not discussed in this ERG report.

The analyses of clinical effectiveness and cost effectiveness in the CS are based on the ITT population and not the ITT-WT or the Teff-high WT populations. The statistical power calculation is thus based on a sample size for a WT population that is slightly smaller than the sample size for the ITT analyses presented in the CS. The ERG notes that the ITT-WT population comprises 87% (n=1040/1202) of the ITT population, so the difference in the size of these two populations is relatively small.

[redacted]

Results of the IMpower150 trial

In the ITT population at the 22nd January 2018 clinical cut-off date (minimum follow up 13.5 months, median follow-up approximately 20 months) median investigator-assessed PFS was longer in the Atezo+Bev+CP group (8.4 months, 95% CI 8.0 to 9.9) than in the Bev+CP group (6.8 months, 95% CI 6.0 to 7.0). The stratified hazard ratio was 0.59 (95% CI 0.50 to 0.69). At an earlier data cut (September 2017) independent review facility (IRF) PFS results were similar to the investigator-assessed PFS.

At the most recent data cut-off (22 January 2018) 192 deaths (48.0%) had been observed in the Atezo+Bev+CP group and 230 (57.5% deaths) in the Bev+CP group. The stratified HR for OS was 0.76 (95% CI 0.63 to 0.93) indicating that among the ITT population, patients in the Atezo+Bev+CP arm had a 24% relative reduction in the risk of death in comparison with the Bev+CP arm. The median survival of 19.8 months (95% CI 17.4 to 24.2) in the Atezo+Bev+CP arm was 4.9 months longer than the Bev+CP arm (median OS 14.9 months, 95% CI 13.4 to 17.1).

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. 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

1.03), p=0.0578 compared with ITT unstratified HR 0.77, (95% CI 0.63 to 0.93). This subgroup analysis should be interpreted cautiously due to the low number of patients included (n=104/800, 13%).

Network meta-analysis

The CS reports two indirect comparisons of atezolizumab with other treatments:

1. A network meta-analysis (NMA) comparing Atezo+Bev+CP versus pemetrexed-based chemotherapy
2. A matched adjusted indirect comparison (MAIC) comparing Atezo+Bev+CP versus pembrolizumab in patients with high PD-L1 expression.

The MAIC is not used to inform the economic evaluation as the company are not seeking NHS reimbursement for pembrolizumab in patients with high PD-L1 expression. We therefore do not provide a critical appraisal of the MAIC in this report.

A total of seven RCTs were included in the NMA, including the IMpower150 trial of atezolizumab. The structure of the OS and the PFS network is identical. Atezo+Bev+CP is compared with two pemetrexed-based regimens:

- Pemetrexed in combination with carboplatin or cisplatin, followed by pemetrexed maintenance (PEM+CARB/CIS then PEM maintenance)
- Pemetrexed in combination with cisplatin followed by placebo maintenance with best supportive care (PEM+CIS then PLAC main + BSC).

The eligibility criteria in the included trials and patient characteristics at baseline were similar with some exceptions, particularly relating to one trial (the PARAMOUNT trial) in which patients were randomised to maintenance treatment only if they had responded to induction therapy. This is in contrast to the other included trials, which required patients to have either no prior treatment for Stage III and/or IV non-squamous NSCLC. To address this, the company reports a scenario analysis in which this trial is omitted.

The company uses a fractional polynomial approach for indirect comparison estimates of OS and PFS. Unlike traditional NMA methods which assume a constant HR over time, a fractional polynomial model aims to better capture variations in the HR over time through fitting a range of polynomial models to the data. The company's justification for using the fractional polynomial approach was based on the assertion that chemotherapy and immunotherapy have different mechanisms of action leading to different survival kinetics. Patients treated with the former demonstrate early survival benefits, whilst those treated with

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.

Description of the company's economic model

The submitted model includes analyses for three populations:

- ITT (the IMpower150 trial population);
- untreated PD-L1 low or negative; and
- EGFR/ALK positive after targeted treatment.

For each population, treatment with Atezo+Bev+CP is compared to pemetrexed + cisplatin (with or without pemetrexed maintenance).

The model uses a partitioned survival approach with three health states (pre-progression, post-progression and death) to estimate costs and QALYs over a 20-year time horizon. Patients enter the model in the pre-progression state at the start of treatment. Rates of progression and mortality are determined by PFS and OS curves for each treatment

- Baseline PFS and OS curves for Atezo+Bev+CP are estimated from IMPower150 clinical trial data and extrapolated using parametric survival modelling.
- For the comparators, PFS and OS curves are estimated by applying time-varying hazard ratios from the company's fractional polynomial NMA to the baseline Atezo+Bev+CP curves.

The company estimated time to treatment discontinuation (TTD) for atezolizumab and bevacizumab in the Atez+Bev+CP intervention from IMPower150 data. In their base case, they assume a maximum of two years treatment with Atezo+Bev+CP with persistence of the survival advantage (relative to the comparator with pemetexed maintenance) for a further three years. Treatment with pemetrexed maintenance is assumed to persist until progression (without a stopping rule or cap on effectiveness) and other treatments are of fixed duration. Subsequent treatments are not modelled explicitly but a cost is added to post-progression state to reflect an average mix of second and subsequent treatments.

The company fitted parametric curves to OS, PFS and TTD data from the Atezo+Bev+CP arm of IMPower150 (exponential, Weibull, log-normal, log-logistic, generalised gamma and Gompertz). They also considered a piecewise approach, with Kaplan-Meier (KM) data up until 20% of patients remain at risk (n=80) and then extrapolation with the six parametric functions. The choice of curves was based on statistical and visual fit to KM data and expert opinion on the plausibility of the extrapolations.

Table 1 Company base case survival curves for Atezo+Bev+CP

Population	OS	PFS	TTD (Atezo and Bev)
ITT	Exponential (log-logistic as a "plausible alternative")	KM + log-logistic	KM + exponential
PD-L1 low/ negative			
EGFR/ALK positive		Log-normal	Exponential
Stopping rule			Maximum 2 years
Effect cap	5 years from baseline mortality rate equal to PEM+CIS/CARBO (with maintenance)		

These curves were adjusted for the two pemetrexed-based comparators (with/without maintenance) using hazard ratios from the fractional polynomial NMA. In their base case, the company used the fixed effects first-order fractional polynomial with P1=0 (Weibull), for the ITT population, and separately for the PD-L1 and EGFR/ALK subgroups.

For their base case, the company used health utilities estimated from EQ-5D-3L data collected in the IMPower150 trial with a proximity to death approach: utility estimates for <35, 34-75, 74- 210 and >211 days before death. The same utilities were applied to all populations and treatment arms and did not include disutility associated with adverse events.

The model includes resource costs associated with drug acquisition, drug administration, subsequent treatment (docetaxel, nivolumab, pembrolizumab and atezolizumab monotherapy), follow-up and monitoring, adverse events and terminal care. These were in line with previous TAs (including TA531).

Company's base case results

The company base case results are shown in Table 1, Table 2 and Table 3 for the ITT, PD-L1 negative/low and EGFR/ALK positive populations, respectively. These results include patient access scheme (PAS) price discounts for atezolizumab and bevacizumab but list prices for comparators and subsequent treatments. We show results with all available price discounts in the confidential addendum to this report.

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).

- The company's base case assumption of a two-year stopping rule for atezolizumab and bevacizumab in the Atez+Bev+CP intervention is consistent with previous NICE guidance for atezolizumab (TA520 and TA525) and other immunotherapies (e.g. TA531). The assumption that pemetrexed maintenance therapy continues until progression is also consistent with committee conclusions in TA402.
- The company assumption of a three-year cap on survival benefits (after the maximum 2-year treatment) for Atez+Bev+CP is reasonably cautious and consistent with previous guidance (e.g. TA520).
- The company's approach to extrapolating OS, PFS and TTD curves is good. They consider a range of baseline extrapolations from the Atezo+Bev+CP arm of the IMpower150 trial, including fully parametric and piecewise (KM with parametric tail). For the piecewise approach, the KM is used up to the time when 20% of trial patients remain at risk, which results in long-term extrapolations that are consistent with the fully parametric curves.
- The company's choice of survival curve extrapolations for PFS and TTD is reasonable and appropriate.
- The company's approach to estimating health state utility values is reasonable and consistent with previous NICE technology appraisals. The use of IMPower150 utility data is preferable to other estimates of utility in this population and we agree that the 'proximity to death' approach has more face validity than the pre/post progression analysis.

Weaknesses and areas of uncertainty

- Median OS has been reached in the IMpower150 RCT, however, final OS data are not yet available.
- The comparators used for the EGFR/ALK positive (pemetrexed + cisplatin with or without pemetrexed maintenance) do no match the NICE scope which includes pembrolizumab and docetaxel. The company has also omitted chemotherapy with carboplatin comparators for the untreated PD-L1 low/negative subgroup which may reflect current practice for patients who cannot tolerate cisplatin.
- There is significant uncertainty over the extrapolation of OS and ICERs are quite sensitive to this uncertainty. We agree that the company's choice of an exponential OS curve for the atezolizumab combination in their base case has a good fit to the trial data and gives clinically plausible extrapolations of survival at five and ten years. We consider that the Weibull distribution is also plausible, with more conservative

survival predictions. The log-logistic gives over optimistic long-term predictions (around 10% survival at 10 years).

- We do not consider the company's assumption of a persistent survival advantage for pemetrexed maintenance throughout the time horizon to be realistic. This is not consistent with committee conclusions in TA402 and is likely to have overestimated the long-term survival gain for Atez+Bev+CP and for the pemetrexed maintenance comparator in comparison with pemetrexed with platinum induction alone. This implies that the ICER for Atez+Bev+CP relative to PEM+CIS without maintenance is likely to be underestimated.
- Cost-effectiveness estimates for the PD-L1 low/negative based on the subgroup analysis of IMpowe150 data are quite similar to the ITT results, and reasonably robust. However, estimates for the EGFR/ALK positive subgroup are much more uncertain as they are based on a small subgroup from the trial (n=41).
- The ERG considers that the utility impact of differences in the incidence of treatment related adverse events between treatments have not been fully captured in the company's base case analysis. It is unclear whether patients treated with Atezo+Bev+ CP have the same health state utility whilst on treatment as those treated with pemetrexed + platinum (with or without pemetrexed maintenance).
- There are some minor discrepancies to some of the cost estimates, which have not been updated correctly.

Summary of additional work undertaken by the ERG

We corrected minor discrepancies in the in the model and re-ran the company's analyses. Changes to the results were minimal.

In addition, we ran the model for an ERG base case, including preferred assumptions and parameters (see table below). This included changes to: the company's baseline Atez+Bev+CP OS curve (Weibull instead of exponential); relative treatment effects excluding the PARAMOUNT trial (which restricts the results to a comparison with pemetrexed maintenance); and inclusion of disutility for adverse events. We also present selected scenario analyses around the ERG base case to reflect key uncertainties.

Table 5 ERG base case and ERG scenarios

	Subgroup	Company base case	ERG base case	ERG scenarios
Baseline OS	All	Exponential	Weibull	• Exponential • Log-logistic
Baseline PFS	ITT & PD-L1 low/-ve	KM + log-logistic	KM + log-logistic	• KM + exponential • KM + Weibull
	EGFR/ALK +ve	Log-normal	Log-normal	• Exponential • Weibull
NMA (OS & PFS)	ITT	FP (FE) ITT	ITT FP excluding PARAMOUNT (FE)	• ITT FP (RE) • ITT PH • Subgroup specific
	PD-L1 low/-ve	FP (FE) PD-L1 low/-ve		
	EGFR/ALK +ve	FP (FE) EGFR/ALK +ve		
TTD	All	KM + exponential for atezo and bev	KM + exponential for atezo and bev	• Bev until progression
		PEM follows PFS	PEM follows PFS	
Stopping rule and effect cap	All	2 year treatment + 3 year OS effects	2 year treatment + 3 year OS effects	• 2 years for OS • 5 years for OS • 3 years for PFS • no stopping rule or effect cap
Utilities	All	IMPower150 EQ-5D time-from-death with no treatment effect	IMPower150 EQ-5D time-from-death + disutility per grade 3+ treatment related AE	• IMpower150 EQ-5D health state model • No AE disutility
Subsequent treatments	All	UK scenario (CS Tab 34)	UK scenario (CS Tab 34)	Exclude nivolumab

FE Fixed effect; FP Fractional polynomial; KM Kaplan Meier; NMA network meta-analysis; RE Random effects

Results from the ERG ITT base case are shown below (with PAS for atezo and bev, list price for other treatments). Scenario analyses are presented in section 4.4.2 below. These indicate that the model is most sensitive t: extrapolations of overall survival and treatment duration, the use of a stopping rule for atezolizumab and bevacizumab as part of Atezo+Bev+CP and the costs of subsequent treatments. Results with all available PAS discounts are shown in an addendum to this report.

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	

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to NICE from Roche Product Limited on the clinical effectiveness and cost effectiveness of atezolizumab in combination for non-squamous non-small-cell lung cancer. It identifies the strengths and weakness of the CS. A clinical expert was consulted to advise the ERG and to help inform this review. Clarification on some aspects of the CS was requested from the manufacturer by the ERG via NICE on 28th September 2018. A response from the company via NICE was received by the ERG on 15th October and this can be seen in the NICE committee papers for this appraisal.

2 BACKGROUND

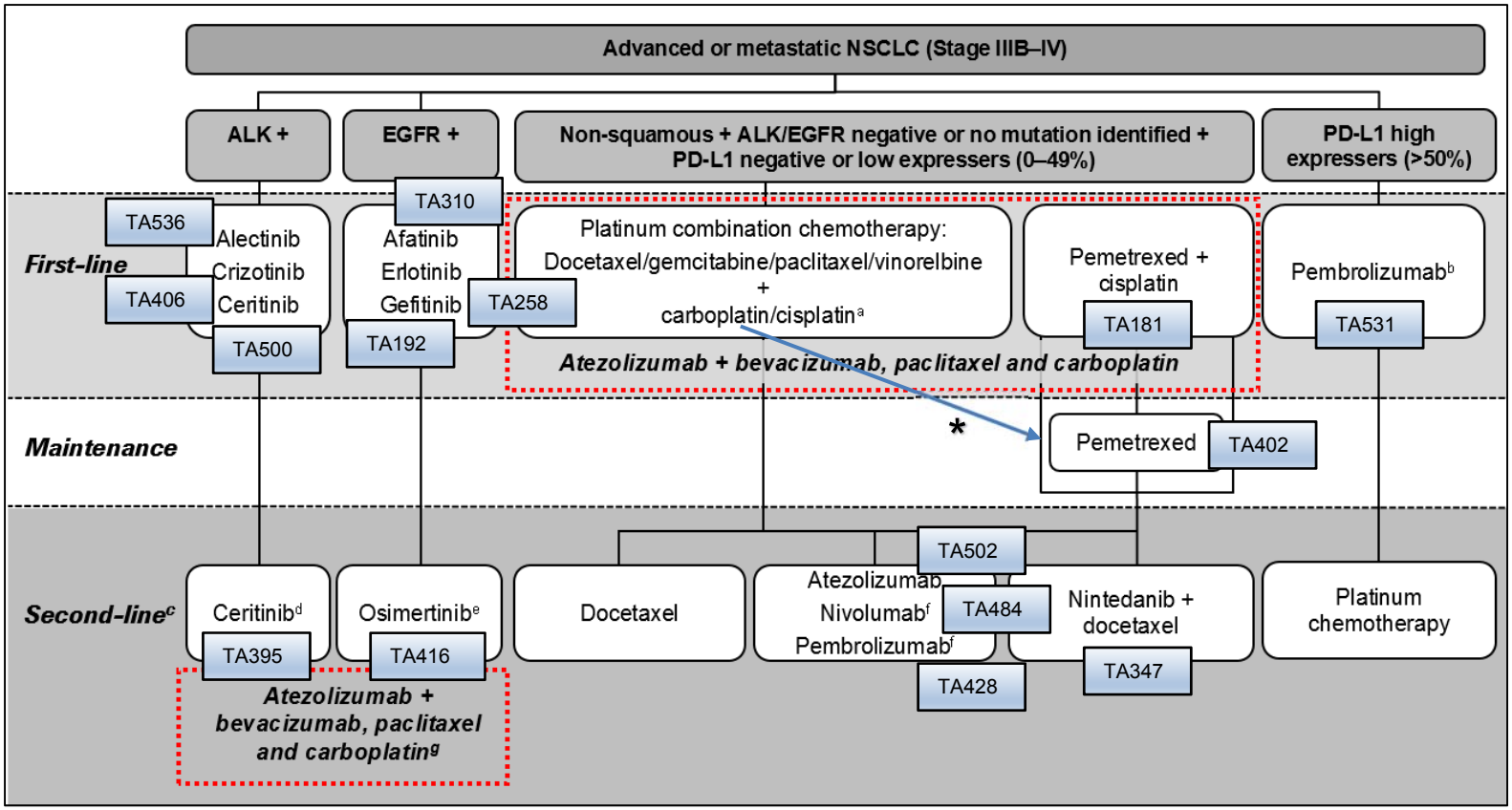
2.1 Critique of company's description of underlying health problem and overview of current service provision

The CS provides a clear and accurate overview of the disease and current service provision, citing relevant NICE guidance and clinical guidelines (including NICE clinical guideline 121[1]). Figure 1 shows the care pathway, reproduced from the CS. Expert clinical advice to the ERG is that the pathway is reflective of current clinical practice, though the advice given was that some patients may be unable to tolerate cisplatin (which is used in combination with pemetrexed), and therefore would therefore commence treatment with platinum combination chemotherapy containing carboplatin, and then receive pemetrexed maintenance therapy.

The CS briefly mentions the key factors that influence choice of treatment for NSCLC, including:

- The presence of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations.
- Programmed Death Ligand 1 (PD-L1) expression (commonly categorised as high expression, or low or negative expression). High expression is defined by a tumour proportion score (TPS) > 50%, TC/IC3. Low or negative expression is defined as a tumour proportion score 0-49%, TC/IC 0,1,2.
- Patient-specific factors such as age, comorbidities, and personal preferences.

Expert clinical advice to the ERG notes that patients with EGFR/ALK mutations tend to have better survival, and respond better to pemetrexed chemotherapy. Patients with high PD-L1 expression are also more likely to respond to pemetrexed chemotherapy. These patient subgroups are included in this company submission and are referred to extensively in this ERG report.



[a]Single-agent chemotherapy with a third-generation drug offered if a platinum combination cannot be tolerated; [b]PD-L1 expression ≥50% TPS; [c]Patients who progress following non-targeted therapy may receive an ALK or EGFR tyrosine kinase inhibitor as a second-line treatment if an actionable mutation is identified or suspected; [d]Certinib after crizotinib failure; not suitable after first-line alectinib; [e]EGFR T790M mutation-positive only; [f]PD-L1 positive patients only; [g]Atezolizumab+bevacizumab, paclitaxel and carboplatin would be available as a second-line treatment option for patients who progress on targeted therapy (after exhausting all available options) and are ineligible for osimertinib, i.e. non T790Mpatients

Adapted from CS Figure 1. TA = Technology appraisal. * The asterisk and arrow reflect the clinical advice to the ERG that patients who are unable to tolerate cisplatin would commence treatment with platinum combination chemotherapy containing carboplatin, and then receive pemetrexed maintenance therapy.

Figure 1 Treatment pathway for advanced or metastatic NSCLC (based on NICE clinical guideline 121), showing intended position of atezolizumab-based therapy

2.2 Critique of company's definition of decision problem

There are some key differences between the decision problem and the NICE scope, as outlined in CS Table 1. The key differences are:

- **Intervention** - The combination of atezolizumab with carboplatin and paclitaxel (without bevacizumab) is not pursued in the anticipated marketing authorisation and therefore not included in the decision problem. Given that NICE only recommends treatments within their marketing authorisation this exclusion is acceptable.
- **Population** – For people without EGFR or ALK tumour mutations there is a restriction to patients with low or negative PD-L1 expression (tumour proportion score 0–49%, TC/IC 0,1,2). Patients with high PD-L1 expression, who currently would be eligible to receive pembrolizumab (NICE TA531), are not included. The justification for this is explained below under 'comparator'. Patients who have EGFR or ALK tumour mutations can have any level of PD-L1 expression, and they are included in the decision problem.
- **Comparator 1 (PD-L1 negative or low patients, ALK/EGFR negative patients)** - the decision problem omits the comparison with chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin), with or without pemetrexed maintenance treatment. Instead, the CS focuses on the comparison with pemetrexed in combination with cisplatin / carboplatin, with or without pemetrexed maintenance treatment. The NICE scope permits this comparison but with the caveat that it applies to adenocarcinoma or large cell carcinoma only (based on NICE TA181) – the CS does not mention this caveat. The ERG notes that the histology of NSCLC is predominantly adenocarcinoma and squamous cell carcinoma, with the remainder of histology sub-types comprising large cell or undifferentiated. The justification for use of pemetrexed in this subgroup, is that pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed maintenance, is the most appropriate 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[2]).Patients who cannot tolerate cisplatin would therefore be treated with a carboplatin-based regimen (i.e. docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with carboplatin), followed by maintenance treatment with pemetrexed (illustrated by the arrow in Figure 1). In practice, however, the findings of

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. 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. Omission of a comparison to pembrolizumab in high expressing or positive PD-L1 patients is supported by clinical opinion.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The CS reports literature searches for clinical effectiveness literature (Appendix D), cost-effectiveness literature (Appendix G), health-related quality of life (HRQoL) (Appendix H), and cost and healthcare resource identification, measurement and valuation (Appendix I). All searches are deemed to be fit for purpose. They are of good quality, contain a balance of descriptor terms, free text terms and suitable study design filters have been applied to identify RCT, cost, resource use & HRQoL. They are well documented and reproducible. A suitable range of databases and grey literature, including ongoing trial databases and pertinent conference proceedings, have been searched. Search results are represented in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow charts. The clinical effectiveness searches were reasonably up to date (February 2018), however the ERG elected to run targeted searches on atezolizumab on Medline, Embase, general internet searches and www.clinicaltrials.gov to check for any recently published material during 2018. No additional sources of information were identified that were relevant to this appraisal.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The company conducted a systematic review to identify and select clinical effectiveness evidence. The inclusion and exclusion criteria for the systematic review are presented in CS Appendix D Table 10. Although the scope of the systematic review is not described, it is apparent from the inclusion and exclusion criteria that the remit was wider than the NICE scope for this appraisal to encompass outcomes of relevance to a network meta-analysis (NMA) and non-NMA outcomes (see section 3.1.7 of this report for a description and critique of the NMA). The population for the systematic review "Adult patients aged over 18 years with any Stage IV non-squamous NSCLC who have not received prior chemotherapy for Stage IV NSCLC" matches that of the NICE scope. Although the systematic review criteria specify stage IV disease and the NICE scope states advanced disease (which could include Stage IIIb and IIIc disease), the NICE scope also indicates that atezolizumab must be used within its marketing authorisation which is the treatment of adult patients with metastatic NSCLC. Metastatic NSCLC would normally be interpreted as stage IV disease.

Ten eligible interventions were specified (four of which included atezolizumab) and the eligible comparators were any pharmacological treatment or placebo. The specified interventions and the broad nature of the comparator are likely to have ensured that the evidence matching the decision problem would be identified (though note that, as discussed earlier, the decision problem and the inclusion criteria exclude some of the comparators specified in the NICE scope). Outcomes were divided into those to consider in the NMA and additional (non-NMA) outcomes. RCTs (phase II to IV) were eligible for inclusion and systematic reviews published in the last five years were used a source of references. Conference abstracts published in the last five years were only included if they provided additional data associated with an included full-text publication. Studies published in Chinese without a detailed abstract in English were excluded. No other restrictions are reported to limit inclusion in the systematic review.

The flow diagram (CS appendix D Figure 1), showing the flow of studies through the inclusion and exclusion screening stages, is provided but no details about how screening was achieved are presented (i.e. how many reviewers involved). In response to clarification question A16 the company stated that two reviewers independently undertook the record selection with a third reviewer involved to adjudicate any disagreements. Furthermore, the company's response to clarification question A12 suggests that the flow-diagram depicts screening against broader criteria for a "global network" (to inform HTA submissions in other countries). The specific UK network criteria for patient eligibility appear to have been applied once a broader set of trials had been identified. The two differences between the UK network and the global network were firstly, for the UK network, the proportion of patients in each study with Stage IV non-squamous NSCLC had to be at least 90% if outcomes were not reported separately for this group. Secondly, only interventions relevant to the UK as shown in CS Appendix D Table 10 were included. CS Appendix D Table 12 lists the 895 full texts documents excluded along with the reasons for exclusion.

> **ERG conclusion:** The ERG believes that the broad scope of the company's systematic review not only encompasses the proposed population and licensed indication for atezolizumab but also the need to identify evidence for the NMA.

3.1.3 Identified studies

The systematic review identified one RCT, the IMpower150 RCT, of atezolizumab in combination with carboplatin plus paclitaxel with or without bevacizumab. A further 13 RCTs, six of which included interventions that were relevant to the UK, were identified for

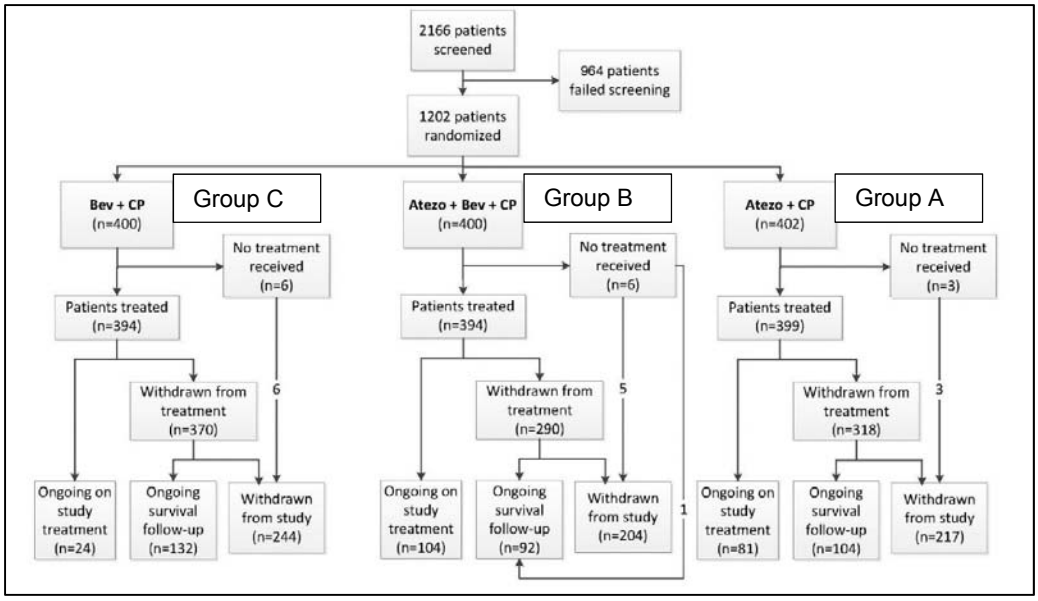
possible inclusion in the NMA. No non-randomised evidence was included in the submission.

Summary details of the IMpower150 RCT, which was sponsored by the company, are provided in the CS. IMpower150 is a Phase III, open-label RCT which enrolled adult chemotherapy-naive patients with stage IV non-squamous NSCLC. Eligible patients were randomised in a 1:1:1 ratio (stratified by gender, PD-L1 expression and the presence of liver metastases) to one of three treatment arms:

- Arm A (n=402): Atezolizumab + carboplatin + paclitaxel (Atezo+CP) induction (four or six 21-day cycles) followed by atezolizumab maintenance (21-day cycles)
- Arm B (n=400): Atezolizumab + bevacizumab + carboplatin + paclitaxel (Atezo+Bev+CP) induction (four or six 21-day cycles) followed by atezolizumab + bevacizumab maintenance (21-day cycles)
- Arm C (n=400): Bevacizumab + carboplatin + paclitaxel (Bev+CP) induction (four or six 21-day cycles) followed by bevacizumab maintenance (21-day cycles).

The marketing authorisation applied for covers Atezo+Bev+CP (Arm B) only and therefore data for Atezo+CP (Arm A) were not included in the CS and this arm is not discussed further in this report.

A flow-chart showing numbers of patients randomised, treated, withdrawn and ongoing either on study treatment or being followed up for survival at the 22nd January 2018 data cut off is reproduced below in Figure 2 (note that groups are presented from left to right in reverse order).



Reproduction of CS Appendix D Figure 19 with group labels added for clarity.

Figure 2 IMpower150 RCT flow chart

Among the ITT population of the Atezo+Bev+CP and the Bev+CP arms of the IMpower150 trial patient characteristics and baseline demographics were well balanced (Table 7). The only exception that the CS highlights (in Appendix D.1.1) is that there were more patients with an ECOG performance status of 1 in the treatment arm (59.9%) than in the control arm (54.9%). The ERG agrees that, other than this, the arms are well balanced. Furthermore, clinical advice to the ERG was that although ECOG performance status is a prognostic factor, the difference between arms is regarded as small and not clinically important.

Results are also presented in the CS for the ITT-WT (wild-type) and EGFR/ALK+ populations (see section 3.1.6 of this report for an explanation of the different analysis populations used in the CS) so the company were asked to provide the baseline characteristics for these populations (clarification question A3). The ITT-WT population baseline characteristics are very similar to those of the ITT population, which is not surprising because the ITT-WT population is 87% of the ITT population. Baseline characteristics of the arms of the ITT-WT population are well balanced. The EGFR/ALK+ population, which is small (n=104 in total across arms B and C of the trial), differs from the ITT population not only in terms of EGFR mutation status and EML-4-ALK rearrangement status, as expected, but additionally the proportion of male participants is lower (approximately 50% compared with approximately 60% in the ITT population), a greater proportion of Asian participants (approximately 35% compared with 13%, respectively) and lower proportion of white participants (approximately 62% compared with 82%, respectively). Activating EGFR mutation and ALK translocations are known oncogenic driver mutations in

NSCLC (i.e. they are responsible for the initiation and maintenance) therefore, the observed greater proportion of participants in the EGFR/ALK+ population who had never smoked (48% compared to 2%, respectively) is not unexpected. There are some imbalances between the trial arms of the EGFR/ALK+ subgroup but these may well be due to the smaller participants numbers and selection bias associated with the non-random nature of this subgroup. Of particular note is the lower proportion of participants in the Atezo+Bev+CP arm with liver metastases at baseline in comparison with the Bev+CP group (12.2% versus 15.9%) (Liver metastases are reported in the CS as being associated with limited therapeutic benefit with checkpoint-inhibitor monotherapy i.e. therapies such as atezolizumab that block immune system checkpoint proteins thus allowing the immune system to kill cancer cells better). There were also imbalances in PD-L1 status between arms. Given these imbalances caution is required in the interpretation of the results of the EGFR/ALK positive subgroup.

The IMpower150 RCT is still ongoing. No other ongoing studies of atezolizumab in this indication are presented by the company (CS section B.2.11) and none were identified by the ERG.

Table 7 Summary of key patient demographics and baseline characteristics in IMpower150 (ITT population)

	Atezo+Bev+CP n=400	**Bev+CP n=400**
Mean age, years (SD) Median age, (range)	63.0 (9.5) 63.0 (31–89)	63.1 (9.3) 63.0 (31–90)
Male, n (%)	240 (60.0)	239 (59.8)
Race, White, n (%)	322 (80.5)	335 (83.8)
ECOG PS, n (%) 0 1	n=397 159 (40.1) 238 (59.9)	n=397 179 (45.1) 218 (54.9)
Smoking status, n (%) Never Current Previous	 82 (20.5) 90 (22.5) 228 (57.0)	 77 (19.3) 92 (23.0) 231 (57.8)
EGFR mutation status, n (%) Positive Negative Unknown	 34 (8.5) 353 (86.3) 10 (2.5)	 45 (11.3) 345 (86.3) 10 (2.5)
EML4-ALK rearrangement status, n (%) Positive Negative Unknown	 11 (2.8) 386 (96.5) 3 (0.8)	 20 (5.0) 376 (94.0) 4 (1.0)

Liver metastases at enrolment from IxRS, n (%)		
Yes	67 (16.8)	69 (17.3)
No	333 (83.3)	332 (82.8)
PD-L1 IHC stratification factor from IxRS, n (%)		
TC0/1/2 and IC0/1	299 (74.8)	301 (75.3)
TC0/1/2 and IC2/3	53 (13.3)	50 (12.5)
TC3 and any IC	48 (12.0)	49 (12.3)

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EML4-ALK, *EML4*-anaplastic lymphoma kinase; IC, tumour-infiltrating immune cell; IHC, immunohistochemistry; IxRS, Interactive Voice/Web Response System; PD-L1, programmed death-ligand-1SD, standard deviation; TC, tumour cell
Source: adapted from CS Table 5

3.1.4 Description and critique of the approach to validity assessment

The company presented an appraisal of aspects of study risk of bias both for the key IMpower150 RCT and the RCTs included in the NMA. For the IMpower150 RCT a summary of the assessment is presented in CS section 2.5, Table 8 using NICE's suggested criteria. Further details are presented in Appendix D Table 32; however, the questions in this table differ from those in CS Table 8. In particular, question 3 in CS Table 8, regarding the similarity of the groups in terms of prognostic factors, is not present in Table 32. Furthermore some questions are answered differently in CS Table 8 and CS Appendix D Table 32 (e.g. question 2 regarding whether the concealment of allocation was adequate where answers are either 'not applicable' or 'yes' depending on which table is consulted). In response to clarification question A6 the company provided a revised version of CS Table 8 and the detailed risk of bias assessment (CS Appendix D Table 32).

Neither the CS nor the published paper for the IMpower150 RCT provided sufficient details for the ERG to complete an assessment of study methods using the NICE suggested criteria. Fortunately, the company had supplied the clinical study report (CSR) for IMpower150 and the ERG used this to complete the assessment (Table 8). The opinion of the ERG and the company differed for one question and partially differed for one question. The reasons for the differences in opinion are provided in the comment rows of Table 8.

> **ERG conclusion:** 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.

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 Unclear for PRO outcomes
Comment: An ITT analysis was conducted for efficacy outcomes. For PFS and OS appropriate censoring methods are described. It is not clear how missing data were accounted for in the analysis of response or of PROs.		

