NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

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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.

Pre-meeting briefing

Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (ID970)

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

1

Non-small cell lung cancer

- In the UK, more than 45,000 people are diagnosed with lung cancer and over 35,000 people die from the condition each year. NSCLC accounts for up to 85 to 90% of lung cancer cases.
- More than half of people with NSCLC present with incurable advanced local or metastatic disease at the time of diagnosis
  - Estimated 5-year survival rate of around 10%
- 2 major histological subtypes
  - Squamous cell carcinoma (25 to 30% of diagnoses)
  - Non-squamous cell carcinoma
    - Adenocarcinoma (30 to 40%)
    - Large-cell carcinoma (10 to 15%)
    - Other cell types (5%)
- Targeted therapy is a growing part of cancer regimens
  - Between 23 and 28% of people with advanced NSCLC have tumours which strongly express PD-L1 (tumour proportion score [TPS] ≥50%)

2

Atezolizumab (TECENTRIQ®)

Anticipated marketing authorisation	for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.
Mechanism	IgG1 monoclonal antibody, binds directly and selectively to PD-L1 preventing it from binding to PD-1 and B7.1.
Administration and dose	• 1,200 mg, every three weeks as intravenous infusion, fixed dose one vial per administration • Treat until loss of clinical benefit or unmanageable toxicity • Based on the OAK trial, the average time on therapy per patient (mean) is 7.78 months, equivalent to 11.3 cycles
Cost	• List price: £3807.69 per 20mL vial. • PAS: Simple discount
Cost of a course of treatment	• The average cost per treatment course is £42,913.66 at list price.

3

Source: company submission pg 26

SPC states treat until loss of clinical benefit (which may be beyond progression), defined as:

- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcaemia]) indicating unequivocal progression of disease
- No decline in ECOG performance status
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilised by protocol-allowed medical interventions prior to repeat dosing
- Evidence of clinical benefit as assessed by the investigator

- Average cost per treatment course = mean cycles * vial price from OAK trial

Patient and professional feedback (I)

- **British Thoracic Society**
  - Welcome the appraisal of atezolizumab, no additional comments.
- **Roy Castle Lung Cancer Foundation**
  - Outlook is poor for people that relapse after platinum based chemotherapy
  - Small improvements in quality and extension of life are significant to individual and family
  - Immunotherapy can 'significantly extend survival'
  - Anecdotal patient experience suggests immunotherapeutic agents are well tolerated compared with current standard therapy
  - Symptoms of NSCLC can be debilitating and difficult to manage clinically (e.g. breathlessness). Anti-tumour therapies provide symptom relief.
  - Until recently, treatment options were limited to docetaxel or docetaxel/nintedanib. Pleased to note the recent NICE approval of Pembrolizumab (PDL-1 positive patients) in second line.
  - The addition of Immunotherapy in the treatment of NSCLC has been a major development.
  - End of life considerations are important for this patient group.

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Comments from consultees

This section summarises comments from:

- British Thoracic Society
- NCRI/RCP/RCR/ACP/BTOG
- Roy Castle Lung Cancer Foundation

Patient and professional feedback (II)

- **NCRI/RCP/RCR/ACP/BTOG**
  - NCCN guidelines recommend atezolizumab for PS0-2 patients after progression on 1st line systemic therapy.
  - Atezolizumb is well tolerated and effective
  - Optimal duration of therapy remains to be identified. Possible that future studies may demonstrate efficacy with a shorter duration of therapy, but at present there is no data to support modifying the treatment regimen.
  - PD-L1 expression appears to help identify a subgroup of patients who derive greater benefit from treatment. For patients with high levels of PD-L1 expression (16% of population had >/=50% PD-L1 expression on tumour cells or >/=10% expression on immune cells), the improvement in OS demonstrated with atezolizumab is even more marked with a median survival of 8.9 months (CI 5.6-11.6) for docetaxel increasing to 20.5 months (CI 17.5 – NR) with atezolizumab, hazard ratio 0.41 (CI 0.27-0.64, p<0.0001)
  - Method for PD-L1 testing for atezolizumab is more complex than other PD-L1 assays and not necessarily interchangeable
  - There will be a reduced incidence of hospital admissions to treat chemotherapy associated toxicity, with consequent improvement in quality of life for patients.

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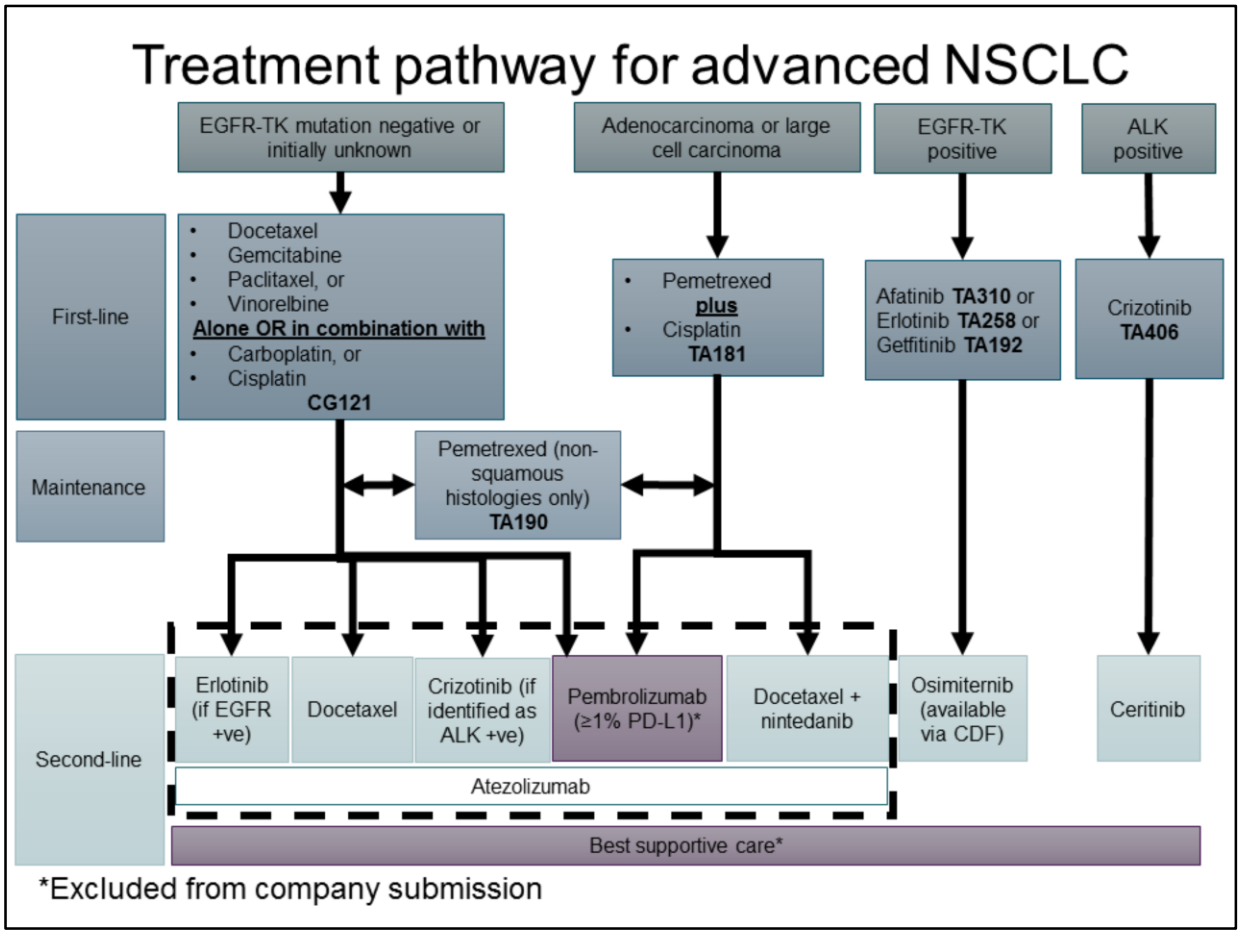

Source: company submission pg 46

The company have positioned atezolizumab 2nd line, within it's anticipated marketing authorisation

COMPANY'S DECISION PROBLEM & DEVIATIONS FROM FINAL SCOPE (1)				
	Final NICE scope	**Company submission**	**Rationale**	**ERG comments**
Population	People with locally advanced or metastatic non-small-cell lung cancer whose disease has progressed after chemotherapy	Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy	No difference	Same as scope
Comparators	1. Docetaxel monotherapy 2. Nintedanib with docetaxel (for people with adenocarcinoma histology) 3. Nivolumab (subject to ongoing NICE appraisal) 4. Pembrolizumab (PD-L1-expressing tumours; subject to ongoing NICE appraisal) 5. Best supportive care	1. Docetaxel 2. Nintedanib with docetaxel	Pembrolizumab • licenced for PDL1 positive only. • not likely to represent standard care. Nivolumab • not recommended for use by NICE in the ACD (October 2016). Best supportive care • clinical expert opinion suggested that people eligible for treatment with atezolizumab would be fit enough for other treatment.	Pembrolizumab • Relevant comparator for PD-L1 expressors • Effectiveness of atezolizumab is similar in PD-L1 -ve and PD-L1 +ve Agrees with exclusion of Nivolumab and BSC

Source: company submission p22-23

Company's justification for difference

Pembrolizumab

- The population is different to the anticipated marketing authorisation for atezolizumab as it is for PDL1 positive NSCLC patients only.
- Accurate comparisons between treatments is not possible due to the differences between tests used in clinical studies to select patients; pembrolizumab studies tested for tumour cell expression only compared to tumour cell and immune cell expression for atezolizumab.
- Unlikely to represent a standard of care at time of submission, as it was only recently approved for use in NSCLC by NICE.

Nivolumab

- Not considered standard of care, not recommended for use by NICE in the Appraisal Consultation Document (ACD), published in October 2016.

Best supportive care

- Clinical expert opinion suggested that patients eligible for treatment with atezolizumab would be considered fit enough for other treatment.

COMPANY'S DECISION PROBLEM & DEVIATIONS FROM FINAL SCOPE (1)				
	Final NICE scope	**Company submission**	**Rationale**	**ERG comments**
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.	In line with final scope	No difference	Same as scope

Subgroups	If the evidence allows, consider subgroups based on biological markers.	Results presented by:
		• baseline characteristics and
		• histology subgroups (squamous and non-squamous)
		• PD-L1 expression presented from OAK trial for
		  • no expression (TC0/IC0) and
		  • more than 1% expression (TC1/2/3 or IC1/2/3)
			No comment	Further subgroups available for PD-L1 expressors, presented in a published paper for:
				• TC3 or IC3, and
				• TC2/3 or IC2/3.

Source: company submission p23

Clinical effectiveness evidence

Company submission section 4

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Key issues – clinical effectiveness

- Pembrolizumab was not included as a comparator
- Atezolizumab targets PD-L1 but the company submission is orientated around the whole population of patients with locally advanced or metastatic NSCLC after prior chemotherapy
- Method used to calculate hazard ratios in both trials assumed proportional hazards holds, but they do not. HRs should be interpreted with caution (method was pre-specified and company could not have known that PH would not hold)
- Indirect treatment comparison
  - Network meta-analysis includes comparators not listed in the scope
  - Nintedanib (licenced for adenocarcinoma) was compared with atezolizumab in the total population (including non-adenocarcinoma histologies)
  - Random effects model would have shown less certainty than fixed effects model
- Stopping rule for atezolizumab and docetaxel differed in both trials:
  - Docetaxel administered until disease progression or unacceptable toxicity. Clinical expert opinion suggests that in practice patients receive 4-6 cycles
  - In line with the draft SPC, atezolizumab was administered for as long as patients experienced a clinical benefit (as assessed by an investigator) in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression.

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Clinical evidence

- Two randomised clinical trials comparing atezolizumab with docetaxel
  - **OAK**, open label phase III study
  - **POPLAR**, open label phase II study
- Both recruited patients regardless of PD-L1 expression

- Direct head-to-head trial data only exists comparing atezolizumab with docetaxel, therefore indirect comparison analyses were done for other comparators

- Safety data from OAK and POPLAR are consistent with safety profile for atezolizumab and other immunotherapies. Company states that atezolizumab was well tolerated with a favourable safety profile compared with docetaxel.

- Ongoing studies
  - OAK is ongoing and the number of patients recruited has increased from 850 to 1,225 to assess OS in patients with high PD-L1 expression
    - Estimated completion date OAK December 2017
  - [redacted]

Source: company submission p49

Clinical evidence from single arm phase II studies for atezolizumab exists and is not discussed in the company submission (BIRCH and FIR).
Phase I data did not demonstrate a clear relationship between PD-L1 expression and response to atezolizumab, therefore patients were recruited to OAK and POPLAR regardless of PD-L1 expression.

Clinical evidence

	OAK (n=1,225*)	POPLAR (n=287)
Design	Randomised, open label, phase III study	Randomised, open label, phase II study
Intervention	Atezolizumab, 1,200 mg every three weeks **(n=425)**	Atezolizumab, 1,200 mg every three weeks **(n=144)**
Comparator	Docetaxel, 75 mg/m^2 every three weeks **(n=425)**	Docetaxel, 75 mg/m^2 every three weeks **(n=143)**
Population Recruited regardless of PD-L1 expression	• NSCLC that is locally advanced or metastatic (that is, Stage IIIB not eligible for definitive chemoradiotherapy, Stage IV, or recurrent) • ≥18 years old • ECOG PS 0 or 1 • Measurable disease by RECIST v1.1 • Adequate haematological and end-organ function • Last dose of prior therapy administered ≥21 days prior to randomisation • Patients with advanced lung cancer and EGFR mutation must have experienced disease progression with an EGFR TKI (e.g. erlotinib, getfitinib)	
Outcomes	**Primary**: Overall survival in ITT population and OS in patients with ≥1%PD-L1 expression **Secondary**: Progression free survival, objective response rate, duration of response, safety and tolerability, EQ-5D-3L, EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module (LC13)	**Primary**: Overall survival **Secondary**: Progression free survival, objective response rate, duration of response, safety and tolerability, EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module (LC13)

*pre-specified analysis of first 850 patients provided sufficient power to test the co-primary endpoints

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Source: company submission p57-61

Eligible patients were randomly assigned 1:1 ratio in both studies. Patients were only allowed to crossover from the control arm to the treatment arm in OAK or POPLAR after the analysis of the primary population.

Inclusion and exclusion criteria were similar for OAK and POPLAR.

OAK:

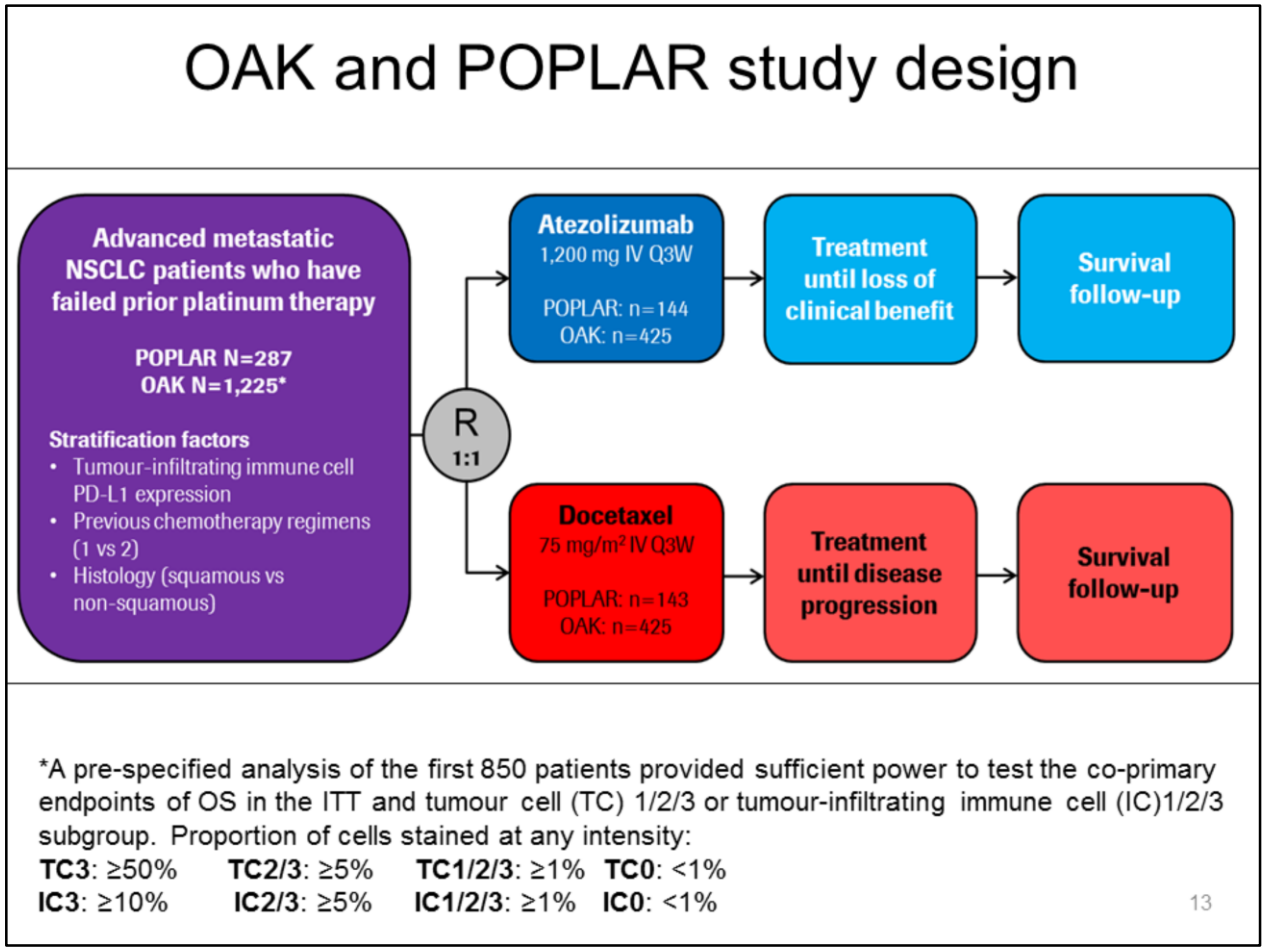
- Primary analysis (clinical cut-off 7th July 2016)

POPLAR:

- Interim analysis (clinical cut-off 30th January 2015)
- Primary analysis (clinical cut-off 8th May 2015)

The sample size for OAK increased from 850 to 1225 (614 atezolizumab arm, 611 docetaxel arm) in order to have at least 220 patients with PD-L1 TC3 or IC3 status. Primary analysis were done on the first 850 randomised patients. The efficacy analyses are based on all 1225 randomised patients.

POPLAR was designed to assess the efficacy and safety of atezolizumab and to estimate OS and PFS hazard ratios for the whole population and PD-L1 immunohistochemistry 2/3 subgroup.



Source: company submission p59

Docetaxel treatment was continued until disease progression.

Atezolizumab treatment was continued as long as patients:

- Experienced clinical benefit as assessed by an investigator
- Did not experience unacceptable toxicity, symptomatic deterioration or worsening laboratory values (e.g. new or worsening hypercalcaemia)
- No decline in ECOG score
- No tumour progression at critical sites (e.g. leptomeningeal)

ERG critique – OAK and POPLAR

- Good quality, well conducted, patient characteristics balanced and eligibility criteria reasonable.
- Open label trials and only investigator assessed PFS results are available from OAK and POPLAR, potential for bias.
- Docetaxel given day 1 of each 21-day cycle until disease progression or unacceptable toxicity. Clinical advice is patients receive between four and six cycles of treatment.

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Source: ERG report p12

PD-L1 expression

- No requirement in draft SPC for PD-L1 testing. Only patients whose tumour sample could be evaluated were included in the study.
- Tumours were tested prospectively for PD-L1 expression in OAK and POPLAR using the VENTANA PD-L1 immunohistochemistry assay, which was designed to stratify PD-L1 expression on tumour-infiltrating immune cells and tumour cells, using the following scoring algorithm:

Description of IHC Scoring Algorithm	PD-L1 expression level
Tumour-infiltrating immune cells (ICs)	
Absence of PD-L1 staining OR presence PD-L1 staining of any intensity in ICs covering < 1% of tumour area*	IC0
Presence of PD-L1 staining of any intensity in ICs covering between ≥1% and <5% of tumour area*	IC1
Presence of PD-L1 staining of any intensity in ICs covering between ≥5% and <10% of tumour area*	IC2
Presence of PD-L1 staining of any intensity in ICs covering ≥10% of tumour area*	IC3
Tumour cells (TCs)	
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in < 1% TCs	TC0
Presence of discernible PD-L1 staining of any intensity in ≥1% and <5% TCs	TC1
Presence of discernible PD-L1 staining of any intensity in ≥5% and <50% TCs	TC2
Presence of discernible PD-L1 staining of any intensity in ≥50% TCs	TC3

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* Tumour area occupied by tumour cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma

Source: company submission p59-60

Baseline characteristics (1)

Study	OAK		POPLAR	
Trial arm	Atezolizumab n=425	Docetaxel n=425	Atezolizumab n=144	Docetaxel n=143
Median age, years (range)	63.0 (33.0–82.0)	64.0 (34.0-85.0)	62.0	62.0
Tobacco use history, n (%)				
Never	84 (20)	72 (17)	27 (18.8)	29 (20.3)
Current	59 (14)	67 (16)	25 (17.4)	21 (14.7)
Previous	282 (66)	286 (67)	92 (63.9)	93 (65.0)
ECOG PS, n (%)			n=142	n=142
0	155 (36)	160 (38)	46 (32.4)	45 (31.7)
1	270 (64)	265 (62)	96 (67.6)	97 (68.3)
Pathology/histology, n (%)				
Non-squamous	313 (74)	315 (74)	95 (66.0)	95 (66.4)
Squamous	112 (26)	110 (26)	49 (34.0)	48 (33.6)

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Source: company submission p74-75

Baseline characteristics (2)

Study	OAK		POPLAR	
Number of prior therapies, n (%)				
1	320 (75)	320 (75)	93 (64.6)	96 (67.1)
2	105 (25)	105 (25)	51 (35.4)	47 (32.9)
Current disease status, n (%)				
Locally advanced	29 (7)	19 (5)	8 (5.6)	5 (3.5)
Metastatic disease	396 (93)	406 (95)	136 (94.4)	138 (96.5)
EGFR mutation	Positive: 42(10) Negative: 318 (75) Unknown: 65 (15)	Positive: 43 (10) Negative: 310 (73) Unknown: 72 (17)	n=83 T790M:1 (1.2) Positive:10 (12.0)	n=83 T790M:0 Positive:8 (9.6)
EML4-ALK mutation	Positive: 2 (<1) Negative: 223 (52) Unknown: 200 (47)	Positive: 0 Negative: 201 (47) Unknown: 224 (53)	n=61 Positive: 0	n=58 Positive: 3 (5.2)

ERG comments:
Baseline characteristics well balanced across treatment arms, broadly representative of patients in NHS, slightly younger and fitter.

