CIC and AIC information 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]– STA

Lead team presentation

1st Appraisal Committee meeting
Committee D
Lead team: Nabeel Alsindi, Paula Parvulescu, Rebecca Harmston
ERG: Southampton Health Technology Assessments Centre
NICE technical team: Emily Eaton Turner, Caron Jones
January 2019

Preview: Key issues - clinical effectiveness

- Are the comparators used by the company for each subgroup relevant to NHS clinical practice?
  - Would most people receive pemetrexed maintenance in clinical practice?
- Median overall survival has not been reached in the EGFR/ALK positive subgroup
  - Is the available overall survival data mature enough for decision making?
- Are the results from the company's network meta-analysis appropriate given the heterogeneity between the included studies?
  - Should the PARAMOUNT trial be included in the network meta-analysis?

[redacted]

Background
Non-small-cell lung cancer (NSCLC)

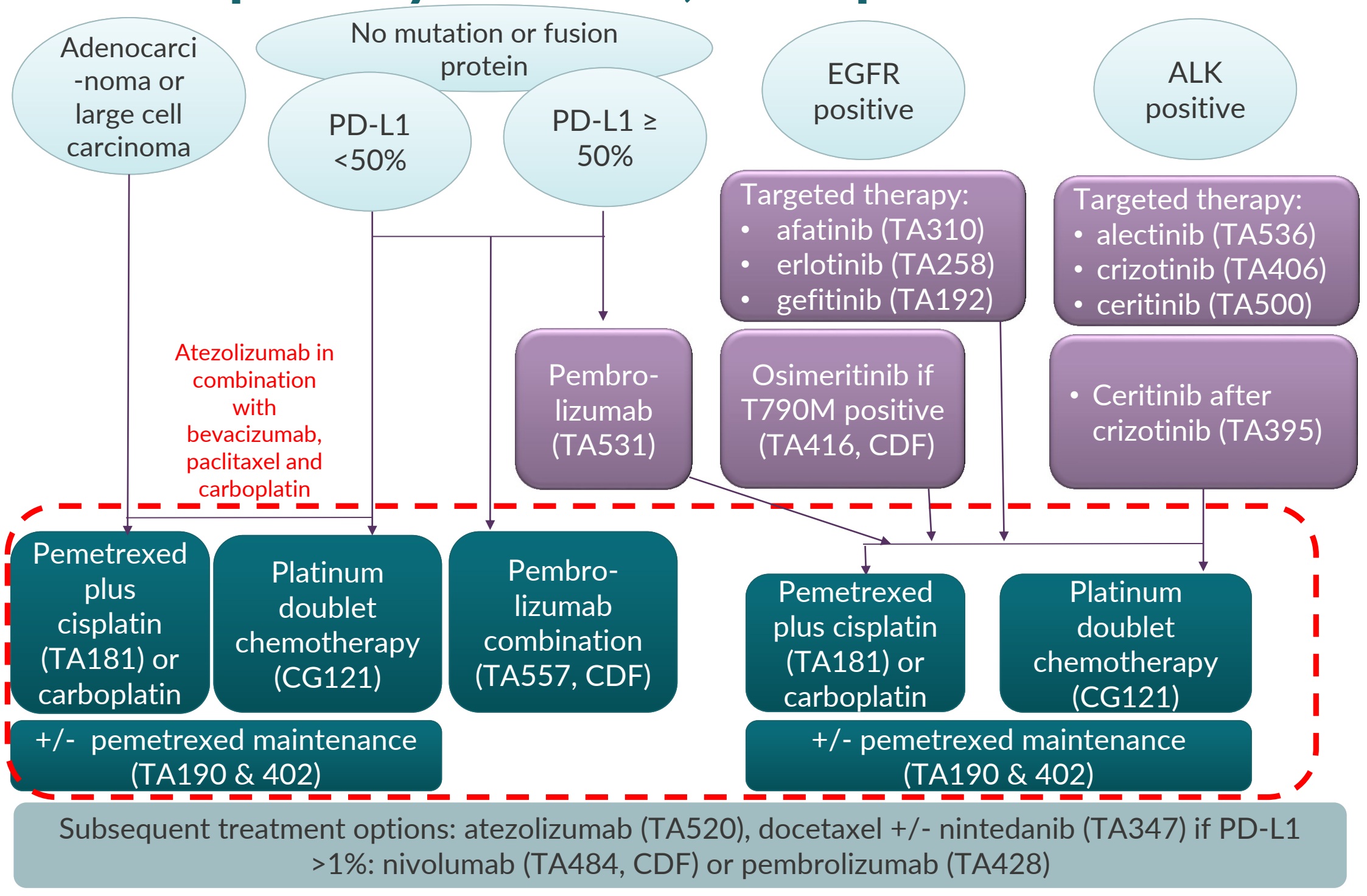
- Approximately 32,500 people were diagnosed with NSCLC in England in 2016, and around 61% had stage IIIB or stage IV disease
  - cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV)
- Approximately 70% of NSCLC are of non-squamous histology and can be either adenocarcinoma (30 to 40%), large-cell carcinoma (10 to 15%) and other cell types (5%)

[redacted]