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.

Overall survival – defined as time from randomisation to death from any cause.

Progression-free survival – Investigator-assessed PFS according to RECIST v1.1. Defined as time from randomisation to first documented progressive disease or death from any cause, whichever occurred first. Although PFS was also assessed by an independent review facility (IRF) these results were not presented in the CS.

Time to treatment discontinuation – this was not defined in the CS but as treatment could continue after progression this could be longer than PFS.

Response rate – Objective Response Rate (ORR) was defined as the proportion of patients with either a complete response (CR) or partial response (PR) as judged by the investigator using RECIST v1.1 with confirmation not required. The ERG notes that the RECIST v.1.1 criteria state that " …. elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded." As far as the ERG can determine no central review of response outcomes took place and hence this outcome may be at risk of bias.

In addition to ORR the CS also reports duration of response (DOR) defined as time from the first documented objective response to documented progressive disease or death from any cause whichever occurred first. Similarly, to ORR, DOR was investigator assessed using RECIST v1.1 with no confirmation required.

Adverse effects of treatment - Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Health-related quality of life – time to deterioration in patient-reported lung cancer symptoms using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality-of-life Questionnaire Core (QLQ-C30) and supplemental lung cancer module (QLQ-LC13). Change from baseline in patient-reported HRQoL as assessed by the EORTC QLQ-C30 and the QLQ-LC13. The CS does not describe these two questionnaires but the ERG can confirm that both the QLQ-C30 core questionnaire and the QLQ-LC13 module are validated instruments. EORTC questionnaires were administered at every cycle during the treatment period until either progressive disease (for the Bev+CP arm) or until loss of clinical benefit (for the Atezo+Bev+CP arm) and after disease progression at 3- and 6-month follow-up visits. For the EORTC QLQ-C30 Global health status, physical functioning and role functioning scales scores range from 0 to 100 with a higher score indicating better quality of life. Clinically meaningful worsening is indicated by a 10-point or greater decrease in mean score. For the EORTC QLQ-LC13 module scores (range 0-100) are produced for dyspnea, coughing, chest pain, arm/shoulder pain, pain in other parts and

pain with a lower score indicating lower symptom severity and a clinically meaningful worsening indicated by an increase in mean score of 10 points or more.

ERG conclusion: The outcomes presented by the company are appropriate.

3.1.6 Description and critique of the company's approach to trial statistics

In this section we describe and critique the statistical approach used in the IMpower150 trial, focusing on the outcome measures that directly inform the economic model (i.e. PFS and OS and HRQoL).

3.1.6.1 Analysis populations

Table 9 provides a summary of the patient analysis populations in the trial at the two data cut-off dates, as discussed in the following sub-sections.

Table 9 Summary of the analysis populations and data cuts in the trial

	PFS			**OS**	
Data cut-off date	September 2017	January 2018	Data cut-off date	September 2017	January 2018
Analysis status	Final	Updated	Analysis status	Interim	2nd interim
Analysis population (method of tumour assessment)			Analysis population		
ITT (INV)	✓	✓	ITT	✓	✓
ITT-WT (INV)	X	✓	ITT-WT	✓	✓
ITT-WT (IRF)	✓	X			
EGFR/ALK+ (INV)[a]	✓	✓	EGFR/ALK+[a]	✓	✓
PD-L1 low/- (INV)[b]	✓	✓	PD-L1 low/-[b]	✓	✓

INV = investigator assessed
IRF = Independent review facility assessed
[a] based on the ITT population
[b] based on ITT population and also the ITT-WT population
Grey shading indicates which populations and data cuts from the IMpower150 trial inform the economic model

The CS reports the following patient analysis populations:

- **ITT (n=1202)** - all randomised patients, regardless of receipt of the assigned treatment. This is the study population used in the analysis of clinical effectiveness and cost effectiveness in the CS. The CS reports that the anticipated marketing authorisation is based on the entire ITT population (i.e. including patients with activating EGFR mutation or ALK translocation).
- **Safety population (n=1187)** - randomised patients who received any amount of any component of study treatment. Patients were grouped according to whether any

amount of atezolizumab was received, including when atezolizumab was received in error.

- **ITT-WT (n=1040)** - intention-to-treat wild type population. This is the same as the ITT population (see below) with the exclusion of patients with activating EGFR mutation or ALK translocation.
  ([redacted]).
    - **Teff-high WT population (n=445)** –patients who had a specific T-effector (Teff) gene signature, excluding patients with an activating EGFR mutation or ALK translocation (thus, a subgroup of the ITT-WT population). The CS reports that since the Atezo+Bev+CP combination demonstrated a clinically meaningful improvement in outcomes regardless of Teff gene signature status, this this biomarker was not deemed to be clinically relevant and therefore this data did not impact the anticipated marketing authorisation. This population is not reported in detail in the CS, and is not mentioned in the NICE scope. Therefore, it is not discussed in this ERG report. Expert clinical advice to the ERG is that, at Southampton General Hospital patients are not routinely tested for this biomarker.

3.1.6.2 Sample size calculation and hypotheses

The determination of patient populations for the primary and secondary analyses has a complex background, as summarised below.

Originally, the primary endpoint analysis was to be performed on the:

- **ITT population**, and the
- **PD-L1 selected population**. (Not explicitly defined, but the ERG assumes this is patients with patients with high PD-L1 expression).

However, there was a protocol amendment during the study (March 2017) which changed the primary-analysis populations to the:

- **ITT-WT population** (i.e. excluding patients with activating EGFR mutation or ALK translocation) and the
- **Teff-high WT** populations

The analyses of PFS and OS in patients defined by their PD-L1 expression status became a secondary analysis.

The sample size calculation was therefore performed for the co-primary endpoints of OS and PFS in the:

- **ITT-WT** patient population (OS and PFS) and the
- **Teff-high WT** population (PFS only).

As mentioned above, the analysis of clinical effectiveness and cost effectiveness in the CS are based on the **ITT population** (effectively a secondary analysis following the protocol amendment), and not the ITT-WT and the Teff-high WT populations (i.e. the primary analysis following protocol amendment). The statistical power calculation is thus based on a sample size for a WT population that is smaller than the sample size for the ITT analyses presented in the CS. The ERG notes that the ITT-WT population comprises 87% (n=1040/1202) of the ITT population, so the difference in the size of these two populations is relatively small.

[redacted]

The sample size was based on the number of events required to demonstrate efficacy with regard to both PFS and OS for the comparison of the Atezo+Bev+CP vs. Bev+CP (Arm B vs Arm C). An 'alpha-spending algorithm' was employed so that if there was a significant difference between Atezo+Bev+CP and Bev+CP then the Atezo+CP arm would be compared with the Bev+CP arm (Arm A vs Arm C). The study was not designed to test a comparison between Atezo+CP and Atezo+Bev+CP (Arm A vs Arm B). Thus, it is not possible to statistically compare a atezolizumab regimen with and without bevacizumab.

The sequence of testing was as follows:

- With a two-sided significance level of 0.05, a two-sided alpha value of 0.012 was allocated to PFS (split equally into 0.006 for each primary-analysis population (the **ITT-WT population** and the **Teff-high WT population**)), and a two-sided alpha value of 0.038 was allocated to OS in the **ITT-WT population.**
- If there was a statistically significant difference in PFS between the Atezo+Bev+CP group and the Bev+CP group, the alpha value would then be recycled for the comparison of OS between the Atezo+Bev+CP group and the Bev+CP group.
- If the result of the comparison of OS between the Atezo+Bev+CP group and the Bev+CP group was significant, the remaining alpha value would be used to compare

both PFS and OS between the Atezo+CP group and the Bev+CP group (i.e. Arm A versus Arm C).

- If there was a statistically significant difference in OS between the Atezo+CP group and the Bev+CP group (A versus C), testing would be extended to the **ITT population**, including patients with EGFR or ALK mutations.

The rationale for this sequence of testing was to maximise statistical power to detect a significant benefit for the addition of atezolizumab to bevacizumab, cisplatin and paclitaxel. If the addition of atezolizumab to this regimen did not provide a significant benefit it was considered unlikely that substituting atezolizumab for bevacizumab in the Bev+CP regimen (i.e. comparing Arm A vs Arm C) would provide significant benefit.

The CS reports that the comparison of Atezo+CP to Bev+CP did not show a statistically significant survival benefit (HR=0.88, 95% CI: 0.72, 1.08; p=0.2041), thus marketing authorisation was only sought for the Atezo+Bev+CP regimen. The CS therefore does not present results for the Atezo+CP arm. Likewise, results for this arm are not reported in this ERG report.

3.1.6.3 Completeness of follow-up

Results are available for two data cuts: September 2017 (final PFS, interim OS), and 22nd January 2018 (updated PFS; second interim OS) (Table 9). The most recent data from the second interim OS results are based on 422 deaths across the two treatment arms relevant to this appraisal, with a median follow-up of approximately 20 months. Median OS has been reached in both treatment arms, however, final OS data analysis will be conducted when there are 507 deaths across the two relevant trial arms (in the ITT-WT population). Analysis is expected in [redacted]. Thus, the PFS results are based on mature data, but the OS data are not fully yet mature, and thus caution is required in the interpretation of the OS results.

3.1.6.4 Tumour progression assessment

Investigator assessed PFS results are presented in the CS. The only reporting of independent review facility (IRF) assessed PFS is for the ITT-WT population, in the trial journal publication (a secondary outcome). Independent assessment of tumour progression can sometimes differ from investigator assessment, and it is informative to conduct and report both. The company were asked to provide IRF PFS results for the ITT, ITT-WT populations and subgroup analyses (clarification question A4). The company provided the IRF-assessed PFS data from the 15 September 2017 data cut and stated that as the IRF was disbanded after the primary endpoint for PFS was met IRF-assessed data are not available for the most recent 22nd January 2018 data cut.

3.1.6.5 Subgroup analyses

The NICE scope included provision for subgroup analysis by level of PD-L1 expression if the evidence allowed. As described earlier in section 2.2, the company's decision problem, for people without EGFR or ALK tumour mutations there is a restriction to patients with low or negative PD-L1 expression (tumour proportion score 0–49%, TC/IC 0,1,2). Patients with high PD-L1 expression are not included (tumour proportion score > 50%, TC/IC3). Within the sub-population of people with EGFR or ALK tumour mutations people with any level of PD-L1 expression are included in the decision problem.

Pre-planned subgroup analyses results are available for OS and PFS by genetic mutation characteristics (e.g. EGFR/ALK status; PD-L1 status) thus including the PD-L1 status subgroups identified in the scope. Additional subgroup results for OS and PFS across a range of baseline demographic variables (e.g. age, race) and disease status (e.g. ECOG performance status; metastases site – liver, lung, lymph node, adrenal gland) are also presented. CS Appendix E reports subgroup results, based on the ITT population, and also based on the ITT-WT population (for PD-L1 status only). Results for other subgroup analyses based on the ITT-WT population are available in the trial journal article and the CSR (by default these do not include the EGFR/ALK status subgroups).

The PD-L1 subgroup analysis provides results according to high, positive, low and negative PD-L1 expression subgroups, and varying combinations of these groups. As noted above, only the PD-L1 low or negative expression subgroups (tumour proportion score 0-49%, TC/IC 0,1,2) are relevant to the company's decision problem and are one of the population groups used to inform the economic model. The low or negative expression PD-L1 subgroups comprise the majority of the randomised patients across the two trial arms relevant to the company's decision problem (n=652/800, 82% in the ITT population).

The ERG asked the company to clarify whether any statistical interaction tests were performed for the subgroups, and also whether any adjustment made for multiple testing among the subgroup analyses (clarification question A11). The company responded that interaction tests and adjustments for multiple testing were not performed therefore, as is commonly the case in clinical trials, caution is required in the interpretation of these subgroup analyses. Some of the subgroups have small sample sizes which may not be sufficiently powered to detect a statistically significant difference (evidenced by wide confidence intervals). Furthermore, the subgroups are effectively observational in nature and carry a risk of potential selection bias between the randomised trial arms (though note,

randomisation was stratified by PD-L1 status, sex and the presence of liver metastases thus the risk of selection bias on these variables is lower).

3.1.6.6 Procedures for handling missing data

Censoring criteria for the assessment of PFS, OS and tumour response are reported in CS Table 6. The PFS censoring criteria appear to be similar to those commonly used in cancer treatment clinical trials. Patients who were alive and without experiencing progressed disease at time of analysis were censored on the date of the last tumour assessment; data for patients with no post-baseline tumour assessment were censored at the date of randomisation plus 1 day. The same censoring criteria were used across the analysis populations (ITT; ITT-WT; PD-L1 status).

The ERG asked the company to clarify the choice of the censoring criteria used for assessing PFS (clarification question A10). The company responded that the criteria were based on those used by the FDA.

The CS does not state whether censoring occurred for patients receiving any subsequent therapies following discontinuation of the study treatment, or for receipt of any non-protocol specified anti-cancer therapy before a PFS or an OS event.

[redacted] (see section 3.3.1).

[redacted] (see section 3.3.2).

As stated in the trial protocol, the impact of missing scheduled tumour assessments on the primary analysis of PFS was evaluated in a sensitivity analysis, using two imputation rules:

- If a patient missed two or more scheduled tumour assessments immediately prior to the date of the PFS event, the patient was censored at the last tumour assessment prior to the first of these missed visits (see section 3.3.1).

- If a patient missed two or more tumour assessments scheduled immediately prior to the date of the PFS event the patient was counted as having progressed on the date of the first of these missing assessments.

To account for patients lost to follow-up a sensitivity analysis for OS was conducted. Patients lost to follow-up were considered as having died at the last date they were known to be alive. Loss to follow-up was very small in the trial (0.3% overall) (CS appendix D Table 31) (see section 3.3.2).

[redacted]

ERG conclusion: the procedures for handling missing PFS, OS and response data in the trial are acceptable.

3.1.6.7 Statistical tests used

The statistical tests used appear to be similar to those commonly used in cancer treatment clinical trials (CS Table 6). Kaplan-Meier methodology was used to estimate median PFS and OS and to construct survival curves. A stratified log-rank test, and stratified Cox regression were performed for the co-primary endpoints of PFS and OS in the ITT-WT population and the ITT population. The stratification factors included: sex, presence of liver metastases at baseline, and PD-L1 tumour expression (i.e. the same as the randomisation stratification factors).

The ERG asked the company to clarify whether any unstratified analyses were performed in the primary analysis (clarification question A8). The company provided the unstratified analyses for PFS and OS for the ITT, ITT-WT and the EGFR/ALK+ populations. The ERG notes that the results of the stratified and the unstratified analyses are similar.

ERG conclusion: The statistical procedures used in the IMPower150 trial are appropriate for use in cancer treatment clinical trials. However, there is a complex background to the analyses populations of the trial. The trial was statistically powered for a sub-group of this trial – the ITT-WT population (87% of the ITT population). However, the assessment of clinical effectiveness and cost effectiveness in the CS is based on the ITT population (all randomised patients), to reflect the anticipated marketing authorisation.

[redacted].

3.1.7 Description and critique of the company's approach to the evidence synthesis

As only one trial of atezolizumab in this indication was included in the submission, IMPower150, a meta-analysis of atezolizumab trials was not possible. The CS provides a narrative review of the trial, with data presented in tables and text.

The CS reports two indirect comparisons of atezolizumab with other treatments:

- A network meta-analysis (NMA) comparing Atezo+Bev+CP versus pemetrexed-based chemotherapy
- A matched adjusted indirect comparison (MAIC) comparing Atezo+Bev+CP versus pembrolizumab in patients with low or negative PD-L1 expression.

The NMA is used to inform estimates of clinical effectiveness in the economic evaluation. The MAIC is not used to inform the economic evaluation as the company are not seeking NHS reimbursement for pembrolizumab in patients with high PD-L1 expression (as discussed earlier in this report, section 2.2). For this reason we do not provide a critique of the MAIC in this report or report its results.

In the following sub-sections we provide a description and critique of the NMA as used to estimate OS and PFS (see also Appendix 9.1 for a quality assessment checklist of this NMA).

3.1.7.1 Evidence networks

The inclusion criteria for the NMA is reported in CS Appendix Table 10. The ERG notes that the inclusion criteria are comprehensive and match the company's decision problem. A total of seven RCTs were included in what the CS describes as the UK network based on these criteria (an additional seven trials were eligible for a "global network" to inform HTA submissions in other countries, which had a wider set of comparators. Citations to these trials are not reported in the CS).

- In three of these trials the experimental treatment under evaluation was pembrolizumab (KEYNOTE-021; KEYNOTE-024; KEYNOTE-189).
- In a further three trials the experimental treatment was pemetrexed-based chemotherapy (ERACLE; PRONOUNCE; PARAMOUNT).
- The remaining trial was the IMpower150 trial of atezolizumab.

The ERG is not aware of any trials relevant to the decision problem that have not been included in the NMA. However, as noted earlier in this report (section 2.2), there are some discrepancies between the decision problem and the NICE scope of the appraisal. Thus, trials comparing pemetrexed with other chemotherapy regimens in the NICE scope (i.e. docetaxel, gemcitabine, paclitaxel or vinorelbine) were not included. The ERG identified a published systematic review and economic evaluation of first-line chemotherapy for locally advanced or metastatic non-small cell lung cancer[4] which reports a mixed treatment comparison for OS and PFS. Pemetrexed + a platinum drug linked to both the OS and PFS networks which contained other platinum containing doublet chemotherapies (e.g. docetaxel + platinum, gemcitabine+platinum). If evidence for chemotherapy regimens such as those reported in the published systematic review[4] had been sought and been possible to include, an indirect comparison between atezolizumab and these other chemotherapies in the NICE scope (clarification question A13) might have been possible.

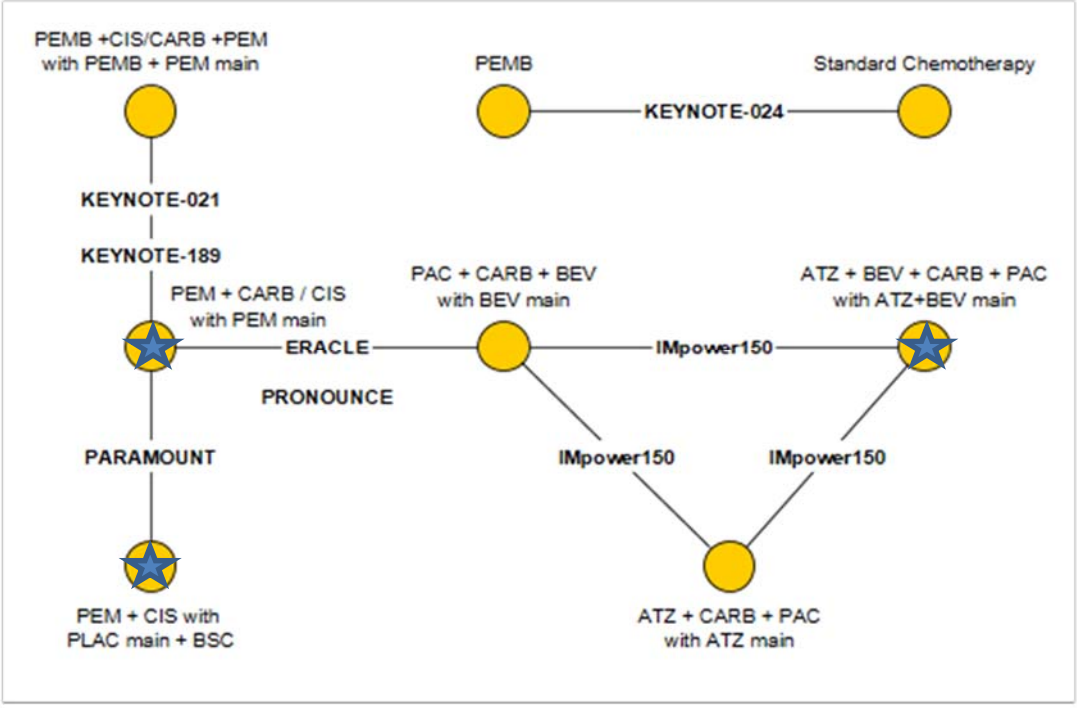
Further, the company argues that the only way to include KEYNOTE-024 in the network "is to assume that all [5] chemotherapy arms are equivalent". They then exclude the study from the network as it "does not share a common treatment arm with any of the other trials". However, we infer that the company, by excluding the docetaxel, gemcitabine, paclitaxel or vinorelbine regimens, did not attempt to connect this study to main network.

A feasibility assessment was undertaken by the company to determine the suitability of the included trials to inform a connected network of evidence for each outcome relevant to the decision problem (see CS Appendix Table 13). Following this assessment, networks were considered feasible for the outcome measures OS, PFS, ORR and adverse events leading to discontinuation. Of these, OS and PFS directly inform the company's economic model, and are the focus in this ERG report.

The structure of the OS and the PFS network is identical, as illustrated in Figure 4. As can be seen, Atezo+Bev+CP is compared with two pemetrexed-based regimens (denoted by a star symbol in the figure):

- Pemetrexed in combination with carboplatin or cisplatin, followed by pemetrexed maintenance (PEM+CARB/CIS then PEM maintenance)
- Pemetrexed in combination with cisplatin followed by placebo maintenance with best supportive care (PEM+CIS then PLAC main + BSC).

Expert clinical advice to the ERG is that, of these two regimens, pemetrexed followed by pemetrexed maintenance therapy is the standard of care in England.



ATZ - Atezolizumab BEV – bevacizumab; BSC – best supportive care; CARB – carboplatin; CIS – cisplatin; MAIN – maintenance; PAC – paclitaxel; PEM-pemetrexed; PEMB – pembrolizumab; PLAC – placebo.

★ denotes relevant NMA treatment comparisons

Source: CS Appendix Figure 2 and Figure 4

Figure 3 Network of studies informing the NMA, for OS and PFS

The network contains only one closed evidence loop, formed of the three arms of the IMpower150 trial. Therefore, there are no relevant treatment comparisons in which both indirect and direct evidence is available hence no assessment of consistency is required.

As noted above, the KEYNOTE-024 trial was not able to be connected to the network, as the control arm contains a mixture of five chemotherapy regimens, thus it is not included in the NMA. It is, however, included in the company's MAIC comparing pembrolizumab to chemotherapy in patients with high PD-L1 expression (not discussed here).

3.1.7.2 Clinical heterogeneity assessment

The eligibility criteria in the included trials and patient characteristics at baseline were similar (CS Appendix Table 15, Table 16 and Table 17), with some exceptions:

- **Induction therapy.** The PARAMOUNT trial had a different study design, with patients randomised to maintenance treatment only if they had responded to induction therapy (Only 539 of the 900 patients included in the induction phase were

randomised). This is in contrast to the other included trials, which required patients to have either no prior treatment for Stage III and/or IV non-squamous NSCLC, no previous systemic treatment, or to be chemotherapy or treatment naïve. Thus, all patients randomised in the PARAMOUNT trial had demonstrated a response to induction treatment, whilst the patients in the other trials would likely comprise a mixture of responders and non-responders to any induction treatment, and thus overall would be less likely to respond to treatment. The ERG agrees with the company's assertion. The CS considers that inclusion of the trial biases results in favour of pemetrexed plus platinum plus pemetrexed maintenance in the base case NMA and in the economic model. To address this, the company reports a scenario analysis in which this trial is omitted (CS Figure 18 and 19), the results of which were more favourable for Atezo+Bev+CP on OS and PFS (NB. the PARAMOUNT trial was the only study which included PEM+CIS then PLAC main + BSC, thus omission of this trial effectively removes this comparator from the analysis).

- **Liver metastases.** Only the IMpower150 trial reported the percentage of patients with liver metastases at baseline (16%-17%). Liver metastases reported in the CS as being associated with limited therapeutic benefit with checkpoint-inhibitor monotherapy, therefore the lack of reporting of this characteristic in the comparator trials creates uncertainty about whether this is a source of clinical heterogeneity in the network.
- **EGFR and ALK mutations**. Only the IMpower150 trial reported inclusion of patients with EGFR and ALK mutations (11.25% of patients in the Atezo+Bev+CP arm). The KEYNOTE trials excluded these patients, and the remaining pemetrexed trials did not report inclusion of any such patients. The base case NMA uses the ITT population of the IMpower150 trial (thus including EGFR and ALK positive patients from IMpower150). A sub-group NMA analysis uses outcome data for EGFR and ALK positive patients from IMpower150 compared to ITT data for the pemetrexed trials (for which it was not reported whether EGFR and ALK positive patients were included). The CS makes the assumption that EGFR and ALK status are not effect modifiers for pemetrexed based regimens. However, expert clinical advice to the ERG did not agree with this assumption. Caution is also advised given that the EGFR and ALK subgroup contains a small percentage of patients (13%).
- **ECOG performance status**. The CS notes substantial variation between (and within) trials in ECOG performance status 0-1. Expert clinical advice to the ERG is that differences in the proportions of patients with either an ECOG performance status of 0 or 1 are unlikely to be clinically significant.

- **Sex.** There was variation in the proportion of males across the trials (37% to 78%). It is unclear what impact this might have on the results of the NMA.

  ERG conclusion: There is some potential clinical heterogeneity in the NMA, primarily associated with the patients in the PARAMOUNT trial who were more likely to respond to treatment than in the other trials. In our base case analysis we exclude the PARAMOUNT trial but we retain it in a scenario analysis (see section 4.4 of this report).

3.1.7.3 Critical appraisal of trials included in the first-line treatment NMA

CS Appendix table 32 provides the company's risk of bias assessment of the trials included in the NMA.

The CS does not provide a narrative summary or discussion of this risk of bias assessment. The ERG has performed an independent risk of bias assessment of the trials included in the NMA (using only the key reference for studies other than IMpower150) which is presented in Appendix 8.2. The ERG's observations broadly concur with the company's assessment with most differences being due to the ERG assessing blinding and missing data separately for different outcomes. The chief risk of bias is that many of the studies were open-label or there was insufficient information in the primary publication for the ERG to determine if blinding was in place.

3.1.7.4 Statistical NMA methods used

The company uses a fractional polynomial approach[5] for indirect comparison estimates of OS and PFS (NB. for the outcomes of ORR and adverse events leading to discontinuation they use a generalised linear modelling approach). Unlike traditional NMA methods which assume a constant HR over time, a fractional polynomial model aims to better reflect the time course of the log-hazard function and as such can be expressed as log-hazard function curves and their parameters (intercept and slope). Credible interval curves can be plotted alongside the log-hazard function curves.

The company's justification for using the fractional polynomial approach was based on the assertion that chemotherapy and immunotherapy have different mechanisms of action leading to different survival kinetics. Patients treated with the former demonstrate early survival benefits, whilst those treated with the latter show a delayed but more sustained survival benefit. Expert clinical advice to the ERG concurs with this assertion. Furthermore, a fractional polynomial approach was also used in the company submission for the NICE

appraisals of atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy (TA520)[6], atezolizumab for treating metastatic urothelial bladder cancer (TA525)[7], and a number of other recent NICE appraisals of cancer treatments.

The CS cites evidence of the difference in survival kinetics in the IMpower150 trial log-cumulative hazard plots (CS section B.3.3) where the curves cross. The ERG observes that the IMpower150 log-cumulative hazard curves do indeed cross (CS Figure 32 and 33), though we also note that the Kaplan-Meier PFS and OS curves appear generally parallel (CS Figures 3 and Figure 4, respectively). Furthermore, the CS does not state whether the proportional hazards assumption holds in the comparator trials in the NMA. A factor which will influence the uncertainty around proportionality of hazards in the trials is the maturity status of the survival data. The more mature the data the less uncertainty there is in the interpretation of proportional hazards. In response to a clarification question (question A27) the company stated that for OS, data maturity ranged from 33% to 72%, and that maturity in some trials was insufficient for median OS to be reached. For PFS, data follow-up were described as reasonably mature (over 50%) in all studies except KEYNOTE-021. The company explains that the time horizon for calculating expected survival was restricted to reduce the influence of extrapolations based on immature data.

On balance, given the expert clinical opinion and previous use in technology appraisals of a fractional polynomial model to differentiate between immunotherapy and chemotherapy we agree the use of fractional polynomial methodology is reasonable. As an alternative to the fractional polynomial time-varying hazards estimation, the company reported a fractional polynomial model approximating an exponential model (i.e. assuming a proportional hazards).

> **ERG conclusion:** The company's clinical rationale for assuming time-varying hazards between treatments is clinically justified. The use of a fractional polynomial model that approximates a proportional hazards exponential model is an informative alternative approach.

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. However, we note U-shaped curves are not represented in the selection of hazard ratios presented. 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 have preferred the range of fractional polynomial models rerun for the subgroup and sensitivity analysis given the different population makeup. Whilst the second order models had lower DIC values (indicating better fit) the company observed that they were not clinically plausible due to unrealistically high survival times. This could also be seen as an

argument in favour of experimenting with other exponents or higher order fractional polynomial models.

> **ERG conclusion:** Having inspected the hazard ratio plots supplied by the company (clarification question A18) the ERG agrees with the company that the second order models are not clinically appropriate, and we note that they are associated with greater uncertainty due to wider credible intervals. Amongst the two first order models tested the ERG agrees with the company's choice of the P1=0 (Weibull) model. This model had a lower DIC value than the P1=1 model, and we include the P1=0 (Weibull) in our own base case analysis (see section 4.4 of this report).

3.1.7.4.2 Outcome data used in NMA

The OS and PFS survival data are reported in CS Table 20 and Table 21. However, these are not the data which input into the NMA.

Individual patient data (IPD) were available for the IMpower150 trial, combined with data reconstructed from the Kaplan-Meier curves (using the Guyot method[8]) from all other studies. It is the binary data (deaths/progression, at risk) extracted from these sources in monthly time periods which populated the NMA model and was reported in vector format in response to clarification question A21. It has not been validated. Furthermore, the company did not state whether the data reconstructed from the Kaplan-Meier graphs was validated against the reported hazard ratios.

The ERG presumes that the company has used the most recent data cuts available for the trials (NB. As discussed above, the company commented on the maturity status of the survival data in the trials in response to clarification question A27). In response to clarification question A28 the company reported that most of the trials included in the NMA used independent review committee assessment of PFS (using the RECIST criteria). The IMpower150 trial and the PARAMOUNT trial used investigator assessed PFS. Since PFS results can differ according to whether investigator-assessed or independent review committee-assessed it would be preferable to use one or the other (or both, separately) in the NMA. Since independent review is frequently more conservative the ERG would have expected a scenario analysis using the earlier (September 2017) data cut for IMpower150 which reported both investigator and independent assessment.

3.1.7.4.3 Choice between random effects and fixed effect models

As stated above, the NMA base case results are reported based on a fixed effect model. In response to a clarification question (A20) the company reported that they only fitted a random effects version of the best fitting fixed effects model (first order FP, P1=0 model) for OS and PFS. The justification the CS provides for using fixed effect model rather than random effects was that the "small differences in DIC indicated a low level of detectable heterogeneity". This is not strictly correct, DIC is simply a measure of relative model fit. It does not indicate heterogeneity or an absence thereof. Nevertheless, DIC is similar across both models and the use of a published informative prior with the random effects is indicative of there not being sufficient data to use a vague prior.

The ERG concurs that the random effects DIC values are similar to the fixed effects DIC values (CS appendix Table 29), but regards this as not a wholly sufficient justification for choice of effect models. Consideration should be given to clinical heterogeneity, and as noted above, there was notable clinical heterogeneity with regard to inclusion of the PARAMOUNT trial. We believe the analysis incorporating PARAMOUNT should use the random effects model, but otherwise the trials are sufficiently similar in terms of ECOG 0-1, disease stage and histology to justify fixed effects (see Section 3.1.7.2).

The results are similar between the two effects models (as would be expected), with the random effects model producing slightly larger credible intervals (clarification question A18, Figure 1 and Figure 2).

> **ERG conclusion:** In principle a random effects model is preferable in the presence of heterogeneity. We retain the fixed effect model in our base case analysis (which omits the PARAMOUNT trial), but we use random effects in a scenario analysis (which includes PARAMOUNT) (see section 4.4 of this report).

3.1.7.4.4 Bayesian modelling methods

The model code was written in Just Another Gibbs Sampler (JAGS) and run via R. JAGS code for selected FP models was provided in response to clarification question A17. The code was validated against published code.[9] However, the code used to approximate a proportional hazards exponential model was not provided so could not be validated. Random effects code was only provided for a first order fractional polynomial as this was the only random effects model run.

Uninformative priors were appropriately used for the fixed effects models. Informative priors as calculated by Turner (2015) were correctly implemented used for the random effects model (checked against Turner Table IV). Given the few trials available and the essentially star-shaped network, informative priors were necessary to estimate between-trial heterogeneity. No random effects model using a vague prior was reported.

A burn-in of 50,000 iterations to ensure convergence was followed by a further 50,000 for estimation, thinned by a factor of 50. Three chains were run giving a total of 3,000 iterations for parameter estimation. Trace plots and Gelman-Rubin statistics were inspected to ensure convergence and the CS model fitting process was reported to be externally validated by an independent statistician. The ERG also ran the P1=0 deterministic model and reported very similar results to the CS.

The NMA output parameters used in the economic model are not reported in the CS documentation. They are reported in the "NMA Raw Inputs" worksheet of the model which only includes the parameters for the proportional hazards and P1=0 fractional polynomial models. The HRs at each timepoint are reported in response to clarification question A17. Coda outputs from JAGS were used in the probabilistic model.

As there were no loops besides those constituted by multi-arm trials, an evaluation of network internal consistency was therefore not required.

ERG conclusion:
Based on the information provided the ERG considers that the methods used to implement the fractional polynomial model are appropriate and correspond to the methods specified in the original methodological texts.[5]

3.2 Summary statement of company's approach

Table 10 provides the ERG's response to a quality assessment checklist for systematic reviews. As can be seen, all of the pre-requisites were met. For example, record selection was independently undertaken by two reviewers with a recourse to a third reviewer for any disagreements.