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Source: company submission p75

Summary of ERG comments on the company's clinical effectiveness evidence

- OAK and POPLAR are well designed and good quality, patients broadly similar to NHS, slightly younger and fitter, open label design could introduce bias
- Stopping rule for atezolizumab and docetaxel differed in both trials:
  - Docetaxel administered until disease progression or unacceptable toxicity. Clinical expert opinion suggests that in practice patients receive 4-6 cycles
  - Atezolizumab administered for as long as patients experienced a clinical benefit (as assessed by an investigator) in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression
- ERG agrees that adverse events data from OAK are consistent with atezolizumab AE profile and it is well tolerated compared with docetaxel
- Method used to calculate hazard ratios in both trials assumed proportional hazards holds, but they do not, so HRs should be interpreted with caution (method was pre-specified and company could not have known that PH would not hold)
- Results show atezolizumab is associated with clinically meaningful and statistically significant improvement in median OS
  - OAK: in all subgroups
  - POPLAR: only in non-squamous histology and ≥1% PD-L1 expression
- No statistically significant difference in PFS in OAK or POPLAR

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Source: Company submission p81-82

OAK – OS, PFS, ORR, and duration of response ITT population

	Endpoint	Atezolizumab n=425	Docetaxel n=425
Primary endpoint	**OS**		
	Median, months (95% CI)	13.8 (11.8, 15.7)	9.6 (8.6, 11.2)
	HR (95% CI)	0.73 (0.62, 0.87)	
	Number of events n (%)	70.1	
	PFS		
	Median (months)	4.0 (3.3, 4.2)	2.8 (2.6, 3.0)
	HR (95% CI)	0.95 (0.82, 1.10)	
	ORR		
	Confirmed ORR % (95% CI)	13.6 (10.53, 17.28)	13.4 (10.32, 17.02)
	Difference in % pembrolizumab compared with standard of care	0.2	
	Duration of response*		
	Median duration of response, months (95% CI)	16.3 (10.0, NE)	6.2 (4.9, 7.6)

Source: Company submission, tables 29, 30

*Note duration of response is based on atezolizumab n=58; docetaxel n=57

ERG comments:
OS and PFS hazard ratios should be interpreted with caution as hazards aren't proportional (calculated with a pre-specified method that assumes they were proportional)

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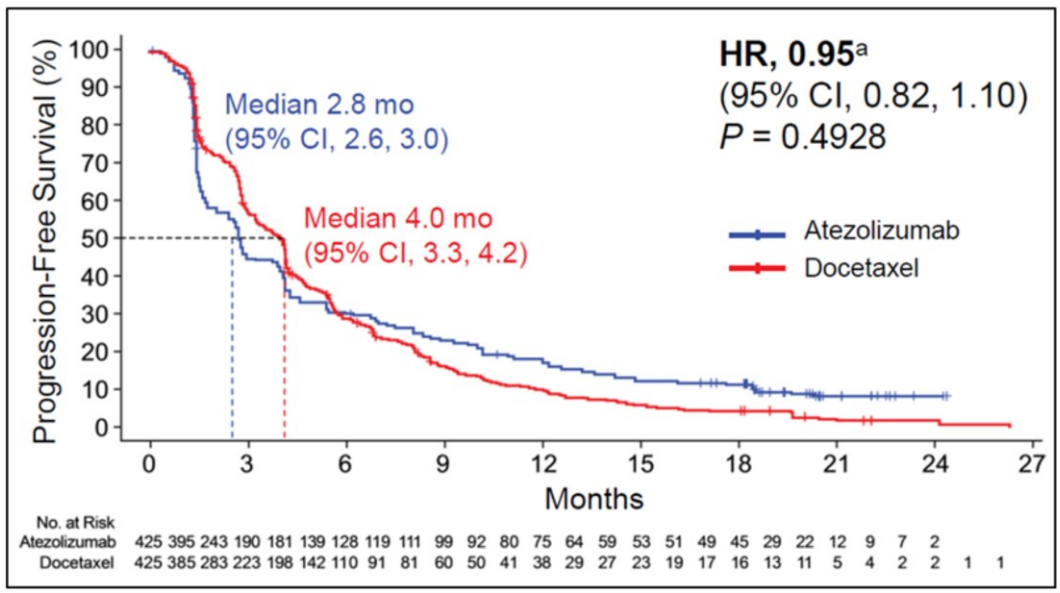
Source: company submission p80-83

OAK Kaplan-Meier plot of progression free survival (ITT)

no statistically significant difference in PFS between atezolizumab and docetaxel



[a] Stratified HR

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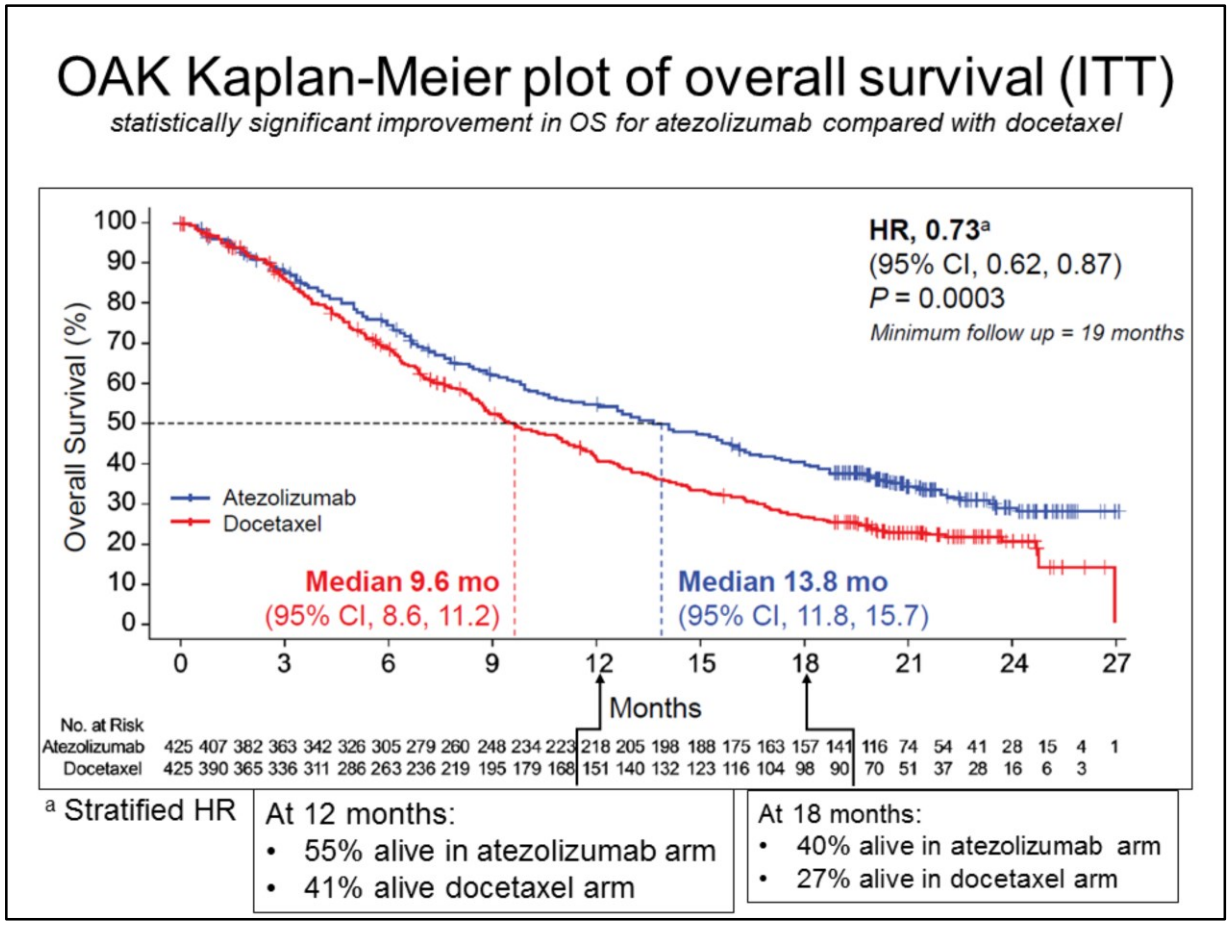
Source: company submission p82
Primary analysis (clinical cut-off 7th July 2016)

The median duration of PFS in the ITT population was:

- 2.8 months (95% CI: 2.6, 3.0) in the atezolizumab arm and
- 4.0 months (95% CI: 3.3, 4.2) in the docetaxel arm

(HR=0.95, 95% CI: 0.82, 1.10)



Source: company submission p81
Primary analysis (clinical cut-off 7th July 2016)

The median overall survival in the ITT population was:

- 9.6 months (95% CI: 8.6, 11.2) in the docetaxel arm and
- 13.8 months (95% CI: 11.8, 15.7) in the atezolizumab arm

There was a statistically significant improvement in OS for treatment with atezolizumab compared with docetaxel in:

- the ITT population (HR 0.73, 95% CI: 062, 0.87; p=0.0003) and
- ≥1 % PD-L1 expression (TC1/2/3 or IC1/2/3) (HR 0.74, 95% CI: 0.58, 0.93; p=0.0102)
- No PD-L1 expression (TC0/IC0) HR 0.75 (95% CI:0.59, 0.96) p=0.0205

Crossover from the docetaxel arm to the atezolizumab was allowed after analysis of the primary population (19 months) (n=850).

POPLAR – OS, PFS, ORR, duration of response ITT population

	Endpoint	Atezolizumab n=144	Docetaxel n=143
Primary endpoint	**OS**		
	Median, months (95% CI)	12.6 (9.7, 16.0)	9.7 (8.6, 12.0)
	HR (95% CI)	0.69 (0.52, 0.92)	
	Number of events n (%)	70	
Secondary endpoints	**PFS**		
	Median (months)	2.7 (2.0, 4.1)	3.4 (2.8, 4.1)
	HR (95% CI)	0.92 (0.71, 1.20)	
	ORR		
	Confirmed ORR (95% CI)	15.3 (9.8, 22.2)	14.7 (9.3, 21.6)
	Difference in % pembrolizumab compared with standard of care	0.6	
	Duration of response		
	Median duration of response, months (95% CI)	18.6 (11.6, NE)	7.2 (5.6, 12.5)

Source: Company submission, table 31, p85-88

*Note duration of response is based on atezolizumab n=22; docetaxel n=21

median DOR more than doubled in the atezolizumab arm compared with docetaxel

ERG comments:
OS and PFS hazard ratios should be interpreted with caution as hazards aren't proportional (calculated with a prespecified method that assumes they were proportional)

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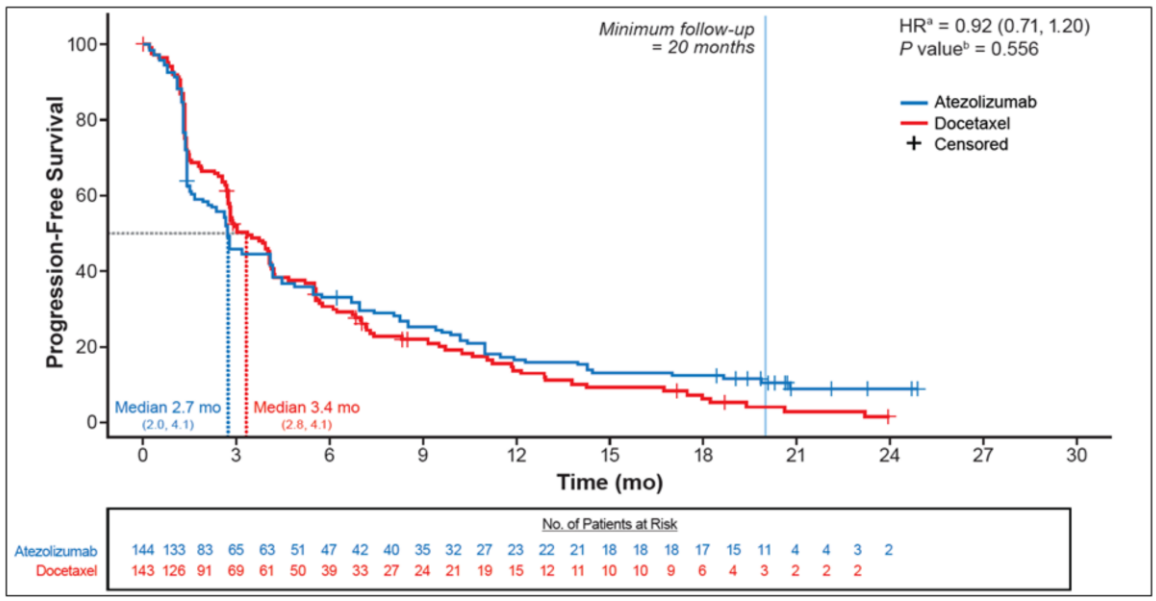
Source: Company submission p85-88

POPLAR Kaplan-Meier plot of progression free survival (ITT)

no statistically significant difference in PFS between atezolizumab and docetaxel



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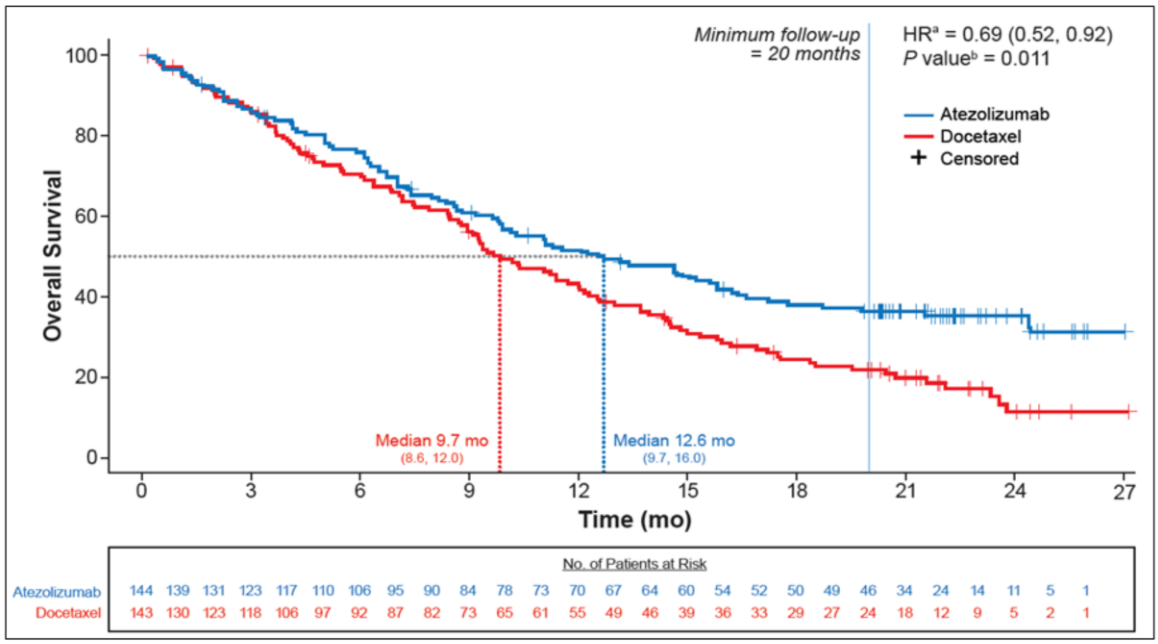
Source: company submission p87

Median PFS in the intention to treat population:

- 3.4 months (95% CI: 2.8, 4.1) in the docetaxel arm
- 2.7 months (95% CI: 2.0, 4.1) in the atezolizumab arm

POPLAR Kaplan-Meier plot of overall survival (ITT)

statistically significant improvement in OS for atezolizumab compared with docetaxel



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Source: company submission p85-86
(clinical cut-off 1st December 2015)

The median overall survival in the ITT population was:

- 9.7 months (95% CI 8.6, 12.0) in the docetaxel arm and
- 12.6 months (95% CI: 9.7, 16.0) in the atezolizumab arm

There was a statistically significant improvement in OS for treatment with atezolizumab compared with docetaxel in the ITT population (HR 0.69, 95% CI: 052, 0.92; p=0.011)

OAK subsequent therapies

- Crossover from the docetaxel arm to the atezolizumab arm was not originally permitted in OAK, however this was subsequently allowed following analysis of the primary population (n=850)
- The company used the Rank Preserving Structural Failure Time (RPSFT) method to assess the impact of cross-over on OS estimates for the primary population
- Based on the results, crossover was considered to only make a marginal impact, hence was excluded from the economic model
- Also true for the nintedanib (plus docetaxel) comparison, within the LUME-Lung 1 trial, treatment switching was balanced across all populations

Treatment, %	Atezolizumab n=425	Docetaxel n=425
Any non-protocol therapy	206 (48.5)	192 (45.2)
Chemotherapy	176 (41.4)	131 (30.8)
Targeted therapy	63 (14.8)	66 (15.5)
Immunotherapy	19 (4.5)	73 (17.2)
Nivolumab	16 (3.8)	58 (13.6)

Subsequent immunotherapies (mostly nivolumab) were received by:
- 5% of patients in the atezolizumab arm, and
- 17% of patients in the docetaxel arm

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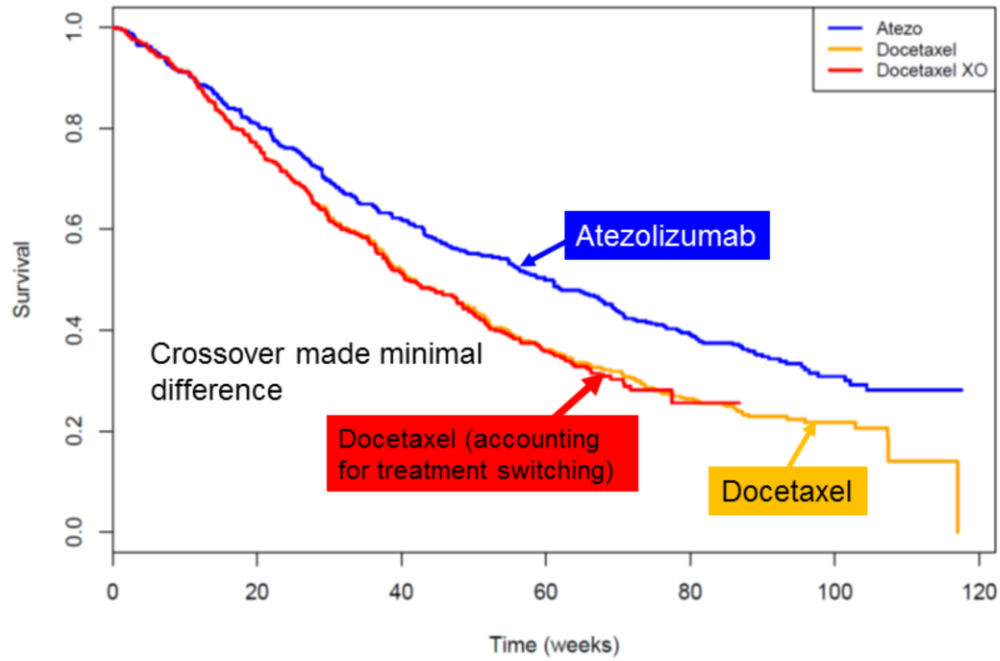
Source: company submission p82

Primary analysis (clinical cut-off 7th July 2016)

OAK – crossover adjusted OS

KM estimates of crossover (RPSFT) adjusted OS in OAK (ITT primary population; 7 Jul 2016 data cut)



XO: Docetaxel OS estimate accounting for treatment switching

26

Source: company submission p163

Subgroup analyses

limited presentation of PD-L1 expression results

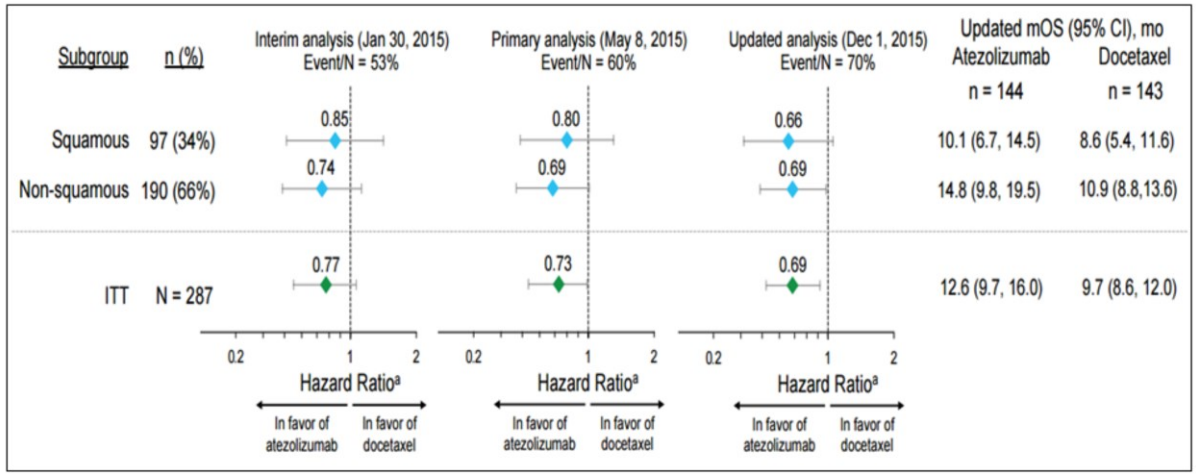
- Subgroups analyses presented in company submission:
  - **Histology**
    - Non-squamous NSCLC
    - Squamous NSCLC
  - **Baseline characteristics**
    - Sex
    - Age
    - ECOG PS
    - No. of prior therapies
    - Tobacco use history
    - Prior liver metastasis
    - Prior bone metastasis
    - KRAS mutation
    - EGFR mutation

27

Source: company submission p92, Figure 17, 18

POPLAR overall survival in histology subgroups

improvement over time of the hazard ratio was greater in the squamous group

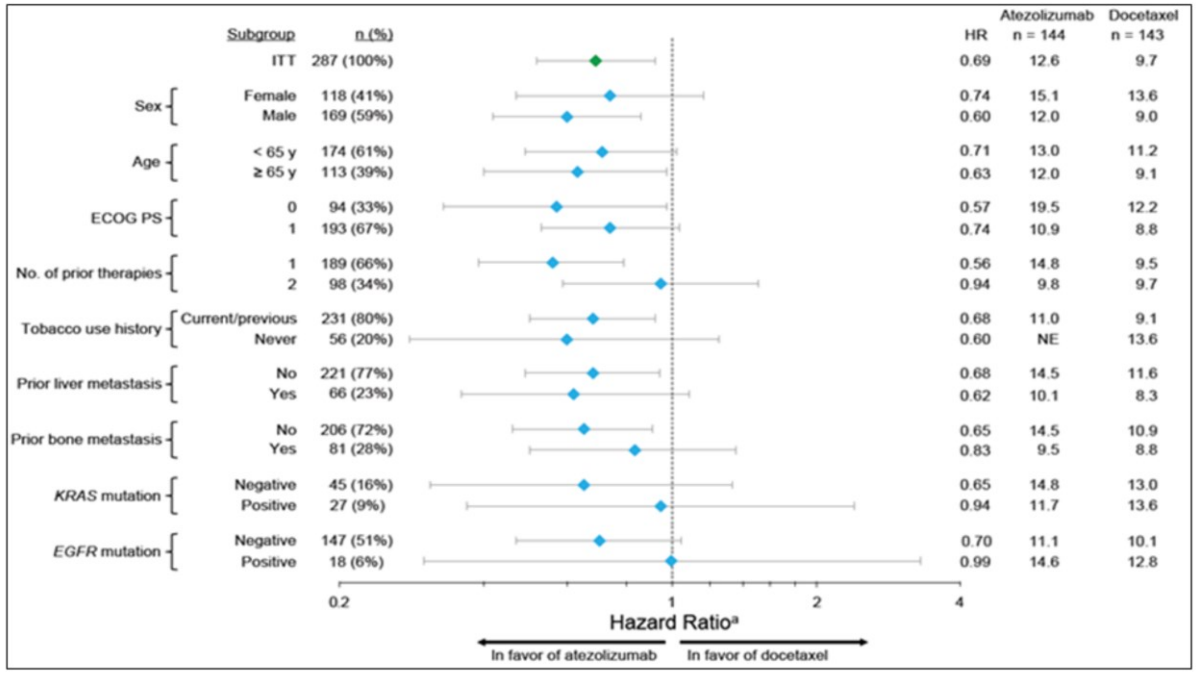


28

Source: CS p92 fig 17

POPLAR overall survival by baseline characteristics

improvement in overall survival generally seen for atezolizumab compared with docetaxel across all baseline characteristics



29

Source: company submission p92 fig 18

OAK overall survival in histology subgroups

longer median overall survival in the non-squamous group for atezolizumab

- Median overall survival improved in patients treated with atezolizumab regardless of histology and was longer in patients with non-squamous NSCLC:
  - squamous (8.9 months, HR 0.73, 95% CI, 0.54, 0.98) and
  - non-squamous groups (15.6 months, HR 0.73, 95% CI, 0.60, 0.89)

30

Source: company submission p88-89

OAK overall survival by baseline characteristics (I)

overall survival improved with atezolizumab compared with docetaxel across all baseline characteristics

Subgroup	n (%)	HR	Median overall survival atezolizumab (n=425)	Median overall survival docetaxel (n=425)
Female	330 (39)	0.64	16.2	11.2
Male	520 (61)	0.79	12.6	9.2
65 years	453 (53)	0.80	13.2	10.5
≥ 65 years	397 (47)	0.66	14.1	9.2
ECOG PS 0	315 (37)	0.78	17.6	15.2
ECOG PS 1	535 (63)	0.68	10.6	7.6
1 prior therapy	640 (75)	0.71	12.8	9.1
2 prior therapies	210 (25)	0.80	15.2	12.0

31

Source: CS p90

OAK overall survival by baseline characteristics (II)

overall survival improved with atezolizumab compared with docetaxel across all baseline characteristics

Subgroup	n (%)	HR	Median overall survival atezolizumab (n=425)	Median overall survival docetaxel (n=425)
Never smokers	156 (18)	0.71	16.3	12.6
Current/previous smokers	694 (82)	0.74	13.2	9.3
CNS mets	85 (10)	0.54	20.1	11.9
No CNS mets	765 (90)	0.75	13.0	9.4
KRAS mutant	59 (7)	0.71	17.2	10.5
KRAS wildtype	203 (24)	0.83	13.8	11.3
EGFR mutant	85 (10)	1.24	10.5	16.2
EGFR wildtype	628 (74)	0.69	15.3	9.5
Intention to treat	850 (100)	0.73	13.8	9.6

32

Source: CS p90 fig 15

OAK - overall survival by PD-L1 expression

Population	n (%)	Median OS (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
ITT	850 (100)	13.8	9.6	**0.73 (0.62, 0.87)**
TC3 or IC3	137 (16)	20.5	8.9	0.41 (0.27, 0.64)
TC2/3 or IC2/3	265 (31)	16.3	10.8	0.67 (0.49, 0.90)
TC1/2/3 or IC1/2/3	463 (54)	15.7	10.3	**0.74 (0.58, 0.93)**
TC0 and IC0	379 (45)	12.6	8.9	**0.75 (0.59, 0.96)**

Company did not present these results in their submission. Presented in ERGR, published data.

Company presented these results in their submission

ERG comments:

- ERG presented OS data by PD-L1 expression from OAK trial published in January 2017 in their report, some results were not presented by the company
- Analyses by level of PD-L1 expression are specified in the protocols for OAK and POPLAR, full results for both trials should be provided by the company
- Scope states that biological subgroups should be presented if data is available

Source: company submission p81, ERG report p81
Primary analysis (clinical cut-off 7th July 2016)

OAK and POPLAR - Health related quality of life

- Health related quality of life assessed in OAK and POPLAR
  - OAK: EQ-5D-5L, QLQ-C30 and QLQ-LC13
- EQ-5D-3L data was collected on the first day of each treatment cycle and at the treatment discontinuation visit (within 30 days of last treatment dose).
- Results from OAK EQ-5D-5L were used in the economic model base case
  - EQ-5D-5L given on
    - cycle 1 day 1,
    - day 1 of each cycle after,
    - Treatment discontinuation visit (within 30 days last treatment)

Summary of health state utility values

	On treatment	Off treatment
≤ 5 weeks before death	0.39	0.35
> 5 and ≤ 15 weeks before death	0.61	0.43
> 15 and ≤ 30 weeks before death	0.71	0.58
> 30 weeks before death	0.77	0.68

34

Source: CS 165

Adverse reactions OAK

Atezolizumab was well tolerated and has a favourable safety profile compared with docetaxel

- Atezolizumab treated patients:
  - had fewer Grade 3 or 4 adverse events
  - had fewer adverse events leading to treatment discontinuation
  - had fewer adverse events leading to dose modifications or interruptions, and
  - did not experience any adverse events (grade-independent) with an incidence that was ≥10% higher compared with docetaxel.
- Patients in the docetaxel arm compared with the atezolizumab arm experienced more (≥5% difference) adverse events including:
  - alopecia, stomatitis, myalgia, fatigue, nausea, diarrhoea, neutropenia, and peripheral neuropathy
- Two adverse events were experienced more frequently in the atezolizumab arm:
  - musculoskeletal pain (10.5% atezolizumab, 4.3% docetaxel) and
  - pruritus (8.2% atezolizumab, 3.1% docetaxel)
- The incidence of fatal adverse events was low in both arms
- The lower incidence of AEs of atezolizumab even with a longer treatment duration than docetaxel

35

Source: CS p115-121

Indirect and mixed treatment comparisons

network meta-analysis included comparators not listed in the final scope

- OAK and POPLAR compare atezolizumab with docetaxel only, so indirect comparisons were needed to get comparative effectiveness estimates for other comparators
- Studies for comparators were identified though a systematic literature review
- Company included 19 reviews in the network meta-analysis on: nintedanib plus docetaxel and comparators not listed in scope (afatinib; dacomitinib; erlotinib; gefitinib; paclitaxel; pemetrexed).
- Proportional hazards assumption did not hold for OS or PFS in the OAK and POPLAR trials, so fractional polynomial framework was used (allows hazard to change over time)
- The company used data from the LUME-Lung 1 trial for nintedanib plus docetaxel, for a broad population of all NSCLC patients and compared this with ITT population from the atezolizumab trial (OAK).
  - Nintedanib is licensed for people with adenomacarcinoma histology, that is narrower than the anticipated marketing authorisation for atezolizumab

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Source: CS p93

Nintedanib (plus docetaxel)

- Licensed only for people with adenocarcinoma histology, which is not consistent with the anticipated marketing authorisation for atezolizumab.
- Therefore the “total population” from the nintedanib (plus docetaxel) trial was compared with the atezolizumab ITT population in an indirect treatment comparison.