Atezolizumab with bevacizumab, carboplatin & paclitaxel

Mechanism of action	**Atezolizumab**: directly & selectively binds to PD-L1 **Bevacizumab:** binds to VEGF **Carboplatin:** alkylating chemotherapy **Paclitaxel:** taxane chemotherapy	
Anticipated marketing authorisation	[redacted]	
Administration & dosage	**Atezolizumab**: 1,200 mg	**Bevacizumab:** 15 mg/kg
	Carboplatin: area under curve of 6 mg/mL/min*	**Paclitaxel:** 200 mg/m^2*
	*during induction phase, 4 or 6 cycles lasting 21-day only all by intravenous infusion every 3 weeks **for 2 years maximum 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 (150mg)	**Paclitaxel:** £9.85 per 16.7 ml vial (100mg)
	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	

NICE's pathway: advanced, non-squamous



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]

Patient expert organisation perspective

Submission received from National Lung Cancer Forum for Nurses

- People with lung cancer often struggle with side effects of the condition → many are breathless and fatigued
- Carers often feel helpless
- People with an ECOG performance status of 0 or 1 are likely to benefit from atezo+bev+CP → people with poor performance status likely to struggle with side effects
- There is an unmet need
- Effective treatments that do no affect quality of life are desired by people with lung cancer and their carers

[redacted]

NHS England perspective (1)

Background

- PD-L1 status is not an important consideration for this appraisal given wording of the anticipated MA

Comparators & clinical interest: Untreated metastatic non-squamous NSCLC TPS 0-49% population

- Platinum-based chemotherapy with pemetrexed plus pemetrexed maintenance = comparator of interest
- Carboplatin in combination with pemetrexed now formally commissioned by NHS England
- Pembrolizumab with platinum-based chemo with pemetrexed then pemetrexed maintenance for PD-L1 0 to 100% TPS is available in the CDF → not a relevant comparator as not routinely recommended but available in clinical practice as a treatment option
- Little clinical interest in the use of atezo+bev+CP in this population & low use likely, if recommended

Comparators & clinical interest: Metastatic non-squamous NSCLC with EGFR/ALK mutations

- Platinum-based chemotherapy with pemetrexed plus pemetrexed maintenance = correct comparator
- **Much more clinical interest** → atezo+bev+CP combination advances the inclusion of immunotherapy to an earlier line in the treatment pathway → benefits in people with EGFR/ALK: mutations who are fit outweigh the benefits of the option of sequential chemotherapy and then immunotherapy

Administration

- Atezo+bev+CP will substantially increase administration time compared to pemetrexed plus a platinum drug & pembrolizumab with pemetrexed (recommended in CDF)

[redacted]

NHS England perspective (2)

Clinical trial data

- Subgroup analyses in the trial mean that the statistical power of the analyses is weakened, particularly in EGFR/ALK positive subgroup
- EGFR/ALK positive subgroup is small & substantial imbalance between arms
- Indirect treatment comparison needed as comparator used in NHS clinical practice not included in trial → issues with heterogeneity & comparison with trials performed a long time ago when the treatment pathway was very different
- Indirect treatment comparison **must be versus platinum-based chemotherapy plus pemetrexed and pemetrexed maintenance**
- Dataset is relatively immature → 13.5 months median follow-up → final trial analysis will be valuable

Adverse events

- Noted higher toxicity in the atezo+bev+CP arm compared with bev+CP in IMpower150 trial

Stopping rule

- 2 year stopping rule important → included in NICE recommendation & in NHS commissioning for atezolizumab monotherapy after platinum-based chemo (TA520) despite not being included in the clinical trial or SmPC → NHS England would commission a 2 year stopping rule if recommended

Subsequent therapies

- Nivolumab not in routine commissioning so should not be included
- Docetaxel plus nintedanib only modest use in clinical practice

[redacted]

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%) ✓	
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	
Subgroups	Level of PD-L1 expression	✓	

Decision problem: comparators

Scope	Company	
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	

- Are the comparators included by the company relevant to NHS clinical practice?
- Is the comparison with pemetrexed plus platinum drug +/- maintenance appropriate for the EGFR/ALK positive subgroup?
- Would most people receive pemetrexed maintenance in clinical practice?

[redacted]

*Chemotherapy: docetaxel, gemcitabine, paclitaxel or vinorelbine

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

Clinical effectiveness

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

[redacted]

Key baseline characteristics in IMpower150

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**				
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)