Table 10 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes

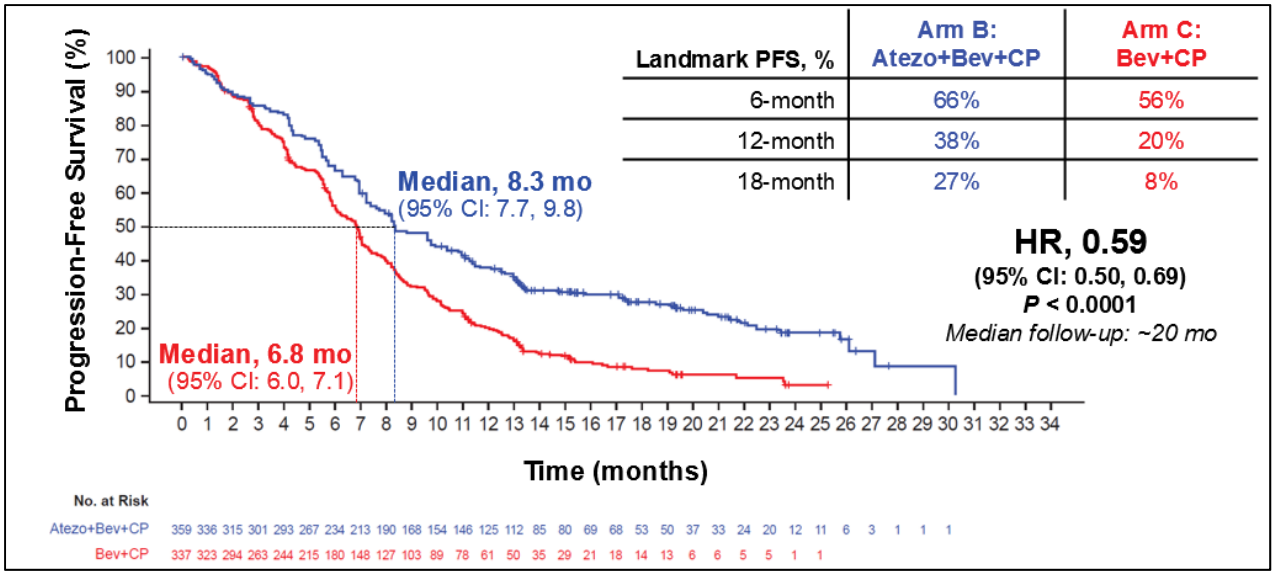
2. Is there evidence of a substantial effort to search for all relevant research? i.e. all studies identified	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.3 Summary of submitted evidence

In the following subsections we summarise the results of the IMpower150 RCT for the most recent data cut available (22nd January 2018) as presented in the CS (see Table 9 earlier for a summary of the endpoints at the different data cuts). The anticipated marketing authorisation is based on the ITT population, (i.e. including the patients with EGFR mutant and ALK-positive NSCLC) and consequently the CS presents data for the ITT population. Data from the ITT population (as well as the PD-L1 and EGFR/ALK+ subpopulations) are also included in the economic model. Therefore, the focus in the following subsections is on the ITT population despite the fact that the co-primary endpoints of the IMpower150 RCT were analysed in the ITT-WT population.

3.3.1 PFS in the ITT population

Investigator-assessed PFS in the ITT population was a secondary outcome of the IMpower150 RCT. At the 22nd January 2018 clinical cut-off date (minimum follow up 13.5 months, median follow-up approximately 20 months) median PFS was longer in the Atezo+Bev+CP group (8.4 months, 95% CI 8.0 to 9.9) than in the Bev+CP group (6.8 months, 95% CI 6.0 to 7.0) (Figure 4). The stratified hazard ratio was 0.59 (95% CI 0.50 to 0.69).



Source: reproduction of CS Figure 3

Figure 4 KM curve – investigator-assessed PFS in the ITT population (clinical cut-off date 22 January 2018)

Upon request the company provided the independent review facility (IRF) PFS results (clarification question A4) for the September 2017 data cut. The IRF was disbanded after this time so this comparison is not possible for the later data cut of January 2018. These results are reproduced in Table 11. As can be seen, the results were similar between the two methods of assessment.

Table 11 Comparison of independent review facility and investigator-assessed PFS in the ITT population (Clinical cut off date September 15, 2017)

PFS assessor	IRF		Investigator	
	Atezo+Bev+CP n=400	Bev+CP n=400	Atezo+Bev+CP n=400	Bev+CP n=400
Patients with event, n (%)	269 (67.3)	296 (74.0)	66.8%	82.8%
Median PFS, months (95% CI)	8.5 (8.1, 9.7)	7.0 (6.1, 7.8)	8.3 (7.9, 9.8)	6.8 (6.0, 7.1)
Stratified HR (95% CI)	0.67 (0.56, 0.79)		0.61 (0.52, 0.72)	
p value	p<0.0001		p value not reported	

HR, hazard ratio; IRF- Independent Review Facility; PFS, progression-free survival

Table compiled by ERG from data presented in the responses to clarification questions, the CS and the published paper for the IMpower150 RCT.

As noted in section 3.1.6.6, a sensitivity analysis was conducted on the September 15 2017 data cut

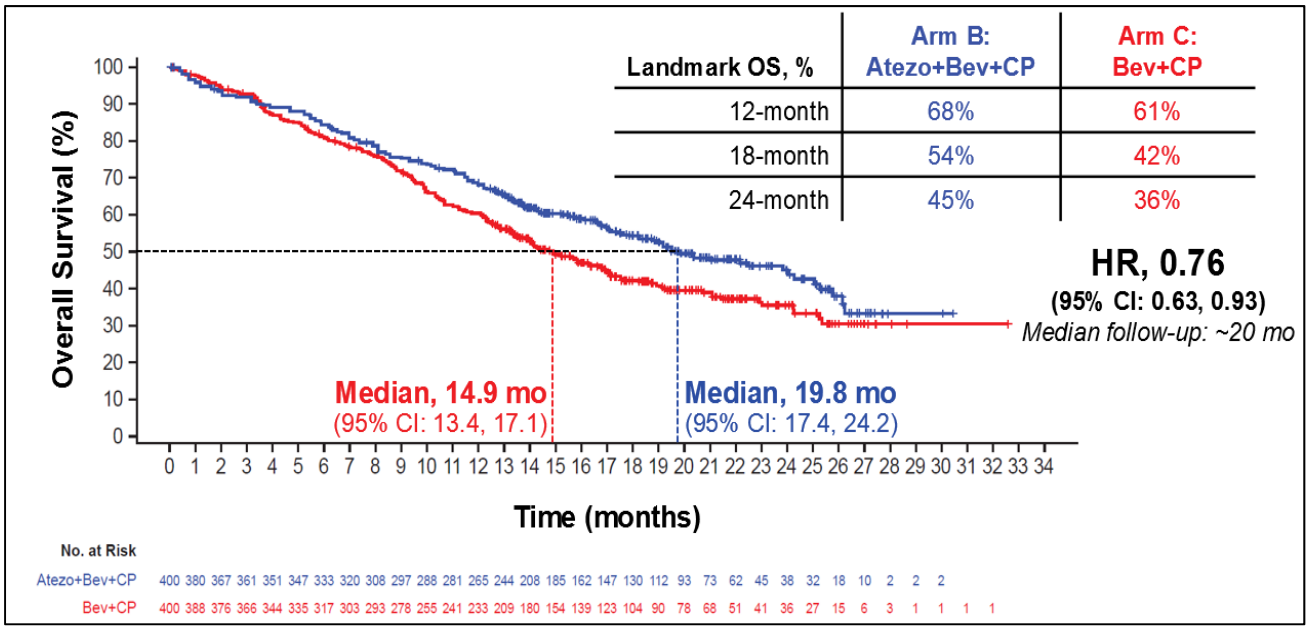
[redacted]

[redacted]. The results of a further sensitivity analysis, conducted to assess the impact of missing tumour assessments, were reported for one of the two imputation rules described in section 3.1.6.6. When patients who missed two or more scheduled tumour assessments immediately prior to the date of the PFS event were censored at the last tumour assessment prior to the first of the missed visits the results were consistent with those of the overall ITT-WT population.

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

3.3.2 OS in the ITT population

At the most recent data cut-off (22 January 2018) 192 deaths (48.0%) had been observed in the Atezo+Bev+CP group and 230 deaths (57.5%) in the Bev+CP group. As Figure 5 shows, the stratified HR was 0.76 (95% CI 0.63 to 0.93) indicating that among the ITT population, patients in the Atezo+Bev+CP arm had a 24% relative reduction in the risk of death in comparison with the Bev+CP arm. The median survival of 19.8 months (95% CI 17.4 to 24.2) in the Atezo+Bev+CP arm was 4.9 months longer than the Bev+CP arm (median OS 14.9 months, 95% CI 13.4 to 17.1).



Source: reproduction of CS Figure 4

Figure 5 KM curve –OS in the ITT population (Clinical cut-off date 22 January 2018)

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).

In the ITT population, a higher proportion of patients in the Atezo+Bev+CP arm (56.4%, 95% CI 51.4 to 61.4) had a confirmed objective response compared with the Bev+CP arm (40.2%, 95% CI 35.3 to 45.2). The odds ratio was in favour of the Atezo+Bev+CP arm (OR =1.94, 95% CI 1.46 to 2.48).

ERG conclusion: A greater proportion of patients obtain an objective response after treatment with Atezo+Bev+CP in comparison to those treated with Bev+CP.

3.3.4 Duration of response

Of the 224 patients in the Atezo+Bev+CP arm with a confirmed objective response 136 (60.7%) had an event (either death or disease progression) with 88 (39.3%) still with an ongoing response at the clinical cut-off date (Table 13). In contrast, in the Bev+CP arm a higher proportion of those with a confirmed objective response experienced an event (88.6%) with just 11.4% of patients with an ongoing response at the clinical cut-off date. The median duration of response in the Atezo+Bev+CP arm was 11.5 months (95% CI 8.9 to 15.7) compared with 6.0 months (95% CI 5.5 to 6.9) in the Bev+CP arm (stratified HR 0.41, 95% CI 0.32 to 0.53; p<0.0001).

Table 13 Duration of confirmed response in the ITT population (Clinical cut-off date 22 January 2018)

	Atezo+Bev+CP n=224	**Bev+CP n=158**
Patients with event, n (%)	136 (60.7)	140 (88.6)
Patients with ongoing response at CCOD, n (%)	88 (39.3)	18 (11.4)
Median DOR, months (95% CI)	11.5 (8.9, 15.7)	6.0 (5.5, 6.9)
Stratified HR (95% CI) p value	0.41 (0.32, 0.53) p<0.0001	

Reproduced from CS Table 12

ERG conclusion: A greater proportion of participants had an ongoing confirmed objective response in the Atezo+Bev+CP arm than in the Bev+CP arm at the 22 January 2018 data cut off.

3.3.5 Summary of health related quality of life

Within the clinical effectiveness section of the CS (Section B.2.6) the only patient reported outcomes reported were those obtained from the EORTC QLQ-C30, which have been presented in a conference abstract.[10] These data are from the September 15th 2017 data

cut (time of final PFS analysis). EQ-5D-3L data, which are used within the economic model (see CS Section B.3.4.1), are not reported in the clinical effectiveness section of the CS. However, the company did supply these on request (clarification question B3).

3.3.5.1 EQ-5D-3L

The company supplied an Excel spreadsheet containing EQ-5D health status data in response to clarification question A5. However, no interpretation of these data was provided by the company. The spreadsheet reports UK index values with numbers of patients, mean, standard error and 95% confidence intervals for each time point. The ERG observes that the number of patients declines over time, but whether this is due to deaths, missing assessments, fewer patients with follow-up to the longer time points, or a combination of these reasons is not explained. At day 1 of the first cycle EQ-5D values in the two treatments groups were almost identical (Table 14).

Table 14 EQ-5D values on day one of the first cycle

Treatment group	Number of patients	Mean EQ-5D value	Standard Error	95% CI
Atezo+Bev+CP	359	0.699	0.014	0.671 to 0.727
Bev+CP	353	0.697	0.014	0.669 to 0.724

Note the ERG have limited the data to three decimal places

3.3.5.2 EORTC QLQ-C30

EORTC QLQ-C30 results were reported as mean change from baseline with a 10-point score change or more being used as the threshold value for clinical meaningful change. The data were interpreted only up to [redacted] Cycle 13 (39 weeks) for the Bev+CP arm because this was the point where approximately 25% or less of the evaluable population remained.

At baseline scores across the different domains of the EORTC QLQ-C30 (global health status, physical functioning and disease burden symptom scores) were comparable between treatment arms. During treatment, average global health status and physical functioning scores numerically worsened but did not cross the threshold for clinically meaningful worsening. Once chemotherapy was completed, scores numerically improved but again did not cross the threshold for clinical meaningful improvement from baseline.

Treatment related symptoms of peripheral neuropathy and alopecia worsened initially in both treatment arms (≥ 30-point mean increase from baseline for peripheral neuropathy; ≥60-point mean increase from baseline for alopecia) but over time this effect was observed to attenuate (data not presented in the CS). No clinically meaningful worsening was observed for a range of other treatment-related symptoms including fatigue, constipation, diarrhea, nausea/vomiting, haemoptysis, dysphagia and sore mouth for the period that data were interpretable (cycle 18 in the Atezo+Bev+CP arm; cycle 13 in the Bev+CP arm).

For lung cancer symptoms both the time taken to deterioration and mean changes from baseline in scores were reported. The time-to-deterioration in each of the individual lung cancer symptoms included (cough, dyspnoea single-item, dyspnoea multi-item, chest pain and pain in arm/shoulder) did not differ between treatment arms. In the ITT population median time-to-deterioration was not reached in any arm for any of the symptom scores. The mean changes from baseline in the patient-reported symptom scores decreased (improved) numerically in all treatment arms to cycle 13 but a clinically meaningful improvement was only observed for coughing scores (i.e. mean scores decreased by 10 points or more from baseline).

> **ERG conclusion**: Treatment with both Atezo+Bev+CP and Bev+CP was reported by patients to lead to worsening peripheral neuropathy and alopecia. 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.

3.3.6 Sub-group analyses results

The decision problem focuses on patients with a low or negative PD-L1 expression (tumour proportion score 0-49%, TC/IC 0,1,2). The ERG notes that a subgroup of participants with low or negative PD-L1 expression can be drawn from both the ITT and ITT-WT populations as shown in Table 15 (i.e. it is possible for patients to have a low or negative PD-L1 expression and be EGFR/ALK+).

Table 15: Patients with low or negative PD-L1 expression in the ITT, ITT-WT and EGFR/ALK+ groups of participants in the IMpower150 RCT

	ITT N=800		ITT-WT n=696		EGFR/ALK+ n=104	
	Atezo+Bev+CP n=400	Bev+CP n=400	Atezo+Bev+CP n=359	Bev+CP n=337	Atezo+Bev+CP n=41	Bev+CP n=63
PD-L1 low or negative sub-population	n=325	n=327	n=288	n=272	n=37	n=55

In this section we focus on

- subgroup results for patients with low or negative PD-L1 expression (tumour proportion score 0-49%, TC/IC 0,1,2) drawn from the ITT population, and
- the EGFR/ALK+ subgroup.

This is because these two patient subgroups are considered in the economic model alongside the ITT population. However, the ERG notes that whereas the hazard ratios for the ITT population reported in the CS are stratified hazard ratios, only unstratified hazard ratios are reported for the subgroups. We also briefly report the company's data for other subgroups based on baseline characteristics.

3.3.6.1 Subgroup of patients with low or negative PD-L1 expression

The subgroup of patients with low or negative PD-L1 expression represented 652/800 (81.5%) of the ITT population and randomisation was stratified by PD-L1 expression status. Investigator assessed PFS in the subgroup of patients with low or negative PD-L1 expression from the ITT population was numerically in favour of the Atezo+Bev+CP group (76.9% PFS events compared to 89.3% PFS events in the Bev+CP group) (Table 16). However, as the unstratified hazard ratio shows, the difference 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).

Overall survival in the subgroup of patients with low or negative PD-L1 expression from the ITT population was also numerically in favour of the Atezo+Bev+CP group (49.2% OS events compared to 58.1% OS events in the Bev+CP group). 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 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).

CS Appendix E Figure 28 (OS) and Figure 29 (PFS) present results for a variety of comparisons between other PD-L1 expression subgroups from the ITT population. Point estimates for PFS and OS hazard ratios were all in favour of Atezo+Bev+CP but for OS in some cases the upper bound of the 95% confidence interval crossed the line of no effect.

Table 16 PFS and OS in the subgroup of patients from the ITT population with low or negative PD-L1 expression

	ITT population			**Low or negative PD-L1 expression[a] (from ITT population)**	
PFS	**Atezo+Bev+CP n=400**	**Bev+CP n=400**		**Atezo+Bev+CP n=325**	**Bev+CP n=327**
Patients with event, n (%)	291 (72.8)	355 (88.8)		250 (76.9)	292 (89.3)
Median PFS, months (95% CI)	8.4 (8.0, 9.9)	6.8 (6.0, 7.0)		8.2 (NR)	6.8 (NR)
Un-stratified HR (95% CI)	0.58 (0.50, 0.68)			0.66 (0.56 to 0.79)	
OS	**Atezo+Bev+CP n=400**	**Bev+CP n=400**		**Atezo+Bev+CP n=325**	**Bev+CP n=327**
Patients with event, n (%)	192 (48.0)	230 (57.5)		160 (49.2)	190 (58.1)
Median OS, months (95% CI)	19.8 (17.4 to 24.2)	14.9 (13.4 to 17.1)		19.1 (NR)	14.9 (NR)
Unstratified HR (95% CI)	0.77 (0.63 to 0.93)			0.80 (0.65 to 0.99)	

[a] tumour proportion score 0-49%, TC/IC 0,1,2

3.3.6.2 Subgroup analysis EGFR/ALK+ patients

The proportion of patients with an EGFR mutation or who were ALK-positive was only 13% of the ITT population (104/800). 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) (Table 17). 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).

Among the EGFR/ALK+ population overall survival was also numerically in favour of the Atezo+Bev+CP group (31.7% OS events compared to 52.4% OS events in the Bev+CP group) but median survival had not been reached the Atezo+Bev+CP group. There is therefore more uncertainty associated with the hazard ratio for overall survival 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 1.03), p=0.0578 compared with ITT unstratified HR 0.77, (95% CI 0.63 to 0.93).

As the numbers of patients in the two arms of the trial that are under consideration (n=41 and n=63) and as the trial was not stratified by EGFR/ALK+ status these subgroup results should be interpreted cautiously.

Table 17 PFS and OS in the subgroup of patients from the ITT population with an EGFR mutation or who were ALK-positive

	ITT population			**EGFR/ALK+ subgroup**	
PFS	**Atezo+Bev+CP n=400**	**Bev+CP n=400**		**Atezo+Bev+CP n=41**	**Bev+CP n=63**
Patients with event, n (%)	291 (72.8)	355 (88.8)		28 (68.3)	57 (90.5)
Median PFS, months (95% CI)	8.4 (8.0, 9.9)	6.8 (6.0, 7.0)		10.0 (7.9 to 15.2)	6.1 (5.6 to 8.4)
Unstratified HR (95% CI)	0.58 (0.50, 0.68)			0.55 (0.34 to 0.90), p=0.0167	
OS	**Atezo+Bev+CP n=400**	**Bev+CP n=400**		**Atezo+Bev+CP n=41**	**Bev+CP n=63**
Patients with event, n (%)	192 (48.0)	230 (57.5)		13 (31.7)	33 (52.4)
Median OS, months (95% CI)	19.8 (17.4 to 24.2)	14.9 (13.4 to 17.1)		NE (17.0 to NE)	17.5 (10.4 to NE)
Unstratified HR (95% CI)	0.77 (0.63 to 0.93)			0.54 (0.29 to 1.03), p=0.0578	

NE= not estimable

3.3.6.3 Other sub-group analyses results

In addition to the subgroup of low or negative PD-L1 expression and the subgroup of EGFR/ALK+ patients reported above there was one further pre-planned subgroup in patients with liver metastases at baseline. Other subgroup analyses by baseline risk factors (sex, TC/IC stratification factor, age group, race, baseline ECOG, tobacco use history, lung metastasis at enrolment, lymph node metastasis at enrolment, adrenal gland metastasis at

enrolment, intended number of induction treatment cycles, EML4-ALK rearrangement status and KRAS mutation status) for overall survival and progression-free survival in the ITT population are presented in CS Appendix E. These were not pre-planned.

The proportion of patients with liver metastases at enrolment was 17%. Liver metastases are known to confer a poor prognosis but in this small subgroup Atezo+Bev+CP treatment still led to a PFS and OS benefit [unstratified HRs: PFS 0.52 (95% CI 0.33 to 0.82); OS 0.41 (95% CI 0.26 to 0.62)].

Across other subgroups analyses by baseline risk factors in the ITT population a PFS benefit was observed in many. However, some subgroups were small and the results uncertain as indicated by wide confidence intervals (e.g. for the subgroup of six participants aged 85 years or over and the 15 participants of Black or African American race). For OS, although a benefit was observed in many subgroups with central OS estimates ranging between 0.47 and 1.06 the upper limit of the 95% confidence interval reaches or crosses 1 for more than half of the subgroups. The results by baseline risk factors should be interpreted cautiously because, other than the PD-L1 expression, EGFR/ALK genetic alteration and liver metastases at baseline subgroups, they were not preplanned, patient numbers are small in some groups and in response to clarification question 11 the company confirmed that no interaction tests or multiplicity adjustment were performed in the subgroup analyses.

> **ERG conclusion**: The PFS and OS benefit for Atezo+Bev+CP versus Bev+CP was maintained across the pre-planned subgroups. The results for the posthoc subgroup analyses are more uncertain due to wide confidence intervals.

3.3.7 Network meta-analysis results

The CS presents forest plots and hazard ratio plots for the fractional polynomial NMA comparing Atezo+Bev+CP with the two comparators included in the decision problem:

A. Pemetrexed in combination with carboplatin or cisplatin, followed by pemetrexed maintenance (PEM+CARB/CIS then PEM maintenance). In the company's economic evaluation this is referred to as 'pemetrexed plus platinum plus pemetrexed maintenance'.
B. Pemetrexed in combination with cisplatin followed by placebo maintenance with best supportive care (PEM+CIS then PLAC main + BSC). In the company's economic evaluation this is referred to as 'pemetrexed plus platinum'.

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).

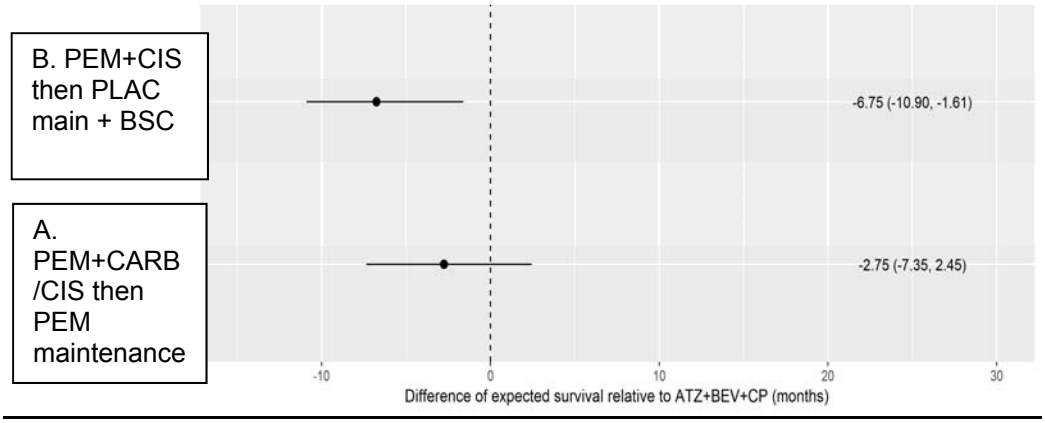
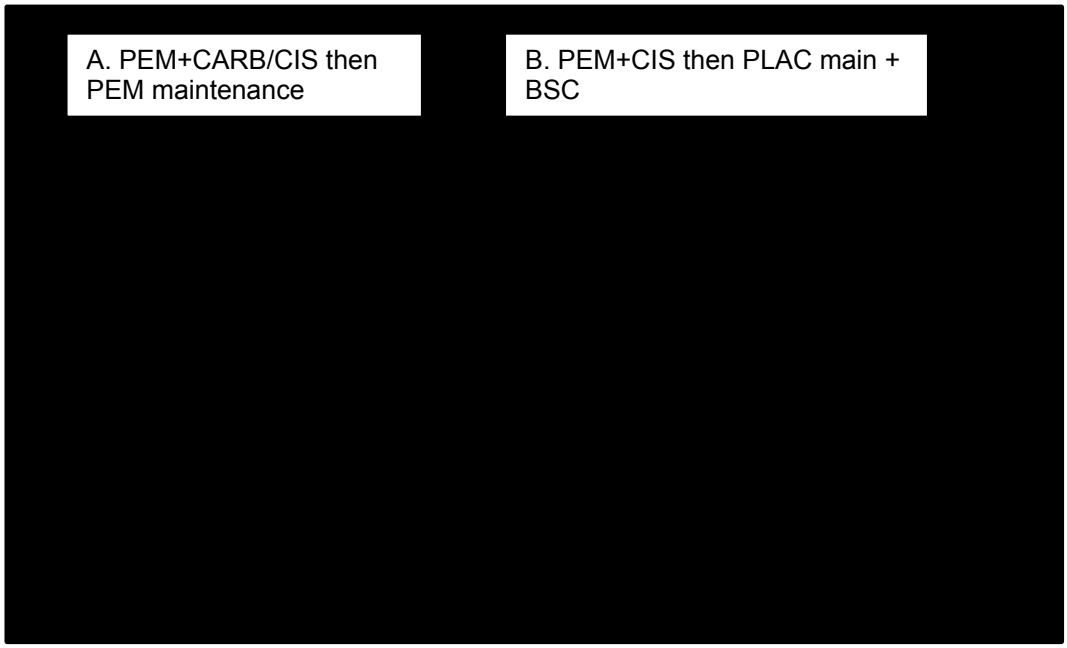


Figure 6 Forest plot of the expected mean OS difference relative to Atezo+Bev+CP (time horizon 60 months)
Reproduced from CS figure 10

- [redacted]7[redacted]

[redacted]7[redacted]

[redacted]

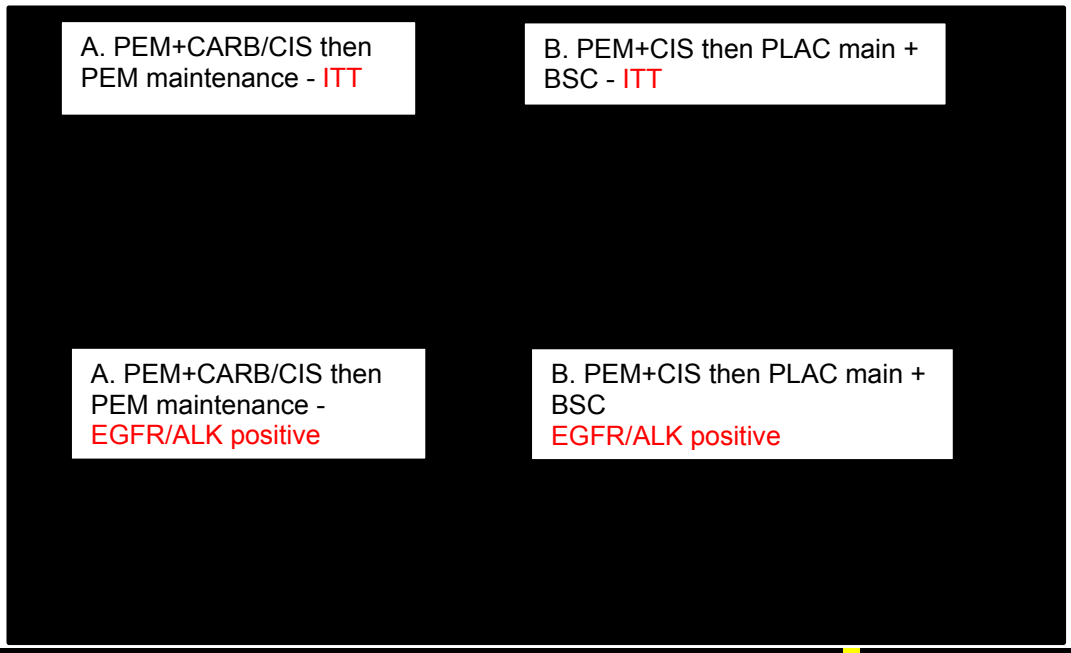


EGFR/ALK positive subgroup

[redacted]8[redacted]

[redacted]

[redacted]



[redacted] 8 [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.

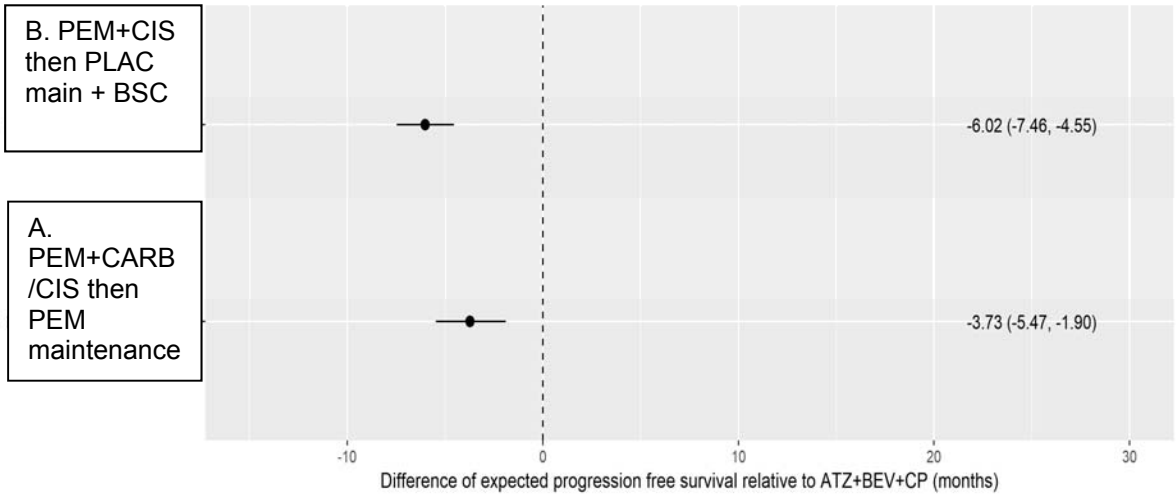
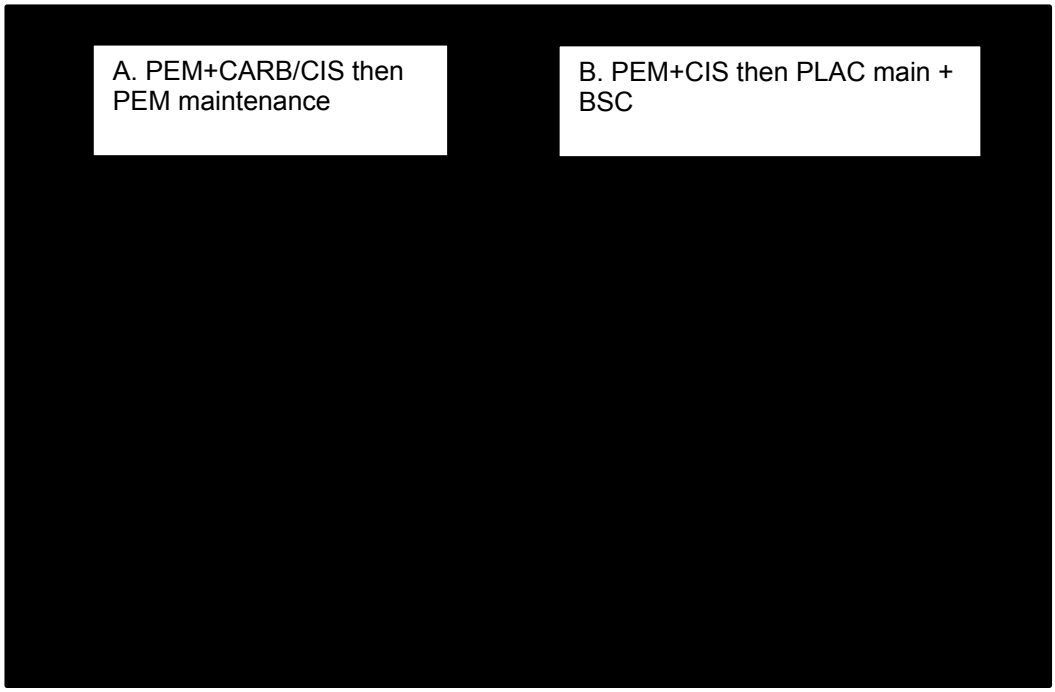


Figure 9 Forest plot of the expected PFS difference relative to Atezo+Bev+CP (time horizon 30 months)
Reproduced from CS Figure 12

The time-varying HR plots (**Error! Reference source not found.**, and CS Figure 13) show similar results to the forest plots:

- [redacted]
- [redacted]

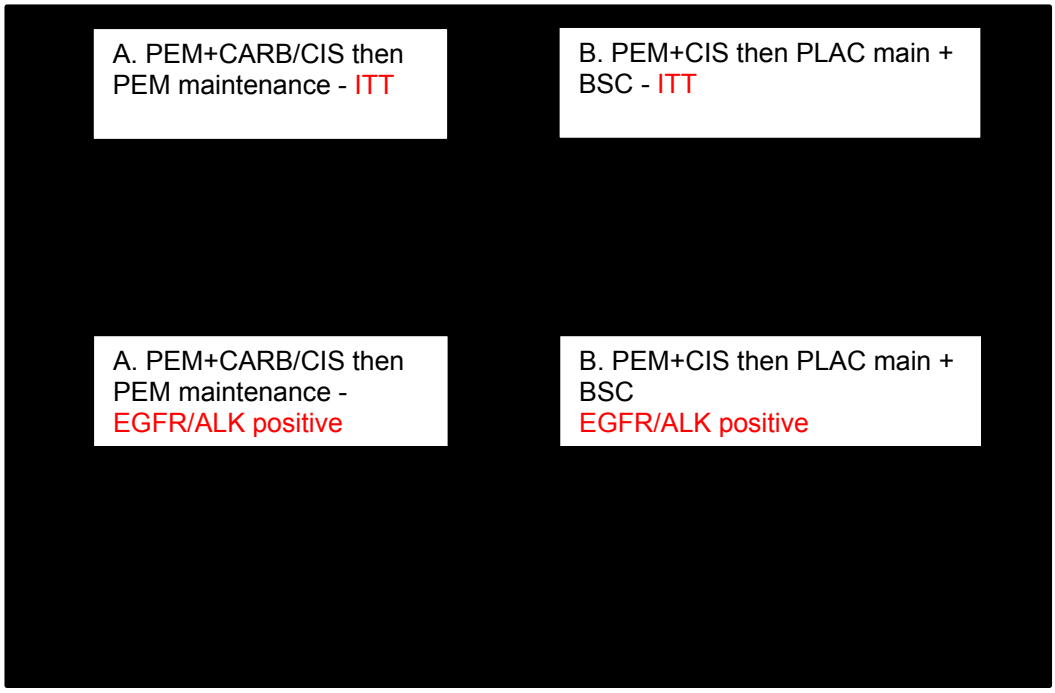


[redacted]

EGFR/ALK positive subgroup:

[redacted]

- [redacted]
- [redacted]



[redacted] **Error! Reference source not found.** [redacted]

PD-L1 low or negative subgroup:

- [redacted]
- [redacted]

[redacted] **Error! Reference source not found.** [redacted]

ERG conclusion: [redacted]

[redacted]

3.3.7.3 NMA s ensitivity 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 and treatment-related serious adverse event were all higher in the Atezo+Bev+CP arm compared with Bev+CP arm.