Results of the indirect and mixed treatment comparison

- Company presented results from full network (including comparators not listed in the scope)
- For OS, the model with p1=0 (Weibull) was the best fit by DIC was the best fit, a 5-year time horizon was used for presenting the FP NMA time-dependent outputs
- For PFS, the model with p1=1 (Gompertz) was the best fit by DIC, a 2.5-year time horizon was used for presenting FP NMA time-dependent outputs

Expected survival difference in months (95% Credible interval) full network

Outcome	Atezolizumab vs docetaxel	Atezolizumab vs nintedanib+docetaxel
OS	4.41 (1.77 to 7.56)	5.31 (2.96 to 8.17)
PFS	-0.41 (-1.63 to 0.69)	0.53 (-0.11 to 1.28)

- ERG requested a reduced network for the indirect treatment comparison that contained comparators relevant to the scope only (to reduce 'noise'):

Expected survival difference in months (95% Credible interval)* reduced network

Outcome	Atezolizumab vs docetaxel	Atezolizumab vs nintedanib+docetaxel
OS	5.84 (3.68 to 8.07)	3.33 (-0.16 to 6.74)
PFS	0.68 (-0.04 to 1.46)	-0.07 (-1.76 to 1.28)

*Results came from the 'best fitting' Weibull fixed effects fractional polynomial model
PFS=progression-free survival; OS=overall survival

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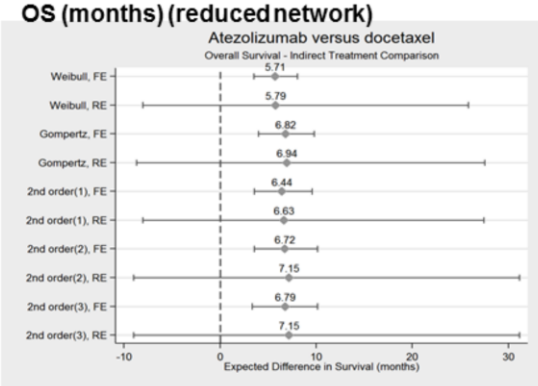
Source: Company submission p109, 112, fig 25, fig 27, ERG report p78 table 26

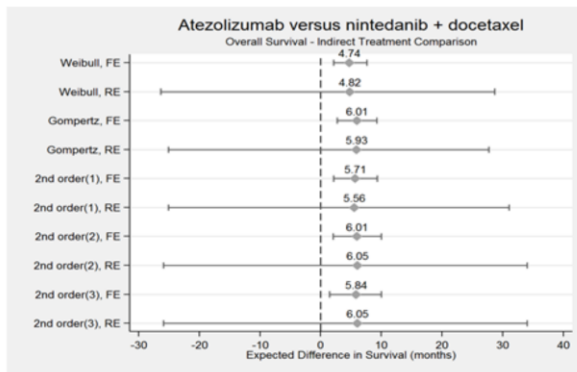
Indirect treatment comparison

Random effects model takes into account heterogeneity of study design

- Company fitted random effects (RE) and fixed effects (FE) models, judged best fitting model based on Deviance Information Criteria (DIC) statistic
- ERG states DIC is a measure of model fit, not statistical heterogeneity and choices between FE and RE models should take in to account similarity of trial design, populations and evidence sources
  - ERG preferred approach is a random effects model, because it takes into account variability of the studies included in the analysis.
  - Confidence intervals are much wider for RE model compared with FE
  - Expected difference in survival is similar across models ranging between 5.7 and 7.2 compared with docetaxel and 4.7 to 6.1 months compared with nintedanib + docetaxel

Results of fixed effects and random effects fractional polynomial models, expected difference in OS (months) (reduced network)





Source: ERG report figure 3 p73

OS results of fractional polynomial models, model fit and heterogeneity (1)

reduced network

FP model	Expected survival difference in months (95% Credible interval)		DIC	SD (95% CrI)
	Atezolizumab vs docetaxel	Atezolizumab vs nintedanib+docetaxel		
Weibull, fixed effects	5.71 (3.49 to 8.03)	4.74 (2.13 to 7.60)	910.4255	NA
Weibull, random effects	5.79 (-8.05 to 25.82)	4.82 (-26.37 to 28.66)	911.4979	0.368 (0.013 to 1.872)
Gompertz, fixed effects	6.82 (3.98 to 9.77)	6.01 (2.69 to 9.26)	934.1241	NA
Gompertz, random effects	6.94 (-8.69 to 27.53)	5.93 (-25.12 to 27.70)	935.3138	0.373 (0.012 to 1.838)

a 2nd order model (1) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(log t)2; CS, page 108

b 2nd order model (2) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(t); CS, page 108

c 2nd order model (3) corresponds to a model of the form: log hazard=beta0+beta1(t)+beta2(t*log t), CS, page 108

NA=not applicable OS=overall survival; SD=standard deviation of the heterogeneity parameter

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Source: ERGR p72 table 24

OS results of FP models, model fit and heterogeneity (2)

FP model	Expected survival difference in months (95% Credible interval)		DIC	SD (95% CrI)
	Atezolizumab vs docetaxel	Atezolizumab vs nintedanib+docetaxel		
2nd order (1)[a], fixed effects	6.44 (3.55 to 9.55)	5.71 (2.09 to 9.32)	837.1486	NA
2nd order (1)[a], random effects	6.63 (-8.06 to 27.42)	5.56 (-25.12 to 31.03)	838.3337	0.384 (0.012 to 1.824)
2nd order (2)[b], fixed effects	6.72 (3.54 to 10.12)	6.01 (2.06 to 9.97)	837.6918	NA
2nd order (2)[b], random effects	7.15 (-9.01 to 31.12)	6.05 (-25.96 to 34.04)	839.1147	0.379 (0.011 to 1.851)
2nd order (3)[c], fixed effects	6.79 (3.33 to 10.15)	5.84 (1.47 to 9.97)	853.9698	NA
2nd order (3)[c], random effects	7.15 (-9.01 to 31.12)	6.05 (-25.96 to 34.04)	854.9049	0.365 (0.010 to 1.858)

a 2nd order model (1) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(log t)2; CS, page 108
b 2nd order model (2) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(t); CS, page 108
c 2nd order model (3) corresponds to a model of the form: log hazard=beta0+beta1(t)+beta2(t*log t), CS, page 108
NA=not applicable OS=overall survival; SD=standard deviation of the heterogeneity parameter

- Company disregards 2nd order models because fitted survival curve plateau at 48 months
- ERG notes, visually 1st and 2nd order models are similar

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Source: ERGR p72 table 24

Results of the indirect and mixed treatment comparison – pembrolizumab

- During clarification the ERG requested results of the network including pembrolizumab as a comparator
- Company provided results comparing atezolizumab in its licenced indication vs pembrolizumab in its licenced indication (PD-L1 positive)
  - risk that relative clinical benefits of pembrolizumab are overestimated
  - not a robust or true reflection of comparative efficacy
- Results for atezolizumab vs docetaxel were similar to results in the network that excluded pembrolizumab
- No statistically significant difference between atezolizumab and pembrolizumab for OS or PFS

Expected survival difference in months (95% Credible interval)*		
Outcome	Atezolizumab vs docetaxel	Atezolizumab vs pembrolizumab
OS	5.79 (3.63 to 8.05)	-0.24 (-5.38 to 4.44)
PFS	1.17 (0.29 to 2.03)	-0.30 (-2.17 to 1.40)
***Results came from the 'best fitting' Weibull FE FP model**		

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Limitations of indirect treatment comparison

Company comments:

- Aggregate level data for all interventions, apart from atezolizumab
- Data in studies reported short period of time so high uncertainty in extrapolation
- Only done for OS and PFS, however TTD more informative endpoint

ERG comments:

- Agree with fractional polynomial approach to ITC, but the results are difficult to interpret and difficult to identify most appropriate combination of relevant factors (influenced by comparators, population, fractional polynomial model)
- Disagree with ITC approach as it includes comparators not listed in the final scope
- Pembrolizumab should have been included in the ITC network. Company did these in response to clarification questions, however used a different population so results should be interpreted with caution
- Company has compared nintedanib outside of its MA using the total trial population (includes non-adenocarcinoma histologies).

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Reduced network used data from the intention-to-treat (ITT) populations of the OAK and POPLAR trials and the adenocarcinoma population from the LUME-Lung 1 trial for atezolizumab vs. docetaxel+nintedanib.

Reduced network using data from the ITT populations of the OAK, POPLAR and KEYNOTE-010 trials (the latter assessing the efficacy of pembrolizumab as a first-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% tumour proportion score.

ERG critique – Indirect Treatment Comparison (I)

- Indirect treatment comparison approach not supported by ERG
  - ERG agree with use of fractional polynomial model
  - Do not agree with using DIC statistic to assess heterogeneity and there is a large amount of statistical heterogeneity in network not accounted for in any ITC analyses
  - The main network includes comparators not listed in the scope
  - Atezolizumab vs Nintedanib: whole LUME-Lung1 trial population used for nintedanib which is broader than its licenced indication for people with adenocarcinoma
  - Pembrolizumab should have been included in ITC network of comparators
  - ITC approach influenced by range of factors (comparators, population, type of FP model), results are difficult to interpret
  - ITT population for atezolizumab vs pembrolizumab (includes ≥50% PD-L1 only), no statistically significant difference in OS or PFS

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ERG critique – Indirect Treatment Comparison (II)

- ERG requested reduced network of comparators from company, results show:
  - Company's best estimate of difference in OS:
    - Atezolizumab vs docetaxel: 6 to 7 months
    - Atezolizumab vs nintedanib + docetaxel: 5 to 6 months
    - No significant difference in PFS
- ERG requested two subgroup analyses from company (Results given are from non-equivalent populations so should be interpreted with caution):
  - ERG requested comparison of atezolizumab and nintedanib + docetaxel in adenocarcinoma subgroups
    - Company provided analysis using data from ITT population for atezolizumab and adenocarcinoma population nintedanib + docetaxel
      - Best estimate of difference in OS for atezolizumab vs nintedanib + docetaxel 3.33 months (4.74 months when total population of LUME-Lung 1 is used)

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Cost effectiveness evidence

Company submission section 5

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Key issues: cost effectiveness

- Mixed cure-rate to model OS for patients receiving atezolizumab:
  - insufficient evidence to apply cure-rate
  - the value for the cure rate used not justified by the company
  - log-logistic function produces implausibly long survival tail (mortality rates, at some points, are lower than the mortality rates of the UK general population of the same age)
- Company's model assumes atezolizumab has a lifetime protective effect

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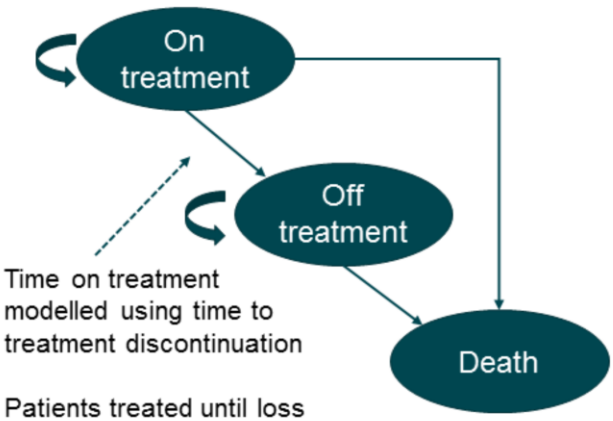
Company's model structure



Time on treatment modelled using time to treatment discontinuation

Patients treated until loss of benefit of treatment

Health states: 'on treatment' and 'off treatment' because treatment beyond progression is common for immunotherapies and past NICE appraisals had shown that the 'progression free survival', 'progressed disease' model was not well suited to this type of treatment.

Proportion of patients in each health state calculated based on TTD and OS curves.

The following parameters were modelled using progression free, post-progression and death structure. Because data for time to discontinuation were not available:

- **Nintedanib plus docetaxel:** treatment duration, supportive care costs and utilities, and;
- **Docetaxel:** supportive care costs.

Time horizon	25 years
Cycle length	One week
Half cycle correction	Yes
Discount rate	3.5% for costs and utilities
Perspective	UK NHS

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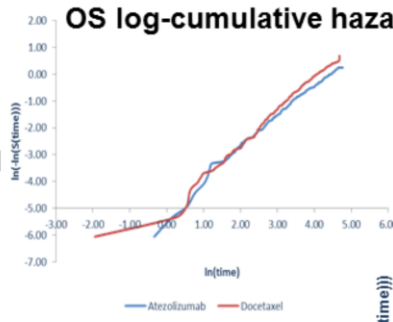
Source: company submission p139-141

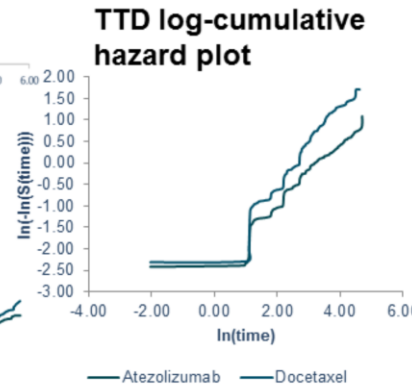
No treatment discontinuation rule for atezolizumab – treatment until loss of clinical benefit (cap at 18 weeks, 6 cycles, in base case). Based on clinical expert opinion.

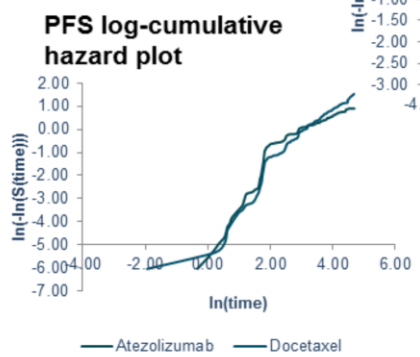
OAK proportional hazards

the proportional hazards assumption does not hold for OS, PFS or TTD

- Visual inspection of log cumulative hazards plots showed curves cross so proportional hazards assumption does not hold for progression free survival, overall survival and time to treatment discontinuation in OAK
- Relationship between schoenfield residuals and time further confirmed this
- Therefore the company used fractional polynomial network meta-analysis, which does not require the proportional hazards assumption







48

Source: company submission p146-148

Proportional hazards did not hold for atezolizumab compared with docetaxel in the OAK trial, the company acknowledges that the DSU advises to separately parameterise treatment and comparator arms in this case. However the company chose to use a fractional polynomial network meta-analyses approach, which does not assume proportional hazards.

Treatment duration assumptions

- The company estimated treatment duration for atezolizumab using time on treatment results from the OAK study

	Treatment duration
Atezolizumab	Based on time to treatment discontinuation
Docetaxel	Capped at 18 weeks. In clinical practice, docetaxel is subject to a cap of 6 cycles.
Nintedanib plus docetaxel	Based on PFS as treatment duration results were not available.

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Source: company submission p195, 212

Time to treatment discontinuation atezolizumab

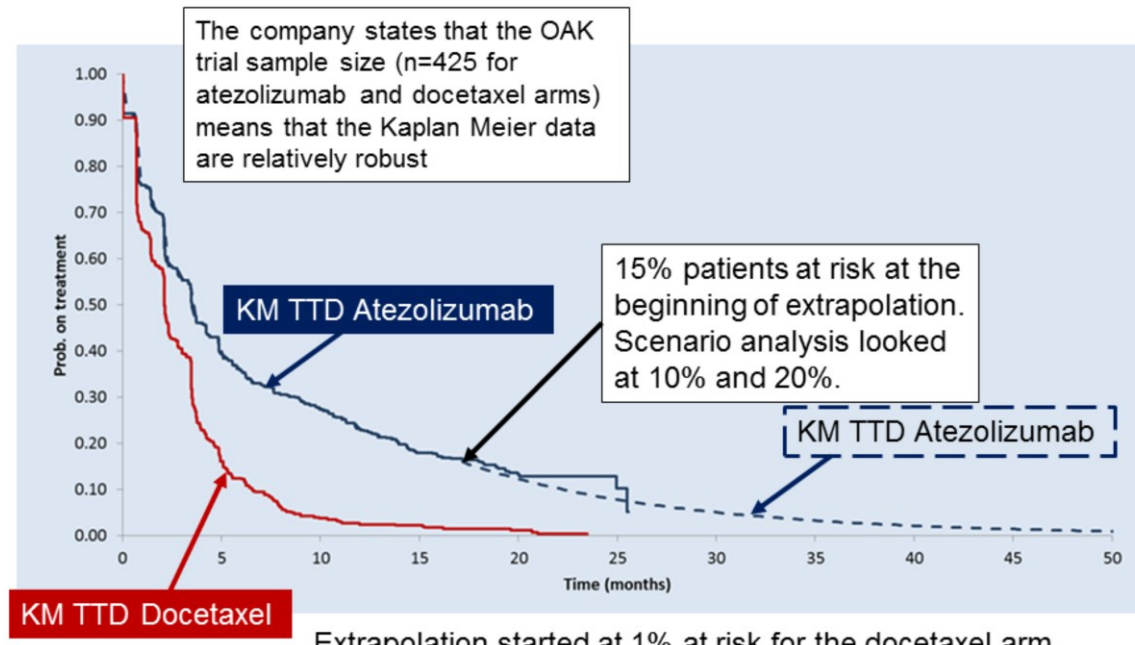
- The company tested extrapolation using akaike information criteria (AIC), Bayesian information criterion (BIC), visual inspection and clinical plausibility.
- The parametric distributions tested were:
  - Exponential, Weibull, Log-normal, Gamma, Log-logistic, and Gompertz
- Gamma was the most appropriate distribution based on statistical fit (AIC, BIC criteria), however the company did not consider any of the distributions to be a good visual fit.
- The company's preferred method was to use Kaplan Meier data that was available and extrapolating the tail only
- The parametric distribution starts when the proportion of patients at risk (OAK) is 15% (mid-point of the Pocock criteria)
- The Gamma distribution was used for the extrapolation of the tail as it had the best statistical and visual fit

50

Source: company submission p149-150
Time to treatment discontinuation: the difference between
Pocock criteria: the parameterised tail should start when there is no greater than 20% or less than 10% patients at risk

Time to treatment discontinuation - atezolizumab vs docetaxel Kaplan Meier and gamma distribution

company's preferred fit



Extrapolation started at 1% at risk for the docetaxel arm (corresponds to 17% at risk for atezolizumab)

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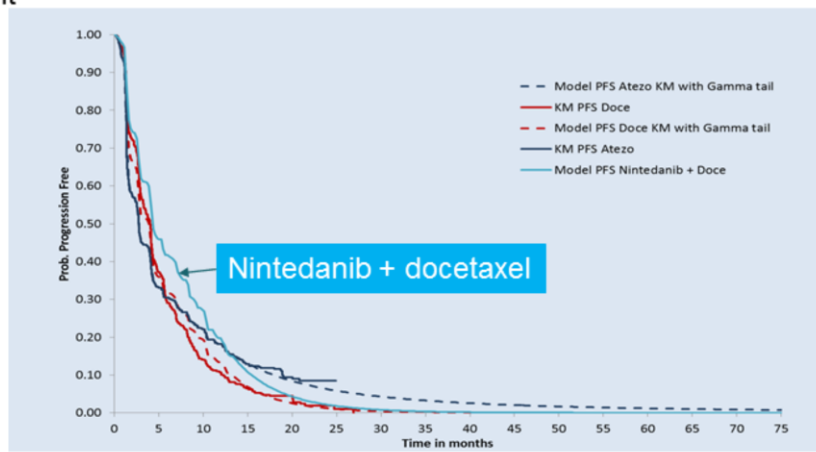
Source: p151 fig 38

Treatment duration - nintedanib plus docetaxel PFS data

- TTD data were not available for nintedanib plus docetaxel so PFS data were used to estimate time on treatment
- Results of the fractional polynomial network meta-analysis were extrapolated
- The extrapolation is constructed by applying time-dependant log hazard ratios to the atezolizumab extrapolation
- Gamma was the most appropriate distribution based on statistical fit (AIC, BIC criteria), however the company did not consider any of the distributions to be a good visual fit



52

Source: company submission p150-151

Company's modelling of OS

the company adjusted OAK trial data for background mortality using a mixed cure-model

- Longest follow up available for OAK intention to treat population was 2 years
- Company assumes lifetime duration of treatment effect assumed for atezolizumab (criticised TA428 pembrolizumab)
- Extrapolation was based on real world data from the national lung cancer audit (NLCA)
- Overall survival estimates were modelled using mixed cure rate methodology (previously used in TA414)
- The company used 'mixture cure rate methodology' to adjust the OAK trial data for background mortality for atezolizumab only, then parametric models were fitted to the adjusted data
- Mixed cure-model assumes a subgroup of patients have the same mortality rate as the general population
- Company states atezolizumab may have a sustained effect for a subgroup of patients with Stage IV NSCLC
- Mixture cure rate
  - cure fraction was estimated using long term survival data from the NLCA
  - Cure fraction of 2% was applied to the OAK trial data.

used in pembrolizumab TA428 by ERG to model OS from year 2 onwards for pembrolizumab and docetaxel

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Source: company submission p156-159

Cure rate fraction: the proportion of patients equally likely to die of non-cancer and cancerous causes
National lung cancer audit: monitors people diagnosed with lung cancer and mesothelioma in the UK, with up to 5 years of data on overall survival for stage IIIB and stage IV NSCLC.

Mixture cure rate methodology - estimates overall mortality risk, at a given point in time, as a mixture between cancer-related and background mortality risk. The company used the observed survival times in the OAK trial and the background mortality risks from life-tables (the latter is known as the cured fraction and represents the proportion of patients who are as like to die from non-cancer causes as from cancer). In summary, the survival function includes patients with a high risk of death from cancer and a low risk of death from cancer – these data are combined to produce and average survival for the whole population

ERG's critique of Mixed cure-rate model

mixed cure model produces results 'inappropriate' for decision making

- Not enough evidence to apply cure rate
- Inappropriate for company to justify use of mixed cure-rate model with TA414
  - Mixed model was used in TA414 because mortality rate of patients decreased at 5 years
    - Demonstrated by phase III head-to-head study (Kaplan-meier 5 year overall survival) and 10 year registry data
- Value of cure rate (2%) used is not justified by the company or supported by evidence
  - In TA414 this was obtained from analysis of the Surveillance, Epidemiology, and End Results (SEER) registry data
  - ERG not aware of any NSCLC registry data that suggests a subgroup of patients with different mortality rates
- The mixed cure-rate model, generates survival gains that are not supported by data from OAK trial.
- The cure rate chosen by the company based on NSCLC data (2%) produces an overestimate of survival for patients treated with atezolizumab by 2.8% and underestimates OS for patients receiving docetaxel by 1.6% (cure rate is not applied for docetaxel, but the curve is dependent on atezolizumab curve).
- Company did not do any adjusted statistical analysis of the NSCLC data (needs to take into account time since diagnosis, number of prior treatments, and progression status.)
- If evidence supporting this existed ERG suggest that it could be modelled by appropriately chosen distributions, based upon available trial data

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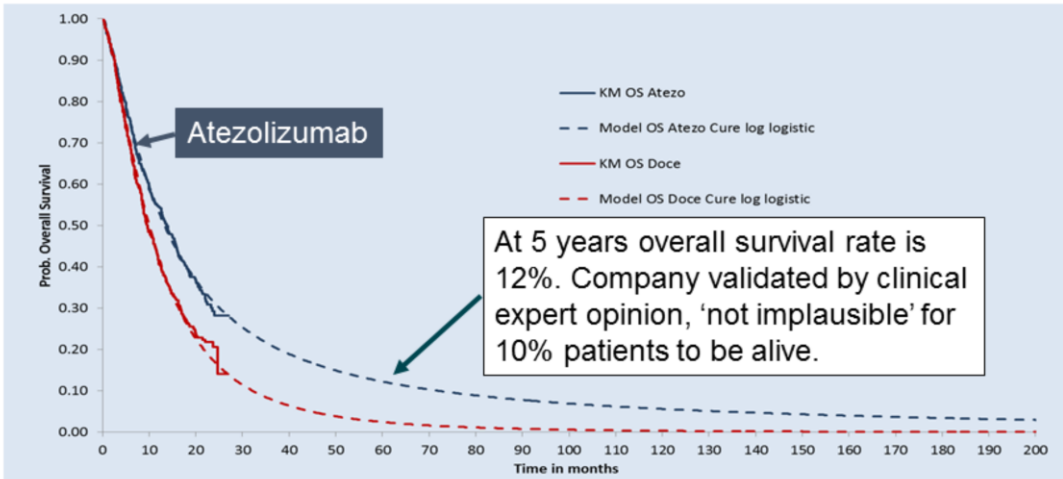
Source: ERGR p103-105

Company's modelling of OS atezolizumab and docetaxel

mix-cure rate cure-log-logistic distribution

- The log-logistic function was the most appropriate statistical (according to AIC and BIC criteria) and visual fit, this was validated by clinical expert opinion
- Company justifies extrapolation based on TA428 and states that under committees preferred assumptions the 5 year OS rate was 9.6%.



ERG comments:

- Implausible tail with log-logistic distribution
- Company assumed that atezolizumab has a lifetime protective effect (previously criticised TA414)

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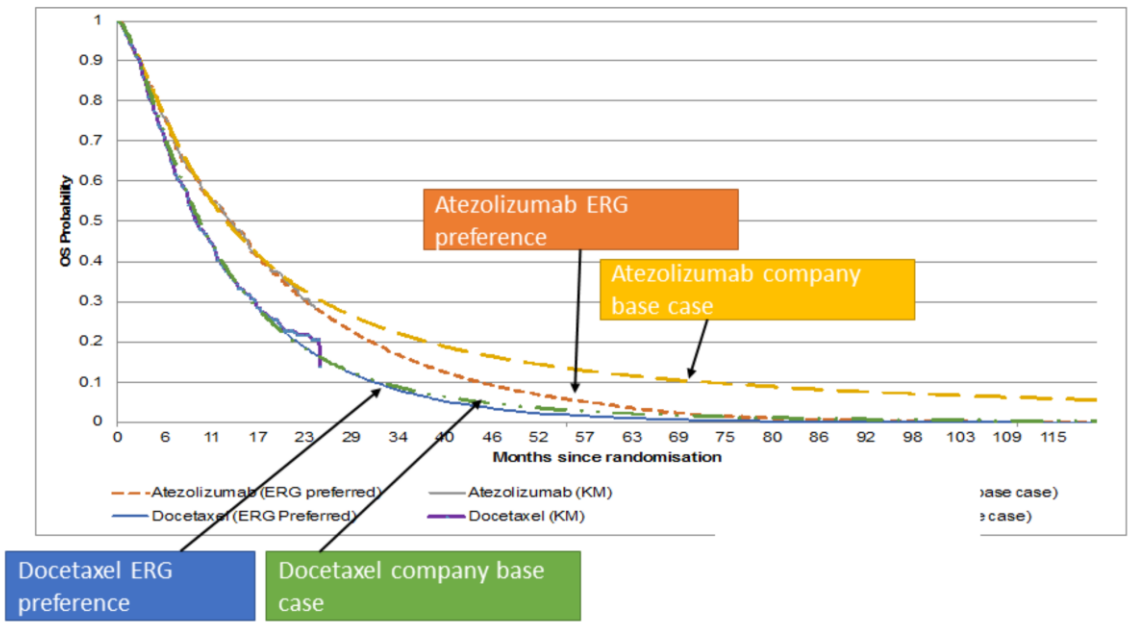
ERG remodelled OS atezolizumab vs docetaxel

- ERGs preferred approach is KM data up to 19 months, followed by exponential extrapolation with HR 1 applied for docetaxel.