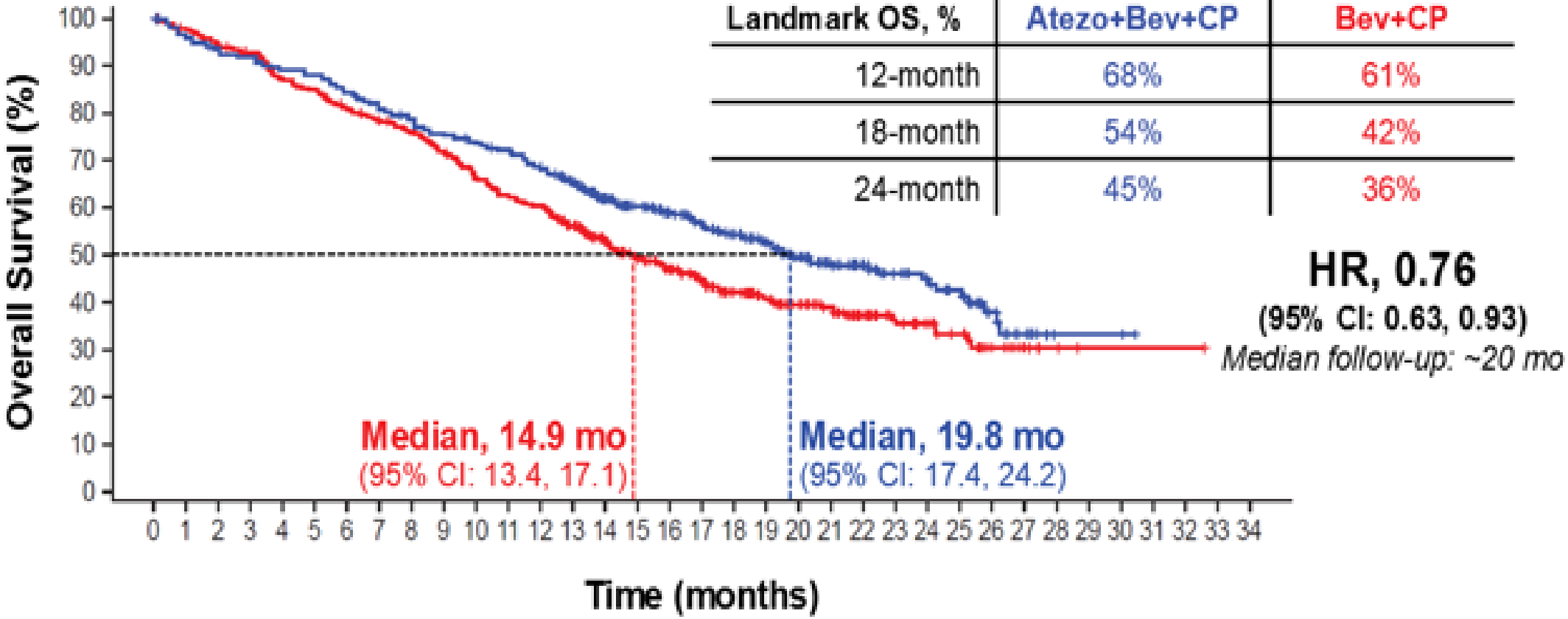
ERG comments: • ITT population is well balanced between arms
• EGFR/ALK+ve population small & differs from the ITT population in numerous baseline characteristics → some imbalance likely due to smaller population size & non-random nature

[redacted]

ITT population: Atezolizumab with bevacizumab, carboplatin & paclitaxel significantly improves OS compared with bev+CP

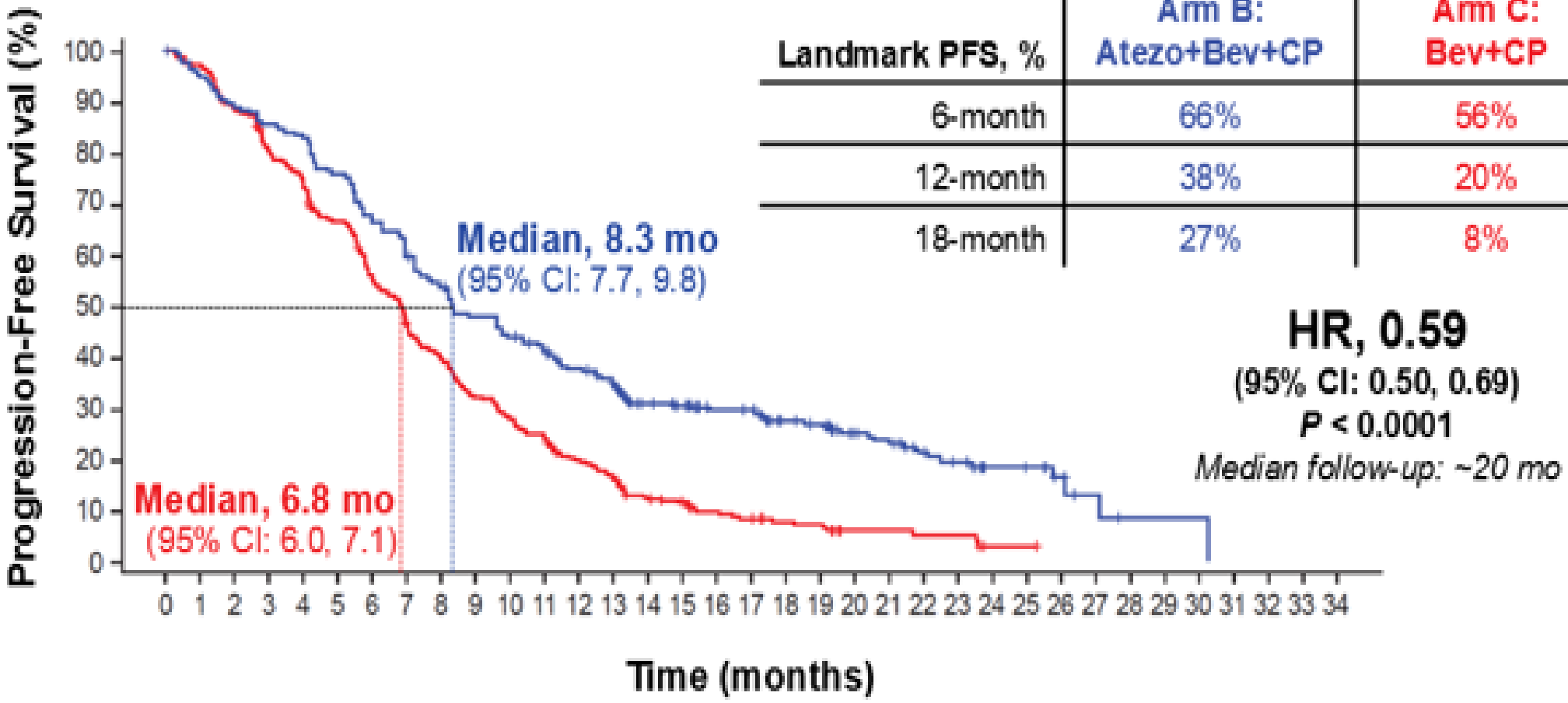
- Median OS reached in both treatment arms, final OS data still to report