Additional details regarding the types of adverse event, types of treatment-related grade 3-4 adverse events, grade 5 adverse events and serious adverse events are summarised in the CS with key information provided below.

Table 18 Overview of the safety profile of Atezo+Bev+CP compared with Bev+CP (Clinical cut-off date 22 January 2018)

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
Total number of events	6419	4630
Total number of patients with at least one:		
Adverse event	386 (98.2)	390 (99.0)
Treatment-related AE	370 (94.1)	377 (95.7)
Grade 3–4 AE	250 (63.6)	230 (58.4)
Treatment-related Grade 3–4 AE	223 (56.7)	191 (48.5)
Grade 5 AE	24 (6.1)	21 (5.3)
Treatment-related Grade 5 AE	11 (2.8)	9 (2.3)
Serious AE	174 (44.3)	135 (34.3)
Treatment-related serious AE	103 (26.2)	78 (19.8)
AE leading to withdrawal from any treatment	133 (33.8)	98 (24.9)
AE leading to any dose modification/interruption	246 (62.6)	188 (47.7)

Reproduced from CS Table 17

Among the total number of patients who experienced at least one adverse event there were some events, shown in Table 19, where there was a difference of at least 5% between treatment arms. With the exception of epistaxis (more commonly known as nosebleed) which was experienced by a greater proportion of patients in the Bev+CP arm, the remaining types of adverse event in Table 19 were experienced by a greater proportion of patients who received Atezo+Bev+CP. However, the CS states that the majority of the common adverse events were of Grade 1 or 2 and were generalised symptoms and events that are consistent with events known to be associated with the Bev+CP chemotherapy backbone.

Table 19 Common adverse events with a difference of at least 5% between treatment arms (Clinical cut-off date 22 January 2018)

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
Total number of patients with at least one AE	386 (98.2)	390 (99.0)
Gastrointestinal disorders		

Nausea	154 (39.2)	125 (31.7)
Constipation	117 (29.8)	92 (23.4)
Diarrhoea	126 (32.1)	97 (24.6)
Stomatitis	51 (13.0)	25 (6.3)
General disorders and administration site conditions		
Fatigue	130 (33.1)	107 (27.2)
Pyrexia	73 (18.6)	34 (8.6)
Nervous system disorders		
Peripheral neuropathy	93 (23.7)	68 (17.3)
Skin and subcutaneous tissue disorders		
Rash	65 (16.5)	26 (6.6)
Pruritus	50 (12.7)	24 (6.1)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	66 (16.8)	87 (22.1)
Metabolism and nutrition disorders		
Decreased appetite	113 (28.8)	83 (21.1)
Hypomagnesaemia	51 (13.0)	23 (5.8)
Hypokalaemia	37 (9.4)	16 (4.1)
Endocrine disorders		
Hypothyroidism	45 (11.5)	11 (2.8)

Reproduced from CS Table 19

Treatment-related adverse events were also comparable between treatment arms (Atezo+Bev+CP 94.1%; Bev+CP 95.7%). The CS provides a summary of the treatment-related Grade 3-4 adverse events that occurred with an incidence of at least 2% (CS Table 20). The most commonly experienced grade 3-4 treatment-related adverse event in both groups was neutropenia (Atezo+Bev+CP 14%; Bev+CP 11.2%). Grade ≥ 3 adverse events with an incidence of ≥2% are included in the economic model (see sections 4.2.4.5 and 4.2.6.6 of this report).

A higher proportion of people in the Atezo+Bev+CP group experienced a serious adverse event than in the Bev+CP group (44.3% versus 34.3% respectively) with the most common serious adverse event being febrile neutropenia (Atezo+Bev+CP 6.4%; Bev+CP 3.8%).

At the 22nd January 2018 clinical cut-off date there had been 189 deaths in the Atezo+Bev+CP arm and 226 in the Bev+CP arm (Table 20). Of these, 81% (153/189) in the Atezo+Bev+CP arm and 87% (197/226) in the Bev+CP arm were due to progressive disease. Approximately 10.8% of deaths were due to adverse events [Atezo+Bev+CP 12.7% (24/189); Bev+CP 9.3% (21/226)] and 4.8 % due to other reasons.

Table 20 Fatal adverse events and causes (Clinical cut-off date 22 January 2018)

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
All deaths	189 (48.1)	226 (57.4)
Adverse event	24 (6.1)	21 (5.3)
Progressive disease	153 (38.9)	197 (50.0)
Other[a]	12 (3.1)	8 (2.0)

Reproduced from CS Table 21

[a] Includes fatal events that are unrelated to study treatment and occur outside the reporting period

Of the grade 5 adverse events (i.e. deaths due to adverse events) fewer than half were judged to be related to any study treatment (Table 21). Among all the grade 5 adverse events the most commonly reported (at least 3 patients) were haemoptysis, pneumonia and febrile neutropenia.

Table 21 Grade 5 AEs [most commonly reported (at least 3 patients), clinical cut-off date 22 January 2018]

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
Any adverse event, grade 5	24 (6.1)	21 (5.3)
Haemoptysis	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Grade 5 events related to any study treatment	11 (2.8)	9 (2.3)

Some of the numbers in this table were sourced from the clinical study report (CIC marked)

Adverse events of special interest were pre-defined in the protocol. They were based on the mechanism of action of atezolizumab and known adverse events associated with other immune-modulating treatments. As Table 22 shows, the majority of adverse events of special interest were of grade 1 or 2 in severity, in the Atezo+Bev+CP arm 12.5% were grade 3-4 in comparison to 3.3% in the Bev+CP arm, and there were no grade 5 events in either arm. Adverse events reported with at least a 2% difference between study arm are summarised in Table 22.

Table 22 Summary of selected adverse events of special interest to atezolizumab (Clinical cut-off date 22 January 2018)

n, (%)	Atezo+Bev+CP n=393	Bev+CP n=394
Total number of patients with at least one AESI	206 (52.4)	112 (28.4)
Total number of patients with at least one:		
Treatment-related AESI	182 (46.3)	70 (17.8)
Grade 3–4 AESI	49 (12.5)	13 (3.3)
Treatment-related Grade 3–4 AESI	42 (10.7)	8 (2.0)
Grade 5 AESI	0	0
Treatment-related Grade 5 AESI	0	0
Serious AESI	25 (6.4)	4 (1.0)
Treatment-related AESI	22 (5.6)	2 (0.5)
AESI leading to withdrawal from any treatment	26 (6.6)	3 (0.8)
AESI leading to any dose modification/interruption	51 (13.0)	16 (4.1)
Patients with at least one (incidence ≥2%)		
Immune-related rash	117 (29.8)	53 (13.5)
Immune-related hepatitis (diagnosis)	54 (13.7)	29 (7.4)
Immune-related hepatitis (laboratory abnormality)	48 (12.2)	29 (7.4)
Immune-related hypothyroidism	56 (14.2)	18 (4.6)
Infusion-related reactions	14 (3.6)	12 (3.0)
Immune-related pneumonitis	13 (3.3)	5 (1.3)
Immune-related hyperthyroidism	16 (4.1)	5 (1.3)
Immune-related colitis	11 (2.8)	2 (0.5)

Reproduced from CS Table 22
AESI, adverse event of special interest;

4 COST EFFECTIVENESS

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

The company presents summary results from a systematic search for economic evaluations of first-line treatments for non-squamous NSCLC (CS section B.3.1 and Appendix G). As stated earlier in this report (section 3.1.1) we regard their search strategy to be comprehensive.

The review identified 66 economic evaluations with full publications in English (CS Appendix G Table 37). Out of these studies, ten used UK data, of which seven were NICE technology appraisals. None of the 66 studies included atezolizumab. Three studies related to NICE appraisals of comparators specified in the scope: TA181 for pemetrexed with cisplatin,[2] TA190 for pemetrexed maintenance after platinum-based chemotherapy[11] and TA447 for pembrolizumab (updated in TA531[12]). We note that NICE has also published guidance on pemetrexed maintenance after pemetrexed and platinum induction in this population (TA402).[13]

Methods and results of the previous NICE appraisals for comparators in the NICE scope for atezolizumab are briefly summarised in Table 23 below. These are a potential source for cross-validation of results from the submitted model (see validation section 4.3.3 below), although none of the results are directly comparable:

- **TA181** had a shorter time horizon, a different source of effectiveness evidence (the JMDB trial) and different model structure.
- **TA402** outcomes relate to a selected population without disease progression after four cycles of PEM+CIS induction therapy and exclude costs and QALYs accrued during the induction period. The evidence base for pemetrexed maintenance in the current submission is also broader; including data from the KEYNOTE, ERACLE and PRONOUNCE trials as well as PARAMOUNT.
- **TA531** used similar methods to the current submission but results relate to a blended Standard of Care (SOC) comparator and a subgroup with high PD-L1.

Table 23 NICE technology appraisals for comparators

Study	Model	Intervention/ comparator	Population	Submitted base case for companies in TA [a]		
				Cost	QALYs	ICERs (£ / QALY)
NICE 2009 **TA181**	Markov (response; stable; PD; death) 6 years	**PEM + CIS** / • GEM+CIS (JMDB) • GEM+CARBO & DOC+CIS (ITC)	Untreated advanced NSCLC	GEM+CIS £10,310 PEM+CIS £11,674 Incr. £1,364	GEM+CIS 0.57 PEM+CIS 0.61 Incr. 0.04	Company: £33,065 **'Most plausible': £17,000 to £25,000** (for adenocarcinoma or LCC subgroup)
NICE 2010 **TA190**	Trial-based analysis (not progressed, progressed, terminal): 6 years	**PEM maintenance** / BSC (placebo) (JMEN trial)	Advanced NS NSCLC **after platinum-based chemotherapy**	BSC £8,318 PEM £17,455 Incr. £9,137	BSC 0.70 PEM 0.97 Incr. 0.27	Company: £33,732 **'Most plausible': £47,000 to £51,000**
NICE 2016 **TA402** (CDF review of TA309)	Markov (PF, PD, death) 16 years	**PEM maintenance** / BSC (placebo) (PARAMOUNT trial)	Advanced NS NSCLC **after PEM+CIS**	At CDF review**:** BSC £9,344 PEM £24,272 *Incr. £14,927*	At CDF review**:** BSC 0.91 PEM 1.12 *Incr. 0.21*	Company: £70,538 (list price) **'Most plausible':** Confidential with CAA
NICE 2018 **TA531** (update of TA447)	Partitioned survival (PF, PD, death) 20 years	**PEMB** / SOC (platinum-based chemo regimen with or without PEM maintenance) (KEYNOTE-024)	Untreated metastatic NSCLC with high PD-L1 (and not EGFR/ALK+)	PEMB £72,353 SOC £43,364 *Incr. £28,989*	PEMB 2.31 SOC 1.35 *Incr. 0.96*	Company: £30,244 **'Most plausible': £30,000 to £50,000**

[a] Results reported in company base case and 'most plausible' ICER from committee conclusions

BSC best supportive care; CAA Commercial Access Agreement; CDF Cancer Drugs Fund; CIS cisplatin; Incr. incremental; PD progressed disease; PF progression free; PEM pemetrexed; SOC standard of care;

4.2 Summary and critique of the company's submitted economic evaluation

Sections B.3.2 to B.3.11 of the CS report on the methods and results of a new economic model developed by the company for this appraisal.

4.2.1 NICE reference case checklist

The ERG assessment of whether the submitted economic evaluation complies with NICE reference case requirements is shown in Table 24. We consider that the company's analysis broadly conforms to the reference case, except that the modelled decision problem differs from the NICE scope. We discuss these differences in the following section.

Table 24 NICE reference case requirements

NICE reference case	Included in submission	ERG comment
Decision problem: The scope developed by NICE	No	The company's economic evaluation does not address the full population and comparators stipulated by NICE. In particular, people with high PD-L1 expression who would be eligible for pembrolizumab are excluded. See CS B.3.2.1 and section 4.2.2.1 below.
Comparator(s): As listed in the scope developed by NICE	No	The company economic analysis omits comparators in the scope, CS B.3.2.3. In particular, we note that none of the comparators specified for EGFR/ALK positive patients are modelled, see 4.2.2.2 below.
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Perspective on costs: NHS and PSS	Yes	CS Table 24
Type of economic evaluation: Cost utility analysis with fully incremental analysis	Yes	The CS does not include a full incremental analysis, but this was provided in response to clarification question B4 (Clarification Response Appendix D)
Time horizon: Long enough to reflect all important differences in costs or outcomes the between technologies being compared	Yes	CS Table 24
Synthesis of evidence on health effects: Based on systematic review	Yes	CS Section 2.9
Measuring and valuing health effects: Health effect should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes	CS Table 24, CS Table 30

Source of data for measurement of health-related quality of life: Reported directly by patients and/or carers	Yes	
Source of preference data for valuation of changes in health-related quality of life: Representative sample of the UK population	Yes	
Equity considerations: An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Evidence on resource use and costs: Costs should relate to NHS and PSS resources and be valued using prices relevant to the NHS and PSS	Yes	CS Table 24
Discounting: The same annual rate for costs and health effects (currently 3.5%)	Yes	CS Table 24

4.2.2 Modelled decision problem

See section 2.2 above for the ERG summary and critique of the company's decision problem. We summarise key differences between the scope and the modelled population and comparators below.

4.2.2.1 Population and subgroups

Two populations are included in the model (CS section B.3.2.1):

- Adults with untreated metastatic non-squamous NSCLC with low or negative PD-L1 (tumour proportion score 0-49%, TC/IC 0, 1 or 2); and
- Adults with metastatic non-squamous NSCLC who are EGFR or ALK positive after targeted therapy (or who cannot have targeted therapy).

This deviates from the NICE scope in two respects. Firstly, although the scope relates to advanced NSCLC, the model is restricted to metastatic disease only. This restriction is appropriate because it follows the anticipated marketing authorisation for Atezo+Bev+CP and is consistent with clinical evidence from the IMpower150 study.

Secondly, the company excludes the subgroup with high PD-L1 expression from the untreated population. This subgroup is included in the anticipated marketing authorisation and the IMpower150 trial population, but the company states that it is not seeking

reimbursement for the high PD-L1 subgroup based on the comparison with pembrolizumab. [redacted]. Expert clinical advice to the ERG concurs with this view (see section 2.2 of this report).

Patient characteristics in the model are based on means across the Atezo+Bev+CP and Bev+CP arms of the IMpower150 trial (Table 25). The same values are used for the EGFR/ALK positive and PD-L1 low/negative populations. We understand that these characteristics are realistic for patients in clinical practice, although EGFR and ALK positive patients are more often younger and female.

Table 25 Patient characteristics used in model

Baseline characteristic	Value (ITT and subgroups)
Age (years)	63
Body weight (kg)	72
Glomerular filtration rate (GFR)	90.4
BSA (m^2)	1.81

4.2.2.2 Intervention and comparators

The model includes three combination therapies for both modelled populations (CS B.3.2.3):

- Atezolizumab with bevacizumab, carboplatin and paclitaxel
- Pemetrexed in combination with a platinum drug (cisplatin or carboplatin)
- Pemetrexed in combination with a platinum drug and pemetrexed maintenance

Intervention

The scope also includes atezolizumab with carboplatin and paclitaxel (without bevacizumab) as an intervention, but this is not covered in the anticipated marketing authorisation. On this basis, it is appropriate to omit it from the economic analysis.

Comparators for the untreated population

The model omits two scoped comparators for the untreated population: pembrolizumab and chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin). We consider it reasonable for the company to have omitted pembrolizumab as a comparator, as they are not seeking NHS reimbursement for the high PD-L1 subgroup for whom pembrolizumab is recommended at first line (TA531).

The company argue that it is reasonable to omit chemotherapy regimens as pemetrexed in combination with a platinum drug is the standard of care, with 83% of the market share for this indication (clarification response B1). The scope specifies that the pemetrexed should be used in combination with cisplatin specifically, in line with NICE guidance (TA181).[2] However, a proportion of patients cannot tolerate cisplatin, due to its side effects. Clinical advice to the ERG is that these patients would have either pemetrexed with carboplatin, or a carboplatin chemotherapy doublet followed by pemetrexed maintenance. As noted in section 2.1 above, UK audit data does suggest that pemetrexed is sometimes given in combination with carboplatin.[3] The company also argue that data on pemetrexed with both platinum drugs were pooled in the NMA for the pembrolizumab appraisal TA531[12], as well as in the NMA for this current appraisal.

Comparators for EGFR or ALK positive people after targeted therapy

The company does not model either of the comparators specified in the scope for the EGFR/ALK positive population: the scope cited NICE TA520, which included docetaxel alone for PD-L1 negative disease and pembrolizumab for PD-L1 positive disease as comparators.[6] In their response to clarification question B1, the company stated that docetaxel and pembrolizumab are not appropriate comparators as they are only licensed and reimbursed for EGFR/ALK positive patients after targeted therapy and after treatment with chemotherapy: "effectively second-line after targeted therapy". We understand that this interpretation is correct and that docetaxel and pembrolizumab should not be considered as comparators for people with EGFR or ALK mutations.

Conversely, the company include pemetrexed-based comparators for EGFR/ALK positive patients after targeted treatment, even though this is not specified in the scope. We understand that in practice, pemetrexed combinations would be used in this population.

> **ERG conclusions**: The decision problem addressed in the company's economic evaluation differs from that specified in the NICE scope. The restrictions to metastatic disease and to the atezolizumab combination with bevacizumab are appropriate, as they are consistent with the proposed marketing authorisation. We also consider the exclusion of the subgroup with untreated disease and high PD-L1 expression to be acceptable, as the company is not seeking NHS reimbursement for this subgroup.
>
> The company restricts the modelled comparators to pemetrexed with platinum, with or without pemetrexed maintenance. Although this is not fully consistent with the scope, we understand that it is a reasonable representation of current practice for

most patients. We note, however, that the model does not compare against carboplatin-based chemotherapy followed by pemetrexed maintenance, 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.

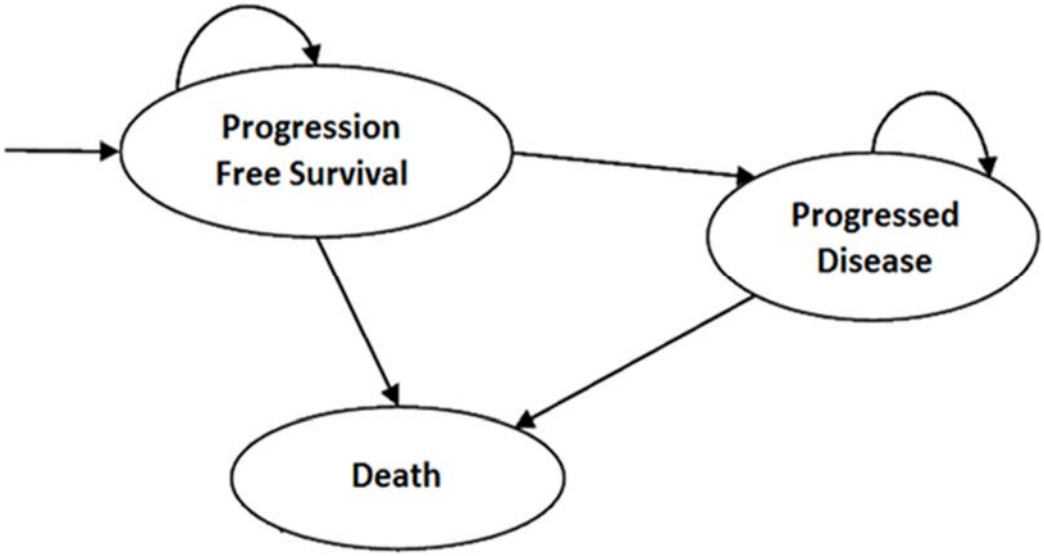


Figure 10 Economic model (reproduced from CS Figure 31)

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.

The company compare key features of their model with those in other related NICE appraisals in CS Table 24. We summarise the ERG view on these and other key assumptions in Table 26 below. The model has a cycle length of one week with a half-cycle correction applied to all relevant outcomes. The time horizon is 20 years. This is sufficient to reflect important cost and outcome differences between the comparators because only a small proportion of the modelled cohort are alive after 20 years. Costs and health outcomes are appropriately discounted at 3.5%.

4.2.3.1 Treatment stopping rule and duration of effect

The model also includes assumptions about the maximum duration of treatment and persistence of survival benefits for Atez+Bev+CP (section B.3.2.2 of the CS). In the base case, treatment with atezolizumab and bevacizumab stops after a maximum of two years and the effect on survival lasts for a further three years (five years from treatment initiation). The company state that these assumptions are conservative, adopted for consistency with other NICE appraisals of atezolizumab (TA520[6] and TA525[7]). They report scenarios with no stopping rule and with longer effects on survival, from 105 to 240 months (CS section B.3.8.3). It is stated in the CS that the effect cap for Atez+Bev+CP is also applied to PFS (section B.3.3.3). However, we note that although the model includes this as an option, the cap on PFS effects is not applied in the company's base case or scenario analyses.

We consider that it is appropriate to limit treatment duration as in previous atezolizumab appraisals, as this was based on clinical concerns over possible consequences of longer-term treatment (paragraph 3.13 TA520[6] and 3.11 in TA525[7]). Similar stopping rules have been applied for other immunotherapies, including pembrolizumab for untreated PD-L1 positive metastatic NSCLC (TA531).[12] In TA520, the committee assumed that the effects of second-line atezolizumab monotherapy would last for up to three years after stopping treatment but noted that the length of any continued effect was uncertain. Based on this, we agree with the company's base case cap on survival effect, but we conduct additional scenario analysis to explore decreases as well as increases in the duration of effects (see section 4.4 below).

The original submitted model only allowed pairwise comparisons of Atez+Bev+CP with the two pemetrexed-based comparators (with and without pemetrexed maintenance). In each comparison, the treatment effect cap was implemented by setting the mortality rate for the atezolizumab combination equal to the pemetrexed comparator. This led to different survival predictions for the intervention depending on the comparator (e.g. see CS Tables 46 and 47). This is counter-intuitive and prevents full incremental analysis.

Table 26 Key assumptions in company's base case (adapted from CS Table 45)

Area	Company base case assumption	ERG comment
Time horizon	20 years (from age 63 to 82 years). Sufficient to reflect differences in costs and effects between treatments. The model predicts less than 1% of patients alive at 20 years for intervention and comparators for ITT population.	We agree that the time horizon is reasonable, as the company's base case and most scenarios predict that few patients would survive to 20 years (except for log-normal and log-logistic extrapolations for Atez+Bev+CP without an effect cap).
Cycle length	One week with half-cycle correction	The cycle length is appropriate, and the half-cycle correction is correctly applied
Treatment stopping rule	Maximum of 2 years treatment with Atezo+Bev+CP. Lack of evidence for a stopping rule, but it is applied for consistency with NICE guidance for atezolizumab (TA520 and TA525). Scenario with no stopping rule.	We agree. Stopping rules for atezolizumab and other immunotherapies in NICE TAs were based on clinical concerns about possible consequences of longer-term treatment. Effect in model is to reduce costs for the intervention and hence ICERs
Duration of treatment effect	Effect of Atezo+Bev+CP on OS lasts for 5 years (3 years after maximum treatment). Lack of evidence but conservative approach following assumption in TA520. Scenarios for increased cap on OS effect, up to 20 years. In the revised model, OS effect cap for Atez+Bev+CP applied relative to pemetrexed maintenance comparator (clarification response B4). No cap on duration of survival effect for pemetrexed maintenance.	We agree with the 5-year cap on survival effect given precedent in related appraisals. We test a scenario with reduced duration of effect as well as increase. Implementation of the OS effect cap relative to the with-maintenance pemetrexed comparator is reasonable but is likely to overestimate survival for both Atez+Bev+CP and PEM+CIS with maintenance.

In response to a clarification question (B4), the company submitted a revised economic model in which the mortality rate for the atezolizumab combination was set equal to that of the with-maintenance pemetrexed comparator after five years, while maintaining the extrapolated survival advantage for pemetrexed with maintenance relative to pemetrexed without maintenance. This is not consistent with committee conclusions in TA402[13]: that patients would receive pemetrexed maintenance until progression but that there was not any

evidence for a post-progression survival benefit for pemetrexed maintenance over placebo (paragraph 4.15). The company's revised base case is therefore likely to overestimate long-term survival for both Atez+Bev+CP and the pemetrexed maintenance comparator, and hence to underestimate the ICER for Atez+Bev+CP compared with PEM+CIS without maintenance.

ERG conclusion: The three-state partitioned survival structure of the company's model is appropriate and correctly implemented. The 20-year time horizon is reasonable given model projections of survival.

We agree with company's base case assumption of a two-year maximum treatment duration for atezolizumab and bevacizumab as part of the Atez+Bev+CP intervention. This is consistent with existing guidance for atezolizumab (TA520 and TA525) and for other immunotherapies (e.g. TA531). The assumption that pemetrexed maintenance therapy continues until progression is also appropriate, given committee conclusions in TA402.

The company assumption of a three-year cap on survival effects (after the maximum 2-year treatment) for Atez+Bev+CP is reasonable. This is consistent with committee assumptions for atezolizumab at second line in TA520, although we note the high uncertainty over the persistence of survival effects after treatment is stopped. The company test scenarios with a longer duration of treatment effect (up to 20 years). We also test a scenario with a shorter duration of effect.

However, we do not consider the company's assumption of a persistent survival advantage for pemetrexed maintenance throughout the time horizon to be realistic. This is not consistent with committee conclusions in TA402 and is likely to have overestimated the long-term survival gain for Atez+Bev+CP and for the pemetrexed maintenance comparator. This implies that the ICER for Atez+Bev+CP relative to PEM+CIS without maintenance is likely to be underestimated.

We comment on the sources and assumptions for model input parameters on clinical effectiveness, utilities and resource use and costs in the following sections.

4.2.4 Clinical effectiveness

The model requires four sets of input parameters for clinical effectiveness:

- OS extrapolations for each comparator (CS section B.3.3.2)
- PFS extrapolations for each comparator (CS section B.3.3.3)
- TTD for atezolizumab and for bevacizumab as part of the Atezo+Bev+CP intervention and for pemetrexed maintenance (B.3.3.4)
- AE incidence for each comparator (CS B.3.5.3)

4.2.4.1 Overview of methods for estimating OS and PFS

The company outline their approach to estimating OS and PFS in section B.3.3.1 of the CS. This was a two-step process.

> **Step 1: Extrapolation of PFS and OS curves for Atez+Bev+CP**
> Parametric survival models were fitted to data from the Atezo+Bev+CP arm of the IMpower150 trial (January 2018 data cut, with investigator-assessed progression).
>
> **Step 2: Estimation of PFS and OS curves for comparators**
> PFS and OS curves for the pemetrexed-based comparators were obtained by applying hazard ratios from the NMA to the fitted Atezo+Bev+CP curves.

We discuss general issues related to the methods of extrapolation in this section and give a more detailed description and critique of the company's selection of OS and PFS curves in the following sections, 4.2.4.2 and 4.2.4.3 respectively.

4.2.4.1.1 Methods used to fit baseline curves for atezolizumab

- *Relevance of IMpower150 to UK population* (section 3.1.3 of this report): We consider this a suitable source of data, as the trial population is broadly reflective of patients with metastatic non-squamous NSCLC in routine practice in the UK NHS.
- *ITT versus subgroup analyses* (section 3.1.6.5): The CS reports results with baseline curves fitted to data for the ITT population and the low/negative PD-L1 and positive EGFR/ALK positive subgroups. On balance, we think that the subgroup analyses are a better source for baseline survival estimates than the ITT analysis - as they are specific to the populations of interest and exclude patients with high PD-L1 expssion for whom pembrolizumab would be a more appropriate treatment. However, the ITT analysis should be more robust as the sample is larger: 400 patients randomised to Atez+Bev+CP, of whom 325 had low or negative PD-L1 and 41 were positive for

EGFR or ALK. The EGFR/ALK subgroup in particular is very small and subject to high uncertainty. We also note that although both subgroups were pre-specified, randomisation was only stratified by PD-L1 high/low status. In ERG analysis, we therefore follow the same approach as the company and report results using baseline curves for the ITT population as well as for the separate subgroups (see section 4.4 below).

- *Separate fitting of parametric curves to one trial arm.* The company argues that this is justified because of different mechanisms of action for immunotherapies and chemotherapies and evidence from log-cumulative hazards plots that proportional hazards do not hold in IMpower150 (see section 3.1.7 above). We agree and note that the other arms in the IMpower150 are not comparators in the economic analysis.
- *Choice of parametric function*. The company selects parametric curves for OS and PFS by considering how well they fit the trial data and the plausibility of the projections; see sections 4.2.4.2 and 4.2.4.3 below.

4.2.4.1.2 Methods used to estimate relative treatment effects

See section 3.1.7.4 above for our explanation and critique of the company's NMA analyses. Key issues arising for the economic analysis are:

- *ITT versus subgroup NMA* (section 3.3.6 above). As with the baseline curves, a decision has to be made whether to use the ITT or subgroup versions of the NMA. The cost-effectiveness results for ITT, EGFR/ALK positive and PD-L1 low/negative populations reported in the CS (B.3.7) each use the corresponding subgroup for the NMA as well as for the fitted baseline curves. Expert clinical advice to the ERG suggests that people with EGFR/ALK mutations and those with high PD-L1 expression are more likely to respond to pemetrexed chemotherapy than other patients. However, analysis of the IMpower150 trial did not show any evidence of effect modification for the EGFR/ALK or PD-L1 subgroups. We consider that the ITT NMA is a more robust source for relative treatment effects than the subgroup NMAs, and so we use the ITT NMA in the ERG base case for both subgroups.
- *Inclusion of PARAMOUNT in the network* (see section 3.1.7.2 above). There is heterogeneity in the NMA, primarily associated with the patients in the PARAMOUNT trial, who were more likely to respond to pemetrexed maintenance. This is not surprising due to the different trial design: in PARAMOUNT, only patients who responded to induction treatment (539 out of 900 patients) were randomised. The company make this point, but include PARAMOUNT in their base case, as this was

the only source of evidence for the pemetrexed comparators without maintenance. However, we consider that the difference in study design is too serious as a likely source of bias for the indirect comparison. We therefore use the NMA excluding PARAMOUNT for ERG base case analyses (section 4.4). We report a scenario including PARAMOUNT to enable comparison against pemetrexed and cisplatin without maintenance (this is the only trial to include this comparison). Expert clinical advice to the ERG is that most patients would receive pemetrexed maintenance therapy.

- *Fixed or random effects NMA* (3.1.7.4.3 above). The company use a fixed effect fractional polynomial NMA model in their base case. In principle, a random effects model is preferable in the presence of heterogeneity. We use the fixed effects model in the ERG base case analysis, as this omits PARAMOUNT, which is the main source of heterogeneity, but we use random effects in the scenario analysis that includes PARAMOUNT.
- *Constant or time-varying hazard ratios* (3.1.7.4 above). The company used a time-varying fractional polynomial model in their base case, based on arguments about the different mechanisms (and hence speeds) of action for immunotherapies and chemotherapies, precedent in previous appraisals and evidence from the IMpower150 trial. We agree with these arguments but note that the comparators in IMpower150 are out of scope and that the company has not presented evidence on proportional hazards for other trials in the network. Nevertheless, we agree with the use of an fractional polynomial to allow for change in relative treatment effects over time.
- *Fractional polynomial model selection* (section 3.1.7.4.1). The ERG also agrees with the company's choice of the first order P1=0 (Weibull) model for their base case, with an alternative, exponential (i.e. proportional hazards) model in scenario analysis.

ERG conclusions: The methods used to extrapolate OS and PFS for the economic model are reasonable. This involved fitting baseline parametric survival curves for the Atez+Bev+CP arm to IMpower150 trial data and then applying time-varying hazard ratios from the NMA to estimate survival curves for the comparators.

- We consider that the baseline curves fitted to data for the PD-L1 low/negative and EGFR/ALK positive subgroups are most relevant to the decision problem: the ITT curves are subject to bias due to inclusion of patients with high PD-L1

expression. However, we also consider results with ITT baseline curves, as these are likely to be more robust.

- There is a lack of evidence of effect modification for the subgroups, so we prefer the ITT version of the NMA. We agree with the company's choice of NMA model (first order FP with P1=0), but consider that the analysis including PARAMOUNT is likely to be biased due to the exclusion of patients who did not respond to pemetrexed with platinum induction. For ERG analysis, we prefer the NMA without PARAMOUNT (fixed effects). This restricts results to the comparison including pemetrexed maintenance, but we understand that this is the most common current practice. To enable comparison against with pemetrexed without maintenance we also run a scenario including PARAMOUNT but with random effects.

4.2.4.2 Overall survival extrapolations

We show KM plots and fitted parametric curves for overall survival in the IMpower150 Atezo+Bev+CP arm ITT (n=400), PD-L1 low/negative (n=325) and EGFR positive (n=41) datasets in Figure 11, Figure 12 and Figure 13 below. The predictions for the PD-L1 low/negative subgroup are similar but slightly less favourable than for the ITT population. The prognosis is better for the EGFR positive subgroup, although these predictions are very uncertain due to the small sample size (n=41).