ERGs preferred OS distributions compared to company modelled OS and K-M data



Source: ERGR p114 figure 18

Estimates of proportions of patients alive at different time points since randomisation

OS curve	Time since randomisation					
	1 year	2 years	5 years	10 years	20 years	25 years
Atezolizumab (K-M)	54.7%	28.1%	-	-	-	-
Atezolizumab (company base case)	53.6%	31.1%	12.2%	5.5%	2.2%	1.4%
Atezolizumab (ERG preferred)	54.7%	28.5%	4.4%	0.1%	0.0%	0.0%
Docetaxel (K-M)	41.7%	20.6%	-	-	-	-
Docetaxel (company base case)	42.5%	16.8%	2.4%	0.0%	0.0%	0.0%
Docetaxel (ERG preferred)	41.7%	17.0%	1.2%	0.0%	0.0%	0.0%

Abbreviations: ERG, Evidence Review Group; K-M, Kaplan-Meier

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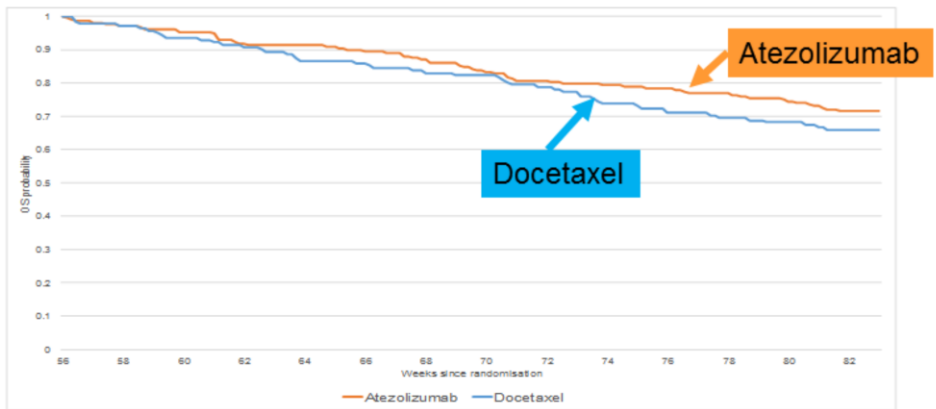
Source: ERGR p112 table 42

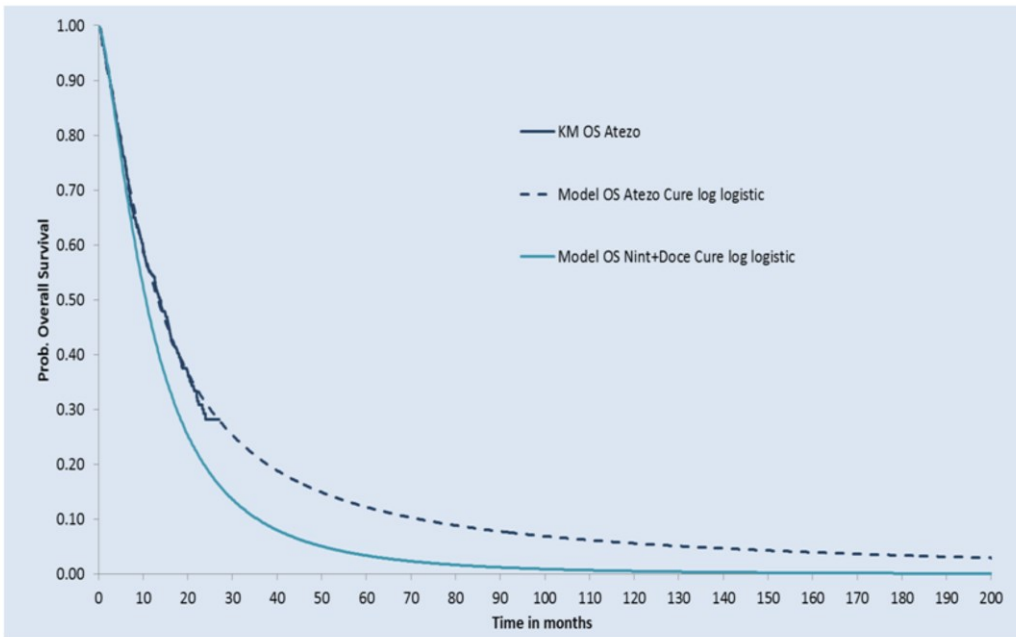
ERG preferred approach to OS modelling atezolizumab vs docetaxel

- The ERG used KM data from OAK up to 19 months then extrapolated
  - Data available were for all patients up to 19 months in OAK (83 WEEKS) and there was limited censoring up to this point, in the ERGs opinion this is best cut off for extrapolation
- The ERG assumed no difference in effectiveness after week 56, HR of 1 applied (only slight separation of curves between week 56-83 & touch twice).
- The ERG caps treatment effect at 3 years (committees view in TA428)

OS K-M data from the OAK trial, weeks 11 to 56 (rebased at week 11)



Company's modelling of OS atezolizumab vs nintedanib



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ERG modelling of OS atezolizumab vs nintedanib + docetaxel

- ERGs preferred approach is to compare atezolizumab with nintedanib + docetaxel in adenocarcinoma population only.
- No statistically significant difference in OS between atezolizumab and nintedanib + docetaxel.
- ERG used KM data up to week 56 and modelled the same OS curve for atezolizumab and nintedanib + docetaxel.
  - QALY gain for atezolizumab falls to 0.027 with the ERG corrected company base case ICER increasing to £1,170,260 per QALY gained (calculated using list prices).
- Company provided atezolizumab (total population OAK and POPLAR) compared with nintedanib + docetaxel
  - This analysis assumes that the effectiveness of atezolizumab is independent of whether a patient has adenocarcinoma

ERG's critique of OS modelling

implausible long-term projection

- Implausible tail with log-logistic distribution
- Company assumed that atezolizumab has a lifetime protective effect (previously criticised TA414)
- Company's base case extrapolation suggests 5.6% alive at 10 years and 1.4% at 25 years.
- No accurate way to set treatment duration within the company's model. Duration of treatment effect can be set to x months, after x months hazard rate for atezolizumab is the same as docetaxel
  - This approach underestimates treatment effect e.g. if treatment effect is set to 3 years then; if patient A stops treatment at 6 months, their duration of treatment effect is 2.5 years. If patient B is still on treatment at 3 years, their treatment effect is 0 years.
  - So treatment effect varies per patient and is not fixed, underestimates true duration of treatment effect.
  - ERG set the treatment effect to 5 years (to simulate a 3 year duration of treatment) given the limitations in the company's model
- Model mortality rates are lower than the general population at some points
  - Between 83-88 years:
    - Model mortality rate 36.9%
    - UK life table mortality rate 39.5%
  - ERG considers it implausible that survival from cancer and all other causes is reduced by atezolizumab.
- ERGs preferred extrapolation use KM data for atezolizumab and docetaxel for as long as possible then extrapolate.

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Adjusting for treatment switching

- Subsequent therapies, mostly nivolumab
  - 5% atezolizumab arm
  - 17% docetaxel arm
- Rank Preserving Structural Failure Time (RPSFT) used to assess impact of cross-over on overall survival estimates
  - Crossover made a marginal impact, so the economic model was not adjusted for treatment switching
  - ICER estimates are conservative

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Health related quality of life data

- Health related quality of life utilities used in the model were collected in the OAK trial
- The company chose 'on treatment' 'off treatment' health states because, progression of disease is often asymptomatic and otherwise utility could be underestimated, if benefit from treatment is still experienced after progression.
- Utilities were decreased based on clinical expert opinion that utility decreases as the patient approaches death

State	Utility value: mean (standard error)	95% confidence interval
Base case: by progression status and time-to-death (weeks)		
On treatment		
≤ 5 weeks before death	0.39	(0.24-0.55)
5 and ≤ 15 weeks before death	0.61	(0.53-0.68)
15 and ≤ 30 weeks before death	0.71	(0.69-0.74)
>30 weeks before death	0.77	(0.75-0.78)
Off treatment		
≤ 5 weeks before death	0.35	(0.27-0.44)
5 and ≤ 15 weeks before death	0.43	(0.37-0.49)
15 and ≤ 30 weeks before death	0.58	(0.55-0.61)
>30 weeks before death	0.68	(0.66-0.71)

ERG considers >30weeks to death utility to be high (0.77) as the population norm aged 63 at start of model is 0.79

Source: company submission p173-174

Adverse event disutilities

- Model includes quality of life decrement of all grade 3-5 AEs, which occurred in ≥2% of patients for intervention and comparator arms

Adverse Event	Disutility	Source
Anaemia	-0.07346	(Nafees et al., 2008)
Fatigue	-0.07346	(Nafees et al., 2008)
Febrile Neutropenia	-0.09002	(Nafees et al., 2008)
Neutropenia	-0.08973	(Nafees et al., 2008)
Leukopenia	-0.08973	Assumed equal to Neutropenia (NICE ID811 and ID900)
Neutropenic sepsis	-0.09002	Assumed equivalent to Febrile Neutropenia
Neutrophil count decreased	0	Assumption (NICE ID811 and ID900)
Pneumonia	-0.008	(Marti et al., 2013)
Respiratory Tract Infection	-0.096	Assumption adapted from Hunter 2015 (Hunter, 2015)
White blood cell count decreased	-0.05	(NICE TA347)

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Source: company submission p172 table 62

Costs

Treatment costs (per cycle)	
Atezolizumab (list)	£3807.69
Docetaxel	£34.39
Nintedanib	£1434.07
Administration atezolizumab	£198.94
Administration docetaxel	£198.94
Administration nintedanib	Table 70
Adverse event management costs	
Atezolizumab	£1313.09
Docetaxel	£3082.59
Nintedanib + Docetaxel	£5612.78
Anaemia	£5612.78
Fatigue	£362.66
Febrile Neutropenia	£362.66
Leukopenia	0
Neutropenia	£2783.99
Neutropenic sepsis	£3515.13
Neutrophil count decreased	£432.47
Health state costs	
On treatment monitoring cost	162.84
On treatment/PFS	£282.96
Off treatment/PD	£128.25
Terminal care	£3679

Administration cost for atezolizumab was assumed to be the same as nivolumab and pembrolizumab (NHS reference cost code SB12Z)

Adverse event costs applied for time on treatment

'Weekly supportive care' costs incorporated as health state costs

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Source: company submission p193 table 81

Company model: Summary

Assumption	Company approach
Treatment continuation	OAK: treated until loss of clinical benefit TTD (atezolizumab).
Time on treatment	OAK: treated until loss of clinical benefit TTD (atezolizumab).
OS extrapolation	OAK: mix-cure rate model, log-logistic distribution. Clinical plausibility of the extrapolation was taken into account and at 5 years 12% of patients are alive. A life time protective effect is assumed for atezolizumab.
TTD extrapolation	OAK: Kaplan meier data, extrapolation tail is gamma distribution.
Long-term treatment effect	'Fractional polynomial' approach to hazards 'the log-HRs increase linearly over time, as the HR from the tail of the observed data continue in the same direction for the extrapolated tail'. Scenario anlayses 'cap' the HR at 2 years, 3 years and 4 years.
Treatment switching	Crossover from the docetaxel arm to the atezolizumab arm was not originally permitted in OAK, however this was subsequently allowed following analysis of the primary population (n=850).
Utilities	OAK: Quality-adjusted life years (QALYs) estimated using EQ-5D-5L data.
AE	KEYNOTE-024: Cost of managing adverse events applied weekly while patients are on treatment. Quality of life decrement of all grade 3-5 AEs, which occurred in ≥2% of patients.
PD-L1 testing	Not included for atezolizumab.

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Company's base case results

list prices

Atezolizumab vs docetaxel							
	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) inc (QALYs)
Docetaxel	£19,941	1.19	0.73	-	-	-	-
Nintedanib + Docetaxel	£37,702	1.31	0.83	£17,761	0.13	0.10	Ext. dominated
Atezolizumab	£73,911	2.22	1.47	£53,970	1.04	0.75	£72,356
Atezolizumab vs nitedanib plus docetaxel							
	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) inc (QALYs)
Docetaxel	£19,941	1.19	0.73	-	-	-	-
Nintedanib + Docetaxel	£37,702	1.31	0.83	-	-	-	-
Atezolizumab	£73,911	2.22	1.47	£36,209	0.91	0.65	£56,076

Note: there is a PAS for nintedanib, with PAS comparaisons with atezolizumab will be presented in part 2b

Abbreviations: ext, extendedly; inc, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Note: numbers may not sum due to rounding

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Source company submission p197

Note: ICERs for atezolizumab compared with nintedanib should be interpreted with caution, because total population of the nintedanib trial was used (outside MA) to be comparable with atezolizumab population, instead of the adenomacarcinoma population. The company states that they do not expect this to have a 'major bearing on the results'

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Company's base case results

Atezolizumab PAS price vs list prices

Atezolizumab vs docetaxel							
	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) inc (QALYs)
Docetaxel	£19,941	1.19	0.73	-	-	-	-
Nintedanib + Docetaxel	£37,702	1.31	0.83	£17,761	0.13	0.10	Ext. dominated
Atezolizumab	[redacted]	2.22	1.47	[redacted]	1.04	0.75	[redacted]
Atezolizumab vs nitedanib plus docetaxel							
	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£) inc (QALYs)
Docetaxel	£19,941	1.19	0.73	-	-	-	-
Nintedanib + Docetaxel	£37,702	1.31	0.83	-	-	-	-
Atezolizumab	[redacted]	2.22	1.47	[redacted]	0.91	0.65	[redacted]

Abbreviations: ext, extendedly; inc, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Note: numbers may not sum due to rounding

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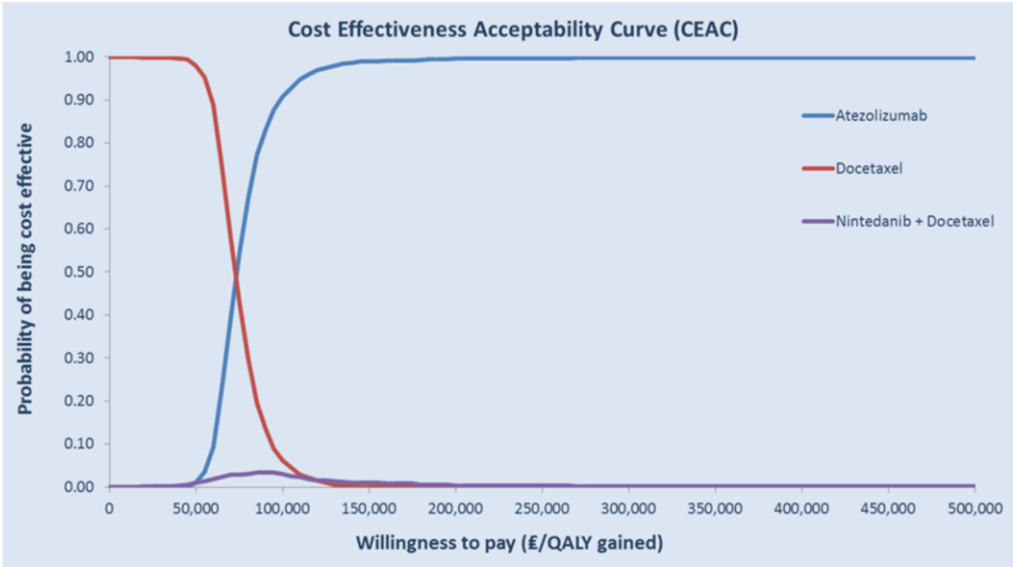
There is a PAS for nintedanimb+docetaxel, PAS vs PAS results will be presented during part 2b of the committee meeting.

Probabilistic sensitivity analysis

list price



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Source: company submission p206 fig 60

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One-way deterministic sensitivity analysis

- Most base case values were varied by +/-50%
- Drug costs were increased by 1% and decreased by 75% (nintedanib PAS discount is unknown)
- The company state that the cure fraction range was chosen to 'aid decision making: providing a sufficient range around our selected base case'

Parameter values that had the biggest impact on the ICER were the cure fraction and cost of atezolizumab:

Parameter	Base case value	Lower value	Higher value
Cure fraction	2%	0%	5%
Monthly cost of atezolizumab	£5,500	[redacted]	+10%
Cost of nintedanib: subsequent cycles	£1,434	-75%	+1%
Discount effects	3.5%	1.5%	6%
Discount costs	3.5%	1.5%	6%
Supportive costs, on treatment, atezolizumab	£282.96	-50%	+50%
Supportive costs, off treatment, atezolizumab	£128.25	-50%	+50%
Supportive costs, on treatment, docetaxel	£282.96	-50%	+50%
Supportive costs, off treatment, docetaxel	£128.25	-50%	+50%
Supportive costs, on treatment, nintedanib+docetaxel	£282.96	-50%	+50%
Supportive costs, off treatment, nintedanib+docetaxel	£128.25	-50%	+50%
Weekly AE cost, docetaxel	£75.87	-50%	+50%
Weekly AE cost, nintedanib+docetaxel	£47.93	-50%	+50%

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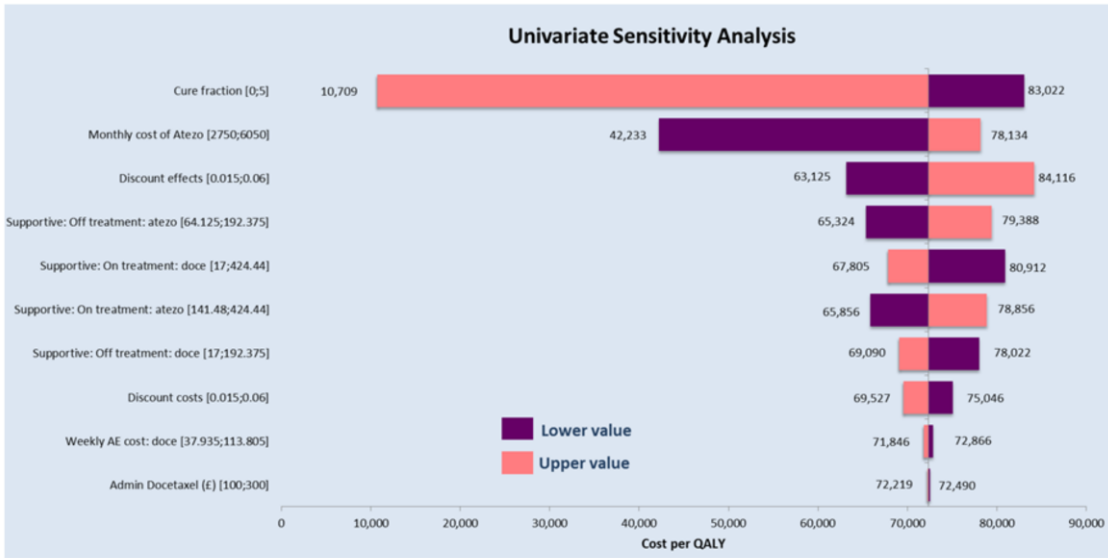
Source: company submission p207 table 94

One-way deterministic sensitivity analysis compared with docetaxel

list price



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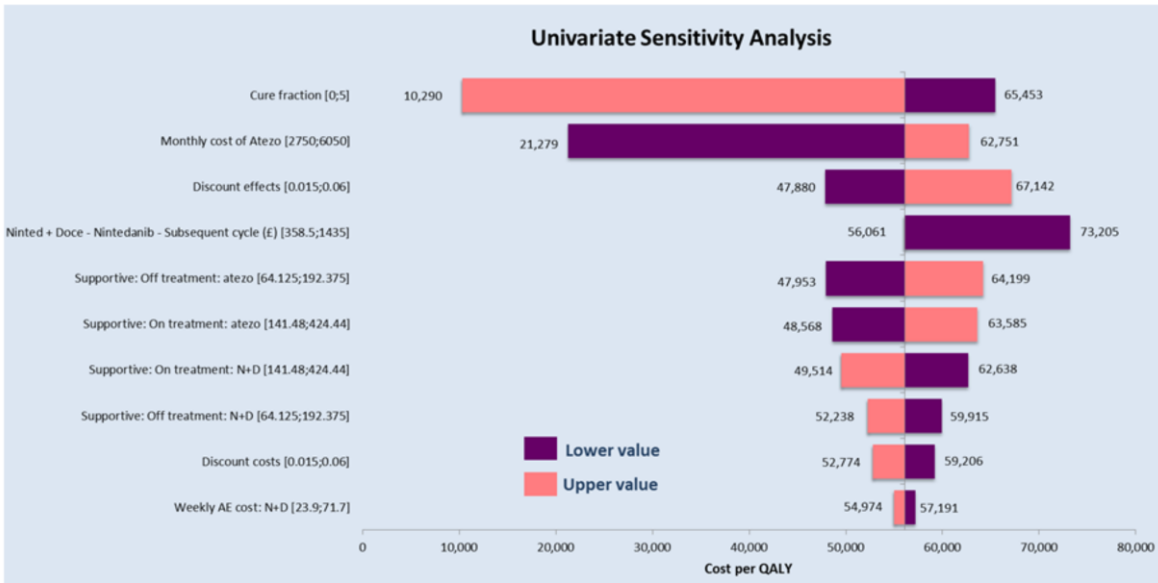
Source: company submission p208

One-way deterministic sensitivity analysis compared with nintedanib plus docetaxel

list price



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Source: company submission p209

Scenario analysis results: atezolizumab vs docetaxel

list price

ICERs were sensitive to changes in the cure fraction for the overall survival extrapolation

	Atezolizumab			Docetaxel			Atezo vs. Docetaxel
Description	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	ICER
Base case	2.22	1.47	£73,911	1.19	0.73	£19,941	£72,365
TTD KM proportion at risk 10%	2.22	1.47	£74,884	1.19	0.73	£19,941	£73,549
TTD KM proportion at risk 20%	2.22	1.47	£72,720	1.19	0.73	£19,941	£70,892
PFS KM proportion at risk 10%	2.22	1.47	£73,911	1.19	0.73	£19,908	£72,239
PFS KM proportion at risk 20%	2.22	1.47	£73,911	1.19	0.73	£19,890	£72,424
Cure fraction 0%	2.07	1.36	£72,885	1.19	0.73	£19,941	£83,022
Cure fraction 1%	2.14	1.42	£73,395	1.19	0.73	£19,941	£77,301
Cure fraction 3%	2.30	1.53	£74,433	1.19	0.73	£19,941	£68,039
Cure fraction 4%	2.39	1.58	£74,961	1.19	0.73	£19,941	£64,237
Cure fraction 5%	2.47	1.64	£75,495	1.19	0.73	£19,941	£60,863
OS HR cap: 24 months (trial follow up)	2.22	1.47	£73,911	1.19	0.73	£19,943	£72,377
OS HR cap: 36 months	2.22	1.47	£73,911	1.19	0.73	£19,941	£72,353
OS HR cap: 48 months	2.22	1.47	£73,911	1.19	0.73	£19,941	£72,356
Treatment until progression	2.22	1.47	£69,548	1.19	0.74	£20,478	£68,029

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Source: company submission p211-212

Scenario analysis results: atezolizumab vs nintedanib plus docetaxel

	Atezolizumab			Nintedanib+Docetaxel			Atezo vs. N+D
Description	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	ICER
Base case	2.22	1.47	£73,911	1.31	0.83	£37,702	£56,076
TTD KM proportion at risk 10%	2.22	1.47	£74,884	1.31	0.83	£37,702	£57,483
TTD KM proportion at risk 20%	2.22	1.47	£72,720	1.31	0.83	£37,702	£54,349
PFS KM proportion at risk 10%	2.22	1.47	£73,911	1.31	0.83	£38,319	£55,214
PFS KM proportion at risk 20%	2.22	1.47	£73,911	1.31	0.83	£37,378	£56,527
Cure fraction 0%	2.07	1.36	£72,885	1.31	0.83	£37,702	£65,453
Cure fraction 1%	2.14	1.42	£73,395	1.31	0.83	£37,702	£60,361
Cure fraction 3%	2.30	1.53	£74,433	1.31	0.83	£37,702	£52,420
Cure fraction 4%	2.39	1.58	£74,961	1.31	0.83	£37,702	£49,263
Cure fraction 5%	2.47	1.64	£75,495	1.31	0.83	£37,702	£46,510
OS HR cap: 24 months (trial follow up)	2.22	1.47	£73,911	1.32	0.83	£37,706	£56,108
OS HR cap: 36 months	2.22	1.47	£73,911	1.31	0.83	£37,703	£56,081
OS HR cap: 48 months	2.22	1.47	£73,911	1.31	0.83	£37,702	£56,077
Treatment until progression	2.22	1.47	£69,548	1.31	0.83	£37,702	£49,743

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Source: company submission p214-215

ERG exploratory analyses

ERG found 3 errors in model

1. Incorrect application of discounting
   - Discounting starts at week 1 (instead of year 2) correcting for this **increases ICER by small amount (£100-£400)**
2. Absence of age-dependent utility decrements
   - Company model does not take into account declining utility with age e.g. at age 63 and 88 if time to death is the same then utility is the same
   - ERG included age related decrements to correct this from Kind et al. (0.02 at 65 and 0.07 at 74). **Increases the company's base case ICER by £2.5-£3k per QALY**
3. Incorrect use of a half-cycle correction to TTD data
   - Treatment is received on day 1 of cycle so half cycle correction isn't needed. Leads to situation where 4.3% of patients don't ever start treatment with atezolizumab.
   - ERG removed half cycle correction applied to TTD data. **Increases the ICER by ~ £2k per QALY**

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ERG exploratory analyses

Atezolizumab vs docetaxel (list prices)

Model scenario & ERG revisions	ICER £/QALY	ICER Change
Company base case	£72,356	-
C1) Discounting algorithms	£72,764	+£408
C2) Age-related utility decrement	£75,316	+£2,960
C3) TTD half-cycle correction	£74,092	+£1,736
ERG corrected company base case (C1-C3)	£77,569	+£5,213
R1) ERG preferred OS for atezolizumab and docetaxel (KM data up to 19 months, followed by exponential extrapolation with HR 1 applied for docetaxel)	£165,310	+£92,954
R2) R1 + atezolizumab treatment duration set to 5 years (to simulate 3 years)	£170,497	+£98,141

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Source: ERG report p117 table 43

ERG exploratory analyses

Atezolizumab vs nintedanib + docetaxel (list prices)

Model scenario & ERG revisions	ICER £/QALY	ICER Change
Company base case	£56,076	-
C1) Discounting algorithms	£55,959	-£117
C2) Age-related utility decrement	£58,608	+£2,532
C3) TTD half-cycle correction	£57,949	+£1,873
ERG corrected company base case (C1-C3)	£60,366	+£4,290
R3) ERG preferred OS for atezolizumab and assumed equal for nintedanib+docetaxel	£1,170,260	+£1,114,185
R4) R3 + treatment duration effect for atezolizumab and nintedanib treatment duration set to 5 years (to simulate 3 years)	£1,170,793	+£1,114,718
R5) ERG preferred OS for atezolizumab, FP ITC for nintedanib+docetaxel OS and treatment duration effect for both set to 5 years	£186,259	+£130,183
R6) ERG preferred OS for atezolizumab, LUME-Lung 1 HR for nintedanib+docetaxel OS and treatment duration effect for both set to 5 years	£225,159	+£169,083

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Source: ERG report p 118 table 44

Innovation

- The company considers that pembrolizumab is an innovative treatment because:
  - Anticipated to be first anti-PD-L1 antibody approved for locally advanced or metastatic NSCLC after prior chemotherapy.
  - Atezolizumab differs from other (anti-PD-1) antibodies approved for the treatment of NSCLC as it results in the dual blockade of PD-1 and B7.1 while leaving the PD-1/PD-L2 interaction intact, thereby potentially preserving peripheral immune homeostasis
  - It is anticipated to be approved for all locally advanced or metastatic NSCLC patients with prior chemotherapy, regardless of PD-L1 expression status.
  - When tumour cells come into contact with immune system via PD-1-PD-L1 checkpoint immune cells attack and destroy tumour cells, with durable responses
    - In OAK median duration of response was more than doubled in the atezolizumab arm (16.3 months, 95% CI: 10.0, NE) compared with the docetaxel arm (6.2 months, 95% CI: 4.9, 7.6)
  - The company considers that treatment with atezolizumab addresses a significant unmet need and represents a clinically significant innovative therapeutic option, which will provide significant positive impact on patients' lives.