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



ITT population: Atezolizumab with bevacizumab, carboplatin & paclitaxel 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%



No. at Risk

Atezo+Bev+CP	359	336	315	301	293	267	234	213	190	168	154	146	125	112	85	80	69	68	53	50	37	33	24	20	12	11	6	3	1	1	1
Bev+CP	337	323	294	263	244	215	180	148	127	103	89	78	61	50	35	29	21	18	14	13	6	6	5	5	1	1					

PD-L1 <50% TPS: Median OS & PFS was longer with atezolizumab with bevacizumab, carboplatin & paclitaxel versus bevacizumab, carboplatin & paclitaxel

	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, 0.76 (0.63 to 0.93)

PFS: difference between arms not as strongly in favour of atezo+bev+CP as it was in the total ITT population, 0.59 (0.50 to 0.69)

EGFR/ALK+ve: Results should be treated with caution as small population & median OS not reached in atezolizumab with bevacizumab, carboplatin & paclitaxel 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 trial not stratified by EGFR/ALK+ve status

❋ Is the available overall survival data mature enough for decision making?

Company's network meta-analysis comparing atezolizumab with bevacizumab, carboplatin & paclitaxel versus pemetrexed-based chemo

- PD-L1 <50% and EGFR/ALK +ve subgroup analyses conducted → **assumptions required** → level of PD-L1 expression and presence of EGFR/ALK mutations are not effect modifiers for pemetrexed-based chemotherapy as subgroups not specified in pemetrexed trials
- 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. Fixed effects model used in base case
- Weibull model chosen for OS & PFS for ITT & subgroup NMA & sensitivity analyses
- PARAMOUNT trial included in company's network → only study connecting pemetrexed + platinum drug to the network
  - different study design **(protocol included induction pemetrexed-based chemotherapy)** compared to other studies in network → possible selection bias

ERG comments: Fractional polynomial approach appropriate & agree with choice of Weibull model. ERG clinical expert **does not agree with assumption that EGFR and ALK status are not effect modifiers. PARAMOUNT not included in ERG base case → main source of clinical heterogeneity**

NMA results

Network	WITH PARAMOUNT (company base case)		WITHOUT PARAMOUNT (ERG base case)
Population	Versus pemetrexed + plat	Versus pemetrexed + plat + maint	Versus pemetrexed + plat + maint
OS	Months with a statistically significant difference in favour of atezo+bev+CP		
ITT	[redacted]	[redacted]	[redacted]
EGFR/ALK +ve	[redacted]	[redacted]	
PD-L1 <50%	[redacted]		
PFS	Months with a statistically significant difference in favour of atezo+bev+CP		
ITT	[redacted]	[redacted]	[redacted]
EGFR/ALK +ve	[redacted]	[redacted]	
PD-L1 <50%	[redacted]	[redacted]	

- Are the results from the company's network meta-analysis appropriate given the heterogeneity between the included studies?
  - Should the PARAMOUNT trial be included in the network meta-analysis?

Key issues - clinical effectiveness

- Are the comparators used by the company for each subgroup relevant to NHS clinical practice?
  - Would most people receive pemetrexed maintenance in clinical practice?
- Median overall survival has not been reached in the EGFR/ALK positive subgroup
  - Is the available overall survival data mature enough for decision making?
- Are the results from the company's network meta-analysis appropriate given the heterogeneity between the included studies?
  - Should the PARAMOUNT trial be included in the network meta-analysis?