Goodness-of-fit to trial data

Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics for the Atez+Bev+CP parametric curves are reproduced in Table 27, Table 28 and Table 29 for the ITT population, PD-L1 low/negative and EGFR positive subgroups respectively. The company state that the best-fitting function for OS is the Weibull, although all models apart from log-normal have similar AIC and BIC values (CS B.3.3.2). We consider that the Gompertz, exponential and Weibull have the best AIC/BIC statistics and a good visual fit to the KM plots for the ITT population and PD-L1 low/negative subgroup. It is difficult to differentiate the EGFR/ALK positive subgroup curves on the basis visual fit, but the exponential has the best AIC and BIC statistics.

Plausibility of survival projections

Five and ten-year survival estimates from the parametric extrapolations for Atezo+Bev+CP and modelled OS curves for the pemetrexed with platinum comparators (with and without pemetrexed maintenance) are reproduced in Table 27, Table 28 and Table 29 for the ITT, PD-L1 low/negative and EGFR positive groups.

Since immunotherapy has only been available for the last two to three years, there is uncertainty over survival expectations for the intervention arm, although there is a clinical expectation that there may be a small proportion of long-term survivors. The company report estimates of five-year survival with Atez+Bev+CP from 10 UK clinicians of between 12% and 27%, with an average of 17%. If correct, this would imply that the exponential, log-normal or log-logistic OS extrapolations are realistic for the ITT and PD-L1 low/negative subgroup. Modelled five-year survival is much higher for the EGFR/ALK positive subgroup.

With regard to the comparator arms, the company compares the model predictions against five-year survival estimates from the NICE appraisal of pembrolizumab for untreated PD-L1 positive metastatic NSCLC (TA531).[12] The TA531 committee concluded that predictions derived from the control arm of the KEYNOTE-024 rial of 8 to 11% survival at five years were plausible for standard care (chemotherapy or pemetrexed with platinum, with or without pemetrexed maintenance). The company also compare against survival estimates from a cohort of newly diagnosed patients with NSCLC from a large US database (the Flatiron database[14]): reported in CS Appendix M pages 376 to 381. This gave five-year survival estimates of 8.3% for pemetrexed with platinum and 12.3% for pemetrexed with platinum and pemetrexed maintenance, similar to the range cited in TA531.[12] Neither source is directly comparable to the IMpower150 population; KEYNOTE-024 was restricted to patients with high PD-L1 high expression and no sensitizing EGFR mutations or ALK translocations; and the Flatiron cohort included patients with stage IIIb disease as well as stage IV. Nevertheless, the target range of 8-11% with comparator treatments appears reasonable.

None of the modelled estimates for the comparator without maintenance fall within the 8-11% range for the ITT or PD-L1 low/negative subgroup. However, for the comparator with maintenance, the exponential and Weibull baseline extrapolations do. We note that with pemetrexed maintenance, the log-logistic and log-normal extrapolations appear unrealistically optimistic, particularly the 10-year extrapolations. The Gompertz and generalised gamma extrapolations for the comparators appear too pessimistic.

Company choice of OS curves

The company present scenario analysis using all six parametric baseline OS functions in Tables 62-66 of the CS (B.3.8.3). These show that expected life years, and hence QALYs and ICERs, are sensitive to the choice of baseline OS curve. The company concludes that the exponential extrapolation provides “appropriate but still conservative” survival estimates.

They use this in their base case analysis, with the log-logistic as an alternative scenario that they consider plausible.

We consider that the Weibull extrapolation also has a good fit to the trial data and produces five-year survival predictions within the plausible range for the pemetrexed combination with maintenance. We also note that a Weibull or exponential extrapolation for Atez+Bev+CP is consistent with the P1=0 FP (Weibull) estimates of relative effects, producing Weibull curves for the comparator arms.

Impact of five-year cap on treatment effect for Atez+Bev+CP

As discussed in section 4.2.3 above, the company base case includes an assumption that the survival advantage for Atez+Bev+CP over the pemetrexed comparators lasts for a maximum of five years (three years beyond the maximum duration of atezolizumab and bevacizumab treatment). The company illustrates the impact of setting the mortality rate for Atez+Bev+CP equal to that for the pemetrexed comparators without maintenance after five years in CS Figures 34 and 35. They argue that the projections for Atezo+Bev+CP without a cap on survival effect is more in line with long-term expectations for immunotherapies, with a small proportion of patients (about 2%) surviving to 10 years.

The impact of applying the five-year cap on survival effect compared with the pemetrexed combination with maintenance is illustrated in CS Figures 36 and 37. This shows a counter-intuitive reduction in survival for the Atezo+Bev+CP when the effect cap is removed. This results from a declining hazard ratio for Atez+Bev+CP compared with the pemetrexed comparator with maintenance over time in the company's preferred FP NMA model (P1=0) when the PARAMOUNT trial is included (clarification response A18 Figure 1). The company argues that this is likely to be a consequence of bias in the PARAMOUNT trial, which only included patients who responded to pemetrexed with cisplatin induction. We agree, and consider the comparison between Atez+Bev+CP and the pemetrexed with maintenance comparator to be more reliable without PARAMOUNT data.

We show the modelled survival curves under the company's base case analysis for the ITT population over a 10-year period in Figure 14. The effect of excluding the PARAMOUNT trial from the NMA is shown in Figure 15 and scenarios with Weibull and log-logistic parametric survival functions for Atez+Bev+CP in Figure 16 and Figure 17 respectively.

ERG conclusion: The company uses an exponential baseline OS curve for the atezolizumab combination in their base case. This has a good fit to the IMPower150

data and clinically plausible extrapolations of survival at five and ten years. We also consider that the Weibull distribution is plausible, with more conservative survival predictions. The log-logistic gives over optimistic long-term predictions (around 10% survival at 10 years).

Table 27 OS Atezo+Bev+CP: ITT population (five-year effect cap)

Baseline distribution	Goodness-of-fit		Atezo+Bev+CP		Pem+plat		Pem+plat with maintenance	
	AIC (rank)	BIC (rank)	5 year	10 year	5 year	10 year	5 year	10 year
Exponential	942.3(3)	946.3(1)	13%	3%	2%	0%	12%	3%
Weibull	941.7(2)	949.7(3)	10%	1%	1%	0%	9%	1%
Log-logistic	947.2(5)	955.2(5)	20%	12%	5%	1%	18%	10%
Log-normal	958.1(6)	966.0(6)	24%	15%	7%	1%	21%	13%
Gamma	942.8(4)	954.7(4)	4%	0%	0%	0%	5%	0%
Gompertz	940.7(1)	948.7(2)	3%	0%	0%	0%	4%	0%

Reproduced from CS Tables 26 and 27, and model

Table 28 OS Atezo+Bev+CP: PD-L1 low/negative (five-year effect cap)

Baseline Distribution	Goodness-of-fit		Atezo+Bev+CP		Pem+plat		Pem+plat with maintenance	
	AIC (rank)	BIC (rank)	5 year	10 year	5 year	10 year	5 year	10 year
Exponential	763.0(4)	766.8(1)	12%	4%	3%	0%	13%	4%
Weibull	760.8(2)	768.4(3)	7%	1%	1%	0%	10%	2%
Log-logistic	765.5(5)	773.1(4)	18%	11%	6%	1%	19%	12%
Log-normal	776.8(6)	784.3(6)	22%	14%	9%	2%	21%	14%
Gamma	762.1(3)	773.4(5)	3%	0%	0%	0%	6%	0%
Gompertz	760.3(1)	767.8(2)	1%	0%	0%	0%	3%	0%

Reproduced from CS Appendix N Tables 62 and 63, and model

Table 29 OS Atezo+Bev+CP: EGFR/ALK positive (five-year effect cap)

Baseline distribution	Goodness-of-fit		Atezo+Bev+CP		Pem+plat		Pem+plat with maintenance	
	AIC (rank)	BIC (rank)	5 year	10 year	5 year	10 year	5 year	10 year
Exponential	80.3(1)	82.0(1)	27%	17%	11%	3%	18%	12%
Weibull	82.3(4)	85.7(4)	26%	16%	11%	3%	18%	11%
Log-logistic	82.1(3)	85.5(3)	35%	28%	15%	9%	22%	18%
Log-normal	81.8(2)	85.2(2)	39%	33%	18%	11%	25%	21%
Gamma	83.8(6)	88.9(6)	42%	36%	20%	13%	26%	23%
Gompertz	82.3(5)	85.7(5)	27%	17%	11%	3%	18%	12%

Reproduced from CS Appendix N Tables 64 and 65, and model

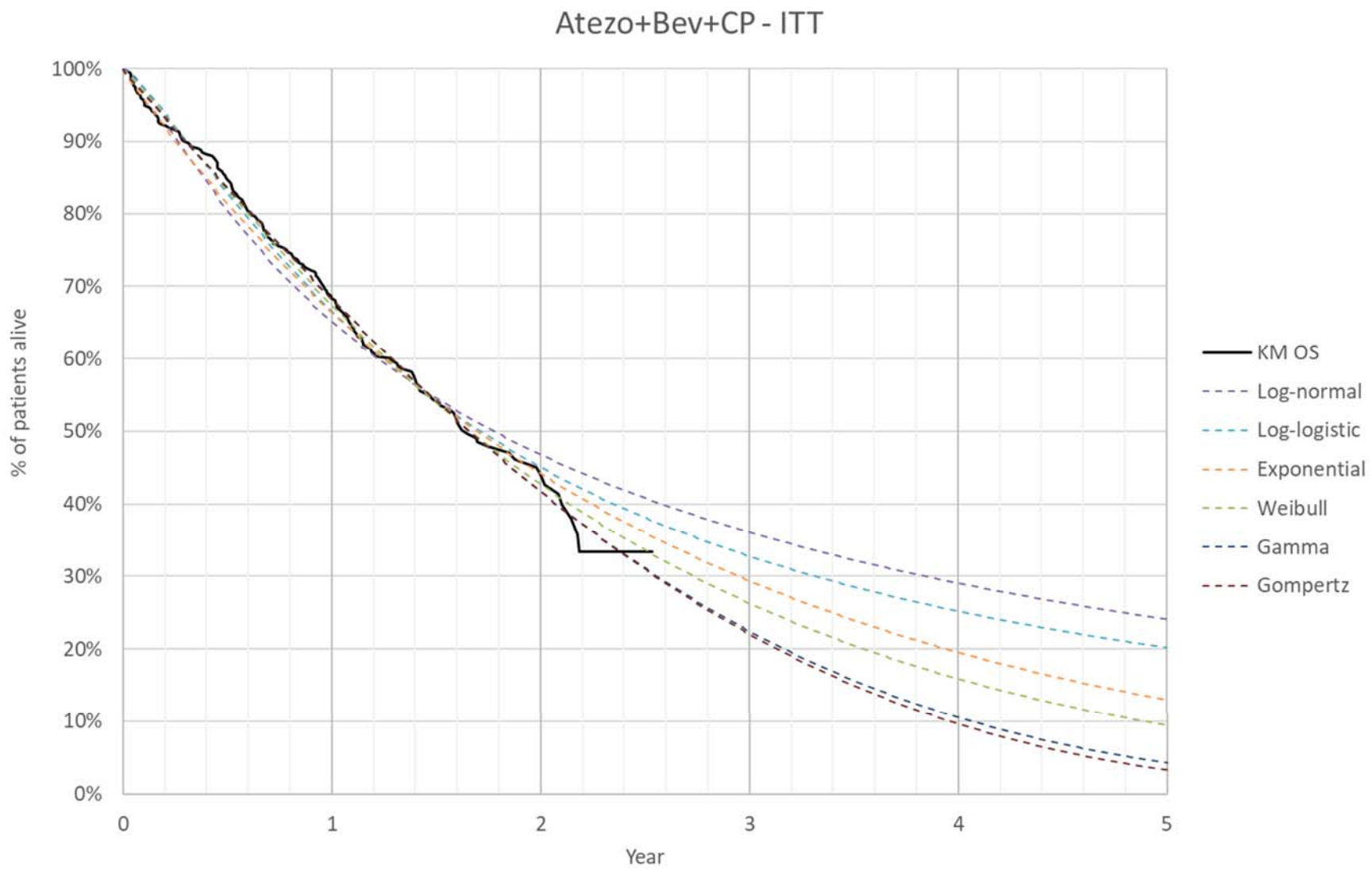


Figure 11 Overall survival curves fitted to IMpower150 Atezo+Bev+CP arm: ITT population

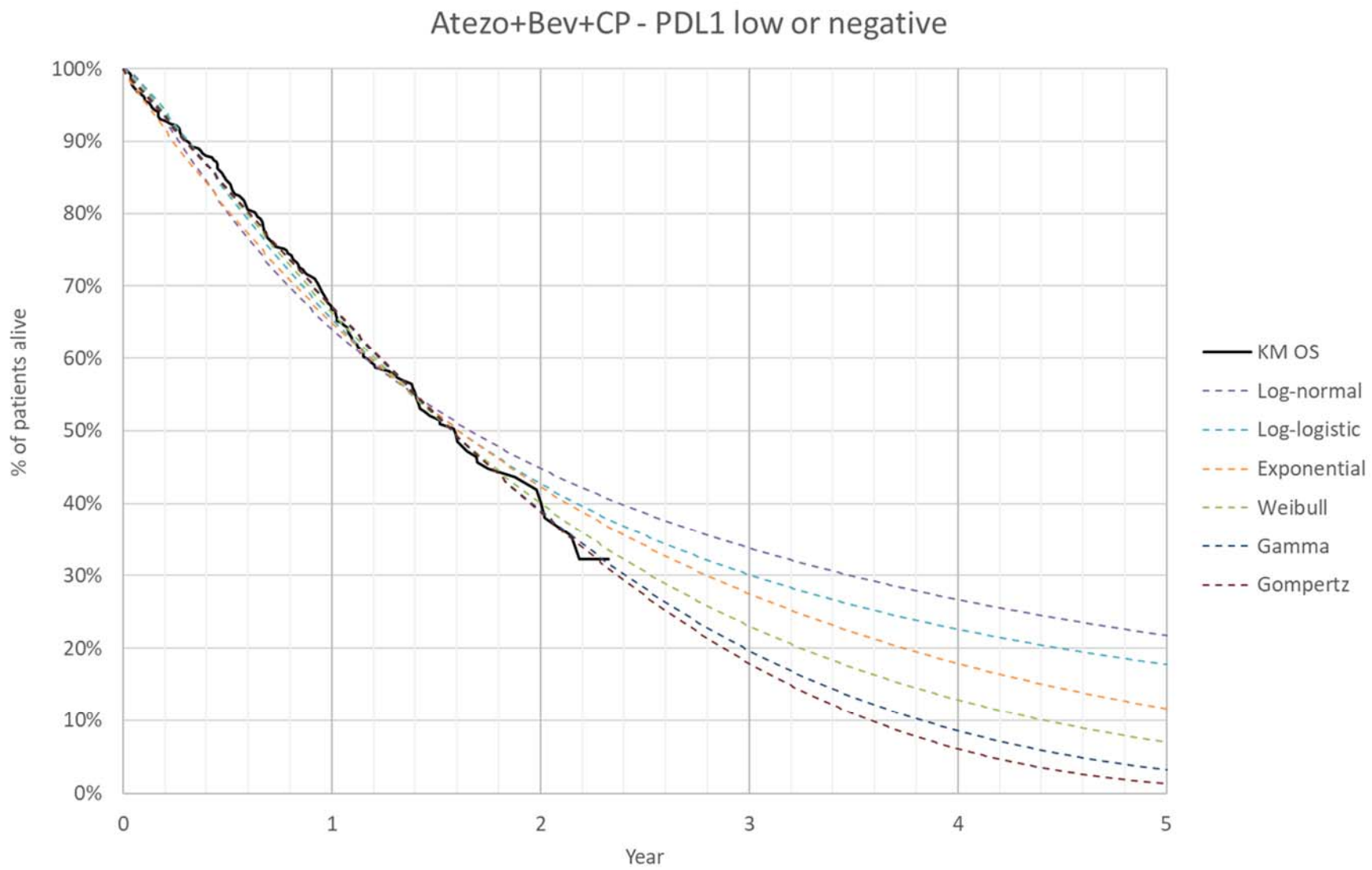


Figure 12 Overall survival curves fitted to IMpower150 Atezo+Bev+CP arm: PD-L1 low or negative subgroup

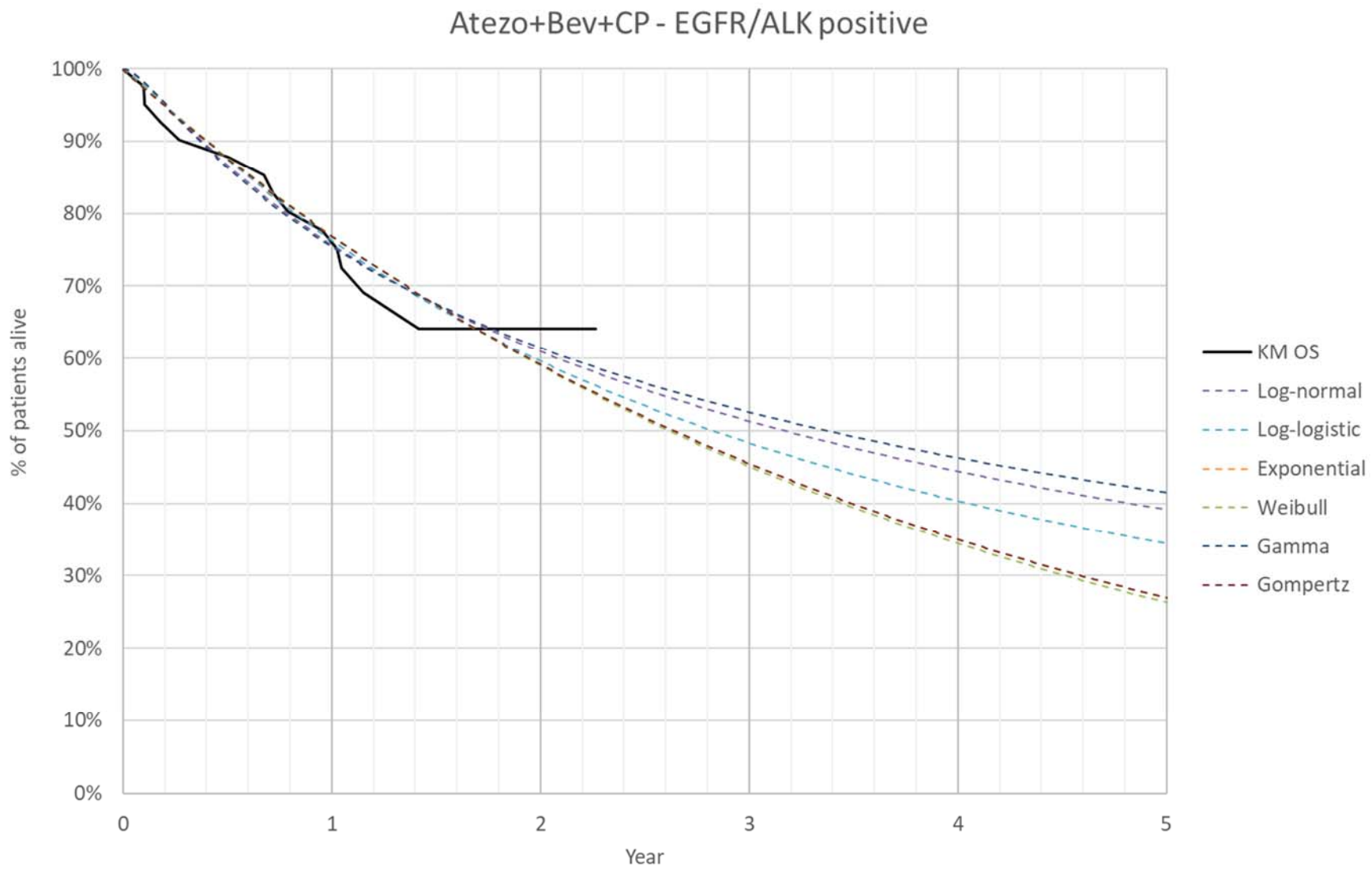


Figure 13 Overall survival curves fitted to IMpower150 Atezo+Bev+CP arm: PD-L1 low or negative subgroup

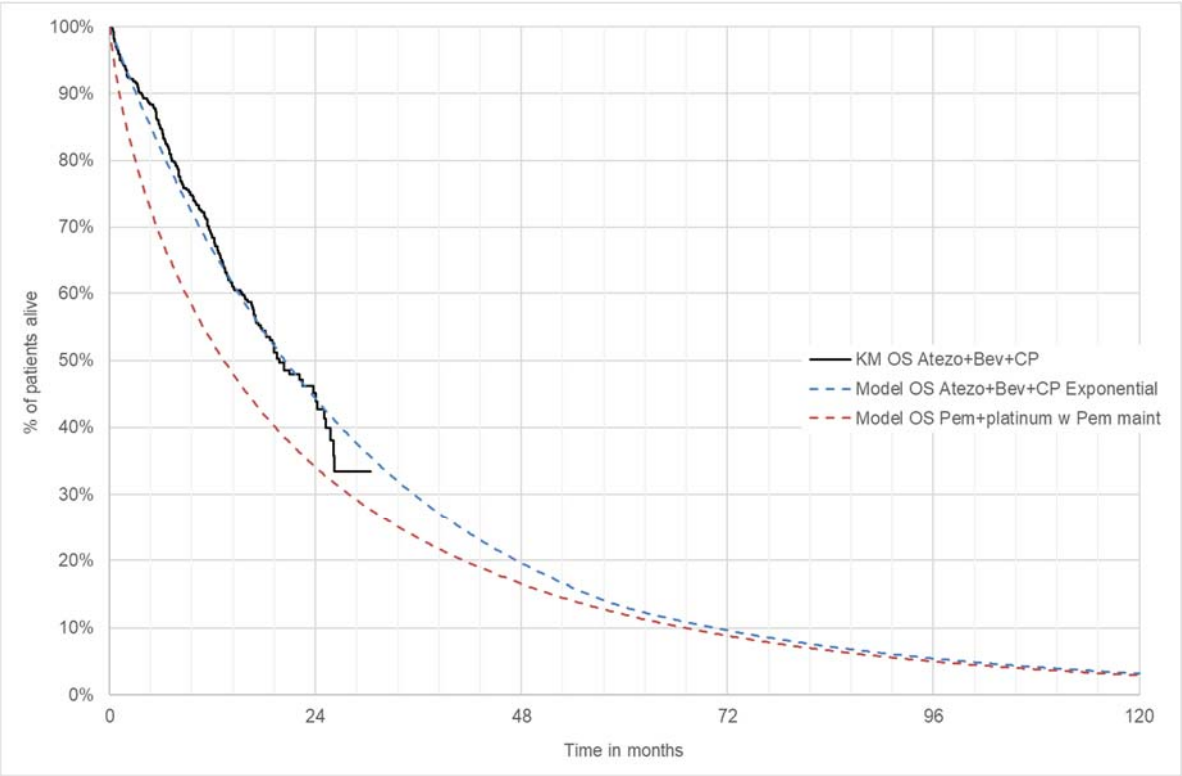


Figure 14 OS company base case ITT (exponential, five-year effect cap)

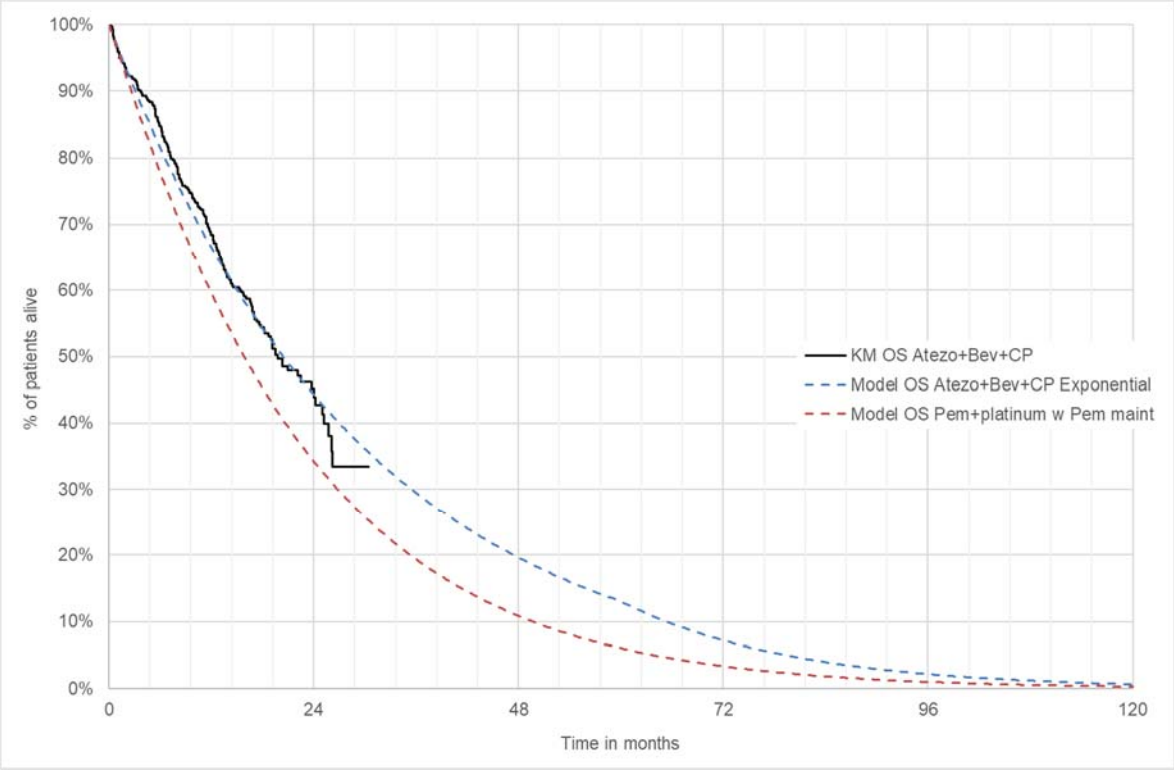


Figure 15 OS company base case ITT, NMA without PARAMOUNT trial

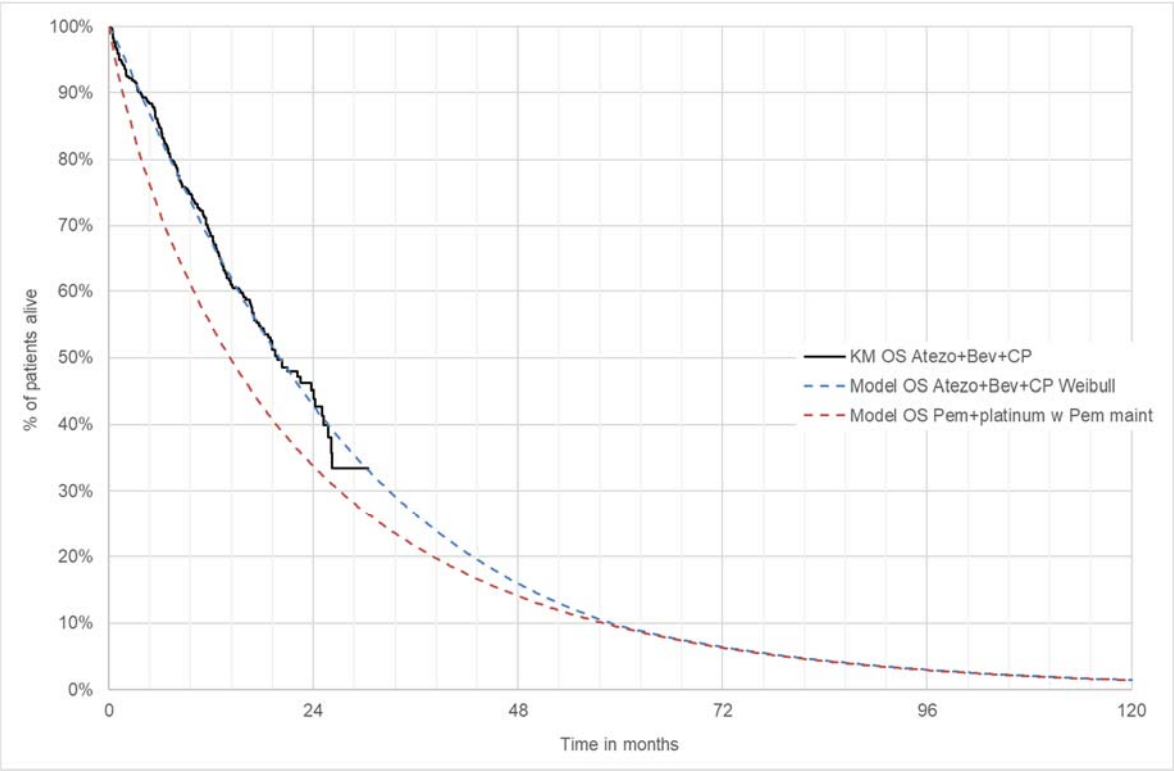


Figure 16 OS company base case ITT, with Weibull survival function

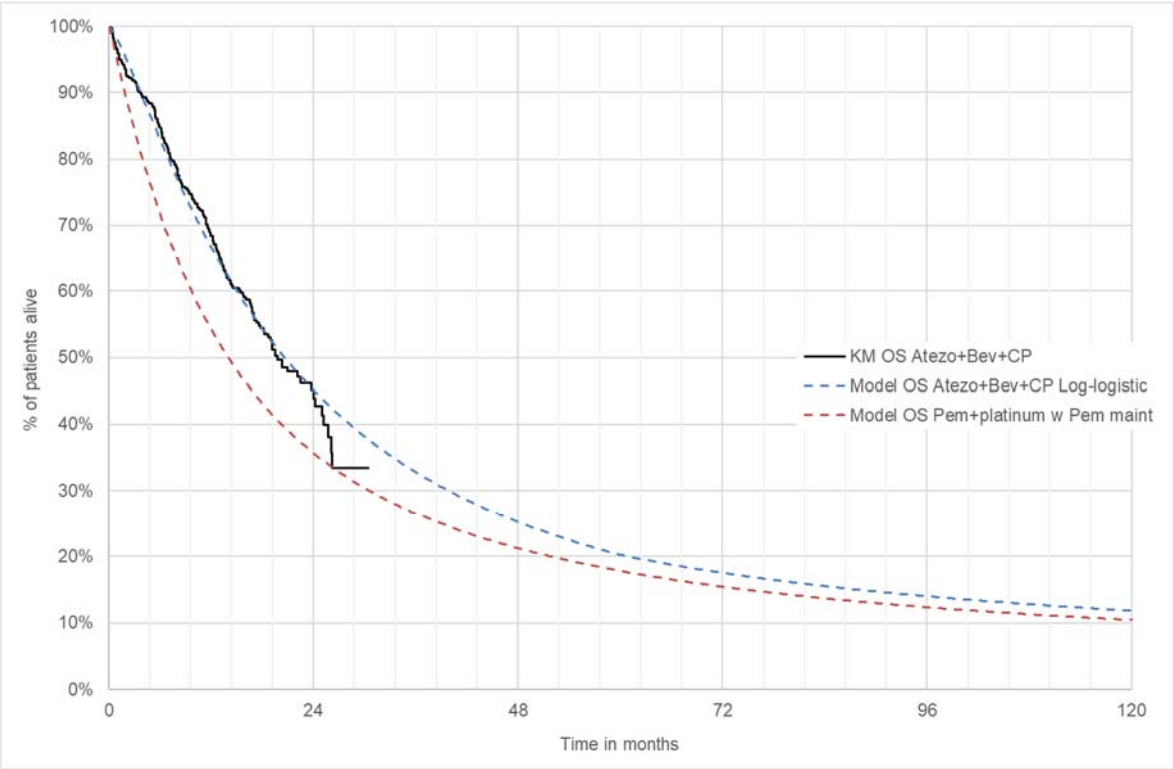


Figure 17 OS company base case ITT, with log-logistic survival function

4.2.4.3 Progression free survival extrapolations

The same approach as for OS was used to fit PFS curves for Atez+Bev+CP and to estimate comparator curves based on time-varying relative effects. PFS data for the IMpower150 trial are relatively complete and cost-effectiveness results are less sensitive to different methods of extrapolating PFS (CS Tables 62 to 65 B.3.8.3).

The company report goodness-of-fit statistics for parametric Atez+Bev+CP PFS distributions in CS Table 28 for the ITT population and Tables 66 and 67 in Appendix O for the PD-L1 and EGFR/ALK subgroups. For the ITT and PD-L1 populations AIC and BIC statistics and visual fit are best for the log-logistic distribution, followed by the Weibull and generalised gamma. These three distributions provide a spread of projections, from about 2% to 5% of patients still alive and free of progression after five years.

For their ITT base case, the company use the KM curve with a log-logistic extrapolation from the point where 20% of patients remain at risk (n=81 at about 15 months). This is reasonable as the KM data are mature with a sufficient sample size, and the extrapolation from the KM is very similar to the fully parametric extrapolation (see Figure 18 below). The curves for the PD-L1 low/negative subgroup are similar but slightly less favourable. For the EGFR/ALK positive subgroup, the log-normal, exponential or log-logistic curves have the best statistical and visual fit to the KM data (see Figure 19). The company chooses a fully parametric log-normal distribution for PFS in the EGFR/ALK positive subgroup, and we consider log-normal, exponential and Weibull distributions to show a range of uncertainty around the extrapolation.

> **ERG conclusion**: The company's approach to extrapolating PFS is reasonable. A similar method was used as for OS, but the model results are much less sensitive to PFS than OS. For the atezolizumab arm, the company use the KM curve with a log-logistic extrapolation for the ITT population and PD-L1 low/negative subgroup. In the EGFR/ALK positive subgroup they used a fully-parametric log-normal distribution. We consider scenarios with exponential and Weibull extrapolations in ERG analysis.