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Source: company submission p36-38

End of life considerations (1)

NICE criterion	Company assessment	ERG assessment
Life expectancy less than 24 months	Yes – median survival for Stage IIIb and Stage IV NSCLC is 7.5 months and 3.4 months, respectively (Section 3.4) (Beckett P et al., 2013)	Yes - agree with company
Extension of life, normally of at least an additional 3 months, compared with current NHS treatment	**Mean OS estimates:** Atezolizumab vs Docetaxel: 7 months Atezolizumab vs nintedanib+docetaxel: 3.7 months **Median OS estimates:** Atezolizumab vs Docetaxel: 3.5 months Atezolizumab vs nintedanib + docetaxel: 2.7 months	**ERG's remodelled OS estimates:** Atezolizumab vs Docetaxel: 4.7 Atezolizumab vs nintedanib+docetaxel: 3.33 months. No statistically significant difference (-0.16 to 6.74) in OS for atezolizumab (total population) compared to nintedanib+docetaxel (adenocarcinoma patients only)

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Source: company submission p126, ERG report p119-120

Equality and diversity

- No equality or equity issues were identified by the company or the ERG

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Key issues – clinical effectiveness

- Pembrolizumab was not included as a comparator
- Atezolizumab targets PD-L1 but the company submission is orientated around the whole population of patients with locally advanced or metastatic NSCLC after prior chemotherapy
- Method used to calculate hazard ratios in both trials assumed proportional hazards holds, but they do not. HRs should be interpreted with caution (method was pre-specified and company could not have known that PH would not hold)
- Indirect treatment comparison
  - Network meta-analysis includes comparators not listed in the scope
  - Nintedanib (licenced for adenocarcinoma) was compared with atezolizumab in the total population (including non-adenocarcinoma histologies)
  - Random effects model would have shown less certainty than fixed effects model
- Stopping rule for atezolizumab and docetaxel differed in both trials:
  - Docetaxel administered until disease progression or unacceptable toxicity. Clinical expert opinion suggests that in practice patients receive 4-6 cycles
  - In line with the draft SPC, atezolizumab was administered for as long as patients experienced a clinical benefit (as assessed by an investigator) in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression.

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Key issues: cost effectiveness

- Mixed cure-rate to model OS for patients receiving atezolizumab:
  - insufficient evidence to apply cure-rate
  - the value for the cure rate used not justified by the company
  - log-logistic function produces implausibly long survival tail (mortality rates, at some points, are lower than the mortality rates of the UK general population of the same age)
- Company's model assumes atezolizumab has a lifetime protective effect

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Authors

- **Jessica Maloney**
  Technical Lead
- **Fay McCracken**
  Technical Adviser
- with input from the Lead Team Gail Coaster, Paul Tappenden, Judith Wardle

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Atezolizumab for treating locally advanced or metastatic non-small cell lung cancer after chemotherapy

Company evidence submission

Roche Products Limited

February 2017

File name	Version	Contains confidential information	Date
ID970 Atezolizumab for locally advanced or metastatic NSCLC after chemotherapy [ACIC]	V1	Yes	16th February 2017
ID970 Atezolizumab for locally advanced or metastatic NSCLC after chemotherapy_April Update [ACIC]	V2	Yes	10th April 2017
ID970 Atezolizumab for locally advanced or metastatic NSCLC after chemotherapy_V3[ACIC]	V3	Yes	16th June 2017

ID970 Atezolizumab for locally advanced or metastatic NSCLC after chemotherapy_FinalRedaction[ACIC]	V4	Yes	28th June 2017

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Abbreviations

ACD	Appraisal Committee Decision
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
AFA	Afatinib
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ASBI	Average Symptom Burden Index
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AWMSG	All Wales Medical Strategy Group
BIC	Bayesian Information Criterion
BID	Twice-daily
BL	Baseline
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
BTOG	British Thoracic Oncology Group
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials;
CER	Ceritinib
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence intervals
CNS	Central nervous system
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRZ	Crizotinib
CSR	Clinical Study Report
CT	Computed tomography
CTLA	Cytotoxic T-lymphocyte associated protein-4

CTSQ	Cancer Therapy Satisfaction Questionnaire
DARE	Database of Abstracts of Reviews of Effects
DIC	Deviance Information Criteria
DOC	Docetaxel
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
ELCC	European Lung Cancer Conference
EMA	European Medicines Agency
EORTC	The European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	EuroQoL-5 dimension
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	European Union
FACT	Functional Assessment of Cancer Therapy
FAD	Final appraisal decision
FDA	Food and Drug Administration
FDG-PET	Flurodeoxyglucose-positron emission tomography
FE	Fixed effects
FP	Fractional polynomial
GBP	Great British Pounds
GEF	Gefitinib
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HTAD	Health Technology Assessment Database
IASLC	International Association for the Study of Lung Cancer
IC	Tumour-infiltrating immune cell
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform Search Portal
IHC	Immunohistochemistry

ILCC	International Lung Cancer Congress
INR	International Normalised Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma
LCS	Lung Cancer Subscale
LCSS	Lung Cancer Symptom Scale
LYG	Life years gained
MA	Marketing Authorisation
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIH	National Institute for Health
NIN	Nintedanib
NIV	Nivolumab
NLCA	National Lung Cancer Audit
NMA	Network Meta-Analysis
NOS	Not otherwise specified
NR	Not reported
NS	Not significant
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PASLU	Patient Access Scheme Liaison Unit
PBO	Placebo

PD	Progressive disease
PD-L1	Programmed death-ligand 1
PEM	Pemetrexed
PEMB	Pembrolizumab
PET	Positron emission tomography
PFS	Progression-free survival
PH	Proportional hazards
PK	Pharmacokinetic
PP	Primary population
PR	Partial response
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal social services research unit
QALY	Quality-adjusted life years gained
QD	Once-daily
QLQ	Quality of Life Questionnaire
RCC	Renal cell carcinoma
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during transfection
RPSFT	Rank Preserving Structural Failure Time
RWD	Real world data
RWE	Real world evidence
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision Making
TAG	Technology appraisal guidance
TC	Tumour cell
TKI	Tyrosine kinase inhibitor
TNBC	Triple negative breast cancer
TRAE	Treatment-related adverse event

TTD	Time-to-treatment discontinuation
TTO	Time trade-off
UBC	Urothelial bladder carcinoma
ULN	Upper limit of normal
VTE	Venous thromboembolism
WBC	White blood cell
WCLC	World Conference on Lung Cancer
WHO	World Health Organization

1. Executive summary

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (n=46,403) in 2014 with approximately 36,000 people dying from lung cancer in the UK in 2014, making it the most common cause of cancer death (Cancer Research UK, 2017).

Lung cancer is classified based upon its histology and can be broadly divided between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC represents approximately 85% of all cancer cases (Molina et al., 2008) and includes several subtypes. For therapeutic purposes, it can be broadly categorised as either squamous or non-squamous (with adenocarcinomas forming the bulk of non-squamous tumours) (Chan and Hughes, 2015, Carnio et al., 2014).

Early diagnosis of NSCLC is difficult, as early-stage disease is often asymptomatic, and symptoms of late-stage or advanced disease are non-specific (Hicks et al., 2007). As a result, the majority of patients with lung cancer are initially diagnosed with disease that is already locally advanced or metastatic (Carnio et al., 2014).

Current UK practice

The majority of patients lack a mutation conferring sensitivity to a targeted agent (i.e. epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK] inhibitors) and are typically treated with chemotherapy, especially platinum-based chemotherapy, which is associated with modest treatment benefits and significant toxicities (Delbaldo et al., 2007).

Docetaxel monotherapy is regarded as the standard of care for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy. Nintedanib in combination with docetaxel is recommended for treating locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy [TA347].

Pembrolizumab has also recently been recommended as an option for adults with locally advanced or metastatic programmed death-ligand 1 (PD-L1) positive

(≥1%) NSCLC treated with at least one chemotherapy regimen (and targeted treatment if they have an EGFR- or ALK-positive tumour) [TA428].

Second-line treatment options for mutation-based NSCLC include osimertinib (within the CDF) after first-line treatment with an EGFR inhibitor and ceritinib in previously treated adults with ALK-positive NSCLC. Patients who have progressed on non-targeted therapy may receive erlotinib if the EGFR mutation is confirmed or mutation status remains unknown and the treating clinician considers the tumour to very likely be EGFR mutation-positive. Crizotinib may also be used in patients who subsequently test positive for the ALK mutation following non-targeted therapy.

Unmet need

Effective treatment options are limited for patients with locally advanced or metastatic NSCLC. The development of targeted therapies led to a paradigm shift that is now well established. While these have dramatically improved outcomes for the minority of patients with actionable mutations, disease progression is still inevitable in most cases and the majority of patients are still reliant on unselective chemotherapy regimens which have substantial toxicity and limited efficacy (Maemondo et al., 2010, Zhou et al., 2011). Therefore, there remains an unmet need for new treatments that improve survival without causing significant toxicity or a deterioration in quality of life, particularly in those patients who are not eligible for targeted therapies and those relapsing after first-line chemotherapy for whom toxic and not very effective docetaxel-based treatments are currently the most widely used.

Atezolizumab

Atezolizumab is a humanised IgG1 monoclonal antibody which binds directly and selectively to PD-L1 on the surface of tumour cells (TCs) and tumour-infiltrating immune cells (ICs), inhibiting the binding to PD-1 and B7.1. This prevents down-regulation of T-cell activity while allowing for the priming of new T cells (Herbst et al., 2014). Atezolizumab differs from anti-PD-1 antibodies approved for the treatment of NSCLC as it results in the dual blockade of PD-1 and B7.1 while leaving the PD-1/PD-L2 interaction intact, thereby potentially preserving peripheral immune homeostasis (Harshman et al., 2014).

Atezolizumab is given at a dose of 1200 mg intravenous (IV) infusion, every 3 weeks.

Clinical efficacy

The efficacy and safety of atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy has been studied in two randomised clinical trials; an open-label Phase III study (OAK, GO28915, NCT02008227) (Clinical Trials.Gov), and an open-label Phase II study (POPLAR, GO28753, NCT01903993) (Clinical Trials.Gov). Patients were recruited to both studies regardless of PD-L1 expression since Phase 1 data did not demonstrate a clear relationship between PD-L1 expression and response to atezolizumab.

The clinical cut-off date for the primary analysis of OAK was 7th July 2016. This analysis confirmed that the OAK study had met its co-primary endpoints; treatment with atezolizumab was associated with a statistically significant and clinically meaningful improvement in overall survival (OS), compared with docetaxel in the intention-to-treat (ITT) population (HR 0.73, 95% CI: 0.62, 0.87; p=0.0003), and in patients with ≥1 % PD-L1 expression (HR 0.74, 95% CI: 0.58, 0.93; p=0.0102). The median overall survival in the ITT population was 9.6 months (95% CI: 8.6, 11.2) in the docetaxel arm and 13.8 months (95% CI: 11.8, 15.7) in the atezolizumab arm. Atezolizumab showed significant improvement in OS for people regardless of PD-L1 status, with a similar effect observed in patients with no measurable PD-L1 expression (TC0/IC0) to that seen in the ITT population (HR 0.75, 95% CI:0.59, 0.96; p=0.0205) (Rittmeyer et al., 2016).

This benefit in OS was observed in all important pre-defined clinical subgroups in OAK. Furthermore, improvements in OS were seen with atezolizumab compared with docetaxel regardless of histology; HR 0.73 (95% CI: 0.60, 0.89; p=0.0015) and 0.73 (95% CI: 0.54, 0.98; p=0.0383), in non-squamous and squamous patients respectively.

Underpinning the improvement in OS seen in patients treated with atezolizumab are very prolonged anti-tumour responses that are much more durable than those seen after conventional cytotoxic chemotherapy. The proportion of patients with a confirmed response per RECIST v1.1 was similar in both arms: 13.6% (95% CI: 10.5, 17.3) in the docetaxel arm and 13.4% (95% CI: 10.3, 17.0) in the atezolizumab arm. Six patients in the atezolizumab arm achieved a complete response compared with one in the docetaxel arm, and a similar proportion of

patients had a partial response (12.2% vs. 13.2%). Among responders, the median duration of response (DOR) was more than doubled in the atezolizumab arm (16.3 months, 95% CI: 10.0, NE) compared with the docetaxel arm (6.2 months, 95% CI: 4.9, 7.6) in the ITT population (HR 0.34, 95% CI: 0.21, 0.55), with 52% of atezolizumab responses ongoing.

Results from OAK were consistent with those seen in the Phase II POPLAR study (Fehrenbacher et al., 2016).

Anticipated role of atezolizumab in English and Welsh clinical practice

Due to the limited efficacy and poor tolerability of existing docetaxel-based treatments, it is anticipated that atezolizumab will replace these as a standard treatment for relapsed NSCLC. Atezolizumab offers significant clinical promise with a tolerable safety profile and minimal impact on NHS resource use or capacity, as compared to current standard of care in England and Wales (principally, docetaxel). As such, it is expected that atezolizumab would become a standard of care, should NICE recommend it for use in metastatic NSCLC.

Indirect treatment comparison

While the OAK trial provides a direct comparison to docetaxel, an indirect treatment comparison was required to appropriately compare atezolizumab to the other comparators of interest (nintedanib (plus docetaxel)).

In line with results for other immunotherapies (in comparison to non-immunotherapy agents), it was acknowledged that the proportional hazards assumption for atezolizumab vs. relevant comparators was unlikely to hold. This was confirmed through visual inspection of the diagnostic plots of the log cumulative hazard for PFS and OS from OAK, and is a result of the prolonged DOR seen with immunotherapies. In order to allow meaningful and more robust analyses, the fractional polynomial model is utilised for the NMA.

Cost effectiveness analysis

A cost-utility analysis was conducted to determine the cost-effectiveness of atezolizumab in metastatic NSCLC vs. relevant comparators. The most relevant comparator in England and Wales for this population is docetaxel (based on use in clinical practice, and the consistency with the anticipated marketing

authorisation for atezolizumab), but the additional comparator of nintedanib plus docetaxel was also included.

A three-state partitioned survival model was built, with a 25 year time horizon. Clinical inputs for the model were derived from OAK, and the results of the indirect treatment comparison. The model takes the perspective of NHS England, and is consistent with the NICE reference case and broadly consistent with the final scope of the appraisal.

Based on the proposed list price of atezolizumab, the base-case incremental cost-effectiveness rations (ICERs) comparing atezolizumab to docetaxel is £72,356, and to nintedanib plus docetaxel is £56,076. A confidential Patient Access Scheme (PAS) for atezolizumab has been submitted to the Department of Health. The equivalent ICERs incorporating the proposed PAS for atezolizumab are [redacted] vs. docetaxel, and [redacted] vs. nintedanib (plus docetaxel). Further results using this price are reported in the confidential PAS appendix.

External expert input

Expert clinical advisory panel

An expert advisory board was convened to provide feedback on the clinical plausibility of results, appraisal comparators, model structure, OS extrapolation methodology, resource use, and utility inputs. The panel consisted of consultant oncologists specialising in the management of patients with locally advanced or metastatic NSCLC, many of whom have experience of atezolizumab from clinical trials. The panel was selected based on their significant clinical and research experience.

Nine expert clinical advisors were consulted. At the one day meeting, invited experts were briefed on the economic model structure and sources of key data inputs; their comments were recorded and taken into account in the subsequent development of the model.

Topics for discussion included:

- Review of the atezolizumab OAK data presented at ESMO 2016
- Current treatment preferences in NSCLC

- Time-until death versus progression free/progressed health state methodologies to elicit utilities
- Appropriate health resource utilisation by health state
- Overall survival extrapolation technique, and expected proportion of patients alive at set time intervals

Expert Health Economist advisory panel

A panel of experienced health economists and clinicians (both UK and non-UK based) were consulted during the development and validation of the economic model, most recently at a one-day meeting in November 2016. Feedback was requested on the potential approaches to the assessment, including specific focus on the methodology used in the NMA, and extrapolation of long term survival.

Topics for discussion included:

- Validation on health states methodology
- Most appropriate OS, PF and TTD extrapolation method
- Mixed cure fraction methodology
- NMA methodology validation

Ad-hoc clinical expert validation

Consultation with a leading oncologist to validate clinical or economic assumptions on an ad-hoc basis has also been conducted.

1.1 Statement of decision problem

The appraisal is consistent with the reference-case and broadly in-line with the final NICE scope.

Not all comparators in the final scope have been included within the submission. The approach to comparators taken in the appraisal has been ratified by the previously described expert clinical advisor panel.

Comparators included in the final appraisal scope were: docetaxel, nintedanib (plus docetaxel), pembrolizumab, nivolumab, and best supportive care (BSC). However, based on clinical feedback, three options were deemed unsuitable for comparison, and excluded from the analysis:

- Pembrolizumab has a marketing authorisation for PD-L1 positive NSCLC patients, and therefore the population is not matched to that of atezolizumab. By including results for pembrolizumab from only PD-L1 positive NSCLC patients within the analysis, there is a risk the relative clinical benefits of pembrolizumab are overestimated, and therefore would not be a true reflection of the comparative effects versus atezolizumab (in the all-comer population which is under consideration). In addition, the tools utilised for pembrolizumab and atezolizumab to assess PD-L1 expression differ significantly, both in how expression is measured (pembrolizumab: TC only; atezolizumab: TC and IC), but importantly also in which patients are considered positive expressors. Hence, even with use of a diagnostic test, the eligible patient populations are not equivalent. Further, pembrolizumab was only recently approved for use in NSCLC by NICE (guidance issued 11th January 2017), and is unlikely to represent a standard of care at time of submission.
- Nivolumab has received a negative recommendation in its Appraisal Consultation Document (ACD) from NICE, and cannot be considered standard of care
- It is considered that patients who are eligible for treatment with atezolizumab would be considered fit enough for other treatment; hence, BSC is not an appropriate comparator.

Hence, the comparators assessed in the economic model include docetaxel, and nintedanib (plus docetaxel). The docetaxel comparison is driven from direct evidence obtained in the OAK trial; the nintedanib (plus docetaxel) comparison is

incorporated through the mixed treatment comparison (or NMA) as described in Section 4.10.

Although nintedanib (plus docetaxel) is licensed (and recommended by NICE) only for those patients with adenocarcinoma histology, in order to conduct a like-with-like comparison versus atezolizumab in its anticipated licence, the "total population" from the nintedanib (plus docetaxel) trial was compared to the atezolizumab ITT population[1]. Consistent with the favorable prognosis seen in patients with non-squamous vs. squamous forms of NSCLC[2] in other trial programmes (Kawase et al., 2012), the OAK and POPLAR studies demonstrated improved outcomes in the subgroup of patients with non-squamous NSCLC (Figure 14, Figure 16). Therefore, the impact of this approach is not anticipated to significantly affect overall results.

[1] Although a similar scenario has been described for the comparison vs. pembrolizumab, the KEYNOTE-010 study did not include a negative-expressor (i.e. all-comer) population.
[2] Adenocarcinoma makes up at least 85% of all non-squamous histologies (see section 3.1 & 4.8)

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 locally advanced or metastatic non-small-cell lung cancer whose disease has progressed after chemotherapy	Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy	No difference
Intervention	Atezolizumab	Atezolizumab	No difference
Comparators	• Docetaxel • Nintedanib with docetaxel (for people with adenocarcinoma histology) • Nivolumab (subject to ongoing NICE appraisal) • Pembrolizumab (PD-L1-expressing tumours) • Best supportive care	• Docetaxel • Nintedanib with docetaxel	Nintedanib (plus docetaxel) is licensed only for patients with adenocarcinoma histology, which is not consistent with the anticipated marketing authorisation for atezolizumab. As such, in order to conduct a like-with-like comparison versus atezolizumab in its anticipated licence, the "total population" from the nintedanib (plus docetaxel) trial was compared to the atezolizumab ITT population in an indirect treatment comparison. Pembrolizumab has a marketing authorization only for PDL1 positive NSCLC patients, and therefore the population is not matched to that of atezolizumab. Furthermore, accurate comparisons between treatments is not possible due to the differences between tests used in clinical studies to select patients; pembrolizumab studies tested for tumour

			cell expression only compared to tumour cell and immune cell expression for atezolizumab. Further, pembrolizumab was only recently approved for use in NSCLC by NICE, and is unlikely to represent a standard of care at time of submission. Nivolumab was not recommended for use by NICE in the Appraisal Consultation Document (ACD), published in October 2016. Hence, cannot be considered standard of care. Due to a clinically-validated assumption that patients eligible for treatment with atezolizumab would be considered fit enough for other treatment, best supportive care has also been excluded.
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life.	No difference
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 appropriate, the appraisal should	The reference case, which stipulates cost effectiveness of treatments be expressed in terms of incremental cost per quality-adjusted life years, will be followed.	The cost of testing for biological markers has not been assessed, as the population considered with this evidence submission is in line with the anticipated marketing authorisation for atezolizumab: i.e. without restriction to patients positive for PD-L1

	include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices. 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.	The time horizon will be appropriate to capture differences in costs and outcomes, with appropriate discounting included. Costs will be considered from an NHS and Personal Social Services perspective. The availability of a patient access schemes for the intervention is accounted for in the confidential PAS Appendix. The patient access scheme available for nintedanib is unknown; however, a sensitivity analysis has been conducted.	expression only.
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups based on biological markers.	No subgroups	Clinical benefit is observed in all subgroups of NSCLC patients treated with atezolizumab. As such no analyses are conducted on restricted populations as compared to the anticipated indication.
Special considerations including issues	None identified	None identified	No difference

related to equity or equality			

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Atezolizumab. EMA and FDA approved brand name: Tecentriq®
Marketing authorisation/CE mark status	EMA, centralised procedure, full submission made. Awaiting CHMP opinion
Indications and any restriction(s) as described in the summary of product characteristics	Anticipated marketing authorisation: *Atezolizumab is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy* The initial Marketing Authorisation Application also seeks approval for use of atezolizumab in the following indication: *Atezolizumab is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible (National Institute for Health and Care Excellence)*
Method of administration and dosage	For patients with locally advanced or metastatic NSCLC, the recommended dose of atezolizumab after prior chemotherapy is 1,200 mg, every three weeks as intravenous infusion

CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; FDA, Food and Drug Administration

1.3 Summary of the clinical effectiveness analysis

The efficacy and safety of atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy has been studied in two randomised clinical trials; an open-label Phase III study (OAK, GO28915, NCT02008227) (Clinical Trials.Gov), and an open-label Phase III study (POPLAR, GO28753, NCT01903993) (Clinical Trials.Gov). The study design, patient inclusion/exclusion criteria and treatment regimens were very similar between the OAK and POPLAR studies.

Eligible patients (OAK N=1225; POPLAR N=287) were randomly assigned in a 1:1 ratio to the two study treatment arms to receive either atezolizumab (OAK n=425; POPLAR n=144) or docetaxel (OAK n=425; POPLAR n=143)[3]. The study populations comprised predominantly white males, with a median age of 64 years and 62 years in OAK and

[3] The primary population for OAK analysis was the first 850 patients, see Section 4.4

POPLAR respectively, and an Eastern Cooperative Oncology Group (ECOG) performance status of 1. The majority of patients had a history of tobacco use. Patients were recruited regardless of PD-L1 expression since Phase 1 data did not demonstrate a clear relationship between PD-L1 expression and response to atezolizumab.

Efficacy in OAK

The OAK study met its co-primary endpoints; treatment with atezolizumab was associated with a statistically significant and clinically meaningful improvement in OS, compared with docetaxel in the ITT population (HR 0.73, 95% CI: 062, 0.87; p=0.0003), and in patients with ≥1 % PD-L1 expression (HR 0.74, 95% CI: 0.58, 0.93; p=0.0102). The median overall survival in the ITT population was 9.6 months (95% CI: 8.6, 11.2) in the docetaxel arm and 13.8 months (95% CI: 11.8, 15.7) in the atezolizumab arm.

Atezolizumab showed significant improvement in OS for people regardless of PD-L1 status, with a similar effect observed in patients with no measurable PD-L1 expression (TC0/IC0) to that seen in the ITT population (HR 0.75, 95% CI:0.59, 0.96; p=0.0205).