[redacted]

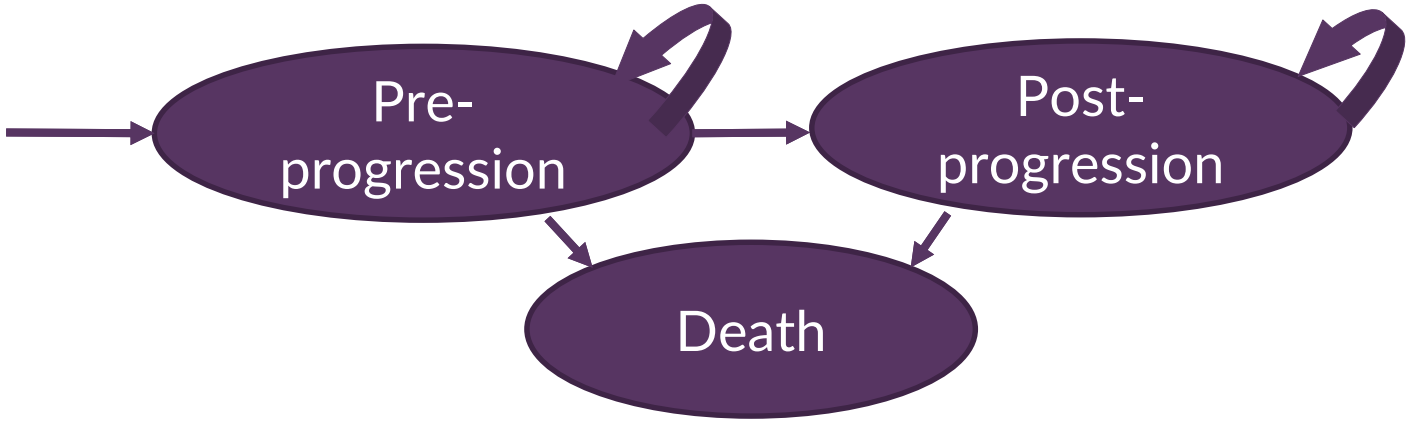
Cost effectiveness

Preview: Key issues - cost effectiveness

- In order to generate the comparator survival curve, are data on relative effect from the subgroup NMA (company approach) or ITT NMA (ERG approach) more appropriate?
- Does the exponential (company) or Weibull (ERG) function give the most appropriate estimates of long-term overall survival?
- Is the company's assumption around the duration of treatment effect reasonable?
  - Is a survival advantage for pemetrexed maintenance over the model time horizon realistic?
- Has the impact on utility value been fully captured?
  - Should disutility for adverse events be included?
- Are the subsequent therapies included in the company's model (docetaxel, nivolumab, pembrolizumab, atezolizumab) reflective of clinical practice in the UK?
  - What proportion of people would receive a subsequent therapy in clinical practice?
- Are the end of life criteria met?

[redacted]

Company's 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	Atezo & bev: 5 years (2 years on treatment + 3 years after discontinuation). Pemetrexed maintenance: assumed continuous benefit
Discount rate	3.5% per year
Perspective	NHS and personal social services

[redacted]

Company & ERG use subgroup specific survival curves for atezolizumab with bevacizumab, paclitaxel & carboplatin but use different outcomes from the NMA for relative effects

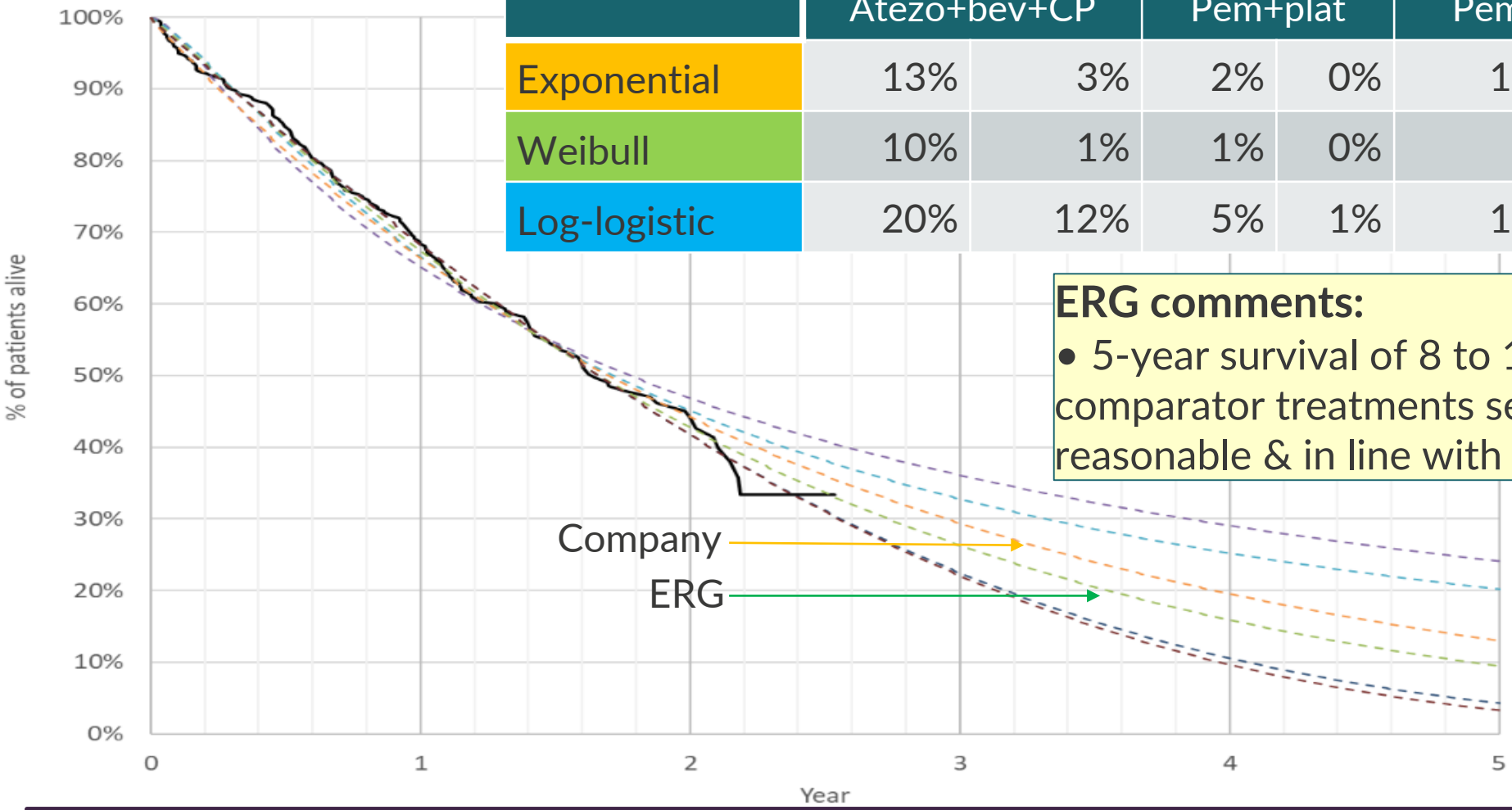
	Survival curve for atezo+bev+CP	NMA used for relative effects
Company	Specific curve for each group: • ITT • EGFR/ALK positive • PD-L1 <50%	Specific NMA for each group: • ITT • EGFR/ALK positive • PD-L1 <50%
ERG	Same as company	Outcomes from the ITT NMA used for both subgroups