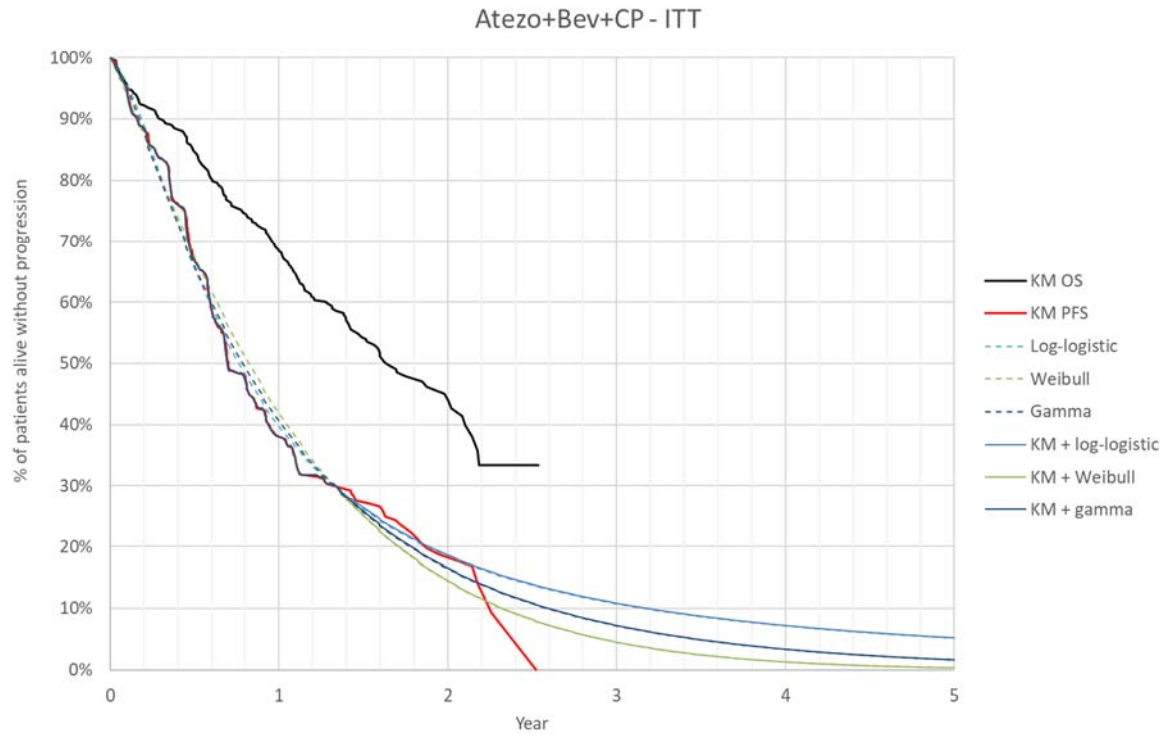


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Figure 18 PFS curves fitted to IMpower150 Atez+Bev+CP data: ITT

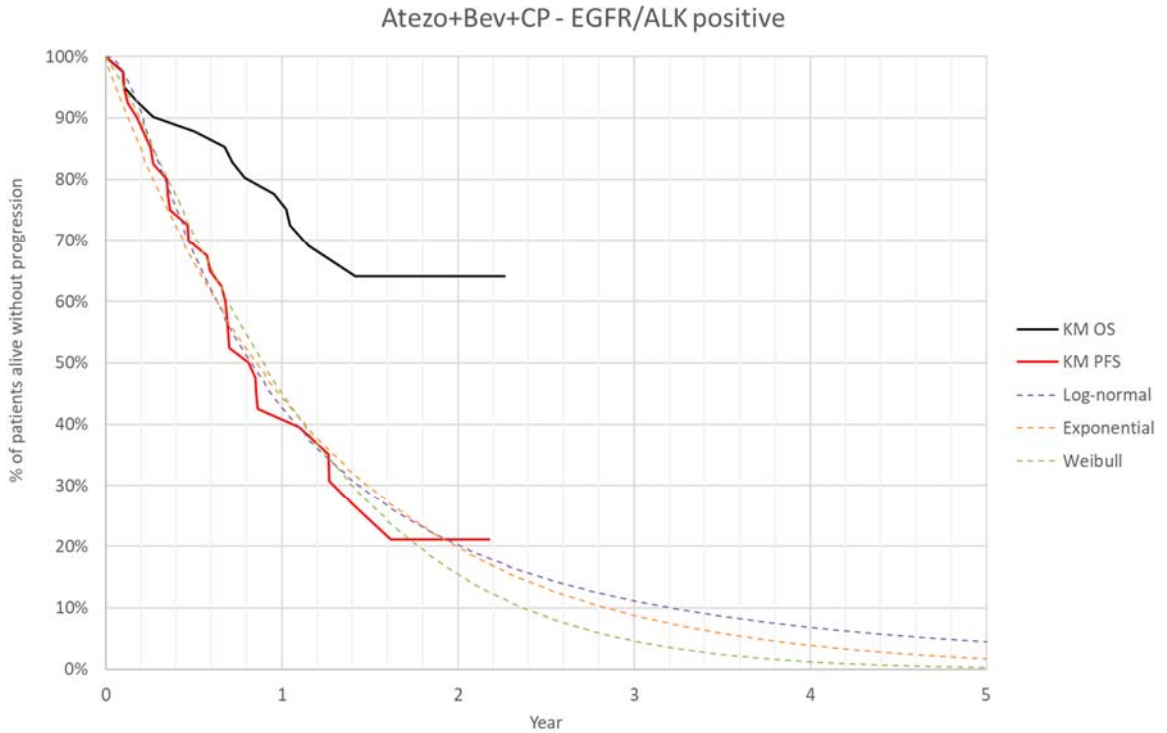


Figure 19 PFS curves fitted to IMpower150 Atez+Bev+CP data: EGFR/ALK positive

4.2.4.4 Treatment duration

TTD curves for atezolizumab and for bevacizumab (separately) were estimated by fitting parametric curves to data from the Atezo+Bev+CP arm of the IMpower150 trial. In the trial, approximately 20% of patients were still being treated with atezolizumab and 10% with bevacizumab after two years. Although the company extrapolates the TTD curves, this has little impact in the base case model due to the use of a two-year stopping rule: see section 4.2.3 above for discussion of the stopping rule and associated assumption about the duration of treatment effects.

Atezolizumab was used until loss of clinical benefit, or unmanageable toxicity. The company states that PFS is not a good surrogate for the duration of treatment with atezolizumab. However, comparison of the KM plots shows that patients tended to stop treatment before progression in the early part of the trial, with similar rates of treatment and progression free survival after about 9 months – see Figure 20. We agree with the company that the exponential curve provides the best visual fit to the KM plot for atezolizumab treatment duration. The company use a KM curve, extrapolated with an exponential curve from the point where 20% of patients remain at risk. This reasonable based on a good visual fit to the trial data.

For bevacizumab, the company notes that although the trial protocol specified that it should be administered in the Atezo+Bev+CP arm until disease progression or unacceptable toxicity, the PFS curve was not a good surrogate for bevacizumab treatment duration. This is supported Figure 21, which shows that progression free survival exceeded bevacizumab treatment duration throughout the trial.

For pemetrexed maintenance, TTD was assumed equal to PFS. This is consistent with committee conclusions in TA181.[13]

> **ERG conclusion**: The ERG agrees with the company's approach to modelling the duration of treatments with atezolizumab and bevacizumab in the Atezo+Bev+CP intervention and of pemetrexed maintenance.

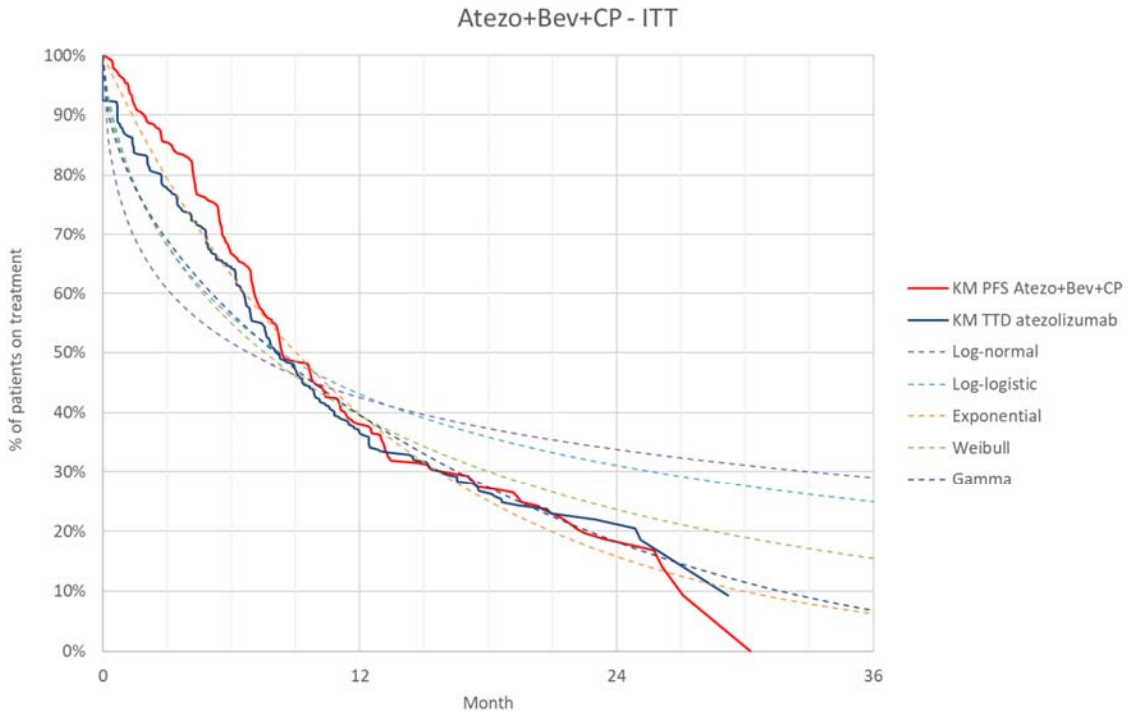


Figure 20 Duration of atezolizumab in Atez+Bev+CP arm of IMpower150: ITT

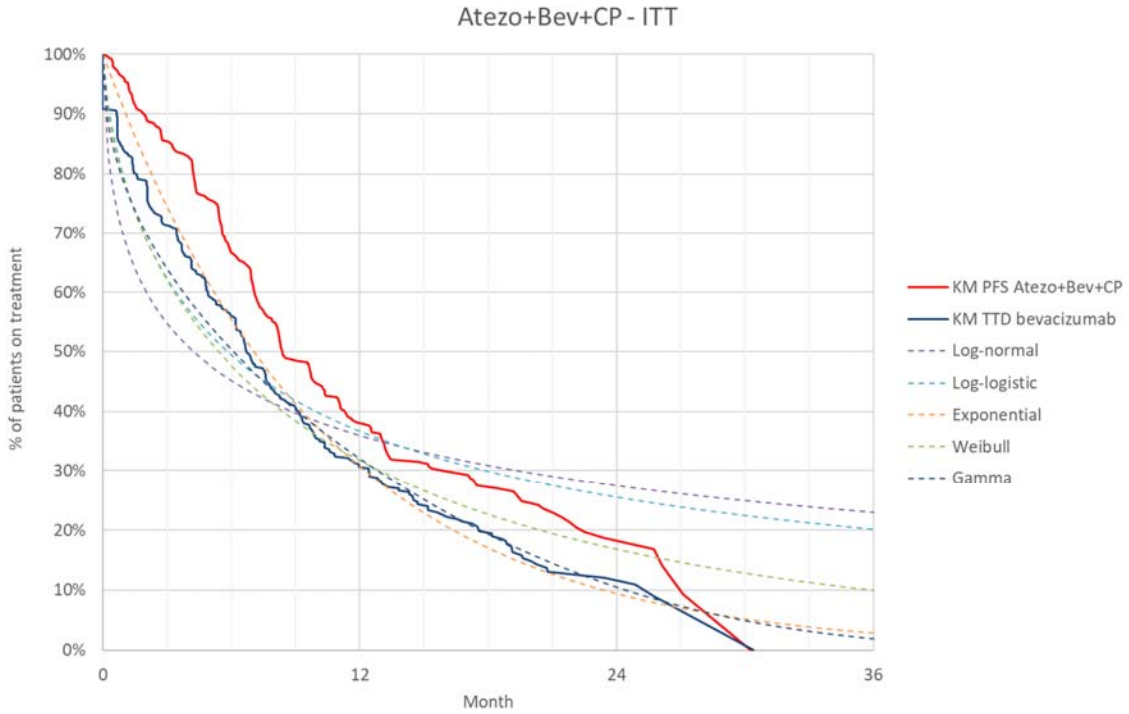


Figure 21 Duration of bevacizumab in Atez+Bev+CP arm of IMpower150: ITT

4.2.4.5 Incidence of adverse events

The base case model includes costs, but not utility loss associated with adverse events. Grade 3+ adverse events with an incidence of in 2% or more in the Atezo+Bev+CP arm of the IMPower150 trial were included in the base case analysis (see CS Table 43). The incidences of the included adverse events for the comparators were sourced from a systematic literature review. The probability of the adverse events per week calculated based on an estimated number of person weeks of follow up in the related trials (clarification question B6).

4.2.5 Health related quality of life

4.2.5.1 Company review of health-related quality of life studies

The company conducted a systematic review to identify evidence in the first-line treatment of patients with non-squamous NSCLC. The original review was completed in September 2016 with an update in February 2018. The search strategy and the inclusion criteria used in the review are detailed in Appendix H of the CS. The review identified 43 publications reporting health state utility values (HSUV) associated with first-line treatment for advanced or metastatic NSCLC, of which five reported the HSUV as graphs only and 21 presented as conference abstracts.

The company reported those studies (n=5) of most relevance to NICE, i.e. those in line with the NICE reference case where utilities were derived directly from patients using EQ-5D with the UK tariff (CS Table 71, Appendix H). Based on the company's review, the CS states that the most suitable studies that were included in the model as scenario analyses were Nafees et al.[15] and Chouaid et al[16] and that these two studies have been used in most of the economic evaluations published in NSCLC. The utility values for both these studies are shown in Table 30.

The ERG considers the company's review to be up-to date and comprehensive and we have not identified any other relevant studies for NSCLC first line treatment. We note that the study by Nafees et al.[15] was not included within the company's list of five most relevant studies as it is for patients receiving second-line treatment. Further, this study does not adhere to the NICE reference case as participants are not patients with the disease. The study has been criticised in previous appraisals for having unrealistically low utility values for patients with progressed disease. Therefore, the ERG suggests that scenario analyses using utility values from the Nafees et al study may be of limited value.

4.2.5.2 Measurement of HRQoL from the IMPower150 trial

The company used utility values in their base case analyses from the utility data collected in the IMPower150 trial. Patients in the study completed the EQ-5D-3L questionnaire and utility values were derived using the UK tariff. EQ-5D data were collected at each scheduled study visit and during survival follow-up at three and six months following disease progression (or loss of clinical benefit).

The company considered two approaches for estimating utility values: 1) proximity to death approach, ii) pre-and-post progression approach. The company used the proximity to death approach and the pre- and post-progression approach was used in scenario analyses. The utility values for both approaches are shown in Table 30. The company justifies the proximity to death approach by stating that this reflects the known decline in cancer patients' quality of life and also that this approach has been used in previous NICE appraisals in NSCLC (TA402,[13] TA428,[17] TA525[6]).

The proximity to death utilities were derived from analyses according to the time before death:

- Group 1: less than 35 days before death
- Group 2: more than 34 and less than 75 days
- Group 3: more than 74 and less than 210 days
- Group 4: more than 211 days

The analysis was based upon HRQoL estimated from those who had died at the time of clinical cut-off (52.2% of patients) for groups 1-3. Group 4 also included those patients still alive with more than 211 days follow-up. The company stated that they fitted a model to include time before death group, assessment time and treatment arm as covariates. The company considered two separate models according to treatment status: on or off treatment. However, the off treatment utilities had wide confidence intervals which overlap for different time to death groups. The company therefore decided to fit and report only utilities by time before death group according to the proximity to death.

Table 30 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 interval

For the pre- and post-progression approach, the company fit a fixed-effects model with covariates for the pre-progression and post-progression periods. They also tested the effects of covariates for treatment arm and adverse events. The company reported that they found no difference between treatment arms and therefore pooled pre-progression mean utility, regardless of treatment arm. The company has provided a scenario analysis using utility values for the pre-progression and post-progression health states (CS Table 62-Table 65). The ERG notes that the results from these scenario analyses have only a small effect on the ICER.

The ERG requested further clarification of the utility values, specifically about the repeated-measures analysis of EQ-5D (clarification question B3). The company provided information on the utility values collected in IMPower150 in Appendix C of their clarification response. These included figures showing how the utilities varied over time for each treatment arm by time before death (Appendix C, Figure 5), before progression (Appendix C, Figure 7), before progression for patients without AEs (Appendix C, Figure 8), and after progression (Appendix C, Figure 9). These figures show that, generally the utility for patients treated with Atez+Bev+CP is worse than for patients treated with Atez+CP but is similar to those treated with Bev+CP. However, as the confidence intervals overlap, the utility for the treatment arms are not statistically different. It is unclear how the health state utility values differ for patients treated with for Atez + Bev + CP differ from the comparators in the economic model (pemetrexed + C; pemetrexed + C + pemetrexed maintenance). The ERG notes that the health state utility values from the PARAMOUNT trial for patients treated with PEM+CIS/CARB + pemetrexed maintenance are [redacted] than those from IMPower150 treated with Atez+Bev+CP (PARAMOUNT: pre-progression 0.77 before randomisation for maintenance, 0.7841 during maintenance phase vs. IMPower150 pre-progression [redacted]). However, as the utility values were taken from different trials in different populations, it is unclear how meaningful these differences are.

The ERG notes that the company has not included any disutility for patients whilst on-treatment or included disutilities for adverse events. The company justified not including the disutility for adverse events because “any disutility has already been incorporated in to the base case health state utilities through the trial derived EQ-5D utilities, and incorporating an additional disutility could be considered double counting”. However, the company included disutilites for adverse events in a scenario analysis. The CS includes details of how the adverse event disutilites have been calculated in Appendix Q. The ERG has concerns with assuming that the utilities would be the same for treatment with Atezo+Bev+CP and pemetrexed plus platinum whilst the adverse

event profile for Atezo+Bev+CP is significantly worse than pemetrexed plus platinum (CS Table 43).

We also note that the scenario for including disutility for adverse events has not been conducted correctly as the same disutility has been used for all treatment arms, whereas in CS Table 70, Appendix Q, the adverse event disutility is lower for pemetrexed plus platinum than for Atezo+Bev+CP. The ERG provides an ERG analysis correcting the adverse event utilities used in section 4.4.

> **ERG conclusion:** The company's approach to estimating health state utility values is reasonable and consistent with previous NICE technology appraisals. The use of IMPower150 utility data is preferable to other estimates of utility in this population. 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).

4.2.6 Resource use and costs

The economic model included the following costs:

- Drug acquisition
- Drug administration
- Subsequent treatment
- Follow up monitoring and care
- Terminal care
- Adverse events

4.2.6.1 Drug acquisition

The company's base uses the list prices for all drugs, as shown in Table 31 below (CS Table 31) and the dosing schedule in Table 32 (CS Table 32). Atezolizumab and bevacizumab, carboplatin and paclitaxel are administered by intravenous infusion every three weeks. Atezolizumab and bevacizumab are administered until unacceptable toxicity or loss of clinical benefit. Carboplatin and paclitaxel are administered for four or six cycles. Pemetrexed and cisplatin are administered by intravenous infusion every three weeks for up to six cycles.

Drug costs are taken from British National Formulary[19] and eMIT[20] and the dosing schedules are taken from the IMPower150 trial[21] and the drug's summary of product characteristics. Atezolizumab and bevacizumab have an agreed confidential patient access scheme (PAS) discount (CS Table 52) and the company provides results using both the list price and the PAS price for atezolizumab and bevacizumab. There are also confidential discounts to the NHS for pemetrexed maintenance and pembrolizumab and the ERG provides results including all existing confidential discounts in a separate confidential appendix to this report.

Table 31 Drug acquisition costs

Drug	Vial/pack concentration	Vial/pack volume	Dose per vial/pack	Cost per vial/pack	Cost per mg	Source
Atezolizumab	60 mg/ml	20 ml	1200 mg	£3807.69	£3.17	BNF
Bevacizumab	25 mg/ml	4 ml	100 mg	£242.66	£2.43	BNF
Bevacizumab	25 mg/ml	16 ml	400 mg	£924.40	£2.31	BNF
Pemetrexed	100 mg powder			£160	£1.60	BNF
Pemetrexed	500 mg powder			£800	£1.60	BNF
Carboplatin	10 mg/ml	15 ml	150 mg	£6.35	£0.04	eMIT
Cisplatin	1 mg/ml	100 ml	100 mg	£10.13	£0.10	eMIT
Paclitaxel	6 mg/ml	16.7 ml	100 mg	£9.85	£0.10	eMIT

Table reproduced from CS Table 31
eMIT: 12 month period until end June 2017

The total drugs cost per combination per cycle is £6,445.89 for Atezo+Bev+CP and for pemetrexed plus cisplatin is £1471.61.

The CS states that the base case analysis assumes full vial sharing (i.e. no wastage) for the administration of all weight based therapies. The ERG notes that the model assumes that 5% of patients share vials for these treatments. The CS includes a scenario analysis where there is no vial sharing. The ERG's preference is to have no vial sharing as the base case analysis, and we remove this assumption in our corrections to the company base case (see section 4.4).

Table 32 Dosing schedule and dose per administration

Drug	Dosing per administration	Frequency of administration	Total dose	Reference for dosing
Atezolizumab	1200 mg fixed	Q3W	1200 mg	SmPC IMpower150
Bevacizumab	15 mg/kg	Q3W	1079 mg	IMpower150
Pemetrexed	500 mg/m²	Q3W	905 mg	SmPC
Carboplatin	6 mg/mL/min (AUC)	Q4W	692 mg	SmPC, IMpower150
Cisplatin	75 mg/m²	Q3W	136 mg	SmPC
Paclitaxel	200 mg/m²	Q3W	362 mg	SmPC, IMpower150
Docetaxel	75 mg/m²	Q3W	136 mg	SmPC
Nivolumab	3mg/kg	Q2W	216 mg	SmPC

Table reproduced from CS Table 32

Q3W, every three weeks; Q4W, every four weeks; AUC, area under the curve

4.2.6.2 Drug administration costs

The drug administration costs used in the economic model are shown in CS Table 38. Costs are taken from NHS reference costs 2016-17.[22] The company assumes that the administration cost for Atezo+Bev+CP (Day case cost £385.99) is higher than that used for pemetrexed + platinum (outpatient / day case cost £327.92) and pemetrexed maintenance (outpatient cost £173.99 due to the longer infusion times. The administration cost for subsequent therapies are £173.99 (outpatient cost) for the single therapies of docetaxel, atezolizumab, pembrolizumab and nivolumab. The company has based the administration costs on those used in previous NICE technology appraisal.[2 12 13]

4.2.6.3 Subsequent therapies

The company's economic model includes subsequent lines of therapy for patients with progressed disease. The company assumes that all patients treated with Atezo+Bev+CP are subsequently treated with docetaxel and patients initially treated with pemetrexed are subsequently treated with an immunotherapy or docetaxel as shown in Table 33 (CS Table 34). The CS justifies this approach by stating that it is in line with UK clinical practice and with the second-line marketing authorisation of immunotherapies and has previously been accepted by

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 33 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 34

Table 34 Drug acquisition costs – subsequent therapies

Drug	Vial/pack concentration	Vial/pack volume	Dose per vial/pack	Cost per vial/pack	Total cost per treatment cycle[1]	Source
Atezolizumab	60 mg/ml	20 ml	1200 mg	£3807.69	£3807.69	BNF
Pembrolizumab	25 mg/ml	4 ml	100 mg	£2630.00	£3781.28	BNF
Pembrolizumab	Powder for concentrate for IV solution		50 mg	£1315.00	£3781.28	BNF
Docetaxel	20 mg/ml	7 ml	140 mg	£20.62	£20.02	eMIT
Docetaxel	20 mg/ml	1 ml	20 mg	£3.85	£20.02	eMIT
Nivolumab	10 mg/ml	4 ml	40 mg	£439.00	£2634.00	BNF

Table reproduced from CS Table 35

eMIT: 12 month period until end June 2017

[1] Values taken from company economic model

4.2.6.4 Follow up monitoring and care

The CS presents the resources used for patients with progression free and progressed disease in CS Table 40 (Table 35). The resource use was consistent with that used for the NICE technology appraisal TA531 for pembrolizumab for NSCLC[17] and the economic evaluation by Brown et al [4] on chemotherapy for NSCLC. The resources used are from the Big Lung trial[23] and a Marie Curie report,[24] which were published in 2005 and 2004 respectively. The Big Lung trial reports on a trial completed in 1999/2000. The ERG is unable to find the values reported in Brown et al[4] in the cited sources. Expert clinical advice to the ERG suggests that it may be counter-intuitive that the number of outpatient visits would be higher in the PFS state than in the progressed disease state. Furthermore, we consider that the resource use data may be out of date as they are from older studies and there have been considerable changes to the management of NSCLC since these studies were conducted. The ERG considers a better approach would have been to collect resource use data from the IMPower150 and use these data in the economic evaluation.

The unit costs for the resources used are shown in Table 36 (CS Table 41). These unit costs have been taken from NHS reference costs 2016/17,[22] PSSRU 2017[25] or from previous NICE technology appraisals and the costs have been inflated to 2016/17 using the PSSRU HCHS index.[25]

Table 35 Resource use for PFS and PD health state

Resource	PFS	PD	Unit	Source
Outpatient visit	9.61	7.91	per annum	NICE TA531
Chest Radiography	6.79	6.5	per annum	NICE TA531
CT scan (chest)	0.62	0.24	per annum	NICE TA531
CT scan (other)	0.36	0.42	per annum	NICE TA531
ECG	1.04	0.88	per annum	NICE TA531
Community nurse visit	8.7	8.7	visits (20 minutes) per patient	Appendix 1 of NICE Guideline CG121 Marie Curie report
Clinical nurse specialist	12	12	hours contact time per patient	Appendix 1 of NICE Guideline CG121
GP surgery	12	0	consultations per patient	Appendix 1 of NICE Guideline CG121
GP home visit	0	26.09	per annum (fortnightly)	Marie Curie report
Therapist visit	0	26.09	per annum (fortnightly)	Appendix 1 of NICE Guideline CG121

Table reproduced from CS Table 40
PFS, progression free state; PD, progressed disease state; GP, general practitioner; CT, computerised tomography; ECG, electrocardiogram; NICE, The National Institute for Health and Care Excellence; CG, clinical guidance

The ERG notes that the company has updated costs incorrectly using the HCHS prices index, rather than using the HCHS pay and prices index. The corrected costs are shown in Table 36 in parentheses in the unit cost column. Some categories on cost are no longer listed in PSSRU in the format reported by Brown et al.[4] The ERG has updated these costs from the latest version of PSSRU that listed these costs.

Table 36 Unit costs (PFS and PD health states)

Resource	Unit cost (ERG estimate)	Unit	Source
Outpatient follow-up visit	£136.43	per visit	NHS Reference Costs 2016-2017, Outpatient attendance data, Consultant Led, Service code 800, Clinical Oncology
Chest Radiography	£27.78 (£27.22)	per case	NICE technology appraisal TA199; (£24.04 in 2009 - inflated to 2016/17 using the PSSRU HCHS index)
CT scan (chest)	£112.07	per case	NHS Reference Costs 2016-2017, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)

CT scan (other)	£112.07	per case	NHS Reference Costs 2016-2017, Diagnostic Imaging, Outpatient, HRG code RD24Z (two areas with contrast)
ECG	£224.99	per case	NHS Reference Costs 2016–2017, Complex ECG, HRG code EY50Z
Community nurse visit	£62.00 (£69.10[1])	per hour	PSSRU 2017 p.159: Cost per hour Band 8a
Clinical nurse specialist	£62.00 (£77.35[1])	per contact hour	PSSRU 2017 p.207: Cost per hour Band 8a
GP surgery visit	£38.00	per visit	PSSRU 2017, p.162: Cost per patient contact lasting 9.22 minutes, including direct care staff costs, including qualifications
GP home visit	£94.82 (£119.95[2])	per visit	PSSRU 2016, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel - inflated to 2016/17 using the PSSRU HCHS index
Therapist visit	£45.00	per visit	PSSRU 2017, p.177: Cost per hour for community occupational therapist, including training

Table reproduced from CS Table 41
GP, general practitioner; CT, computerised tomography; ECG, electrocardiogram; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; NICE, The National Institute for Health and Care Excellence; HRG, Healthcare Resource Groups; HCHS, hospital and community health services

[1] Costs updated from PSSRU 2015 to 2016/17.
[2] Costs updated from PSSRU 2013 to 2016/17.

The total cost per week in the PFS health state is £61.80 and for the PD state £117.00. The corrected health state costs using the ERG estimates shown in the Table above is £65.53 for the PFS and £139.39 for the PD health state.

4.2.6.5 Costs of terminal care

The company's economic model includes terminal care costs reflecting the resources used by patients in various care settings. The resources have been taken from Brown et al.[4] and were originally reported in a Marie Curie report.[24] The company has updated the unit costs to 2016/17. As noted above for health state costs, the company has incorrectly updated the unit costs using the HCHS prices index, rather than the HCHS pay and prices index. The ERG has corrected the unit costs and these are shown, together with the resource use in Table 37 (CS Table 42). The total cost of terminal care used in the model is £4456.13 and the corrected ERG estimate is £4556.88.

Table 37 Resource use and unit costs for terminal care/end of life

Resource	Unit cost (ERG estimate)	Number of consumption	% of patients in each setting	Assumptions / Source
Community nurse visit	£62.00 (£69.10) per hour	28.00 hours	27%	PSSRU 2017, p.159: Cost per hour Band 8a
GP Home visit	£94.82 (£119.95) per visit	7.00 visits	27%	PSSRU 2016, p.145: Cost per home visit including 11.4 minutes for consultations and 12 minutes for travel - inflated to 2016/17 using the PSSRU HCHS index
Macmillan nurse	£41.35 (£46.07) per hour	50.00 hours	27%	Assumed to be 66.7% of community nurse cost
Drugs and equipment	£574.57 £562.73 per patient	Average drug and equipment usage	27%	Value from Brown et al study (2013) inflated to 2016/17 using the PSSRU HCHS index
Terminal care in hospital	£4003.46 (£3921.95) per episode	1 episode (9.66 days)	56%	NICE TA531, inflated to 2016/17 using the PSSRU HCHS index[25]
Terminal care in hospice	£5004.33 (£4902.44) per episode	1 episode (9.66 days)	17%	NICE TA531, assumed 25% increase on hospital inpatient care
Total cost	£4456.13 (£4556.88) per episode			

Table reproduced from CS Table 42

4.2.6.6 Adverse events

The company's economic model includes the costs for treating adverse events. Adverse event data for patients treated with Atezo+Bev+CP are taken directly from IMPower150 for grade ≥ 3 grade adverse events with an incidence of ≥2%. For the comparator treatment, the company conducted a systematic literature review (CS Appendix D). The frequency of adverse events is shown in CS Table 43. The unit costs for treating the adverse events are shown in CS Table 44 (Table 38). The unit costs are based on NHS Reference costs 2016/17. As noted for health care costs, the company has incorrectly updated some of the costs by using the HCHS prices index instead of the HCHS pay and prices index. The costs of adverse events corrected by the ERG are shown in Table 38.

The adverse event costs per patient in the economic model are £1227.68 for Atezo+Bev+CP, £272.54 for pemetrexed + platinum and £723.78 for pemetrexed + platinum + pemetrexed

maintenance. The corrected adverse event costs estimated by the ERG produce a total cost per patient of £1334.27 for Atezo+Bev+CP, £289.67 for pemetrexed + platinum and £861.56 for pemetrexed + platinum + pemetrexed maintenance

Table 38 Unit cost per adverse event used in the economic model

Adverse Event	Unit cost	ERG estimate	Reference
Anaemia	£2,748.57	£2692.61	NICE TA531[12] - inflated to 2016/17 using the PSSRU HCHS index
Asthenia	£2,914.59	£2855.25	Assumed same as fatigue
Fatigue	£2,914.59	£2855.25	Brown 2013[4] (inflated to 2016-17 using PSSRU inflation indices)
Febrile neutropenia	£7097.41	£7045.41	NICE TA531[12] - inflated to 2016/17 using the PSSRU HCHS index
Leukopenia	£376.80	£1209.92	Assumed same as neutropenia
Nausea	£1019.12	£998.38	Brown 2013[4] (inflated to 2016-17 using PSSRU inflation indices)
Neutropenia	£601.23	£1209.92	Brown 2013[4] (inflated to 2016-17 using PSSRU inflation indices)
Thrombocytopenia	£123.51	£120.99	NICE TA484,[26] NICE TA520,[6] NICE TA525[7]
White blood cell count decreased	£449.34	£440.19	NICE TA484,[26] NICE TA520,[6] NICE TA525[7]

Table reproduced from CS Table 44
[1] Costs inflated using HCHS pay and prices index, rather than HCHS prices index
[2] Brown et al (2013) assumes two episodes of hospital treatment, rather than one episode

ERG conclusion: 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. The resources use estimates used in the model are from outdated sources and need updating. The ERG suggests that the resource use could have been taken from the IMPower150 trial, if these data were available.

4.3 Cost effectiveness results

4.3.1 Company's base case results

The CS presents results of the base case economic analysis in a pairwise format, comparing Atezo+Bev+CP to each comparator separately (CS Tables 46 – 51, B.3.7.1). In response to ERG clarification question B4, the company produced an incremental analysis comparing the two included comparators, as well as results of pairwise analysis (Clarification response Appendix D). We reproduce the results with PAS discount price discounts for atezolizumab and

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 39 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)
	Costs (£)	QALYs		
PEM+plat	[redacted]	[redacted]		£16,419
PEM+plat+PEM maint	[redacted]	[redacted]	£35,985	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	-

Table 40 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)
	Costs (£)	QALYs		
PEM+plat	[redacted]	[redacted]		£13,424
PEM+plat+PEM maint	[redacted]	[redacted]	£38,943	Dominant
Atezo+Bev+CP	[redacted]	[redacted]	Dominant	-

Table 41 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)
	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	-

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 42 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)
	Costs (£)	QALYs		
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.