This benefit in OS was observed in all important pre-defined clinical subgroups in OAK. Furthermore, improvements in OS were seen with atezolizumab compared with docetaxel regardless of histology, with statistically significant and clinically meaningful benefits in both non-squamous and squamous NSCLC; HR 0.73 (95% CI: 0.60, 0.89; p=0.0015) and 0.73 (95% CI: 0.54, 0.98; p=0.0383), respectively.

Consistent with the known profiles and mechanism of action of immunotherapies, there was no statistically significant difference in progression-free survival (PFS) between atezolizumab and docetaxel in the primary analysis of OAK. The median duration of PFS in the ITT population was 2.8 months (95% CI: 2.6, 3.0) in the atezolizumab arm and 4.0 months (95% CI: 3.3, 4.2) in the docetaxel arm (HR=0.95, 95% CI: 0.82, 1.10). Likewise, the proportion of patients with a confirmed response per RECIST v1.1 was similar in both arms: 13.6% (95% CI: 10.5, 17.3) in the docetaxel arm and 13.4% (95% CI: 10.3, 17.0) in the atezolizumab arm. Six patients in the atezolizumab arm achieved a complete response compared with one in the docetaxel arm, and a similar proportion of patients had a partial response (12.2% vs. 13.2%).

Among responders, the median DOR was more than doubled in the atezolizumab arm (16.3 months, 95% CI: 10.0, NE) compared with the docetaxel arm (6.2 months, 95% CI: 4.9, 7.6) in the ITT population (HR 0.34, 95% CI: 0.21, 0.55), with 52% of atezolizumab responses ongoing at the time of the most recent data cut, compared with 18% in the docetaxel arm.

Efficacy in POPLAR

Treatment with atezolizumab was associated with a clinically meaningful and statistically significant prolongation in OS compared with docetaxel (HR 0.69, 95% CI: 052, 0.92; p=0.011); the median OS in the ITT population was 9.7 months (95% CI 8.6, 12.0) in the docetaxel arm and 12.6 months (95% CI: 9.7, 16.0) in the atezolizumab arm.

As in OAK, median PFS and the proportion of patients with a confirmed response per RECIST v1.1 was similar in both arms, with a greater median DOR among responders with atezolizumab (18.6 months, 95% CI: 11.6, NE) compared with docetaxel (7.2 months, 95% CI: 5.6, 12.5) (HR 0.32, 95% CI: 0.15, 0.70).

Safety of atezolizumab in NSCLC

The safety data from OAK and POPLAR are consistent with the known safety profile of atezolizumab and immunotherapies generally, with no new safety signals observed. Atezolizumab was well tolerated, with a favourable safety profile compared with docetaxel.

Specifically in OAK, atezolizumab treated patients had fewer Grade 3 or 4 adverse events (AEs) (especially for those deemed related to study treatment per the investigator); AEs leading to treatment discontinuation; and AEs leading to dose modifications or interruptions which can be interpreted as those that are dangerous or intolerable to the patient. Patients in the atezolizumab arm did not experience any AEs with an incidence that was at least 10% higher compared with docetaxel. Events of pneumonia and febrile neutropenia reported as serious AEs were observed at higher frequencies (≥2% difference) in patients in the docetaxel arm compared with the atezolizumab arm.

Only two AE preferred terms, musculoskeletal pain and pruritus, were reported with a higher incidence (≥5%) in patients receiving atezolizumab than docetaxel after adjustment for exposure. They were seen in 10.5% and 8.2% of atezolizumab treated patients compared with 4.3% and 3.1% of docetaxel treated patients respectively, with the majority of cases of mild-moderate severity and less than 1% of patients experiencing either event at Grade 3.

The incidence of fatal AEs was low in both arms, and no grade 5 immune-mediated AEs or adverse events of special interest (AESIs) were observed.

1.4 Summary of the cost-effectiveness analysis

The cost-utility analysis was implemented in line with the NICE reference case, to determine the incremental-cost-effectiveness-ratio (ICER) for atezolizumab in metastatic NSCLC as

compared to standards of care in current clinical practice. A de novo model was developed to evaluate the cost-effectiveness of atezolizumab as a second-line treatment after prior chemotherapy. A three-state partitioned survival model was built, and included health-states for “on treatment”, “off treatment” and death. A 25 year time horizon was used to capture life-time costs and benefits, with discounting applied at 3.5% for costs and effects.

Clinical inputs for the model were derived from OAK for atezolizumab, and the results of the indirect treatment comparison (ITC) for comparators. Utility inputs were derived from EQ-5D data collected from the OAK trial. All costs are derived from UK literature.

The model expressed treatment effect in quality-adjusted life years (QALYs). Costs for all therapies included drug cost, administration cost, resource use, and adverse event management. Time-to-treatment discontinuation data were available for atezolizumab and docetaxel. For the comparison to nintedanib (plus docetaxel), these data were not publically available; as such, PFS was used as a proxy for treatment duration, consistent with the approach used in other oncology appraisals.

Atezolizumab was projected to provide 2.22 life-years, an increase of 1.04 compared to docetaxel, and 0.91 compared to nintedanib (plus docetaxel). This is a result of the significant survival benefit that atezolizumab is expected to provide over current treatment options. Atezolizumab is estimated to provide an incremental QALY gain of 0.75 over docetaxel, and 0.65 over nintedanib (plus docetaxel). The utility differential is derived from both the “on treatment” and “off treatment” health states, with the largest proportion generated from extending patient life.

The base-case ICERs comparing atezolizumab at list price to docetaxel is £72,356 and to nintedanib (plus docetaxe)l is £56,076. A confidential PAS for atezolizumab has been submitted to the Department of Health. The equivalent ICERs incorporating the proposed PAS for atezolizumab are [redacted] vs. docetaxel, and [redacted] vs. nintedanib (plus docetaxel).

The ICER associated with the nintedanib (plus docetaxel) versus docetaxel comparison should be interpreted with caution. This is an artefeact of the data used for nintedanib (plus docetaxel) (total population as opposed to adenocarcinoma population). However, as this is an assessment of atezolizumab, and based on the rationale and assumptions set out in section 5.2, this is not anticipated to have a major bearing on the results.

Table 3: Incremental cost-effectiveness results (list price)

				Versus Docetaxel				Versus N+D			
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	£19,941	1.19	0.73	-	-	-	-	-	-	-	-
Nintedanib + Docetaxel	£37,702	1.31	0.83	£17,761	0.13	0.10	Ext. dominated	-	-	-	-
Atezolizumab	£73,911	2.22	1.47	£53,970	1.04	0.75	£72,356.07	£36,209	0.91	0.65	£56,076.16

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

Note: numbers may not sum due to rounding

Table 4: Incremental cost-effectiveness results (with-PAS)

				Versus Docetaxel				Versus N+D			
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	£19,941	1.19	0.73	-	-	-	-	-	-	-	-
Nintedanib + Docetaxel	£37,702	1.31	0.83	£17,761	0.13	0.10	Ext. dominated	-	-	-	-
Atezolizumab	[redacted]	2.22	1.47	[redacted]	1.04	0.75	[redacted]	[redacted]	0.91	0.65	[redacted]

2. The technology

2.1 Description of the technology

Brand name: Tecentriq®

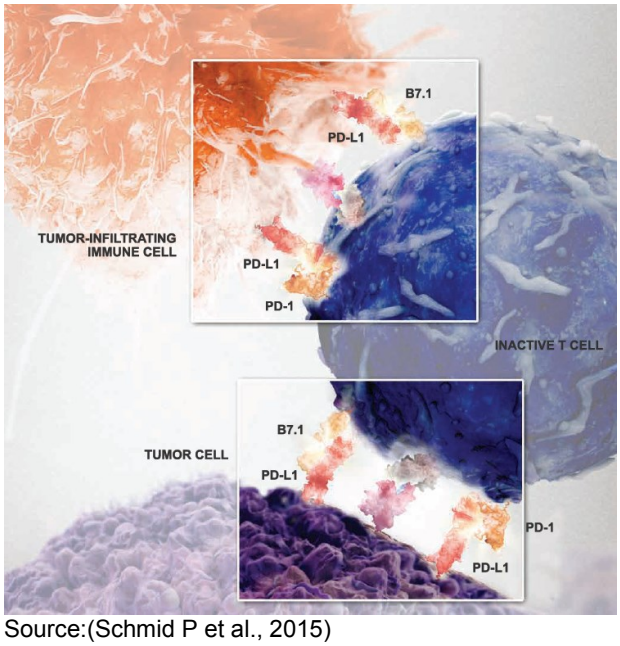
Generic name: atezolizumab

Therapeutic class: anatomical therapeutic chemical (ATC) code: not yet confirmed

Overview of atezolizumab: Atezolizumab is a monoclonal antibody that binds to and inactivates a protein called programmed death-ligand 1 (PD-L1), which leads to downstream activation of T cells that can detect and attack tumour cells (F. Hoffmann-La Roche Ltd, 2016u).

PD-L1 is an immune checkpoint protein expressed on both tumour cells (TC) and tumour-infiltrating immune cells (IC) (Meng et al., 2015). PD-L1 binds to two known inhibitory receptors expressed on activated T cells (PD-1 and B7.1) to inhibit T-cell proliferation, cytokine production and cytolytic activity and thus restrict tumour cell killing (Chen and Mellman, 2013, Herbst et al., 2014, Schmid P et al., 2015).

Figure 1: PD-L1 expression in the tumour microenvironment



Source:(Schmid P et al., 2015)

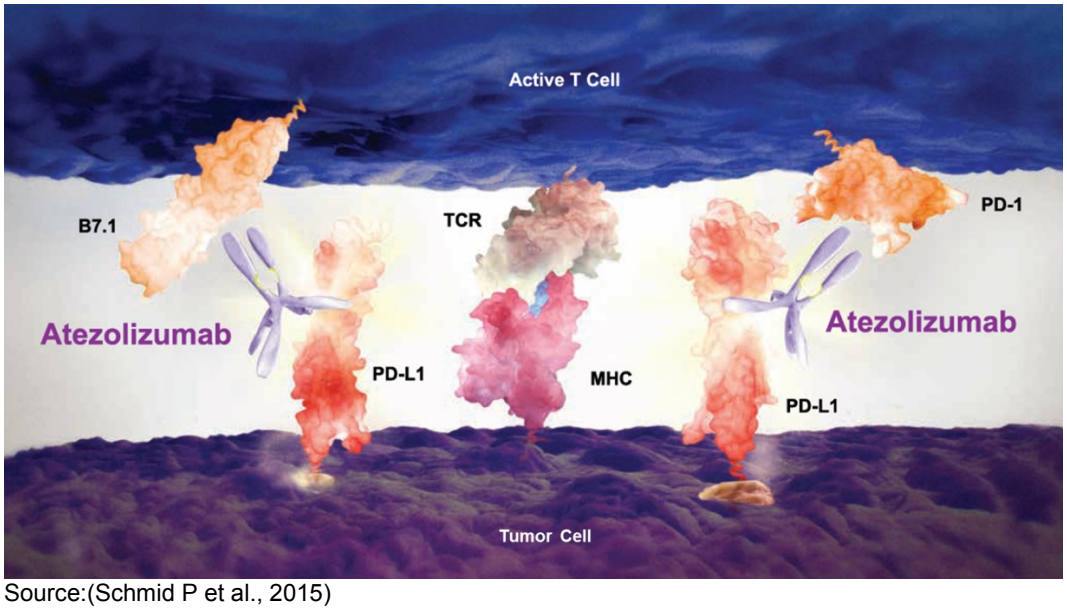
Overexpression of PD-L1 in tumour cells has been associated with poor prognosis in patients with several cancers (Thompson et al., 2006, Hamanishi et al., 2007, Hino et al., 2010, Mu et al., 2011). Therefore, interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathway

represents an attractive strategy for anti-tumour response (Chen and Mellman, 2013, Ohaegbulam et al., 2015).

Programmed death-ligand 2 (PD-L2) is an alternative ligand that can bind to PD-1 if PD-L1 is inhibited (Herbst et al., 2014). Based on this, targeting PD-L1 rather than PD-1 preserves the PD-L2/PD-1 interaction, and potentially avoids autoimmune reactions in healthy tissue (Harshman et al., 2014).

Atezolizumab is a humanised IgG1 monoclonal antibody which binds directly and selectively to PD-L1 on the surface of TCs and ICs, preventing it from binding to PD-1 and B7.1. This prevents down-regulation of T-cell activity while allowing for the priming of new T cells. Atezolizumab does not cause antibody-dependent cell-mediated cytotoxicity (ADCC) as it is FcγR-binding deficient, therefore it cannot bind to Fc receptors on phagocytes. This is important because PD-L1 is heavily-expressed by T cells and other leukocytes and binding of a monoclonal antibody to their cell membrane could result in ADCC-mediated depletion of tumour-specific T cells; an event which could worsen antitumor immunity rather than improving it (Inman et al., 2016, Herbst et al., 2014).

Figure 2: Mechanism of action of atezolizumab



Source:(Schmid P et al., 2015)

A summary of the clinical development programme for atezolizumab in NSCLC is summarised below.

Table 5: Atezolizumab in NSCLC clinical development programme

Study ID, Phase and Design	Objectives	Patient population
PCD4989g Open-Label, Phase Ia	Safety, tolerability, PK, immunogenicity, exploratory PD, and preliminary evidence of biologic activity	Locally advanced or metastatic solid tumours or haematologic malignancies (including NSCLC, UBC, clear cell RCC, TNBC)
GO28625 (FIR) Single-arm, Phase II	Safety and efficacy Evaluate whether archival or fresh tumour tissue is more predictive of response to atezolizumab. Understand the role of using FDG-PET to define response in patients receiving immunotherapy	PD-L1-positive locally advanced or metastatic NSCLC
GO28754 (BIRCH) Single arm, Phase II	Safety, efficacy and pharmacokinetics	PD-L1-positive locally advanced or metastatic NSCLC
GO28753 (POPLAR) Randomized, Open-Label, Phase II	Safety and efficacy compared with docetaxel as measured by OS	Locally advanced or metastatic NSCLC who have failed a prior platinum-containing regimen
GO28915 (OAK) Randomised, open-label, Phase III	Safety and efficacy compared with docetaxel as measured by OS	Locally advanced or metastatic NSCLC who have failed a prior platinum-containing regimen

For the purpose of this submission, evidence from the randomised Phase III (OAK) and Phase II (POPLAR) studies will be discussed. Single-arm Phase II studies (FIR and BIRCH) will not be discussed as these studies enrolled PD-L1 positive patients only and are therefore not relevant to the anticipated indication of atezolizumab.

2.2 Marketing Authorisation/CE marking and health technology assessment

An application for UK Marketing Authorisation was made for atezolizumab on 20th April 2016. Committee for Medicinal Products for Human Use (CHMP) opinion is anticipated in June 2017, with regulatory approval expected in [redacted].

The following indication wording has been submitted; however, this may be modified following comments from the CHMP:

- Atezolizumab is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible
- Atezolizumab is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy

As noted in the draft SmPC (Appendix 1), this medicine will be contraindicated to people who demonstrate hypersensitivity to atezolizumab or to any of the excipients below:

- L-Histidine
- Glacial Acetic Acid
- Sucrose
- Polysorbate 20
- Water for injections

The CHMP opinion has not yet been received; therefore, the European public assessment report (EPAR) is not available. As such, information regarding key regulatory issues or special conditions of Marketing Authorisation is not yet available.

Atezolizumab will be routinely available once Marketing Authorisation is received. Atezolizumab is currently available for UK patients with metastatic urothelial carcinoma under the Early Access to Medicines Scheme (EAMS).

In October 2016 the US Food and Drug Administration (FDA) approved atezolizumab for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy.

The FDA also gave accelerated approval to atezolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (May 2016).

Regulatory approval for both of these indications has also been received in Kuwait and South Korea.

Atezolizumab is also being assessed by NICE for the treatment of locally advanced or metastatic urothelial carcinoma after prior chemotherapy and patients who are considered cisplatin-ineligible (National Institute for Health and Care Excellence). This appraisal was submitted on 18th January 2017. It is anticipated submissions will be made for both indications to the Scottish Medicines Consortium (SMC). Timelines will follow the usual SMC process.

2.3 Administration and costs of the technology

A patient access scheme (PAS) has been submitted to the Patient Access Scheme Liaison Unit (PASLU), with details provided in the confidential PAS appendix.

Table 6: The technology being appraised

	Cost	Source
Pharmaceutical formulation	Concentrate for solution for infusion	SmPC (see Appendix 1)
Acquisition cost (excluding VAT)	List price: £3807.69 per 20mL vial A PAS has been submitted to the Department of Health.	PAS template (see Confidential Appendix) Status: pending confirmation with Department of Health
Method of administration	Intravenous infusion	SmPC (see Appendix 1)
Doses	1,200 mg every 3 weeks	SmPC (see Appendix 1)
Dosing frequency	Every 3 weeks until loss of clinical benefit or unmanageable toxicity	SmPC (see Appendix 1)
Average length of a course of treatment	Based on the OAK trial, the average time on therapy per patient (mean) is 7.78 months, equivalent to 11.3 cycles	OAK clinical trial
Average cost of a course of treatment	The average cost per treatment course is £42,913.66 at list price (mean cycles * vial price)	OAK clinical trial
Anticipated average interval between courses of treatments	Treatment regimen is continuous until loss of clinical benefit or unmanageable toxicity	OAK clinical trial
Anticipated number of repeat courses of treatments	Repeated treatment is not anticipated	SmPC (see Appendix 1)
Dose adjustments	No dose adjustment is expected	SmPC (see Appendix 1)
Anticipated care setting	Atezolizumab is anticipated to be administered in the hospital setting	

2.4 Changes in service provision and management

No additional tests, investigations or infrastructure are required to treat patients with atezolizumab. Atezolizumab is administered on a 3-weekly cycle in a secondary care (i.e. hospital setting) with no inpatient stay required. The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be administered over 30 minutes (F. Hoffmann-La Roche Ltd, 2017). This dosing schedule and administration time is lower compared to some of the chemotherapies available at present.

Atezolizumab is administered until loss of clinical benefit or unmanageable toxicity. Atezolizumab is generally well tolerated by patients with NSCLC, with a significantly improved adverse event profile in comparison to Docetaxel (Rittmeyer et al., 2016). In addition, as seen with other immunotherapies, atezolizumab is expected to provide durable benefit for a proportion of patients treated. Therefore, the main resource use to the NHS associated with the use of atezolizumab is expected to be that which is related to the management of patients whilst on treatment, including the long-term treated patients, who can be anticipated to receive ongoing follow-up including scanning.

2.5 Innovation

Targeting T cell receptors to modulate the immune response and target cancers has been gaining momentum over recent years, starting with Cytotoxic-T-lymphocyte associated antigen (CTLA)-4 inhibition, for which ipilimumab is indicated in advanced melanoma (Bristol Myers Squibb, 2016). More recently PD-1 inhibition is indicated in advanced melanoma, advanced NSCLC, advanced renal cancer and classical Hodgkin lymphoma (Bristol Myers Squibb, 2017, Merck Sharp & Dohme, 2017). As the first drug developed within these T cell modulators, ipilimumab has the longest survival follow up, with 1,861 melanoma patients treated in a pooled analysis. The three year survival rate was 21% with an apparent plateau in the survival curve at three years, which extended up to 10 years in some patients (Schadendorf et al., 2015). This provides substantial credibility to the durability of such immunomodulatory mechanisms.

Many tumour types, including NSCLC, express PD-L1 either on the tumour cells themselves or on immune cells that are infiltrating the tumour, and this is often associated with aggressive tumour behaviour (Inman et al., 2016). The PD-1 receptor and its ligand, PD-L1, comprise one of the main immune checkpoint pathways that downregulate immune activity (Inman et al., 2016). Rather than mistakenly recognising tumour cells as part of the normal human body and being deactivated when they come into contact with tumour cells via the PD-1-PD-L1 checkpoint, they remain active and detect, attack, and destroy tumour cells. By exposing tumour cells to the immune system and utilising the body's own immune system in this way, responses can be both complete and durable in some patients.

Lung cancer is the leading cause of cancer death globally. Each year 1.59 million people die as a result of the disease; this translates into more than 4,350 deaths worldwide every day (Jemal et al., 2011). In the UK alone, there were approximately 36,000 deaths from lung cancer in 2014 (Cancer Research UK, 2017).

Effective treatment options are limited for patients with locally advanced or metastatic NSCLC. Patients without a mutation conferring sensitivity to a targeted agent are typically treated with chemotherapy, especially platinum-based chemotherapy, which is associated with modest treatment benefits and significant toxicities (Delbaldo et al., 2007). The development of targeted therapies led to a paradigm shift that is now well established. They have dramatically improved outcomes for the minority of patients with actionable mutations but even for these patients, disease progression is still inevitable in most cases and the majority of patients are still reliant on unselective chemotherapy regimens which have substantial toxicity and limited efficacy (Maemondo et al., 2010, Zhou et al., 2011). Therefore, there remains an unmet need for new treatments that improve survival without causing significant toxicity or a deterioration in quality of life, particularly in those patients who are not eligible for targeted therapies and those relapsing after first-line chemotherapy for whom toxic and not very effective docetaxel-based treatments are currently the most widely used.

Atezolizumab is anticipated to be the first anti-PD-L1 antibody to be approved for locally advanced or metastatic NSCLC after prior chemotherapy. Atezolizumab differs from other (anti-PD-1) antibodies approved for the treatment of NSCLC as it results in the dual blockade of PD-1 and B7.1 while leaving the PD-1/PD-L2 interaction intact, thereby potentially preserving peripheral immune homeostasis (Herbst et al., 2014).

The anticipated approval of atezolizumab is based on the strength of Phase II (POPLAR) and Phase III (OAK) data (see Section 4). The OAK study demonstrated an overall survival benefit of 4.2 months with atezolizumab compared with docetaxel (HR 0.73; 95% CI: 0.62, 0.87, p=0.0003) (Rittmeyer et al., 2016). Atezolizumab is anticipated to be approved for all locally advanced or metastatic NSCLC patients with prior chemotherapy, regardless of PD-L1 expression status.

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 OAK, the median duration of response was more than doubled in the atezolizumab arm (16.3 months, 95% CI: 10.0, NE) compared with the docetaxel arm (6.2 months, 95% CI: 4.9, 7.6) in the ITT population (HR 0.34, 95% CI: 0.21, 0.55), with 52% of atezolizumab responses ongoing at the latest data cut. 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.

Taken together, Roche believes that atezolizumab addresses the significant unmet need for this patient population and represents a clinically significant innovative therapeutic option for the treatment of patients, which will provide significant positive impact on patients' lives.

3. Health condition and position of the technology in the treatment pathway

3.1 Disease overview

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (n=46,403) in 2014. It is responsible for 22% of all cancer deaths in the UK, making it the most common cause of cancer death. Around 35,900 people died of lung cancer in the UK in 2014. One in 13 men and 1 in 17 women will be diagnosed with lung cancer during their lifetime (Cancer Research UK, 2017).

Lung cancer is classified based upon its histology and can be broadly divided between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC represents approximately 85% of all lung cancer cases (Molina et al., 2008) and includes several subtypes.

Patient populations in trials of drugs for the treatment of NSCLC often make reference to two histological subtypes, squamous and non-squamous. Differentiation between these classifications is important as they have very different prognoses, with significantly poorer overall survival observed in the squamous population than non-squamous (Kawase et al., 2012). Furthermore, squamous tumours are inherently less sensitive to pemetrexed, which has become a dominant cytotoxic agent in the treatment of non-squamous cancers. "Non-squamous" is a collective categorisation used to define several histologic subtypes which can be treated in a similar manner (Travis et al., 2011). However, the term "non-squamous" is not used in pathological reports on lung cancer histology; instead the International Associate for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society recommend that lung cancer of non-squamous histology is reported as adenocarcinoma or NSCLC not otherwise specified (NOS) (Travis et al., 2011). A study by Ho et al (2015) demonstrated that, within a group of 680 non-squamous patients, adenocarcinoma accounted for 96% of cases (Ho et al., 2015). This corresponds with figures reported in the CheckMate-057 trial (93%) and the LUME-Lung 1 trial (87%) (National Institute for Health and Care Excellence, 2016d, National Institute for Health and Care Excellence, 2015n).

Incidence rates of lung cancer in the UK are summarised in Table 7 below (Cancer Research UK, 2017).

Table 7: Number of New Cases, Crude and European Age-Standardised Incidence Rates per 100,000 Population by gender

		England	Wales	Scotland	N. Ireland	UK
Males	Cases	20,127	1,288	2,714	640	24,769
	Crude rate*	75.2	84.7	104.5	70.9	77.9
	AS rate (95% CI)	91.6 (90.3, 92.8)	91.9 (86.8, 96.9)	122.6 (117.9, 127.2)	95.0 (87.6, 102.3)	94.3 (93.1, 95.5)
Females	Cases	17,326	1,095	2,639	574	21,634
	Crude rate*	62.9	69.7	95.9	61.2	66.0
	AS rate (95% CI)	65.2 (64.2, 66.2)	65.0 (61.2, 68.9)	95.4 (91.8, 99.0)	70.5 (64.8, 76.3)	68.0 (67.1, 68.9)
Overall	Cases	37,453	2,383	5,353	1,214	46,403
	Crude rate*	69.0	77.1	100.1	66.0	71.8
	AS rate (95% CI)	76.6 (75.8, 77.4)	76.6 (73.5, 79.6)	106.7 (103.9, 109.6)	80.7 (76.2, 85.3)	79.3 (78.6, 80.0)

*per 100,00 population
AS, age-standardised rates; CI, confidence interval
Source:(Cancer Research UK, 2017)

Early diagnosis of NSCLC is difficult, as early-stage disease is often asymptomatic, and symptoms of late-stage or advanced disease are non-specific (Hicks et al., 2007). As a result, the majority of patients with lung cancer are initially diagnosed with disease that is already locally advanced or metastatic (Carnio et al., 2014).

The diagnosis of lung cancer can result from either evaluation of suspicious symptoms or, in around 5% of patients, it may be incidental to an imaging investigation carried out for other reasons (Hicks et al., 2007). More prominent symptoms typically arise with late-stage or advanced NSCLC as tumour mass increases and begins to impact the surrounding tissues.

For patients presenting with lung cancer, the extent of the disease is evaluated by staging, as this determines the most appropriate form of treatment and provides an indication of prognosis. The tumour, node, metastases (TNM) system is defined as the size and level invasiveness of the primary tumour (T), degree of regional lymph node involvement (N) and the metastatic spread to distant organs and lymph nodes (M). The TNM forms the basis of staging in NSCLC. This submission will focus on locally advanced and metastatic NSCLC, i.e. unresectable Stage IIIA, Stages IIIB and IV.