ERG comments:
• IMpower150 trial did not show any evidence of effect modification for the EGFR/ALK positive or PD-L1 <50% subgroups
ITT NMA considered a more robust source for relative treatment effects than subgroup NMAs

☼ What is the most appropriate approach (company's or ERG's)?

ITT: Company & ERG preferred different functions for OS extrapolation

Distribution	5 & 10-year survival, respectively					
	Atezo+bev+CP		Pem+plat		Pem+plat+maint	
Exponential	13%	3%	2%	0%	12%	3%
Weibull	10%	1%	1%	0%	9%	1%
Log-logistic	20%	12%	5%	1%	18%	10%



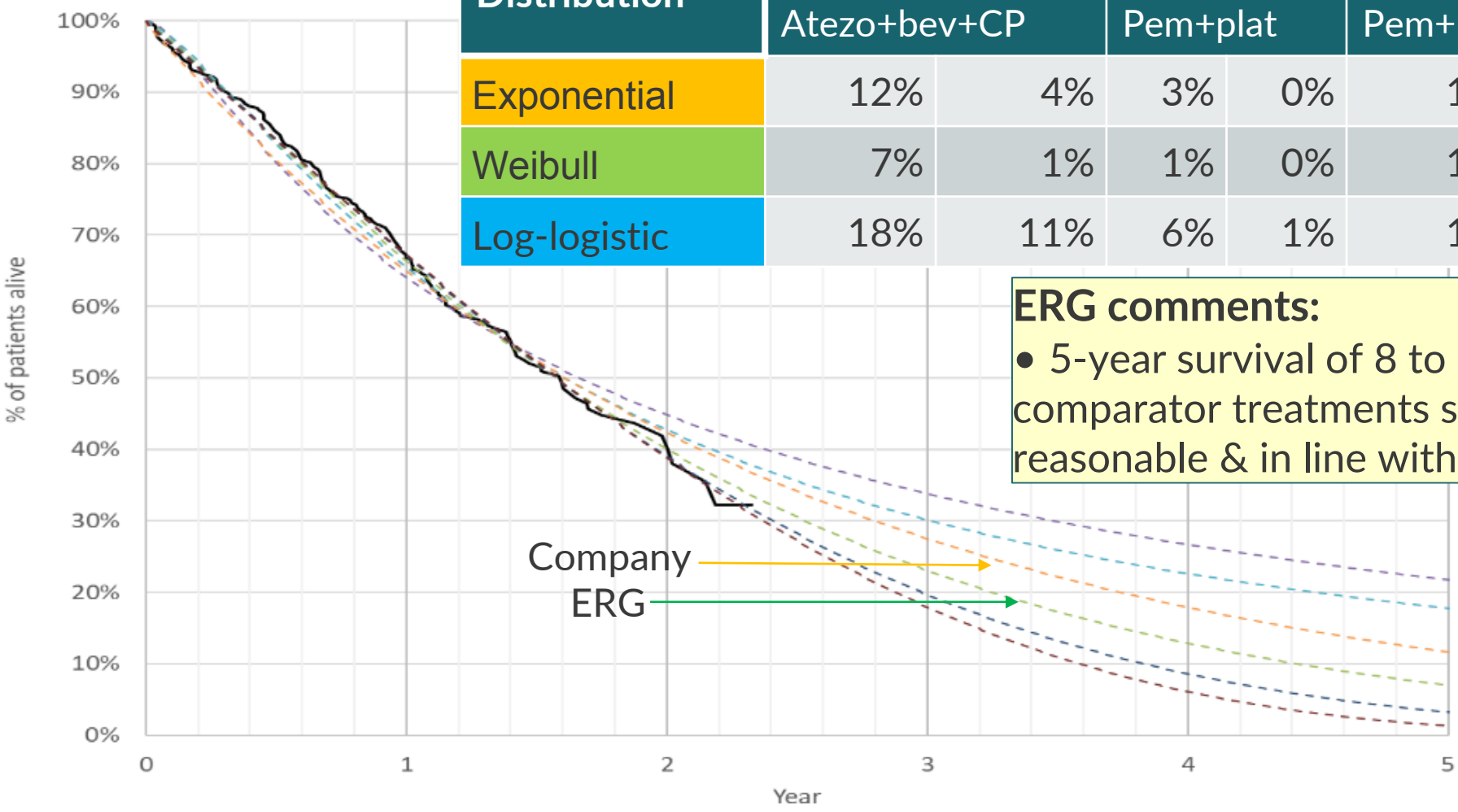
ERG comments:

- 5-year survival of 8 to 11% with comparator treatments seems reasonable & in line with NICE TA531

❊ What is the most appropriate extrapolation to use for overall survival?

PD-L1 < 50% groups: Company & ERG preferred different functions for OS extrapolation

Distribution	5 & 10-year survival, respectively					
	Atezo+bev+CP		Pem+plat		Pem+plat+maint	
Exponential	12%	4%	3%	0%	13%	4%
Weibull	7%	1%	1%	0%	10%	2%
Log-logistic	18%	11%	6%	1%	19%	12%



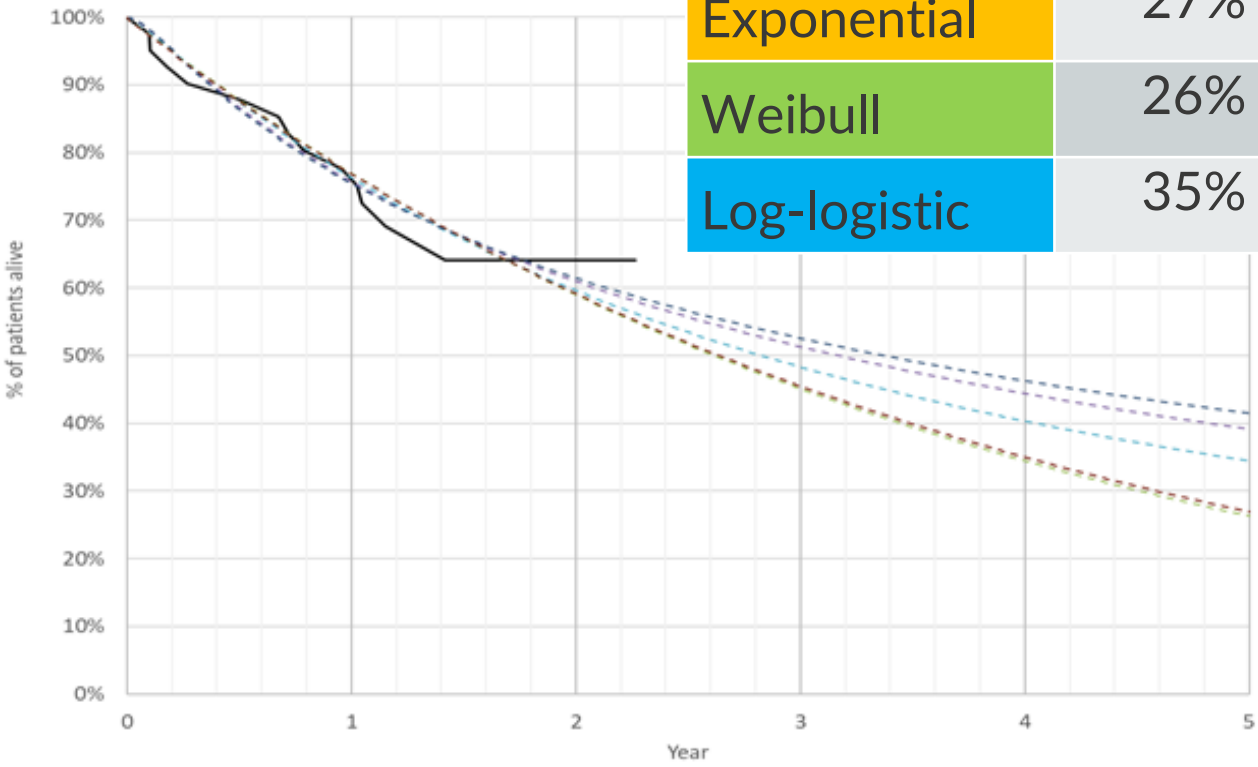
ERG comments:

- 5-year survival of 8 to 11% with comparator treatments seems reasonable & in line with NICE TA531

❊ What is the most appropriate extrapolation to use for overall survival?