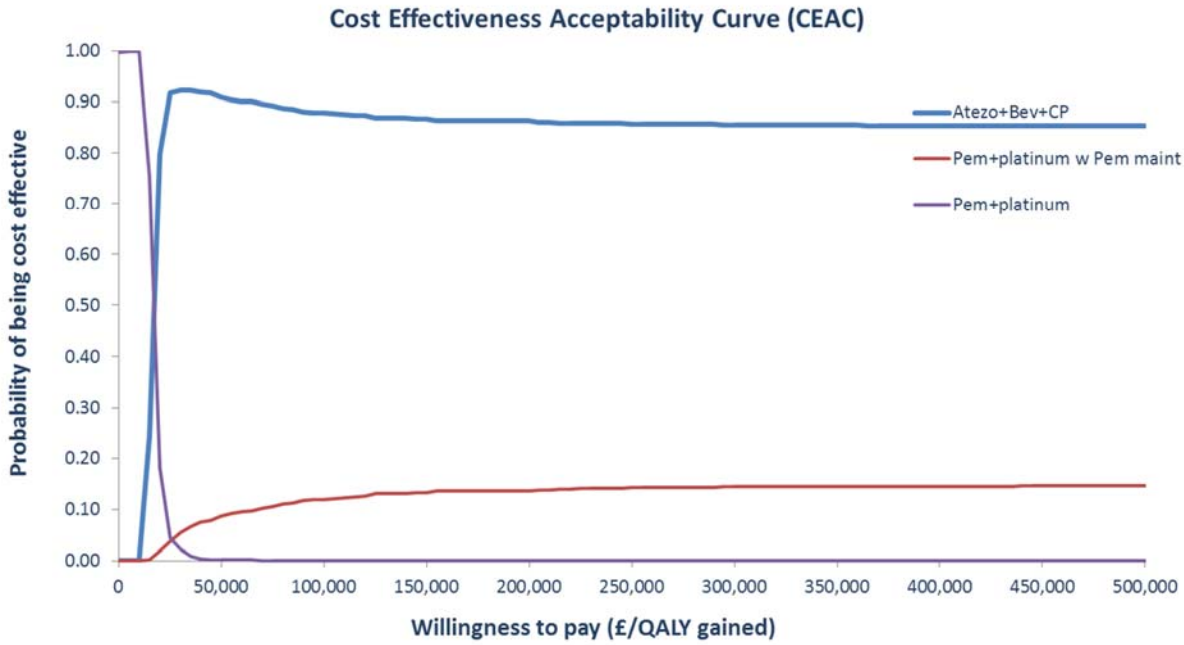
4.3.2.1 Company's probabilistic sensitivity analyses

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.

Probabilistic estimates of costs, QALYs and ICERs were very similar to the mean probabilistic values (company clarification response, Appendix D, Tables 38 and 39). We reproduce the company's base case CEAC for the ITT population (with PAS discounts for the intervention only) in Figure 22. The curves are similar for the PD-L1 low/negative and EGFR/ALK positive populations.

Figure 22 Cost-Effectiveness Acceptability Curve (PAS for atezolizumab and bevacizumab, list price for comparators and subsequent treatments) – ITT population



Reproduced from the company's clarification response (Appendix D, Figure 16)

4.3.2.2 One-way sensitivity analysis

The company produced tornado plots to illustrate the effect of one-way sensitivity analysis on the ICERs in Appendix D of their clarification response (Figures 25 to 34). We reproduce the plot for the ITT population for the comparison with pemetrexed plus platinum in Figure 23 below (PAS discounts for atezolizumab and bevacizumab only). The CS states that the most influential parameters are the discount rates for costs and health outcomes, the administration cost for Atezo+Bev+CP, the utility value for the interval of >30 weeks before death and the weekly AE costs for Atezo+Bev+CP. Similar results are found for the subgroups and comparison including pemetrexed maintenance.

However, we note that the one-way deterministic sensitivity analysis does not include uncertainty over the treatment effects (either the baseline curves for Atezo+Bev+CP or relative effects versus the comparators). The company also uses arbitrary variations of +/- 5% for some of input parameters. The ERG is of the opinion that treatment effect is potentially a key driver of cost-effectiveness and should be varied according to the confidence intervals for PFS and OS.

ERG conclusion: The one-way sensitivity analyses do not capture the full uncertainty of the parameters because some parameters have only been varied by +/- 5% and the treatment effect has not been included.

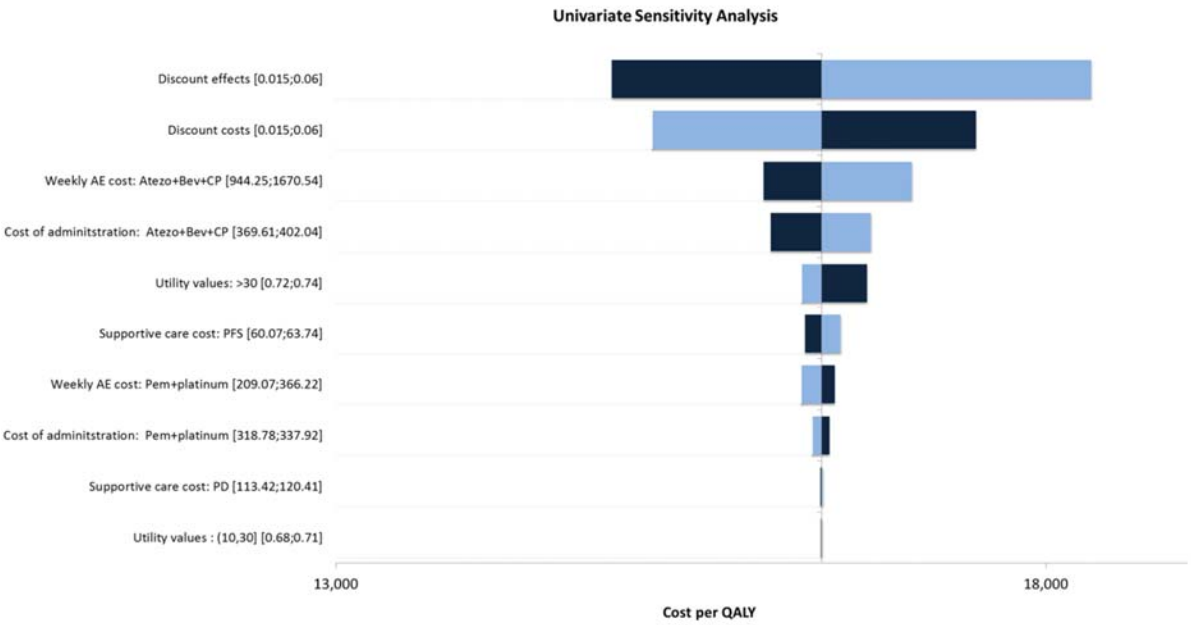


Figure 23 Tornado diagram – ITT population vs. pemetrexed plus platinum (PAS for atezolizumab and bevacizumab but not comparators or subsequent treatments)
Reproduced from Figure 27 in company's clarification question response

4.3.2.3 Scenario analyses

The company used deterministic scenario analyses to assess the impact of uncertainty around some other parameter inputs and structural assumptions: They explored the following scenarios:

- Alternative OS extrapolations
- Alternative PFS extrapolations
- Alternative TTD extrapolations
- Alternative NMA networks and models
- No treatment stopping rule for atezolizumab and bevacizumab
- Alternative time points for cap of treatment effect duration
- Alternative drug vial wastage assumptions
- Alternative utility values
- Alternative subsequent therapy approach
- Disutility for AEs

The company provided updated results in their clarification response document. We reproduce the results for the ITT population in Table 43 below (PAS discounts for atezolizumab and bevacizumab only). Other subgroups and PAS scenario analyses are in Appendix D of the company's clarification responses.

The scenario analyses show that the model results are most sensitive to changes to the choice of parametric curve for OS, treatment effect duration, treatment stopping duration, and the choice of studies to include in the NMA.

The economic model includes a macro which runs all the scenarios, with the exception of the subsequent treatment scenario. As noted in section 4.2.5 of this report, the ERG disagrees with the company's approach to estimating disutilities for the comparators. The ERG conducts a scenario including disutilities in section 4.4.

As observed with the company's base case analysis, the ERG was not able to exactly replicate the results for the scenario analyses for the EGFR/ALK positive population on the company's updated model.

> **ERG conclusion**: The company's choice of scenarios is comprehensive and informative.

Table 43 Company scenario analyses - ITT (PAS for atezolizumab and bevacizumab only)

Scenario		Pairwise ICER Atezo+Bev+CP vs	
		PEM+platinum	PEM+platinum w PEM maint
OS distribution	Exponential (base case)	£16,419	Dominant
	Weibull	£18,470	Dominant
	Log-normal	£11,840	Dominant
	Gen Gamma	£23,304	Dominant
	Log-logistic	£12,376	Dominant
	Gompertz	Does not converge	Dominant
PFS distribution	KM - Log-logistic tail (base case)	£16,419	Dominant
	Exponential	£18,324	£130
	Weibull	£18,073	Dominant
	Log-normal	£16,738	Dominant
	Gen Gamma	£17,637	Dominant
	Log-logistic	£16,418	Dominant
	Gompertz	£18,428	£612
TTD distribution	KM- Exponential tail (base case)	£16,419	Dominant
	Exponential	£17,533	Dominant
	Weibull	£15,639	Dominant
	Log-normal	£18,191	Dominant
	Gen Gamma	£14,558	Dominant
	Log-logistic	£20,885	£546
	Gompertz	Does not converge	Does not converge
Alternative NMA network	ITT (base case)	£16,419	Dominant
	ITT exclude KEYNOTE	£16,501	Dominant
	ITT exclude PARAMOUNT	Comparison not feasible - no connected network	Dominant
Alternative NMA model	NMA - Fract Poly (FE) (base case)	£16,419	Dominant
	NMA - PH	£20,028	Dominant
	NMA - Fract Poly (RE)	£16,523	Dominant
Treatment stopping rule	At 2 years (base case)	£16,419	Dominant
	No treatment stopping rule	£25,865	£12,234
Treatment effect duration	5 years (base case)	£16,419	Dominant
	105 months	£17,223	Dominant
	150 months	£17,522	Dominant
	195 months	£17,586	Dominant
	240 months (lifetime)	£17,595	Dominant
Wastage	With vial sharing (base case)	£16,419	Dominant

	No vial sharing	£16,427	Dominant
Utility values	IMpower150 (Proximity to death) (base case)	£16,419	Dominant
	IMpower150 (Pre/Post progression)	£17,090	Dominant
	Pembrolizumab utilities (US publication)	£14,960	Dominant
	Chouaid et al. 2013	£16,974	Dominant
	Nafees et al. 2008	£18,438	Dominant
Subsequent treatments	Base case	£16,419	Dominant
	IMpower150	£20,866	£1,201
AE disutility	No (base case)	£16,419	Dominant
	Yes	£16,502	Dominant

Reproduced from the company's clarification response (Table 43 and Table 44)

4.3.3 Model validation and face validity check

The company described their approach to model validation in CS section B.3.10.1. The CS states that "all outcomes of the economic model have been extensively compared to and validated against all available evidence, as well as clinical expert opinion, to assess the accuracy of the modelled survival".

For Atez+Bev+CP, the company compare the model extrapolations with 5-year survival estimates from 10 UK clinicians (4.2.4.2CS B.3.3.2). For the pemetrexed-based comparators, the company compare against predictions of 5-year survival under standard care from the pembrolizumab appraisal TA531 (8 to 11%), and against estimates from the Flatiron study[14]: 8.3% for pemetrexed with platinum and 12.3% for pemetrexed with platinum and pemetrexed maintenance (CS Appendix M). A critique of the company's selection of respective time-to-event distributions and extrapolation techniques can be found in section 4.2.2 of this ERG report.

Additional parameters validated by the company include health state inclusion, relevant comparators and resource use. To verify that these parameters were reflective of clinical practice, the company consulted UK clinical experts. The company reports that internal quality control and external validation of their economic model was conducted by a consultancy. The CS further describes other methods used to validate the model outputs such as cell-by-cell validation and pressure tests using extreme values.

The ERG checked the company's economic model for transparency and validity. The model was developed in Microsoft Excel and the visual basic codes were accessible.

We conducted a range of 'white box' tests to verify model inputs, calculations and outputs which consisted of:

- Cross-checking of all parameter inputs against values in the CS and cited sources;
- Checking that model outputs such as base case deterministic results and results of scenario analysis reported in the CS were reproducible by manually running the model;
- Checking individual equations and formulas within the model;
- Testing the logic of formulas in the model by substituting model inputs with a range of extreme values;
- Checking that visual basic codes did what they were designed to do.

Generally, we found the economic model to be of a good quality, with a few errors in input parameters, logic or coding. We identified a few small errors that we report and correct in section 4.4 below. However, these errors did not make any substantive difference to the results of economic analysis.

We also attempted to validate the outcomes from the company model (Table 39) against estimates from related NICE appraisals (summarised in Table 23, section 4.1 above).

- The company's ITT base case QALY estimate for pemetrexed with platinum (1.01 QALYs) is lower than that estimated in TA181 (0.61). However, this may be explained by the longer time horizon (20 years compared with 6 years in TA181).
- The QALY gain with pemetrexed-based treatment with vs. without maintenance (0.38 QALYs in the company's ITT base case) is not directly comparable with the incremental QALY gain in the pemetrexed maintenance appraisal (TA402) (0.21), because the latter does not include the induction period.
- The estimate of 1.35 QALYs attributed to standard care in the pembrolizumab appraisal (TA531) compares with 1.01 QALYs for pemetrexed with platinum and 1.39 for pemetrexed with platinum plus pemetrexed maintenance in the current company ITT base case. The standard of care comparator in TA531 includes chemotherapy regimens as well as pemetrexed-based ones, so the estimates from the current company base case are rather lower than might be expected.

4.4 Additional work undertaken by the ERG

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the company's cost-effectiveness analyses. This consists of corrections to

the model for discrepancies in costs, changes to the population used for the NMA, changes to the trials included in the NMA, using alternative assumptions for the duration of the treatment effect, changes to the parametric curves using for the survival extrapolations and inclusion of adverse event disutilities.

We firstly correct discrepancies in the model and we then run the model for our preferred base case. Table 44 details the corrections made to the company model. Our base case is explained and justified in Table 45. We conduct additional analyses by varying the ERG base case and these scenarios are shown in Table 46.

Table 44 ERG corrections to company model

Parameter	Company estimate	ERG Correction	Explanation
Vial sharing	5%	0%	No vial sharing is more appropriate
Pembrolizumab	£3781.28	£4453.13	As in TA428[17]
PFS health state cost	£61.80	£65.53	Some cost discrepancies in CS
PD health state cost	£117.00	£139.39	Some cost discrepancies in CS
Terminal care	£4456.13	£4556.88	Some cost discrepancies in CS
Adverse event cost Atezo+Bev+CP	£1227.68	£1334.27	Some cost discrepancies in CS
Adverse event cost PEM + platinum	£272.54	£289.67	Some cost discrepancies in CS
Adverse event cost PEM + platinum + PEM main	£723.78	£861.56	Some cost discrepancies in CS

Table 45 ERG additional analysis

Model aspect	Company analysis	ERG base case
Decision problem		
Population	Company reports results for ITT as well as PD-L1 and EGFR/ALK subgroups. The latter use subgroup-specific extrapolations for the atezolizumab arm survival curves and relative effects from the subgroup NMAs. • ITT curves & NMA • PD-L1 curves & NMA • EGFR/ALK curves & NMA	The ERG base case uses subgroup-specific survival curves for the atezolizumab arm for the PD-L1 & EGFR/ALK subgroups combined with relative effects from the ITT NMA, as this is more robust and there is no evidence of effect modification from the IMpower150 trial. ERG base case:: • PD-L1 curves + ITT NMA • EGFR/ALK curves + ITT NMA
Intervention	Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel Combination without bevacizumab not pursued in anticipated marketing authorisation	No change
Comparators	Pemetrexed in combination with cisplatin/carboplatin, with or without pemetrexed maintenance The company is not seeking reimbursement for patients eligible for pembrolizumab (PD-L1 high expressors) The company does not model other comparators that are in scope, arguing that PEM+CIS/CARBO is 'standard of care' in the UK.	No change We agree that it is acceptable to omit pembrolizumab from analysis as reimbursement is not sought for the subgroup who meet NICE TA531 criteria.[12] We consider that the platinum-based chemotherapies listed in the scope should have been included as comparators. Expert advice to the ERG is that patients who cannot tolerate cisplatin will have carboplatin-based chemotherapy, followed by pemetrexed maintenance. Model does not include any comparator specified in the scope for the EGFR/ALK subgroup. We report cost-effectiveness relative to the pemetrexed comparators for this subgroup, but note that this is out of scope.
Structure and assumptions		
Time horizon	20 years, from age 63 to 82	No change

Stopping rule	2 year maximum in the base case. Scenario with no limit on treatment duration. This aligns with stopping rules for atezolizumab after chemotherapy (TA520) and pembrolizumab (TA531).	No change
Effect duration	5 year cut off for OS (3 years after stopping), with scenario analysis from 8.75 to 20 years In the revised model this was applied by setting the mortality rate for Atezo+Bev+CP equal to that for PEM+plat with maintenance.	No change for base case, but extend the scenario analysis due to uncertainty over the duration of effects after discontinuation of immunotherapies (e.g. as noted in TA 520).
Clinical parameters		
Fitted survival curves for atezolizumab combination	ITT & PD-L1 low • OS exponential • PFS KM + log-logistic tail • TTD exponential	ERG base case: The ERG prefers the Weibull distribution for OS extrapolation (section 4.2.4.1). The choice of parametric curves for PFS and TTD are reasonable, except for PFS curves for EGFR/ALK +ve subgroup. For this curve, the ERG prefers the log-logistic distribution.
	EGFR/ALK +ve subgroup • OS exponential • PFS log-normal • TTD exponential	
	KM tails attached where 20% of patients remain at risk Parametric curves fitted separately to Atezo+Bev+CP arm of IMpower150 (Jan 2018 cut off with investigator-assessed PFS).	
Relative effects	HR from ITT NMA FP (FE) P1=0 Weibull (scenarios: PH and RE NMA models, excluding KEYNOTE, excluding PARAMOUNT)	The ERG prefers the analysis excluding the PARAMOUNT trial (due to heterogeneity), with first order Weibull, fixed effects.
AE rates	See CS Tab 43 p132	No change
Utilities		
Health state	IMpower150 EQ-5D IPD time from death analysis (IMpower150 PF/PD, Huang, Nafees, Chouaid)	No change to health state utilities, however company has not included any differences in utility between the treatments.

AE disutilities	Not included in base case. Scenario with disutility estimated from trial EQ-5D analysis	ERG prefers to include disutilities due to adverse events (see above).
Resource use and costs		
Drug acquisition	Vial sharing (no vial sharing)	ERG prefers no vial sharing (ERG correction).
Price discounts	List prices and PAS discount (atezolizumab & bevacizumab)	PAS atezolizumab PAS bevacizumab CAA nivolumab CAA pemetrexed maintenance
Drug admin	Higher costs for atezolizumab - takes longer for infusion.	No change
Subsequent treatment		No change
Health state costs		Some discrepancies in cost calculations due to incorrect updating of costs (ERG correction).
Terminal care		Some discrepancies in cost calculations due to incorrect updating of costs (ERG correction).
AE costs		Some discrepancies in cost calculations due to incorrect updating of costs (ERG correction).

CAA commercial access agreement; FE Fixed effect; FP Fractional polynomial; HR hazard ratio; KM Kaplan Meier; NMA network meta-analysis; PAS Patient access scheme; PH Proportional hazards; RE Random effects

Table 46 ERG base case and ERG scenarios

	Subgroup	Company base case	ERG base case	ERG scenarios
Baseline OS	All	Exponential	Weibull	• Exponential • Log-logistic
Baseline PFS	ITT & PD-L1 low/-ve	KM + log-logistic	KM + log-logistic	• KM + exponential • KM + Weibull
	EGFR/ALK +ve	Log-normal	Log-normal	• Exponential • Weibull
NMA (OS & PFS)	ITT	FP (FE) ITT	ITT FP excluding PARAMOUNT (FE)	• ITT FP (RE) • ITT PH • Subgroup specific
	PD-L1 low/-ve	FP (FE) PD-L1 low/-ve		
	EGFR/ALK +ve	FP (FE) EGFR/ALK +ve		
TTD	All	KM + exponential for atezo and bev	KM + exponential for atezo and bev	• Bev until progression
		PEM follows PFS	PEM follows PFS	
Stopping rule and effect cap	All	2 year treatment + 3 year OS effects	2 year treatment + 3 year OS effects	• 2 years for OS • 5 years for OS • 3 years for PFS • no stopping rule or effect cap
Utilities	All	IMPower150 EQ-5D time-from-death with no treatment effect	IMPower150 EQ-5D time-from-death + disutility per grade 3+ treatment related AE	• IMpower150 EQ-5D health state model • No AE disutility
Subsequent treatments	All	UK scenario (CS Tab 34)	UK scenario (CS Tab 34)	Exclude nivolumab

AE Adverse events; FE Fixed effect; FP Fractional polynomial; KM Kaplan Meier; NMA network meta-analysis; RE Random effects

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 47 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 48 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 49 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 50 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
	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	£14,467

Treatment stopping rule	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 51 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
		Total QALYs	Total costs	Total QALYs	Total costs	
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					Does not converge
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 52 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 53 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 54 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 55 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+	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

	treatment related AE (base case)					
	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

Results of the ERG analyses with all available PAS discounts are in the separate confidential addendum.

4.4.3 Conclusions on cost effectiveness

4.4.3.1 Comparators

The comparators used for the EGFR/ALK positive (pemetrexed + cisplatin with or without pemetrexed maintenance) do not match the NICE scope which includes pembrolizumab and docetaxel. The company has also omitted chemotherapy with carboplatin comparators for the untreated PD-L1 low/negative subgroup, which may reflect current practice for patients who cannot tolerate cisplatin.

4.4.3.2 Model assumptions

The model structure is appropriate for NSCLC and correctly implemented. The use of a 20-year time horizon is reasonable, given the model projections of survival. We also agree with company's base case assumptions of a 2-year stopping rule for the Atez+Bev+CP intervention and the 5-year cap on the survival benefit for this combination. These assumptions are consistent with committee assumptions in previous appraisals of atezolizumab and other immunotherapies.

4.4.3.3 Extrapolation of OS, PFS and TTD

The company's base case extrapolations for OS are reasonable. The exponential distribution for the atezolizumab combination has a good fit to the IMPower150 data and, when coupled with a five-year cap on effects relative to the pemetrexed comparator with maintenance, clinically plausible extrapolations of survival at 5 and 10 years. We consider that the Weibull distribution is also plausible and gives more conservative survival predictions. The parametric curves chosen for PFS and TTD are reasonable and appropriate.

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 undiscounted life years from the company's model. The 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 56 Company base case undiscounted life years

Absolute life years (undiscounted)	PEM+platinum	PEM+platinum with PEM maint
ITT	1.53	2.18
PD-L1	1.55	2.27
EGFR/ALK +ve	2.04	3.15

Table 57 ERG base case undiscounted life years

Absolute life Years (undiscounted)	PEM+platinum with PEM maint
ITT	1.72

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 undiscounted life years gained. For all populations the estimates exceed 3 months.

Table 58 Company modelled undiscounted life years gained

Life years gained (undiscounted)	Versus Pem+platinum	Versus PEM+platinum w PEM maint
ITT	1.08	0.42
PD-L1	1.01	0.29
EGFR/ALK +ve	3.08	1.97

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

Table 59 ERG modelled undiscounted incremental life years gained

LY gained (undiscounted)	Versus PEM+platinum w PEM maint
ITT	0.46

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.

The biological justification for combining an immunotherapy drug such as atezolizumab with chemotherapies (i.e. bevacizumab, carboplatin/paclitaxel) is described. The ERG notes that atezolizumab is an immune checkpoint inhibitor (specifically a PD-L1 blocking antibody) where as bevacizumab inhibits angiogenesis (development of blood supply for the tumour), cisplatin stops or slows tumour growth by interfering with DNA replication and the mitotic inhibitor paclitaxel, inhibits cell division. The CS highlights the synergistic effect of atezolizumab in combination with chemotherapies to enhance anti–PD-1– dependent anti-tumour effects.

Expert clinical advice to the ERG suggests that atezolizumab can be considered a treatment innovation as, apart from pembrolizumab for PD-L1 high expressers, there is no immunotherapy option for patients in the first line advanced setting. However, the regimen would be considered a more attractive option to clinicians if it did not contain bevacizumab due to the additional cost of this drug, and potential for additional adverse effects. As discussed earlier in this report (section 3.1.6), the IMPower150 trial was not designed to compare an atezolizumab plus bevacizumab regimen to an atezolizumab regimen without bevacizumab, and the anticipated marketing authorisation is for atezolizumab in combination with bevacizumab.

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26. National Institute for Health and Care Excellence. Nivolumab for previously treated non-squamous non-small-cell lung cancer [TA484], 2017.

8 APPENDICES

8.1 NMA Critical appraisal checklist

Checklist		Response yes/no
Does the CS present an NMA?		Yes
Are the NMA results used to support the evidence for the clinical effectiveness of the intervention		Yes
Are the NMA results used to support the evidence for the cost-effectiveness of the intervention		Yes
Homogeneity		
	1. Is homogeneity considered?	Yes
	2. Are the studies homogenous in terms of patient characteristics and study design?	Yes, with the exception of the PARAMOUNT trial
	3. Is the method used to determine the presence of statistical heterogeneity adequate? (e.g. Chi-squared test, I-squared statistic)	Yes. Pairwise meta-analyses were used where network links were informed by more than one study. The I^2 statistic was reported.
	4. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	Yes. Subgroup analyses were done (PD-L1 low/-ve patients, and EGFR/ALK +ve patients), and sensitivity analyses were conducted (removing particular trials thought to be heterogeneous).
Similarity		
	1. Is the assumption of similarity stated?	No
	2. Have they justified their assumption?	N/A
Consistency		
	1. Does the analysis explicitly assess consistency?	N/A. There were no closed loops in the network, apart from the 3 arms of the IMPower150 trial.
	2. Does the method described include a description of the analyses/ models/ handling of potential bias/ inconsistency/ analysis framework?	N/A
	3. Are patient or trial characteristics compared between direct and indirect evidence trials?	N/A
	4. If Q3 is yes, and inconsistency is reported, is this accounted for by not combining the direct and indirect evidence?	N/A

N/A = Not applicable

Criterion	ERG assessment
NMA purpose	
1. Are the NMA results used to support the evidence for the clinical effectiveness of the intervention?	Yes, for the indirect comparison of Atezo+Bev+CP versus pemetrexed-based chemotherapy regimens.
2. Are the NMA results used to support the evidence for the cost-effectiveness of the intervention?	Yes, as above.
Evidence selection	
3. Are inclusion/exclusion criteria adequately reported?	Yes, following clarification question (question A12). Criteria are specified in CS Appendix Table 10.
4. Is quality of the included studies assessed?	Yes. CS appendix D.1.3.
Methods – statistical model	
5. Is the statistical model described?	Yes, briefly in the CS, and in more detail in the appendix (D1.1)
6. Has the choice of outcome measure used in the analysis been justified?	Yes. A feasibility assessment was done to determine whether connected networks could be formed for a range of outcomes within the scope of the appraisal (Appendix D1.1). Networks were constructed for OS, PFS, ORR and adverse events leading to discontinuation. Of these, OS and PFS are used to inform the economic model (and are the focus of this ERG report).
7. Has a structure of the network been provided?	Yes
8. Is homogeneity considered?	Yes
9. Are the studies homogenous in terms of patient characteristics and study design?	Yes, with the exception of the PARAMOUNT trial
10. If the homogeneity assumption is not satisfied, is clinical or methodological homogeneity across trials in each set involved in the indirect comparison investigated by an adequate method? (e.g. sub group analysis, sensitivity analysis, meta-regression)	Yes. Subgroup analyses were done (PD-L1 low/-ve patients, and EGFR/ALK +ve patients), and sensitivity analyses were conducted (removing particular trials thought to be heterogeneous).
11. Is the assumption of similarity stated?	No explicit statement is given.
12. Is any of the programming code used in the statistical programme provided (for potential verification)?	Yes, following a clarification question request (question A21).
Sensitivity analysis	
13. Does the study report sensitivity analyses?	Yes. Results scenario analysis results are presented for the FP NMAs with the exclusion of the PARAMOUNT trial and the KEYNOTE trials (021, 189) (CS B.2.9.1). A scenario analysis assuming

	proportional hazards (analogous to an exponential FP model) is reported.
Results	
14. Are the results of the NMA presented?	Yes, in CS section B.2.9, and in Appendix D1.4. Additional results for all FP models tested, and random effects FP models and were supplied on request (clarification question A18 and A20).
15. Does the study describe an assessment of the model fit?	Yes. CS appendix D1.1 (Table 29) reports DIC values for fixed effect FP models. It is also stated that fit was assessed by visual inspection of hazard curves, survival curves and validation of the clinical plausibility of the extrapolated survival curves.
16. Has there been any discussion around the model uncertainty?	Yes, CS section B.2.9.1.
17. Are the point estimates of the relative treatment effects accompanied by some measure of variance such as confidence intervals?	Yes, 95% credible intervals are illustrated in hazard ratio plots (in light grey shaded regions surrounding the hazard ratio line).
Discussion - overall results	
18. Does the study discuss both conceptual and statistical heterogeneity?	Yes
Discussion - validity	
19. Are the results from the indirect/NMA compared, where possible, to those just using direct evidence?	N/A

8.2 ERG independent assessment of risk of bias for the trials included in the clinical systematic review and in the NMA.

Author / trial ID Company & ERG assessment	Was the allocation sequence adequately generated?	Was the concealment of treatment allocation adequate?	Was knowledge of the allocated interventions adequately prevented from participants and personnel	Was knowledge of the allocated interventions adequately prevented from outcome assessors	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of bias?
IMpower150							
Company	Yes	Yes	N/A (open label study)	Unclear	Yes	No	Yes
ERG	Yes	Yes	No	No	Yes for PFS/OS Unclear for PRO outcomes	Yes	Yes
KEYNOTE-024							
Company	Yes	Yes	N/A (open label study)	Yes	Yes	Yes	Yes
ERG	Yes	Yes	No	Yes (central review PFS & response). Unclear (other outcomes)	Yes for PFS, OS & response.	Yes	Yes
ERACLE							
Company	Yes	Yes	No	No	No	Yes	Yes
ERG	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes
KEYNOTE-021							
Company	Yes	Yes	No	Yes	Yes	Yes	Yes
ERG	Yes	Yes	No	Yes (central review objective response & PFS).	Yes	Yes	Yes

				Unclear (duration of response)			
KEYNOTE-189							
Company	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ERG	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PARAMOUNT							
Company	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
ERG	Yes	Yes	Yes	Yes (PFS, response)	Unclear	Yes	Yes
PRONOUNCE							
Company	Unclear	Unclear	No	No	Unclear	Yes	Yes
ERG	Unclear	Unclear	No	No	Unclear	Yes	Yes

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer [ID1210]

You are asked to check the ERG report from Southampton Health Technology Assessments Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Tuesday 20 November** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Inclusion of relevant comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 11) states that: *"Patients who cannot tolerate cisplatin would therefore be treated with a carboplatin-based regimen (i.e. docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with carboplatin), followed by maintenance treatment with pemetrexed. This treatment regimen is not included in the CS"* A similar statement is made in page 20, 24, 26, 124	*"Patients who cannot tolerate cisplatin can be treated with a carboplatin-based regimen (i.e. docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with carboplatin), followed by maintenance treatment with pemetrexed. This treatment regimen is not included in the CS.* *However, UK clinical expert opinion and UK market share data have confirmed pemetrexed plus carboplatin or cisplatin (with or without pemetrexed maintenance) is the standard of care chemotherapy for the vast majority of untreated non-squamous NSCLC patients. These comparators are included in the CS"*	It is factually correct that guidance from NICE (TA190) recommends pemetrexed maintenance for NSCLC after platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel (1). However, ten UK clinical experts consulted by Roche have confirmed that the vast majority or "almost all" of untreated non-squamous NSCLC patients are treated with either carboplatin or cisplatin in combination with pemetrexed, with or without pemetrexed maintenance. Pemetrexed-based chemotherapy should therefore be considered the UK standard-of-care for untreated non-squamous NSCLC. Cisplatin plus gemcitabine is not routinely used for treatment of non-squamous NSCLC patients, based on results of the JMDB trial (2) which showed that cisplatin in combination with pemetrexed was clinically and statically superior to cisplatin plus gemcitabine. Cisplatin plus docetaxel or paclitaxel is also not routinely used in non-squamous NSCLC	We acknowledge this point, but it is not a factual error – no change made.

		patients due to the Schiller J et al study (3), which showed that all platinum-based therapies were equivalent in terms of efficacy, although gemcitabine had a more tolerable safety profile. Furthermore, during the TA181 NICE appraisal, clinical experts also confirmed that docetaxel is not widely used in the UK because of its adverse-event profile (4). We acknowledge in our submission that patients who cannot tolerate cisplatin will receive carboplatin-based chemotherapy. A recent Cochrane meta-analysis has shown no difference between carboplatin and cisplatin regimens in terms of overall survival, although differences in safety and tolerability exist (5). UK clinical experts consulted by Roche agree that approximately half of patients will receive carboplatin plus pemetrexed in first-line non-squamous NSCLC, with the other half receiving the cisplatin plus pemetrexed combination. Therefore, we do not consider that any standard-of-care chemotherapy option for first-line non-squamous NSCLC has been excluded from our submission or economic model, since pemetrexed plus carboplatin or cisplatin (with or without	

		pemetrexed maintenance) are both included as relevant comparators.	

Issue 2 Inclusion of relevant comparators – EGFR/ALK positive patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 24) does not state that whilst in the NICE final scope, docetaxel or pembrolizumab are not appropriate comparators in patients with EGFR-or ALK-positive advanced, non-squamous NSCLC previously treated with targeted therapy. A similar statement is made in page 20, 124.	Please add statement "*We understand that docetaxel and pembrolizumab should not be considered as comparators for people with EGFR or ALK mutations",* as per the conclusion in page 80 of the ERG report.	The ERG states in page 80: *"We understand that this interpretation is correct and that docetaxel and pembrolizumab should not be considered as comparators for people with EGFR or ALK mutations"*	We have made the requested change which was applicable to page 27 (not page 24) of the ERG report.