Table 8: Lung cancer Stage III and IV grouping

Stage	T, N, M		
Stage IIIA	T1a,b, T2a,b	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

M, metastasis; N, node; T, tumour; Source:(Peters et al., 2012)

A number of genetic events have been identified as oncogenic drivers in NSCLC, including epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations, anaplastic lymphoma kinase (ALK), and rearranged during transfection (RET) gene rearrangements. Molecular mechanisms such as these, which drive the pathophysiology of NSCLC, are increasingly the focus of new research and have led to new therapeutic options that are now approved or in early- to late-stage NSCLC (Stinchcombe, 2014). Indeed, the discovery of the EGFR mutations (Lynch et al., 2004) and rearrangements of the ALK gene (Soda et al., 2007) have led to a paradigm shift with the advancement of targeted therapies for the 10-20% of patients with metastatic NSCLC whose tumours harbour these oncogenic alterations.

Despite this, disease progression is still inevitable in the majority of patients treated with targeted therapies (Maemondo et al., 2010, Zhou et al., 2011). Furthermore, patients without a mutation conferring sensitivity to a targeted agent are typically treated with chemotherapy, especially platinum-based chemotherapy, which is associated with modest treatment benefits and significant toxicities (Delbaldo et al., 2007). Therefore, there remains an unmet need for new treatments without causing significant toxicity or a deterioration in quality of life that improve survival for those patients who progress following targeted therapy and for patients ineligible for targeted therapy that relapse after first-line chemotherapy for whom toxic and not very effective docetaxel-based treatments are currently the most widely used.

3.2 Effects of the disease on patients, carers and society

The symptoms of lung cancer include persistent coughing (sometimes with blood present), chest pain, shortness of breath, recurrent chest infections, weight loss and tiredness (National Health Service). The high symptom burden in patients with advanced NSCLC has a highly negative impact on health-related quality of life (HRQoL), well-being and on family functioning (Sarna et al., 2002).

Due to its severe toxicity profile, chemotherapy is often associated with various complications and diminished HRQoL in patients with lung cancer (Pearman, 2008). A major consequence of using chemotherapy is its effect on bone marrow (Ettinger, 2005). Myelosuppression can lead to severe complications such as neutropenia, febrile neutropenia, anaemia, thrombocytopenia and leukopenia (Ettinger, 2005, Stokes et al., 2009). These events are severe and can lead to life-threatening complications (Stokes et al., 2009). Other side effects of chemotherapy include nausea and vomiting, cardiac toxic effects, renal toxic effects, diarrhoea, hypersensitivity reactions, weakness and neuropathy (Schiller et al., 2002).

In addition to the complications associated with the treatment of advanced NSCLC, disease progression can itself have a marked impact on patients' HRQoL. In a UK study, the utility values for patients with metastatic NSCLC receiving second-line therapy ranged from 0.653 for stable patients with no toxicity to 0.473 in patients with disease progression: this corresponds to an 18% decrease in quality of life (p=0.0001) (Nafees et al., 2008).

Furthermore, advanced lung cancer can also have a significant impact on the emotional and social wellbeing of the patient's family. The lives of patients and their families may become centred around clinic appointments, while increasing physical limitations can lead to changes in interpersonal roles and relationships, adversely affecting family relationships (Rowland et al., 2016).

Lung cancer is also associated with a significant burden on caregivers, which can include social isolation, psychological impairment and poorer quality of life. A study investigating the consequences of caring for patients with lung cancer in five European countries (including the UK) concluded that caregivers had significantly higher odds of being diagnosed with depression, headache, insomnia and gastrointestinal symptoms, and worse HRQoL, compared with non-caregivers. Moreover, caregivers also shoulder an economic burden with higher annual indirect costs with presenteeism-related impairment (impairment while working) and overall work impairment (Jassem et al., 2015). A modelling study estimated the mean cost of providing informal care to lung cancer patients at the end of life in England and Wales to be £73m, approximately one third of the total cost of care for this patient group (Round et al., 2015).

The direct costs associated with the treatment of lung cancer places a considerable burden on healthcare budgets, especially since the diagnosis, treatment and follow-up of lung cancer predominantly occurs within secondary care. Data for UK healthcare costs in lung cancer are limited; however, a recent retrospective, descriptive cohort study was conducted to evaluate the direct costs of hospital care in the diagnosis and management of 3,274 lung cancer patients, using routine NHS data (costs adjusted to 2013–14 prices). Mean cumulative costs were £5,852 at 90 days and £10,009 at one year. The majority of costs (58.5%) were accrued within the first 90 days, with acute inpatient costs the largest contributor at one year (42.1%) (Kennedy et al., 2016).

3.3 Clinical pathway of care

The information presented below is based on the current NICE guidelines for the diagnosis and management of lung cancer [CG121] (National Institute for Health and Care Excellence, 2016ce).

First-line chemotherapy for advanced or metastatic NSCLC

Chemotherapy is offered to patients with stage III or IV NSCLC without a known mutation and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life. Chemotherapy should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug; either cisplatin if patients can tolerate the toxicity, or carboplatin if not. Pemetrexed is the preferred third-generation drug in patients with non-squamous cancer, but it is unsuitable for squamous tumours [TA181]. Single-agent chemotherapy with a third generation drug may be offered to patients who are unable to tolerate a platinum combination.

The first-line treatment options available to patients whose tumours test positive for EGFR tyrosine kinase (TK) mutation include afatinib [TA310], erlotinib [TA258] and gefitinib [TA192]. Crizotinib is approved as a first-line treatment for patients whose tumours test positive for the ALK mutation [TA406].

Maintenance chemotherapy for advanced or metastatic 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].

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].

Second-line chemotherapy for advanced or metastatic NSCLC

Docetaxel monotherapy is regarded as the standard of care for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy.

Nintedanib in combination with docetaxel is recommended, within its Marketing Authorisation, as an option for treating locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy [TA347].

Pembrolizumab has recently been recommended as an option for treating locally advanced or metastatic PD-L1-positive (≥1%) NSCLC in adults who have had at least one chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour), providing pembrolizumab is stopped at 2 years of uninterrupted treatment and that no documented disease progression is observed [TA428]. As it has recently been approved, and the marketing authorisation is only for PD-L1 positive patients, pembrolizumab has not been included as a comparator in this submission.

For mutation-based NSCLC, a number of other treatment options are recommended for use:

- Osimertinib is recommended as an option for use within the CDF for treating locally advanced or metastatic EGFR T790M mutation-positive NSCLC in adults whose disease has progressed only after first-line treatment with an EGFR-TK inhibitor [TA416].

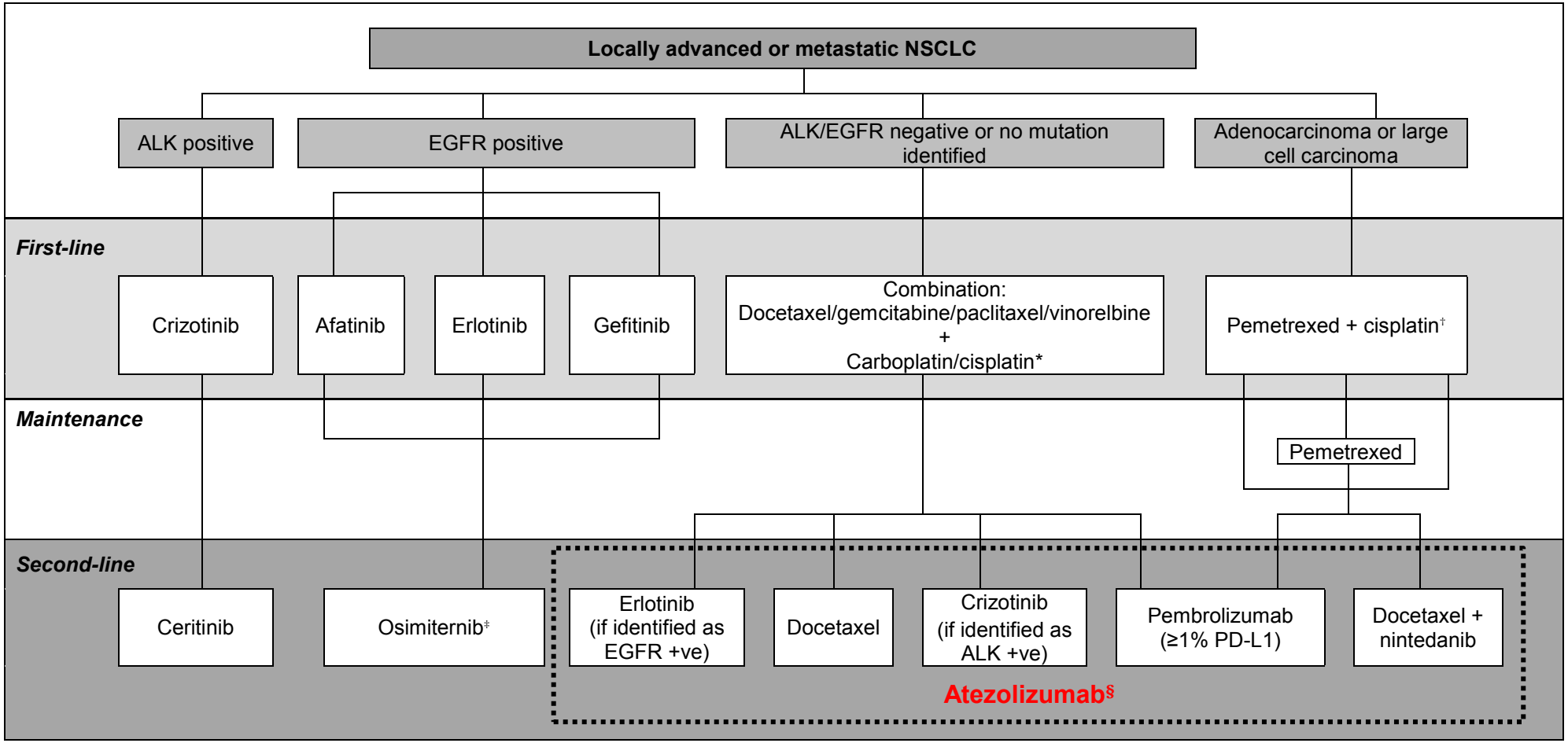
- Erlotinib is recommended as a treatment option for people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is EGFR-TK mutation-positive. It is also an option for patients who have progressed after non-targeted chemotherapy in people with tumours of unknown EGFR-TK mutation status, but only if the result of an EGFR-TK mutation diagnostic test is unobtainable because of an inadequate tissue sample or poor-quality DNA; the treating clinician considers that the tumour is very likely to be EGFR-TK mutation-positive; and there is an observed response within the first 2 cycles of treatment. However, erlotinib is not recommended for patients with EGFR-TK mutation-negative tumours that have progressed after non-targeted chemotherapy. Gefitinib is not recommended for second-line treatment after non-targeted chemotherapy in people with tumours that are EGFR-TK mutation-positive [TA374].

- Crizotinib is recommended by NICE as a second-line treatment in previously treated adults with ALK positive NSCLC [TA422] after a rapid re-review from the CDF.

- Ceritinib is also recommended as an option for treating advanced ALK positive non-small-cell lung cancer in adults who have previously had crizotinib [TA395].

Although no treatment options are included in the NICE guidance beyond second line, clinical experts have informed Roche that patients who progress on targeted therapy are likely to be treated with platinum-based chemotherapy regimens (see Section 1). As discussed previously in Section 2.5, effective treatment options are limited for patients with locally advanced or metastatic NSCLC, particularly those who cannot receive targeted therapy. The proposed positioning of atezolizumab in the NICE clinical guidance for lung cancer pathway is represented in Figure 3; based on the anticipated indication, atezolizumab will provide an alternative treatment option for all patients who have progressed on a prior chemotherapy regimen (indicated by dotted box), although clinical expert opinion indicates targeted therapy treatment options are likely to be preferred over immunotherapy in patients with confirmed EGFR or ALK mutations. Based on this feedback, along with the final scope of the appraisal, no comparison to targeted therapies is made in this submission

Figure 3: Advanced or metastatic NSCLC treatment pathway based on NICE guidance CG121



§Dotted box indicates proposed position of atezolizumab based on anticipated indication, i.e. after prior chemotherapy. Nb. targeted therapies are likely to be preferred option in patients with confirmed or suspected mutation; therefore targeted therapies are excluded from economic analysis in this submission.
*If patients cannot tolerate a platinum combination, offer single-agent chemotherapy with a third-generation drug;
†Other regimens possible for this patient population, including gemcitabine+cisplatin;
‡via CDF

3.4 Life expectancy of people with the disease in England

Overall, survival for patients with NSCLC is very poor. Lung cancer was the most common cause of cancer death in the UK in 2014 (~35,900 deaths in total) and it accounted for 22% of all cancer deaths in the UK that year (Cancer Research UK, 2017).

As discussed previously, there are limited treatment options for patients with locally advanced or metastatic disease; this is reflected in the decline in median survival and 5-year survival rate as disease progresses and performance status declines (Beckett P et al., 2013).

Table 9: Median survival (months) and 5-year survival in NSCLC

	Stage Ia	Stage Ib	Stage IIa	Stage IIb	Stage IIIa	Stage IIIb	Stage IV
Median survival (months) All patients	58.6	34.6	36.6	18.3	12.2	7.5	3.4
5-year survival (%) All patients	48	39	37	25	12	7	3

Source:(Beckett P et al., 2013)

3.5 Guidance related to the condition

Details of relevant NICE guidance for the diagnosis and management of lung cancer are listed below, based on the final scope.

- Lung cancer: diagnosis and management [CG121] (National Institute for Health and Care Excellence, 2016ce)
- Lung cancer in adults: quality standards [QS17] (National Institute for Health and Care Excellence, 2012)
- Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non‑small cell lung cancer [TA347] (National Institute for Health and Care Excellence, 2015n)
- Pembrolizumab for treating PDL1-positive non-small-cell lung cancer after chemotherapy [TA428] (National Institute for Health and Care Excellence, 2017)

3.6 Other clinical guidelines

There are a number of other clinical guidelines related to NSCLC, including ESMO Clinical Practice Guidelines, 2016 (Novello et al., 2016) and NCCN Clinical Practice Guidelines (National Comprehensive Cancer Network, 2016).

3.7 Issues relating to current clinical practice

Other than the limited treatment options available beyond second-line for patients with locally advanced or metastatic NSCLC (as discussed above), we are not aware of any issues relating to current clinical practice.

3.8 Equality Issues

No equality issues have been identified.

4. Clinical effectiveness

Summary of clinical effectiveness

- Evidence for the efficacy and safety of atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy is sourced from two randomised clinical trials; an open-label Phase III study (OAK) and an open-label Phase II study (POPLAR) [evidence from the single arm Phase II studies (BIRCH and FIR) will not be discussed; see Section 4.11]
- Patients were enrolled into OAK and POPLAR regardless of PD-L1 expression since Phase 1 data did not demonstrate a clear relationship between PD-L1 expression and response to atezolizumab. PD-L1 expression was a pre-determined stratification factor for both OAK and POPLAR; however, interim data from POPLAR showed that the OS treatment benefit extended beyond the TC3 or IC3 subgroup and as such, data discussed in this submission is not restricted by PD-L1 expression
- The OAK study met both co-primary endpoints; there was statistically significant and clinically meaningful improvement in OS with atezolizumab compared with docetaxel in the ITT population (HR 0.73, 95% CI: 0.62, 0.87; p=0.0003) and in patients with ≥1 % PD-L1 expression (HR 0.74, 95% CI: 0.58, 0.93; p=0.0102)
    - The median overall survival in the ITT population was 9.6 months (95% CI: 8.6, 11.2) in the docetaxel arm and 13.8 months (95% CI: 11.8, 15.7) in the atezolizumab arm
- A significant improvement in OS with atezolizumab was observed regardless of PD-L1 status, with a similar effect observed in PD-L1 negative patients (TC0/IC0) to that seen in the ITT population (HR 0.75, 95% CI:0.59, 0.96; p=0.0205)
- The proportion of patients with a confirmed response per RECIST v1.1 was similar in both arms: 13.6% (95% CI: 10.5, 17.3) in the docetaxel arm and 13.4% (95% CI: 10.3, 17.0) in the atezolizumab arm
    - Six patients in the atezolizumab arm achieved a complete response compared with one in the docetaxel arm
- Among responders, the median DOR was more than doubled in the atezolizumab arm (16.3 months, 95% CI: 10.0, NE) compared with the docetaxel arm (6.2 months, 95% CI: 4.9, 7.6) in the ITT population (HR 0.34, 95% CI: 0.21, 0.55), with 52% of atezolizumab responses ongoing at the time of the most recent data cut
- Results from OAK were consistent with those seen in the Phase II POPLAR study
- The safety data from OAK and POPLAR are consistent with the known safety profile of atezolizumab and immunotherapies generally, with no new safety signals observed. Atezolizumab was well tolerated, with a favourable safety profile compared with docetaxel

4.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant published and unpublished RCT evidence relating to second and further-line pharmacological treatments used for locally advanced/metastatic NSCLC.

The SLR was conducted according to the NICE Guide to the Methods of Technology Appraisal 2013 and therefore adhered to the Centre for Reviews and Dissemination guidance for undertaking systematic reviews in health care.

The systematic search was run on electronic databases (i.e. MEDLINE, MEDLINE In-Process, EMBASE and Cochrane) and was supplemented by hand searches to ensure that all relevant studies had been included. Each database was searched individually.

SLR search strategy

The complete search strategy for this review is provided in Appendix 2. The following sources were searched, using search terms that combined population, interventions and study types:

- Electronic databases, searched separately:
    - EMBASE (from 1988)
    - MEDLINE and MEDLINE In-Process (from 1946)
    - Cochrane Central Library of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) (January 2012–June 2016)
- Congress proceedings were also searched manually from 1st January 2013 to 17th June 2016:
    - American Society of Clinical Oncology (ASCO)
    - European Society for Medical Oncology (ESMO)
    - International Association for the Study of Lung Cancer (IASLC)/World Conference on Lung Cancer (WCLC)
    - International Lung Cancer Congress (ILCC)
    - European Lung Cancer Conference (ELCC)
    - British Thoracic Oncology Group (BTOG)
- Clinical trial registries were also searched (not restricted by time period):
    - ClinicalTrials.gov of the US National Institute of Health (NIH) (1st January 2012 to 21st July 2016)
    - WHO's meta-registry "International Clinical Trials Registry Platform Search Portal" (ICTRP) (1st January 2012 to 21st July 2016)

    - EU Clinical Trial Registry (1st January 2012 to 30th August 2016)
- The reference lists of included articles were hand-searched for potentially relevant studies

Inclusion and exclusion criteria

The eligibility criteria used for the SLR are presented in Table 10.

Although no language restrictions were posed in the search strategy, a decision was made to exclude Asian language publications from the data extraction process because of the extra complexity associated with translating these articles and the limited relevant additional data that these would provide.

Table 10: Eligibility criteria for systematic literature review of RCT evidence

Criteria		Inclusion	Exclusion
STUDY DESIGN	**Abstract selection**	Phase II-IV controlled clinical trials (RCTs and non-RCTs) Cross-over studies were included but highlighted as having a cross-over design.	Phase I clinical trials Post-hoc or retrospective analyses Cost-effectiveness analyses Observational studies Reviews or meta-analyses* Methodology studies or protocols Case studies (sample size of 1 patient) Studies with less than 10 patients per arm Single arm studies – were listed, but excluded from data extraction.
	Full-text selection	Phase II-IV, controlled clinical trials (RCTs and non-RCTs) (full-text or abstracts) Cross-over studies were included but highlighted as having a cross-over design.	
POPULATION	**Abstract selection**	Adult patients (≥18 years) with advanced/metastatic NSCLC eligible for second-line or further-line treatment, who had received 1 or more prior systemic therapies Studies that included adults and children	Studies with only healthy patients Studies that included all NSCLC patients (1st and further line), but did not report data for second or further-line treatment patients separately. These studies included a comment that they had 1st and further line of treatments reported together. Studies that included only children Studies that included adults and children but did not report data for adults separately
	Full-text selection	Adult patients (≥18 years) with advanced/metastatic NSCLC eligible for second-line or further-line treatment, who had received 1 or more prior systemic therapies Studies that include all NSCLC patients (1st and further line) and reported data for second or further-line treatment patients separately Adults (≥ 18 years) Studies that included adults and children and reported data for adults separately	Studies with only healthy patients Studies that included all NSCLC patients (1st and further line), but did not report data for second or further-line treatment patients separately. These studies included a comment that they had1st and further line treatments reported together. Studies that included only children Studies that included adults and children but did not report data for adults separately Studies that included only first-line treatment NSCLC patients

TREATMENT / INTERVENTION	**(abstract and full-text selection)**	All second and further line pharmacological treatments (licensed and investigational – Phase II-IV) reported in the articles for treatment of locally advanced/metastatic NSCLC were of interest.	All pharmaceutical interventions not treating NSCLC Non-pharmaceutical interventions used to treat NSCLC.
COMPARATOR	**(abstract and full-text selection)**	Studies that compared second and further line pharmacological treatments (licensed and investigational – Phase II-IV) for locally advanced/metastatic NSCLC patients to each other or to placebo or standard of care were included.	Studies that compared treatments for NSCLC to non-pharmaceutical interventions. Non-pharmaceutical interventions were only included if they represented a standard of care, otherwise they were excluded.
OUTCOMES	**Abstract selection**	No selection on outcomes during the abstract screening	
	Full-text selection	Reported results for one of the following outcomes (for all treatments): **Efficacy and safety outcomes:** • Overall survival • Progression-free survival (RECIST V1.1, RECIST (initial version) and modified RECIST) • Disease control rate (RECIST v1.1, RECIST (initial version) and modified RECIST)Overall or objective response rate (RECIST v1.1, RECIST (initial version) and modified RECIST) • Partial response rate (RECIST v1.1, RECIST (initial version) and modified RECIST) • Complete response rate (RECIST v1.1, RECIST (initial version) and modified RECIST) • Stable disease • Progressive disease • Unknown response • Duration of response (RECIST v1.1, RECIST (initial version) and modified RECIST) • Time to progression (weeks) (RECIST v1.1, RECIST (initial version) and modified RECIST) • Any Adverse events • Serious Adverse events • Any grade 3 or higher adverse event	Outcomes not of interest.

		• All withdrawals; • Withdrawals due to AEs; • Withdrawals due to lack of efficacy; • Withdrawals due to loss of follow-up • Withdrawals due to mortality • Mortality **PRO and HRQoL outcomes:** • EORTC QLQ-C30 (The European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire) • EORTC QLQ-LC13 • Cancer Therapy Satisfaction Questionnaire 16 items (CTSQ-16). • Lung Cancer Symptom Scale (LCSS) • Average Symptom Burden Index (ASBI) • FACT-L score • Lung Cancer Subscale (LCS) • EQ-5D (3L or 5L)	
* Reviews and meta-analysis were excluded from data extraction since the pooled results could not be used in our analysis. However, good quality meta-analysis and reviews (i.e. Cochrane reviews) were used for cross-checking of references to ensure that the search did not omit any articles.			

AE: Adverse event; ASBI: Average Symptom Burden Index; CTSQ: Cancer Therapy Satisfaction Questionnaire; EGFR: Epidermal growth factor receptor; EORTC: The European Organisation for Research and Treatment of Cancer; FACT-L: Functional Assessment of Cancer Therapy – Lung; HRQoL; Health-related quality of life; LCS: Lung Cancer Subscale; LCSS: Lung Cancer Symptom Scale; NSCLC: Non-small cell lung cancer; QLQ: Quality of Life Questionnaire; PRO: Patient reported outcome; RCT: Randomised Controlled Trial; RECIST: Response Evaluation Criteria in Solid Tumours

Review strategy

All citations were independently screened by two analysts, with any discrepancies resolved by discussion. A third independent researcher was consulted when consensus could not be reached.

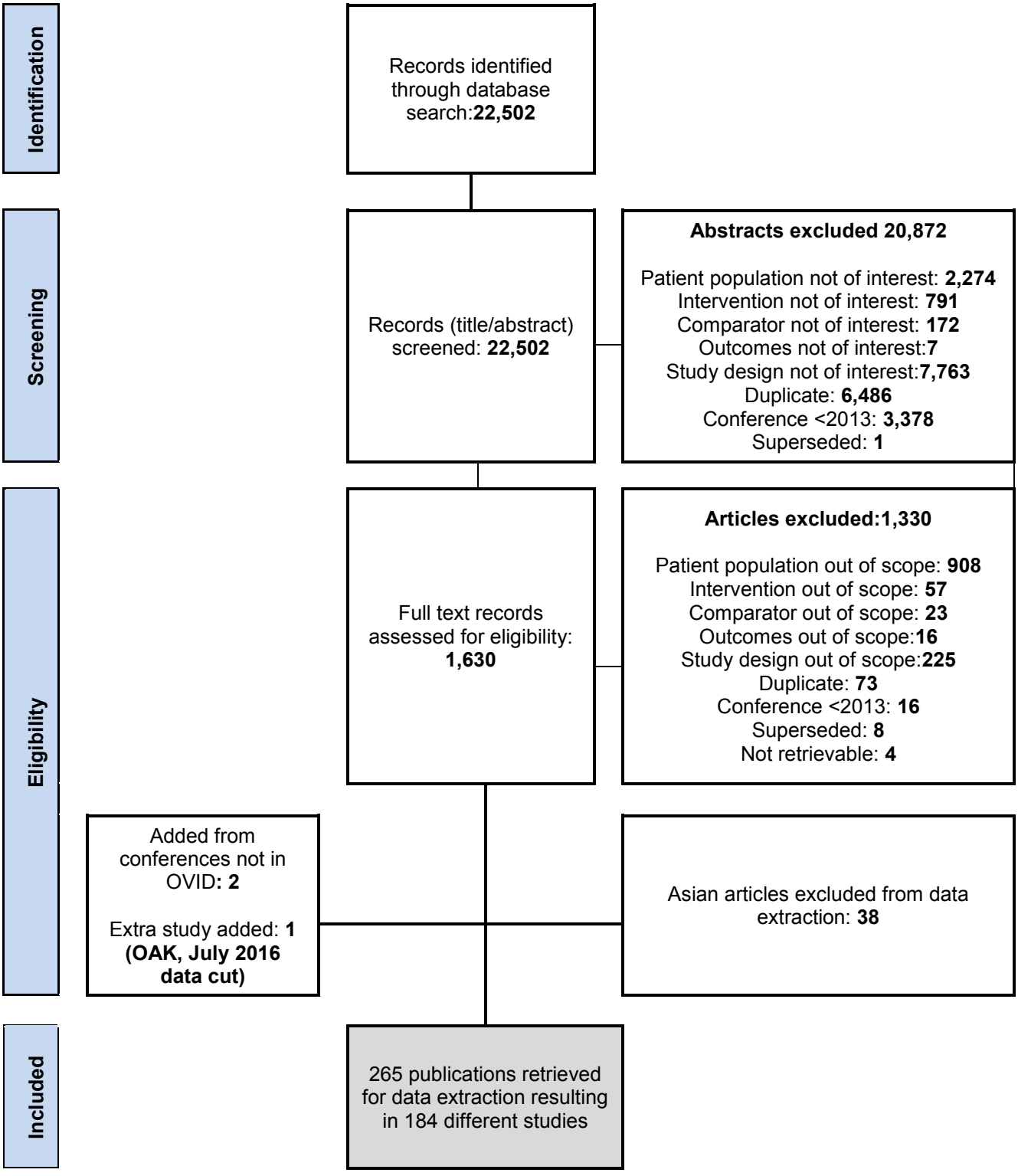
Once eligible publications were identified, full papers were obtained and screened again on the basis of the complete manuscript – rather than abstract only – to ensure eligibility. As per the first step, two analysts conducted independent reviews of the full publications with a third reviewer consulted for any disagreements. When the survival probabilities were not reported in the individual studies, they were extracted from figures using the DigitizeIt software

Search results

A total of 22,502 citations were identified with the search strategies in Medline, EMBASE and Cochrane databases. During the abstract screening phase, 20,872 abstracts were excluded. Thirty-one percent of identified citations were duplicates between databases. The most common reason for exclusion was inappropriate study design (37%). During full text screening, an additional 1,330 publications were excluded, leaving 300 publications. An additional 2 records were obtained from conference websites, with the atezolizumab Phase III study (OAK) added since the data were not yet published at the database and conference search date. Thirty-eight Asian language articles were excluded, resulting in the final 265 publications for data extraction representing 184 studies (Figure 4).