EGFR/ALK+ve: Company & ERG preferred different functions for OS extrapolation

Distribution	5 & 10-year survival, respectively					
	Atezo+bev+CP		Pem+plat		Pem+plat+maint	
Exponential	27%	17%	11%	3%	18%	12%
Weibull	26%	16%	11%	3%	18%	11%
Log-logistic	35%	28%	15%	9%	22%	18%



ERG comment:

- Difficult to differentiate on the basis of visual fit
- Exponential has the best statistical fit

❊ What is the most appropriate extrapolation to use for overall survival?

[redacted]

Company modelled a 3 year duration of treatment effect beyond discontinuation

- 3 years for atezolizumab and bevacizumab & no cap on duration of survival effect for pemetrexed maintenance
- 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:

- 3-year cap seems reasonable but high uncertainty
- **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 & **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

❊ Are company's assumptions around duration of treatment effect reasonable?

- ◌ Is the survival advantage for pemetrexed maintenance realistic?

Company included a 2 year stopping rule

- Consistent with previous NICE guidance for atezolizumab (TA520 for NSCLC and TA525 for urothelial carcinoma) and other immunotherapies (e.g. TA531)
- No stopping rule in IMpower150 trial → 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 included in the company base case using proximity to death approach

- Company applied same utilities to all populations and treatment arms

Category	Base case utilities		Source
	Mean value	95% CI	
≤ 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:

- Agree more face validity with proximity to death approach than pre/post-progression
- Utility impact not fully captured
- No disutility included while on treatment or for adverse events in company base case. Scenario analysis run to include AEs but assumed the same for both arms when atezo+bev+CP AE profile significantly worse. ERG suggest values in table →

Treatment	Disutility per grade 3+ TRAE
Atezo+bev+CP	-0.0058
Pem + plat	-0.0009
Pem + plat + maint	-0.0042

Source: Utility decrements from Nafees et al. 2008 & applied to frequency of AEs

❊ Should disutility for adverse events be included?

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

- 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

❊ Are the subsequent therapies included in the company's model reflective of clinical practice in the UK?
❊ What proportion of people would receive a subsequent therapy in clinical practice?

Company's probabilistic base case (with PAS for atezolizumab and bevacizumab only[a])

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]

[a] Excludes PAS discounts for pemetrexed maintenance, pembrolizumab, nintendanib and nivolumab

Company's scenario analysis results vs pemetrexed + platinum drug (with PAS for atezolizumab and bevacizumab only)

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 (2 years on and 3 years off treatment)	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

Company's scenario analysis results vs pemetrexed + platinum drug + maintenance (with PAS for atezolizumab and bevacizumab only)

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	PARAMOUNT excluded	Dominant	-	-
OS extrapolation	Exponential	Log-logistic	Dominant	Dominant	£6,963
		Weibull	Dominant	Dominant	£6,918
Duration of treatment effect	5 years (2 years on and 3 years off treatment)	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

ERG's preferred base case assumptions

- Discrepancies in the model were corrected by the ERG → minor impact on results

Parameter	Subgroup	Company base case	ERG base case
Baseline OS	All	Exponential	Weibull (a plausible alternative to exponential & more conservative)
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

[redacted]

ERG's deterministic base case with PAS for atezolizumab and bevacizumab only[a]

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]	£3,352

[a] Excludes PAS discounts for pemetrexed maintenance, pembrolizumab, nintendanib and nivolumab

ERG's scenario analysis results: ITT population with PAS for atezolizumab and bevacizumab 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 atezolizumab and bevacizumab 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

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 (13.3)	1.72 (20.6)	1.32 (15.8)
	PD-L1 <50%	1.55 (18.6)	1.14 (13.7)	2.27 (27.2)	0.99 (11.9)	-	-
	EGFR/ALK+ve	2.04 (24.5)	0.91 (10.9)	3.15 (37.8)	0.49 (5.9)	-	-
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 (5.8)	0.42 (5.0)	0.59 (7.1)	0.46 (5.5)	0.32 (3.8)
	PD-L1 <50%	1.01 (12.1)	0.46 (5.5)	0.29 (3.5)	0.61 (7.3)	-	-
	EGFR/ALK+ve	3.08 (37.0)	1.73 (20.8)	1.97 (23.6)	2.15 (25.8)	-	-

☼ Are the end of life criteria met?

Equality and Innovation

Equality

- The company & professional organisation identified no equality issues

Innovation (company view)

- Early Access to Medicines Scheme granted for “the treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) with EGFR activating or ALK-positive tumour mutations after failure of appropriate targeted therapies.“ (December 2018)
- 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

[redacted]

Key issues - cost effectiveness

- In order to generate the comparator survival curve, are data on relative effect from the subgroup NMA (company approach) or ITT NMA (ERG approach) more appropriate?
- Does the exponential (company) or Weibull (ERG) function give the most appropriate estimates of long-term overall survival?
- Is the company's assumption around the duration of treatment effect reasonable?
  - Is a survival advantage for pemetrexed maintenance over the model time horizon realistic?
- Has the impact on utility value been fully captured?
  - Should disutility for adverse events be included?
- Are the subsequent therapies included in the company's model (docetaxel, nivolumab, pembrolizumab, atezolizumab) reflective of clinical practice in the UK?
  - What proportion of people would receive a subsequent therapy in clinical practice?
- Are the end of life criteria met?

[redacted]