Issue 3 Impact of the use of additional comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 81) states that: *"We note, however, that the model does not compare against carboplatin-based chemotherapy followed by*	*"We note, however, that the model does not compare against carboplatin-based chemotherapy followed by pemetrexed maintenance, which is an option for patients who cannot tolerate cisplatin. It is unclear how this*	We disagree with the statements that: 1. "… *the model does not compare against carboplatin-based chemotherapy followed by pemetrexed maintenance*". • In the model we do compare with carboplatin or cisplatin in	Point 1 – the point we were making is that the model does not compare against carboplatin in combination with chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) which is a scoped comparator. We have amended the

pemetrexed maintenance, which is an option for patients who cannot tolerate cisplatin. It is unclear how this omission affects the incremental cost-effectiveness results"	*omission affects the incremental cost-effectiveness results"*	combination with pemetrexed, with or without pemetrexed maintenance, so effectively carboplatin-based chemotherapy is accounted for in the model 2. *"It is unclear how this omission affects the incremental cost-effectiveness results"* • Pemetrexed-based chemotherapy has demonstrated better efficacy compared to other chemotherapy combinations in untreated non-squamous NSCLC, based on results of the JMDB trial (2). Therefore, by comparing to the chemotherapy with the highest efficacy in the economic model, it is reasonable to assume that the comparison to other chemotherapy options will be more favourable for Atezo+Bev+CP in terms of clinical outcomes.	sentence to make this clearer. NOTE: The company's 'Description of proposed amendment' doesn't seem any different to our original text. Point 2 – relates to the clarification we have made for point 1 above. Not a factual error, no change proposed.

Issue 4 Updated indication wording

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 11) states that: *"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 ineligible*	Can the second bullet point please be amended to read: "patients who have progressed on targeted therapies for epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) tumour mutations."	Text of ERG report to reflect the updated indication wording of our anticipated marketing authorisation: [redacted]	Change made as requested.

for, intolerant to or who have progressed on targeted therapy for epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) tumour mutations."			

Issue 5 Outcomes for patients with PDL1 low/negative expression and EGFR/ALK mutations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 24) states that: *"Expert clinical advice to the ERG notes that patients with EGFR/ALK mutations tend to have better survival, and respond better to pemetrexed chemotherapy. Patients with high PD-L1 expression are also*	*"UK clinical expert opinion and published literature have confirmed that level of PDL1 expression is not an effect modifier status for pemetrexed-based chemotherapy. Evidence to support that EGFR/ALK mutation is an effect modifier for pemetrexed-based chemotherapy are*	Roche consulted with four UK clinical experts to establish whether the level of PD-L1 expression and the presence of EGFR/ALK mutations are effect modifiers for pemetrexed-based chemotherapy in the studies included in the NMA. This would enable a connected network in	Not a factual error, no change made.

more likely to respond to pemetrexed chemotherapy" The ERG report (page 46) states that: *"The CS makes the assumption that EGFR and ALK status are not effect modifiers for pemetrexed based regimens. However, expert clinical advice to the ERG did not agree with this assumption."* The ERG report (page 86) states that: *"Expert clinical advice to the ERG suggests that people with EGFR/ALK mutations and those with high PD-L1 expression are more likely to respond to pemetrexed chemotherapy than other patients."* A similar statement is made in page 88.	*however more inconclusive. Nonetheless, four UK clinical experts consulted in the CS suggested that the assumption of EGFR/ALK status is not an effect modifier for chemotherapy is reasonable and necessary in order to be able to perform an indirect treatment comparison for the EGFR/ALK subgroup of patients"*	order to perform subgroup NMAs • For the level of PD-L1 expression, the OAK study in second-line NSCLC and KEYNOTE-189 in first-line NSCLC have demonstrated that there is no significant effect of the level of PD-L1 expression on the clinical efficacy of chemotherapy. (6, 7). UK clinical experts agreed with this. • The assumption that EGFR mutation is not an effect modifier for chemotherapy efficacy is supported by the literature (8, 9). When asked, the four UK clinical experts considered that there is inconclusive evidence to support whether patients with EGFR/ALK mutations have better health outcomes on chemotherapy compared to non-mutated patients. However, they appreciated that this assumption is reasonable and necessary in order to be able to perform an indirect treatment comparison within the EGFR/ALK subgroup of patients.	

Issue 6 Evidence of effect modification in study IMPower 150

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>The ERG report (page 86) states that:

"However, analysis of the IMpower150 trial did not show any evidence of effect modification for the EGFR/ALK or PD-L1 subgroups. We consider that the ITT NMA is a more robust source for relative treatment effects than the subgroup NMAs, and so we use the ITT NMA in the ERG base case for both subgroups."

A similar statement is made in page 88, 124</td>
<td>"… analysis of the IMpower150 provides and an indication of effect modification in the relevant subgroups of interest, especially for EGFR/ALK+ patients."</td>
<td>We disagree with the statement "there is no evidence of effect modification from the IMpower150 trial".

Based on the results presented on the following table we believe there is an indication of effect modification in the relevant subgroups of interest, especially for EGFR/ALK positive patients. In EGFR/ALK positive patients we see a reduction in the risk of death of 46% whereas in the ITT we see a reduction of 24%. Meanwhile, the median OS in the control arm (Bev+CP) is similar in the ITT and in relevant subgroups (PD-L1 low/negative and EGFR/ALK+) indicating that level of PD-L1 expression and presence of EGFR/ALK mutation status are not prognostic factors.
<table>
<tr><th></th><th colspan="2">Median and 95% CI</th><th></th></tr>
<tr><th></th><th>Bev + CP</th><th>Atezo + Bev + CP</th><th>Hazard Ratio</th></tr>
<tr><td>ITT</td><td>14.9 (13.4 , 17.1)</td><td>19.8 (17.4 , 24.2)</td><td>0.76 (0.63, 0.93)</td></tr>
<tr><td>PD-L1 low/neg</td><td>14.9 (13.5 , 17.1)</td><td>19.1 (16.8 , 23.8)</td><td>0.80 (0.65, 0.99)</td></tr>
<tr><td>EGFR/ALK+</td><td>17.5 (10.4 , NE)</td><td>NE (17.0 , NE)</td><td>0.542 (0.285, 1.03)</td></tr>
</table>
</td>
<td>Not a factual error, no change proposed.

(NB. The Cox models the company cite were not reported in the CS or in response to our clarification question). The models do not show evidence of effect modification. Given the small size of the EGFR/ALK subgroup, interpreting the difference in HRs as evidence of modification isn't justified.)</td>
</tr>
</table>

		Interaction tests for exploring the treatment effect in subgroups of patients were not pre-planned in study IMPower150. In addition, interaction tests require a large sample size to reach a definite conclusion (stated to be 16 times higher than the sample size to estimate an interaction than to estimate a main effect[1]). Therefore, inconclusive results should be treated with caution, due to the statistical power needed for such tests. Nonetheless, we performed interaction tests, by fitting two Cox models including: • Treatment, presence of EGFR/ALK+ (yes/no) and the interaction between both. The p-value for the interaction is: 0.3023 • Treatment, presence of PD-L1 low and negative (yes/no) and the interaction between both. The p-value for the interaction is: 0.3855 Whilst the results of the interaction tests are not statistically significant, this does not mean that presence of PD-L1 low/negative expression or EGRF/ALK+ are not effect modifiers. The results of study IMPower150 shown above provide an indication of effect modification in relevant subgroups, especially for EGFR/ALK+ patients.	

[1] "You need 16 times the sample size to estimate an interaction than to estimate a main effect", https://andrewgelman.com/2018/03/15/need-16-times-sample-size-estimate-interaction-estimate-main-effect/

Issue 7 ERG conclusion for the EGFR/ALK subgroup NMA results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 70) states that: *"The EGFR/ALK subgroup results were less favourable than the ITT analyses but should be viewed with caution due to small numbers of patients included."* This also stated in pages 16 and 68.	*"The EGFR/ALK subgroup results are more favourable than the ITT analyses but should be viewed with caution due to uncertainty introduced by the small numbers of patients included."*	This ERG conclusion is factually inaccurate. Please note that that while estimates for the EGFR/ALK positive subgroup come with a higher degree of uncertainty, the point estimates indicate a more favourable outcome for Atezo+Bev+CP compared to the ITT analysis, contrary to what is stated. This can be demonstrated in terms of expected survival difference for OS at 60 months. The expected OS difference is more pronounced in favour of the atezolizumab combination in the EGFR/ALK population compared to the ITT, against both pemetrexed-based comparators (please see page 59 in CS and page 159 in Appendix D). In terms of OS hazard ratio, this is initially higher (i.e. more favourable for Atezo+Bev+CP) in the EGFR/ALK population compared to the ITT analysis. This higher hazard ratio then drops off faster than for the main analysis. The overall impact of this difference however is a larger difference in expected OS in favour of Atezo+Bev+CP in the EGFR/ALK positive population compared to the ITT.	We have amended the text on page 68 to say: [redacted] We have amended the text on pages 16 and 70 to say: [redacted]

Issue 8 Representation of hazard in NMA models

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 49) states that: *"However, we note U-shaped curves are not represented in the selection of hazard ratios presented."*	Please remove this sentence.	The range of second order models that were evaluated does allow U-shaped hazard patterns, which in turn would make U-shaped hazard ratio curves possible.	Sentence removed

Issue 9 OS extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 20) states that: *"We consider that the Weibull distribution is also plausible, with more conservative survival predictions."* A similar statement is made in page 91.	*Please consider revising to: "We consider that the Weibull distribution is also plausible, but with overly conservative survival predictions."*	Our company submission outlined that Weibull provides overly conservative OS at 5 years for Atezo+Bev+CP based on UK clinical expert opinion and validation against other NICE TAs in the same indication.	Not a factual error. It is the ERG's view that the Weibull distribution is a plausible distribution, based on the evidence provided. Reasons for this are given in the ERG report.

Issue 10 Utility analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 20) states that: *"It is unclear whether patients treated with Atezo+Bev+ CP have the same health state utility whilst on treatment as those treated with pemetrexed + platinum (with or without pemetrexed maintenance).."*	Please consider removing this sentence.	Page 117 of our company submission states that when calculating utilities following the proximity to death approach: *"Initially we considered two separate models according to the treatment status: on and off treatment. However, results for off-treatment utilities produced broad confidence intervals which would overlap. This would produce unrealistic results in the probabilistic sensitivity analysis (PSA) of the economic model where patients closer to death would have higher utility than those further away from death. Therefore, we decided to fit and to report only utilities by time before death group according to the proximity to death as it is shown in the following figure."*	Not a factual error. This statement is not about the validity of the proximity to death approach, but is concerning the fact that Atezo+Bev+CP and pemetrexed + platinum (with or without pemetrexed maintenance) have not been directly compared in a trial.

Issue 11 End of life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Tables 56 and 58 of the ERG report (pages 136-137), only mean OS is reported from the CS	Please update Table 56 to report mean and median OS from the CS, and to also include evidence on OS for pemetrexed-based chemotherapy from published studies. These can be found in page 91 of the CS. Please also update Table 58 to include both incremental mean and incremental median OS.		Median OS estimates have now been included in Tables 56-59

Issue 12 ERG amended base case model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG amended base case model does not reflect the ERG base case results.	Please send an updated model to reflect ERG base case results for ITT and relevant population subgroups	We cannot reproduce the ERG base case and scenarios (Section 4.4.2) from the ERG base case model that NICE have shared with us, without having to make adjustments	We apologise. The correct model that we used for our base case analysis has been sent to NICE with instructions on how to replicate our analysis.

Issue 13 EORTC QLQ-C30 results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 11) states that: *"Treatment with both Atezo+Bev+CP and Bev+CP was reported by patients to lead to worsening peripheral neuropathy and alopecia:*	*"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."*	Consistency with what is stated in page 59 of the ERG report: *"Treatment related symptoms of peripheral neuropathy and alopecia worsened initially in both treatment arms (≥ 30-point mean increase from baseline for peripheral neuropathy; ≥60-point mean increase from baseline for alopecia) but over time this effect was observed to attenuate (data not presented in the CS)".*	The ERG finds the text highlighted by the company on page 14 (not page 11). In trying to keep the ERG summary succinct the ERG lost some of the detail from page 14 which is presented on page 59 of the ERG report. The ERG has amended page 14 as suggested by the company.

Issue 14 Missing data in the PROs analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report (page 24) states that: *"It is not clear how missing data were accounted for in the analysis of response or of PROs"*	Given that the ERG had access to both the CS and the CSR, please consider removing this statement.	Page 103 of the CSR outlines that for PROs: • The EORTC QLQ-C30 and EORTC QLQ-LC13 were scored according to the EORTC scoring manual (Fayers et al. 2001). The QLQ-C30 and QLQ-LC13 consisted of both multi-item scales and single-item measures such as functional scales, symptom scales, and a	The information on handling of missing PRO data is not reported or cited in the CS and therefore it was not clear to the ERG how missing PRO data were accounted for (note this is reported on ERG report page 34, not page 24). The ERG agree procedures for handling missing EORTC QLQ-C30 quality of life data are provided in the CSR, however procedures do not appear to be

		global health status/quality-of-life scale. • For multi-item subscales, if ≤50% of items within the multi-item subscale were missing at a given time point, the multi-item score was calculated on the basis of the non-missing items. If ≥50% of items were missing or if a single-item measure was missing, the subscale was missing.	reported for the EQ-5D. The ERG has clarified the text on p.34.

Issue 15 Confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Update confidentiality marking	Please ensure the following updates are made: • Page 11: the sentence "clinicians would be unlikely to treat patients with a regimen containing four drugs (i.e. Atezo+Bev+CP) instead of one drug (pembrolizumab)." Should be CIC • Page 19: only with-PAS ICERs should be unredacted. The rest should be CIC • Page 23: only with-PAS ICERs should be unredacted. The rest	To reflect the updated confidentiality marking of the company submission and to amend some parts of text the report that were not appropriately redacted.	Page 11 - marking updated Page 19 – total costs and QALYs marked as CIC Page 23 - total costs and QALYs marked as CIC Page 56 – marking updated Page 64 - marking updated Page 66 – marking updated Page 70 - marking updated Page 104 – marking updated Page 109 - marking updated

	should be CIC • Page 56: All of the second paragraph should be marked as AIC • Page 64: first paragraph of Section 3.3.7.1 and Figure 6 to be unredacted • Page 66: first paragraph of Section 3.3.7.2 and Figure 9 to be unredacted • Page 70: Section 3.3.7.3 to be unredacted • Page 104: IMPower 150 utility values to be unredacted • Page 109: Subsequent therapies anticipated market shares to be unredacted • Page 114: In Tables 39-42 only with-PAS ICERs should be unredacted. The rest should be CIC • Pages 128-135: In Tables 47-55 only with-PAS ICERs should be unredacted. The rest should be CIC In the addendum to the ERG report: • All fields of result tables at list price (Tables 1-12) should be		Page 115 (not 114) - total costs and QALYs marked as CIC in Tables 39-42 Pages 128-135 - total costs and QALYs marked as CIC in Tables 47-55

	redacted as CIC • In Table 13 (page 11) only with-PAS ICERs should be unredacted. The rest should be CIC		

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2. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543-51.
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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 **Error! Reference source not found.**,

[redacted]

[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) 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 1 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).

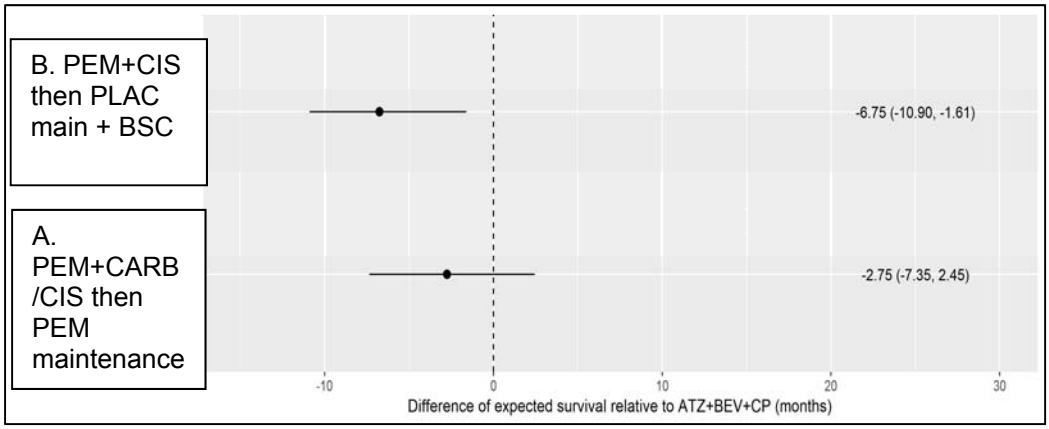
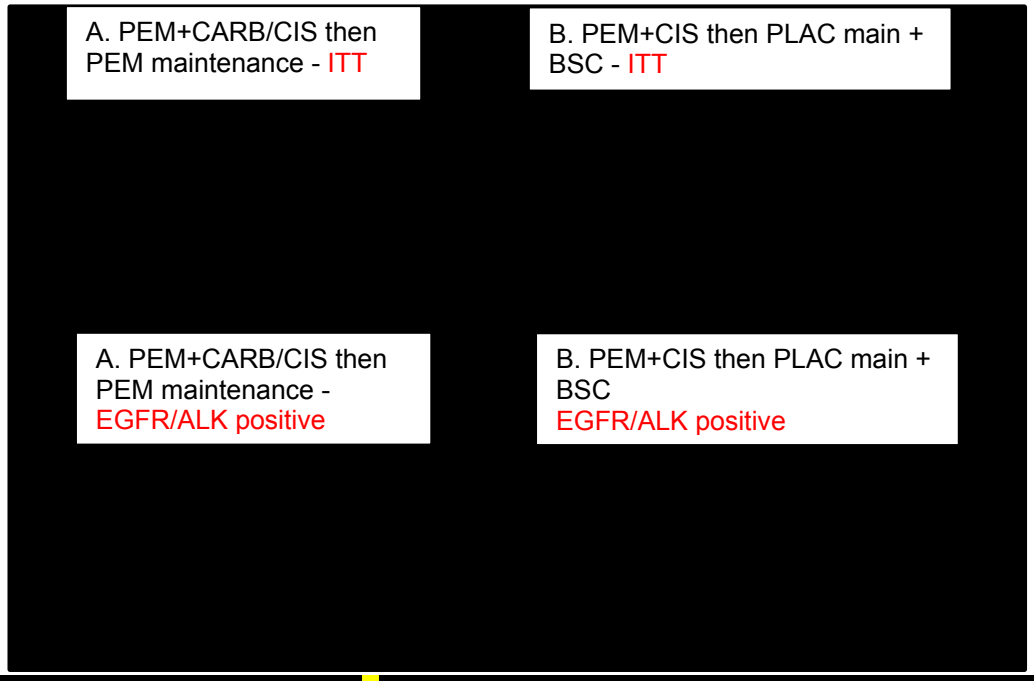


Figure 1 Forest plot of the expected mean OS difference relative to Atezo+Bev+CP (time horizon 60 months)
Reproduced from CS figure 10

[redacted] Error! Reference source not found. [redacted]



2

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

-
-

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 3 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.

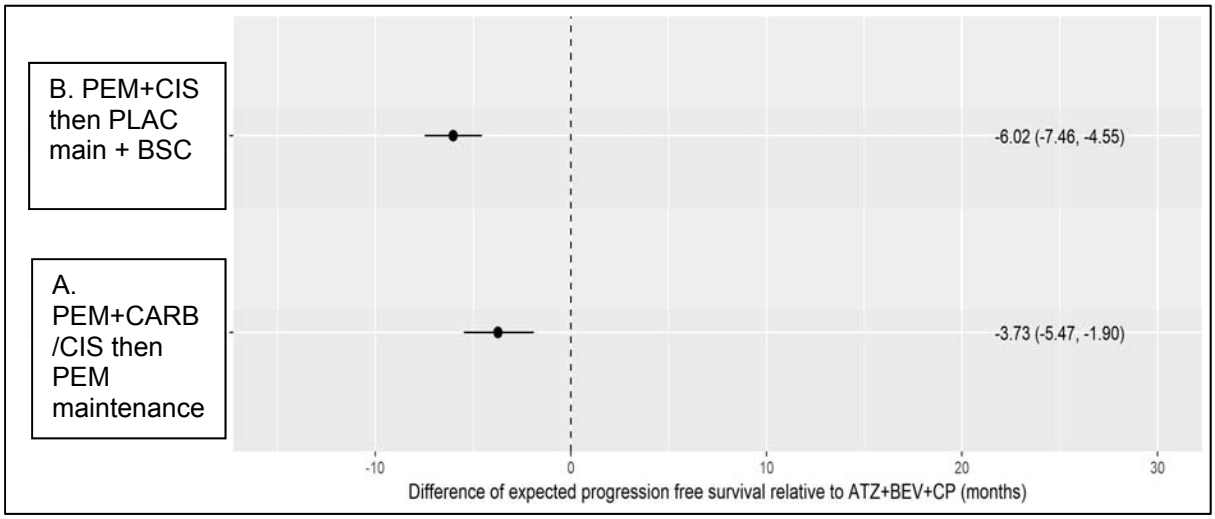


Figure 3 Forest plot of the expected PFS difference relative to Atezo+Bev+CP (time horizon 30 months)
Reproduced from CS Figure 12

The time-varying HR plots ([redacted]4, and CS Figure 13) show similar results to the forest plots:

[redacted]
A. PEM+CARB/CIS then PEM maintenance
B. PEM+CIS then PLAC main + BSC
4

EGFR/ALK positive subgroup

[redacted]**Error! Reference source not found.**[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 **Error! Reference source not found.**).

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 **Error! Reference source not found.**. 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 **Error!**

Reference source not found. 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.

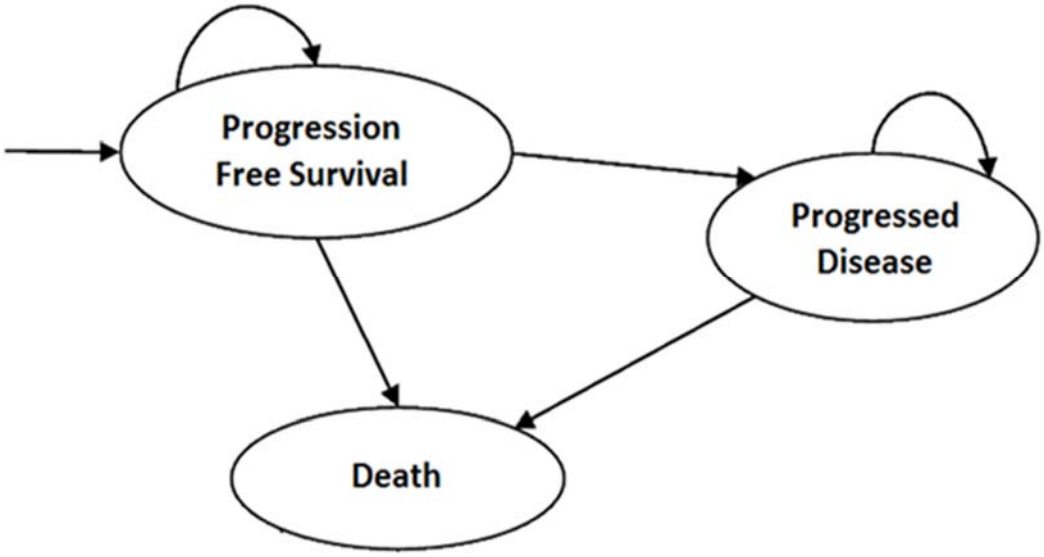


Figure 12 Economic model (reproduced from CS Figure 31)

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 **Error! Reference source not found.** (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 3, Table 4 and Table 5 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 5. The results when the ERG ran the company model are shown in Table 6. 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 7 - Table 9, with PAS price for atezolizumab and bevacizumab and list price for comparators and subsequent treatments. The ERG corrections (**Error! Reference source not found.**) 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 10 and Table 11 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 12 (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 13 and Table 14.

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 15. 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 16 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 17).

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 18 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 19).

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.

CONFIDENTIAL UNTIL PUBLISHED

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

Additional Erratum

Replacement pages in addition to Erratum following the factual accuracy check by Roche Product Limited

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Stopping rule	2 year maximum in the base case. Scenario with no limit on treatment duration. This aligns with stopping rules for atezolizumab after chemotherapy (TA520) and pembrolizumab (TA531).	No change
Effect duration	5 year cut off for OS (3 years after stopping), with scenario analysis from 8.75 to 20 years In the revised model this was applied by setting the mortality rate for Atezo+Bev+CP equal to that for PEM+plat with maintenance.	No change for base case, but extend the scenario analysis due to uncertainty over the duration of effects after discontinuation of immunotherapies (e.g. as noted in TA 520).
Clinical parameters		
Fitted survival curves for atezolizumab combination	ITT & PD-L1 low • OS exponential • PFS KM + log-logistic tail • TTD exponential EGFR/ALK +ve subgroup • OS exponential • PFS log-normal • TTD exponential KM tails attached where 20% of patients remain at risk Parametric curves fitted separately to Atezo+Bev+CP arm of IMpower150 (Jan 2018 cut off with investigator-assessed PFS).	ERG base case: The ERG prefers the Weibull distribution for OS extrapolation (section 4.2.4.1). The choice of parametric curves for PFS and TTD are reasonable.
Relative effects	HR from ITT NMA FP (FE) P1=0 Weibull (scenarios: PH and RE NMA models, excluding KEYNOTE, excluding PARAMOUNT)	The ERG prefers the analysis excluding the PARAMOUNT trial (due to heterogeneity), with first order Weibull, fixed effects.
AE rates	See CS Tab 43 p132	No change
Utilities		
Health state	IMpower150 EQ-5D IPD time from death analysis (IMpower150 PF/PD, Huang, Nafees, Chouaid)	No change to health state utilities, however company has not included any differences in utility between the treatments.

4.4.2 ERG base case and scenarios

Results for the ERG base case analysis for the ITT population are shown in Table 1 (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 2 and Table 3.

Table 1 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 2 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 3 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]		£3,352
Atezo+Bev+CP	[redacted]	[redacted]	£3,352	

The results of scenarios around the ERG ITT base case are shown in **Error! Reference source not found.**. 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 survival and treatment duration, the use of a stopping rule for

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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

Addendum to the ERG report: Results with list prices for all treatments

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Date completed 8th November 2018

This is an addendum to the ERG report dated 8th November 2018. In this addendum we present the company's base case results, ERG corrected company base case results, ERG corrected company scenario analyses, ERG base case analyses and ERG scenario analyses, all of which are based on available list prices. In addition to the above, this addendum contains an additional ERG scenario analysis in which one of the subsequent treatment options for patients progressing on first line treatment is nintedanib in combination with docetaxel (based on PAS discount prices for atezolizumab and bevacizumab).

Analyses based on all available PAS analyses are available in a separate confidential addendum (dated 8th November 2018).

1.1 Cost-effectiveness results at list prices

1.1.1 Company base case results (from clarification response)

The company base results for the three populations at list price for all treatments are shown in Table 1-Table 3.

Table 1 Company base-case results ITT population – list price, deterministic (Clarification response Table 31)

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
Pem+plat	[redacted]	[redacted]		[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	-

Table 2 Company base-case results PD-L1 negative/low population – list price, deterministic (Clarification response Table 32)

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
Pem+plat	[redacted]	[redacted]		[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	-

Table 3 Company base-case results EGFR/ ALK positive population – list price, deterministic (Clarification response Table 33)

Technologies	Total costs (£)	Total QALYs	ICER (£) fully incremental analysis	ICER (£) pairwise; Atezo+Bev+CP vs comparator
Pem+plat	[redacted]	[redacted]		[redacted]
Pem+plat+pem maint	[redacted]	[redacted]	[redacted]	[redacted]
Atezo+Bev+CP	[redacted]	[redacted]	[redacted]	-

1.1.2 Company base case results (with ERG corrections)

The company base case results for the three populations with ERG corrections are shown in Table 4-Table 6 with list price for all treatments.

Table 4 Company base case results with ERG corrections for ITT population – list price

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

Table 5 Company base case results with ERG corrections for PD-L1 population – list price

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

Table 6 Company base case results with ERG corrections for EGFR/ALK+ population – list price

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

1.2 Company scenarios with ERG corrections at list price

Table 7 and Table 8 show the scenario analyses with ERG corrections for the ITT population with list price for all treatments.

Table 7 Scenario analysis results- ITT population vs. Pemetrexed plus platinum plus pemetrexed maintenance – list price

	Description	Atezo+Bev+CP			Pem+platinum w Pem maint			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	(£/QALY)
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS distribution	KM with Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution	KM with Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
Alternative NMA network	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ITT exclude Keynote	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ITT exclude Paramount	[redacted]						
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]						
	NMA - PH	[redacted]						
	NMA - Fract Poly (RE)	[redacted]						
Treatment stopping rule	At 2 years (base case)	[redacted]						
	No treatment stopping rule	[redacted]						
Treatment effect duration	5 years (base case)	[redacted]						
	105 months	[redacted]						
	150 months	[redacted]						
	195 months	[redacted]						
	240 months (lifetime)	[redacted]						
Wastage	With vial sharing (base case)	[redacted]						
	No vial sharing	[redacted]						
Utility values	IMpower150 (Proximity to death) (base case)	[redacted]						
	IMpower150 (Pre/Post progression)	[redacted]						
	Chouaid et al. 2013	[redacted]						
	Nafees et al. 2008	[redacted]						
Subsequent treatments	Base case	[redacted]						
	Impower 150	[redacted]						
AE disutility	No (base case)	[redacted]						
	Yes	[redacted]						

Table 8 Scenario analysis results- ITT population vs. Pemetrexed plus platinum – list price

	Description	Atezo+Bev+CP			Pem+platinum			ICER
		Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	(£/QALY)
OS distribution	Exponential (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
PFS distribution	KM with Log-logistic tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution	KM with Exponential tail (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Does not converge						
Alternative NMA network	ITT (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ITT exclude Keynote	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ITT exclude Paramount	Does not converge						
Alternative NMA model	NMA - Fract Poly (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NMA - PH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NMA - Fract Poly (RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	At 2 years (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

1.2.1 ERG analyses

Table 9 - Table 11 show the ERG base case results for the three populations with list price for all treatments.

Table 9 ERG base case results for ITT population– list price

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

Table 10 ERG base case results for PD-L1 population– list price

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

Table 11 ERG base case results for EGFR/ALK population – list price

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

Table 12 shows the scenario analyses with the ERG base case for the ITT population with list price for all treatments.

Table 12 ERG scenario analysis for ITT population – list price

	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]	[redacted]
	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS distribution	KM+log-logistic (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	KM + Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	KM+Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD distribution	KM + Exponential and pemetrexed follows PFS (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Bevacizumab until progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative NMA network/model	ITT FP excluding PARAMOUNT (FE) (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ITT FP (RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ITT PH (excluding PARAMOUNT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment stopping rule/treatment effect	2 years treatment + 3 years OS effect (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	2 years OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5 years OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 years PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No stopping rule or effect cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility values	IMPower150 EQ-5D, using time from death + disutilities (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IMPower EQ-5D health states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	disutilities per grade 3+ treatment related AE (base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No AE disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	IMpower150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exclude nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Include nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.2.2 Additional scenario analysis - subsequent treatments

We have included an additional scenario for subsequent (second line) treatments in which nintedanib in combination with docetaxel is an available option for patients progressing on pemetrexed-based chemotherapy. This scenario analysis is not reported in the main ERG report. Costs for nintedanib were taken from NICE technology appraisal TA347 (i.e. 21 day cycle cost of nintedanib of nintedanib £1434.07; docetaxel £20.02; treatment given for 5.35 months). We assumed that 15% of patients received nintedanib and docetaxel, and kept the

proportion of all other treatments unchanged. The model rescales the proportion on all treatments to equal 100%. (Rescaled proportion for patients receiving nintedanib 13%).

Error! Not a valid bookmark self-reference. shows the additional scenario analysis in the ERG base case with subsequent treatment for nintedanib + docetaxel for the ITT population (based on PAS discount for atezolizumab and bevacizumab).

Table 13 ERG scenario analysis for ITT population including nintedanib + docetaxel – (PAS price for atezolizumab and bevacizumab)

	Description	**Atezo+Bev+CP**		**Pem+platinum+Pem Maintenance**		**ICER (£/QALY)**
		Total QALYs	Total costs	Total QALYs	Total costs	
Subsequent treatments	Base case	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Include nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

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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

ERG scenarios for reduced use of subsequent treatments

Contains Patient Access Scheme discount prices for atezolizumab and bevacizumab only

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Date completed **18 January 2019**

ERG scenario with reduced use of subsequent treatments

The company model assumes that all patients with progressed disease have subsequent treatment, with 100% of those who progress after Atezo + Bev + CP having docetaxel; and 15%, 34%, 34% and 17% of those who progress after pemetrexed-based regimens having docetaxel, nivolumab, pembrolizumab and atezolizumab respectively (CS Table 34).

The ERG ran a set of scenarios with reduced proportions of patients proceeding to any subsequent treatment, while holding the above mix of subsequent treatments constant. We ran the analyses for the ERG base case with the ITT population and the PAS price discounts for atezolizumab and bevacizumab but list prices for pemetrexed and all subsequent treatments.

Results are reported in Table 1 below. ICERs are sensitive to the uptake of subsequent therapy and vary between dominant in the base case, to £55,706 per QALY gained.

Table 1 Reduced uptake of subsequent therapy: ERG base case ITT population (PAS for atezolizumab and bevacizumab only)

Proportion of patients with subsequent therapy	Atezo+Bev+CP		Pem+platinum+Pem maintenance		ICER (£ per QALY)
	Total QALYs	Total costs	Total QALYs	Total costs	
Base case 100%	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
90%	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
80%	[redacted]	[redacted]	[redacted]	[redacted]	£4,619
70%	[redacted]	[redacted]	[redacted]	[redacted]	£13,133
60%	[redacted]	[redacted]	[redacted]	[redacted]	£21,648
50%	[redacted]	[redacted]	[redacted]	[redacted]	£30,162
40%	[redacted]	[redacted]	[redacted]	[redacted]	£38,677
30%	[redacted]	[redacted]	[redacted]	[redacted]	£47,191
20%	[redacted]	[redacted]	[redacted]	[redacted]	£55,706