Of these, two were found to be relevant to the decision problem in question. The total 184 studies are further considered in section 4.10 and the articles excluded from the systematic review at the full-text review stage can be found in Appendix 3.

Figure 4: PRISMA flow diagram for clinical SLR



4.2 List of relevant randomised controlled trials

The efficacy and safety of atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy has been studied in two randomised clinical trials; an open-label Phase

III study (OAK, GO28915, NCT02008227) (Clinical Trials.Gov) and an open-label Phase II study (POPLAR, GO28753, NCT01903993) (Clinical Trials.Gov).

A summary of the OAK and POPLAR clinical trials and available publications is provided in Table 11.

Table 11: List of relevant RCTs and publications

Trial number (name)	NCT02008227 (OAK)	NCT01903993 (POPLAR)
Phase	III	II
Sponsor	F. Hoffmann-La Roche, Ltd.	F. Hoffmann-La Roche, Ltd.
Intervention	Atezolizumab, 1,200 mg every three weeks	Atezolizumab, 1,200 mg every three weeks
Comparator	Docetaxel, 75 mg/m^2 every three weeks	Docetaxel, 75 mg/m^2 every three weeks
Population	• ≥18 years old • ECOG PS 0 or 1 • Measurable disease by (RECIST v1.1) • Adequate haematological and end-organ function	• ≥18 years old • ECOG PS 0 or 1 • Measurable disease by (RECIST v1.1) • Adequate haematological and end-organ function
Study references	**Primary analysis, clinical cut-off date: 7th July 2016** • Barlesi F, et al. Oral presentation from abstract LBA44, ESMO 2016 (Barlesi F et al., 2016) • Gadgeel S, et al. Oral presentation from abstract PL04A.02, IASLC World Conference on Lung Cancer (Gadgeel S et al., 2016) Rittmeyer A, et al. Lancet 2016 (Rittmeyer et al., 2016)	**Third interim analysis, clinical cut-off date: 30th January, 2015** • Spira A, et al. Oral presentation from abstract 8010, ASCO 2015 (Spira et al., 2015) **Primary analysis, clinical cut-off date: 8th May 2015, 2015** • Vansteenkiste J, et al. Oral presentation from abstract 14LBA, ESMO 2015 (Vansteenkiste et al., 2015) • Fehrenbacher L, et al. Lancet 2016;387;137-46 (Fehrenbacher et al., 2016) **Updated analysis, clinical cut-off date: 1st December, 2015** • Smith D, et al. Poster from Abstract 9028, ASCO 2016 (Smith et al., 2016)

ASCO, American Society of Clinical Oncology; ECOG PS, Eastern Cooperative Oncology Group performance status; ESMO, European Society for Medical Oncology; RECIST, Response Evaluation Criteria in Solid Tumours

4.3 Summary of methodology of the relevant randomised controlled trials

The study design, patient inclusion/exclusion criteria and treatment regimens were very similar between the OAK and POPLAR studies. In the interest of brevity and succinctness,

this section of the company submission will summarise the methodology of both studies together, with any differences between studies highlighted as necessary. Unless otherwise stated, information on the POPLAR study was sourced from the primary manuscript and clinical study report (Fehrenbacher et al., 2016, F. Hoffmann-La Roche Ltd, 2015a); information from OAK was obtained from the Barlesi F, et al ESMO 2016 presentation, clinical study report and the Rittmeyer, et al primary manuscript (Barlesi F et al., 2016, F. Hoffmann-La Roche Ltd, 2016b, Rittmeyer et al., 2016).

Trial design

OAK is a Phase III, open-label, multicentre, randomised study to investigate the efficacy and safety of atezolizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC who had progressed during or following a platinum-containing regimen. POPLAR is a Phase II open-label, multicentre, randomised study investigating the same treatment regimens in this patient population.

The following data analyses from OAK and POPLAR have taken place

Table 12: Data analyses from OAK and POPLAR

OAK	POPLAR
• Primary analysis (clinical cut-off 7th July 2016); data taken from primary population	• Interim analysis (clinical cut-off 30th January 2015) • Primary analysis (clinical cut-off 8th May 2015) • Updated efficacy analysis (clinical cut-off 1st December 2015)

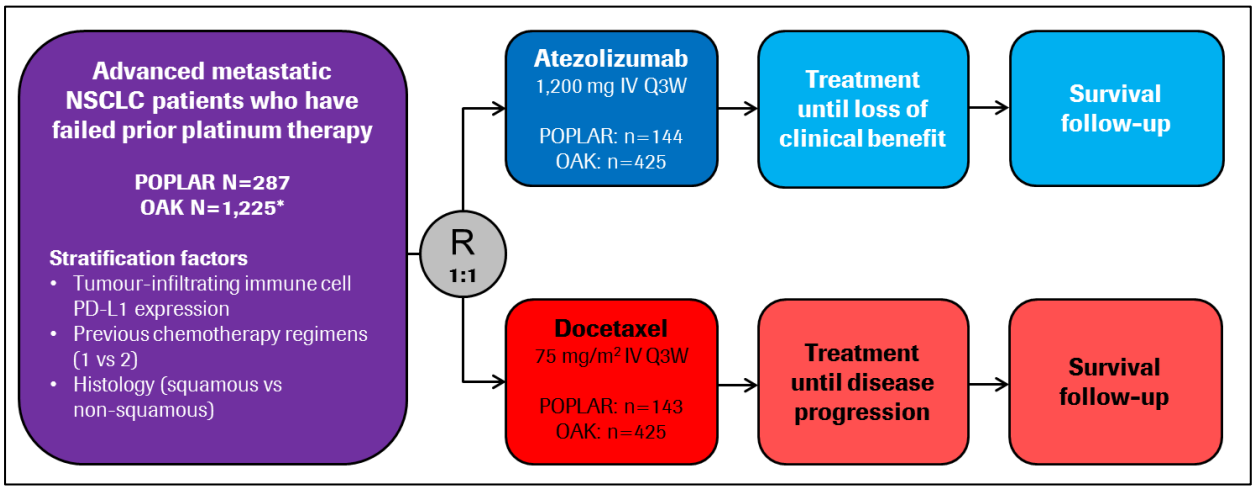
Eligible patients (OAK N=850 [primary population]; POPLAR N=287) were randomly assigned in a 1:1 ratio to the two study treatment arms to receive either atezolizumab (OAK n=425; POPLAR n=144) or docetaxel (OAK n=425; POPLAR n=143). Patients were stratified by previous lines of chemotherapy (one vs two), and histology (non-squamous vs squamous), then permuted block-randomised (1:1) with a block size of four to receive either atezolizumab or docetaxel using an interactive voice or web response system.

Patients were recruited to OAK and POPLAR regardless of PD-L1 expression. Phase I data demonstrated responses per RECIST v1.1 and prolonged stable disease in the subgroup of patients with low/no levels of PD-L1(Horn L et al., 2015), and therefore patients negative for PD-L1 expression were included in POPLAR and OAK as they may also potentially experience an overall survival benefit with atezolizumab and less toxicity relative to docetaxel. PD-L1 expression was, however, a pre-determined stratification factor for both OAK and POPLAR. Based on the results of these trials (Section 4.7), along with the

anticipated marketing authorisation, this submission focuses on patients with metastatic NSCLC, without restriction to patients positive for PD-L1 expression only.

The study schema for OAK and POPLAR is summarised in Figure 5 below.

Figure 5: OAK and POPLAR study design schematic



*A prespecified analysis of the first 850 patients provided sufficient power to test the co-primary endpoints of OS in the ITT and tumour cell (TC) 1/2/3 or tumour-infiltrating immune cell (IC)1/2/3 subgroup (≥1 PD-L1 expression)
IV, intravenous; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1; Q3W, every three weeks

Atezolizumab treatment could be continued as long as patients experienced a clinical benefit as assessed by an investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

Patients were permitted to continue atezolizumab treatment after RECIST v1.1 criteria for progressive disease if they met 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 hypercalcaemia]) 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 for whom approved therapies exist must have provided written consent to acknowledge deferring these treatment options in favour of continuing study treatment at the time of initial progression.

Patients treated with atezolizumab in whom radiographic disease progression was confirmed at a subsequent tumour assessment could be considered for continued study treatment at the discretion of the investigator if they continued to meet the criteria above.

Docetaxel 75 mg/m^2 was administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

No crossover was allowed from the control arm to the experimental arm in either OAK (although this is now possible following analysis of the primary population) or POPLAR, however subsequent treatments were allowed (see Table 28).

Tumour specimens from eligible patients for OAK and POPLAR were prospectively tested for PD-L1 expression by a central laboratory using the VENTANA PD-L1 (SP142) immunohistochemistry (IHC) assay. The study enrolled all patients whose tissue was evaluable for expression testing, regardless of PD-L1 expression status. The PD-L1 IHC scoring system was developed to stratify PD-L1 expression on tumour-infiltrating immune cells (ICs) and on tumour cells (TCs).

Table 13: Criteria for PD-L1 expression

Description of IHC Scoring Algorithm	PD-L1 expression level
Tumour-infiltrating immune cells (ICs)	
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in ICs covering < **1%** of tumour area occupied by tumour cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC0
Presence of discernible PD-L1 staining of any intensity in ICs covering between **≥1% and <5%** of tumour area occupied by tumour cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC1
Presence of discernible PD-L1 staining of any intensity in ICs covering between ≥ **5% and** <**10%** of tumour area occupied by tumour cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC2
Presence of discernible PD-L1 staining of any intensity in ICs covering ≥**10%** of tumour area occupied by tumour cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC3
Tumour cells (TCs)	
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in < **1%** TCs	TC0
Presence of discernible PD-L1 staining of any intensity in ≥**1% and** <**5%** TCs	TC1
Presence of discernible PD-L1 staining of any intensity in ≥**5% and** <**50%** TCs	TC2
Presence of discernible PD-L1 staining of any intensity in ≥**50%** TCs	TC3

IC, tumour-infiltrating immune cell; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; TC, tumour cell

Eligibility criteria

The specific inclusion and exclusion criteria (for both OAK and POPLAR) are detailed in Table 14 and Table 15 below, respectively.

Table 14: OAK and POPLAR inclusion criteria

Inclusion criteria
• Aged ≥ 18 years • Histologically or cytologically documented NSCLC that is locally advanced or metastatic (i.e., Stage IIIB not eligible for definitive chemoradiotherapy, Stage IV, or recurrent) NSCLC • Representative formalin-fixed paraffin-embedded tumour specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to be evaluable for tumour PD-L1 expression o Patients with fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with Medical Monitor o Patients who do not have tissue specimens meeting eligibility requirements may undergo a biopsy during the screening period • Disease progression during or following treatment with a prior platinum-containing regimen for locally advanced, unresectable/inoperable or metastatic NSCLC or disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen o Adjuvant/neoadjuvant chemotherapy or chemoradiation counts as a prior chemotherapy regimen if < 6 months between the last dose and the date of recurrence o Combined treatment with chemotherapy and radiation constitutes a single regimen; surgery is not considered a regimen o Patients may have received one additional cytotoxic chemotherapy regimen (maximum of two prior cytotoxic chemotherapy regimens) o Patients with advanced lung cancer and a sensitising EGFR mutation will additionally be required to have experienced disease progression (during or after treatment) with an EGFR TKI (erlotinib, gefitinib, etc.) ▪ Patients with unknown EGFR mutational status not previously treated with an EGFR TKI but whose tumour may harbour a sensitising EGFR will be tested by a central laboratory prior to enrolment o Patients with a previously detected ALK fusion oncogene must additionally have experienced disease progression (during or after treatment) with crizotinib or another ALK inhibitor o The last dose of prior systemic anti-cancer therapy must have been administered ≥21 days prior to randomisation ▪ In POPLAR: ≥14 days for vinorelbine or other vinca alkaloids or gemcitabine and within 4 weeks or five half-lives, whichever was shorter for immunostimulatory agents ▪ In OAK: the exception being TKIs approved for treatment of NSCLC have to be discontinued ≥7 days prior to Cycle 1, Day 1 o The last dose of treatment with any investigational agent or participation in another interventional study must have ended ≥28 days prior to randomisation • Measurable disease, as defined by RECIST v1.1 • ECOG performance status of 0 or 1 • Life expectancy ≥12 weeks • Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment: o ANC ≥1500 cells/µL

- WBC counts >2500/μL
- Lymphocyte count >500/ μL
- Serum albumin ≥2.5 g/dL
- Platelet count ≥100,000/μL
- Haemoglobin ≥9.0 g/dL
- AST and ALT ≤2.5 x ULN, with alkaline phosphatase ≤ 2.5 x ULN or AST and ALT ≤1.5 x ULN, with alkaline phosphatase > 2.5 x ULN
- Serum bilirubin ≤1.0 x ULN
- INR and aPTT ≤1.5 x ULN
- Creatinine clearance:
  - POPLAR: ≥50 mL/min
  - OAK: ≥30 mL/min

- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use highly effective form(s) of contraception and to continue its use for 6 months after the last dose of atezolizumab
- Able and willing to provide written informed consent and to comply with the study protocol

ALK, anaplastic lymphoma kinase; ALT, alanine transaminase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; EGFR, epidermal growth factor receptor; INR, International Normalised Ratio; NSCLC, non-small cell lung cancer; PD-L1 programmed cell death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitors; ULN, upper limit of normal; WBC, white blood cell

Table 15: Key OAK and POPLAR exclusion criteria

Exclusion criteria
• Active or untreated CNS metastases as determined by CT or MRI evaluation during screening and prior radiographic assessments • Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥2 weeks prior to randomization • Leptomeningeal disease • Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures • Uncontrolled tumour-related pain • Uncontrolled hypercalcaemia (>1.5 mmol/L ionized calcium or Ca >12 mg/dL or corrected serum calcium >ULN) or symptomatic hypercalcaemia requiring continued use of bisphosphonate therapy or denosumab • Malignancies other than NSCLC within 5 years prior to randomisation, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, or ductal carcinoma in situ treated surgically with curative intent) • Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina **Related to docetaxel:** • Prior treatment with docetaxel • History of severe hypersensitivity to docetaxel • Grade ≥2 peripheral neuropathy as defined by NCI CTCAE v4.0 criteria **Related to atezolizumab** • History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanised antibodies or fusion proteins • History of autoimmune disease

- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation
- Known tumour PD-L1 expression status from other clinical trials (OAK only)
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organising pneumonia, or evidence of active pneumonitis on screening chest CT scan
- Patients with active hepatitis B, hepatitis C, or positive test for HIV
- Prior treatment with CD137 agonists, anti-CTLA-4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications within 2 weeks prior to randomisation, or anticipated requirement for systemic immunosuppressive medications during the trial

CNS, central nervous system; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte associated protein-4; MRI, magnetic resonance imaging; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; PD-1 programmed cell death protein-1; PD-L1, programmed cell death ligand-1

Settings and locations of data collection

The number and locations of investigational sites for OAK and POPLAR are summarised below.

Table 16: OAK and POPLAR investigational site locations

	OAK	POPLAR
Patients randomised, N	1225	287
Number of centres	194	61
Countries, number of patients (centres)	Total: 31 • USA,330 (55) • France, 114 (20) • Spain, 112 (10) • Japan, 101 (16) • Germany, 92 (9) • South Korea, 85 (6) • Italy, 79 (12) • Poland, 54 (5) • United Kingdom, 31 (8) • Turkey, 26 (2) • Hungary, 20 (4) • Chile, 19 (3) • New Zealand, 17 (3) • Thailand, 16 (3) • Norway, 16 (1) • Canada, 15 (4) • Taiwan, 14 (4) • Switzerland, 13 (3) • Portugal, 12 (3) • Finland, 9 (3) • Netherlands, 8 (3) • Ukraine, 8 (3) • Greece, 8 (2) • Austria, 5 (3) • Russia, 5 (2)	Total:13 • USA, 132 (26) • Poland, 27 (4) • Germany, 24 (4) • Spain, 18 (4) • France, 16 (5) • South Korea, 16 (3) • Thailand, 15 (3) • United Kingdom, 11 (4) • Belgium, 10 (1) • Turkey, 7 (2) • Canada, 5 (2) • Italy, 5 (2) • Sweden, 1 (1)

	• Serbia, 5 (2) • Brazil, 4 (1) • Guatemala, 4 (1) • Argentina, 1 (1) • Panama, 1 (1) • Sweden, 1 (1)	

Trial drugs and concomitant medications

Patients were randomised in a 1:1 ratio to the following treatment arms:

Atezolizumab

- The dose of atezolizumab tested in OAK and POPLAR was 1,200 mg administered by IV infusion q3w
- Selection of an every-21-day dosing interval is supported by preliminary pharmacokinetic evaluations and allowed for a convenient integration with common chemotherapeutic regimens
- Treatment continued until loss of clinical benefit (see above)

Docetaxel

- Docetaxel was administered at a starting dose of 75 mg/m^2 q3w, consistent with the approved label for NSCLC (European Medicines Agency, 2012)
- All patients randomised to receive docetaxel had to be premedicated with corticosteroids according to local practice, for example oral dexamethasone 8 mg twice daily for 3 days starting a day prior to docetaxel administration, in order to reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity reactions
- Treatment continued until disease progression, unacceptable toxicity, or death

The permitted and prohibited concomitant medications for OAK and POPLAR are detailed below.

Table 17: Permitted concomitant medications

Permitted medications
• Any prescription medications or over-the-counter preparations used between the 7 days preceding the screening evaluation and the treatment discontinuation visit • Anti-pyretics (ibuprofen preferred), diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice for the symptomatic treatment of infusion-associated symptoms • Serious infusion-associated events manifested by dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress were managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and

β2-adrenergic agonists)
- Systemic corticosteroids and tumour necrosis factor-α inhibitors administered at the discretion of the treating physician
- For patients randomised to atezolizumab, alternatives to corticosteroids could be considered if feasible, but premedication could be administered for Cycles 2 and beyond
- Megestrol administered as an appetite stimulant was acceptable
- Oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy or other allowed ongoing therapies or medications

The following medications were permitted for patients in the **docetaxel** arm:
- Granulocyte colony-stimulating factor treatment
- Anti-emetics, anti-allergic measures, and other treatments for concomitant docetaxel toxicities could be used at the discretion of the investigator

Table 18: Prohibited concomitant medications

Prohibited medications
Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, was prohibited, including but is not limited to the following: • Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy The following medications were excluded for patients in the **atezolizumab arm**: • Traditional herbal medicines • RANKL inhibitor (denosumab) • Immunomodulatory agents, including but not limited to interferons or interleukin-2, during the entire study • Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide • Initiation or increased dose of granulocyte colony-stimulating factors • No other immunomodulatory agents for 10 weeks after study treatment discontinuation As docetaxel is a CYP3A4 substrate, patients in the **docetaxel arm** had to avoid using concomitant strong CYP3A4 inhibitors; furthermore, concomitant treatment with CYP3A4 inducers could only be used with caution

Study endpoints

The outcome measures for OAK and POPLAR are summarised below. The primary aims of treatment in NSCLC are to reduce tumour burden, delay disease progression and ultimately prolong life. The primary endpoint of overall survival (OS) was selected to explore the impact of atezolizumab in reaching these aims. While progression-free survival (PFS) is an appropriate endpoint to assess the activity of agents that are likely to elicit rapid control of tumour growth, it may be less suitable for therapies where tumour control may develop over time, such as immunotherapies.

Table 19: Outcome measures

	OAK	POPLAR
Primary endpoint	Co-primary: • OS (time from the date of randomisation to the date of death due to any cause) in the ITT • OS in patients with ≥1 % PD-L1 expression (TC1/2/3, IC1/2/3)	OS - time from the date of randomisation to the date of death due to any cause
Secondary endpoints	• PFS – interval between date of randomization and date of first documented PD as determined by investigator using RECIST v1.1 or death from any cause • ORR per RECIST v 1.1as determined by investigator - proportion of patients achieving best overall response of partial response or complete response • DOR - interval between first documented objective response (CR or PR) and first documented PD as determined by investigator using RECIST v 1.1 or death	• PFS per RECIST v1.1 - interval between date of randomisation and date of first documented PD or death • ORR per RECIST v1.1 - proportion of patients achieving confirmed best response of CR or PR per RECIST v1.1 • DOR per RECIST v1.1 - interval between first documented objective response (CR or PR) and first documented PD or death
Safety endpoints	• Safety and tolerability of atezolizumab compared with docetaxel	• Safety and tolerability of atezolizumab compared with docetaxel
Patient reported outcomes	• EQ-5D-3L, time-to-deterioration of lung cancer symptoms, patient functioning, and HRQoL between treatment arms as measured by the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module (LC13)	• Time-to-deterioration of lung cancer symptoms, patient functioning, and HRQoL between treatment arms as measured by the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module (LC13)

*atezolizumab arm only

CR, complete response; DOR, duration of response; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQoL-5 dimension; HRQoL, health-related quality of life; PD progressive disease; PFS progression free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; ORR, objective response rate; OS overall survival

Subgroup analyses

The consistency of both OAK and POPLAR study results in subgroups was examined based on the ITT populations of the trials. The subgroups were defined by demographic (e.g., age, sex, race) and baseline prognostic characteristics (e.g., ECOG performance status, prior lines of chemotherapy, histology (non-squamous vs squamous), smoking history and EGFR

mutational status). Efficacy was also evaluated in the PD-L1 subgroups (Table 13) to explore how the expression level of biomarkers predicted any treatment benefit with atezolizumab.

Safety reporting and analyses

The primary safety analyses were based on all randomised patients who received any dose of study drug during the study treatment period.

Adverse events of special interest for the purposes of expedited reporting were pre-defined in the protocol based on the known mechanism of action for atezolizumab and concerns reported with other immune modulating agents (Table 20).

Table 20: Protocol defined adverse events of special interest

Adverse Events of Special Interest
• Conditions (regardless of grade) suggestive of an autoimmune disorder, including but not limited to hepatitis, pneumonitis, thyroiditis, colitis, rheumatoid arthritis, Type I diabetes mellitus, vasculitis, neuritis, systemic lupus erythematosus, Sjögren's syndrome, multiple sclerosis, and endocrinopathy • Grade ≥3 events suggestive of hypersensitivity, cytokine release, systemic inflammatory response, or infusion reaction syndromes, including but not limited to fever, chills, rash, urticaria, dyspnoea, wheezing, angioedema, tachycardia, and hypotension, occurring within 24 hours of infusion • Grade ≥2 rash or pruritus (POPLAR); Grade ≥3 rash or pruritus (OAK) • Grade ≥2 diarrhoea (POPLAR); Grade ≥3 diarrhoea (OAK) • Grade ≥2 colitis • Grade ≥3 AST/ALT/total bilirubin elevations lasting >48 hours, asymptomatic • Grade ≥2 AST/ALT/total bilirubin elevations lasting >48 hours, with constitutional symptoms • Grade ≥2 dyspnoea not attributable to lung cancer or other pulmonary disease present at baseline (e.g., chronic obstructive pulmonary disease) • Grade ≥ 2 hypoxia not attributable to lung cancer or other pulmonary disease present at baseline (e.g., chronic obstructive pulmonary disease) • Grade ≥ 2 pleural effusion • Grade ≥ 2 pericardial effusion • Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law • Suspected transmission of an infectious agent by study drug

All adverse events of special interest (AESI) apply to both POPLAR and OAK unless specified.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Unless otherwise stated, information for OAK and POPLAR are sourced from the protocols and primary CSRs for each study (F. Hoffmann-La Roche Ltd, 2013, F. Hoffmann-La Roche Ltd, 2015a, F. Hoffmann-La Roche Ltd, 2015g, F. Hoffmann-La Roche Ltd, 2016b).

OAK

The following analysis of OAK has taken place:

- Primary analysis (clinical cut-off 7th July 2016)

Determination of sample size for OAK

An enrolment of 850 patients in the ITT population was initially planned for OAK so that approximately 255 PD-L1 IC2/3 patients and 425 PD-L1 IC1/2/3 patients would be enrolled. With emerging data, the sample size of OAK was increased to approximately 1100 patients (up to a maximum of 1300) in order to ensure at least 220 patients with PD-L1 TC3 or IC3 status, assuming a 20% prevalence of the TC3 or IC3 subgroup. The final enrolment in OAK was 1225 patients.

Interim data from POPLAR showed that clinical efficacy was observed in all PD-L1 subgroups, including PD-L1 negative patients. Study design assumptions in OAK based on these POPLAR results would lead to a fully powered study for OS evaluation in an ITT population with fewer than 1225 patients. Therefore, the primary OS analyses in OAK were conducted on the primary population (PP) of the first 850 randomised patients at the primary analysis time. If the null hypothesis in this primary OS analysis on the PP at this time was rejected, the OS secondary analyses for the secondary population of 1225 randomised ITT patients would be tested at the secondary analysis time (F. Hoffmann-La Roche Ltd, 2015g).

OAK analysis populations

Randomised population (ITT)

- The PP is the first 850 randomised ITT patients, regardless of whether they received any study drug
- The secondary population for efficacy analyses will consist of all 1225 randomised ITT patients

Safety population

- The primary safety analyses will be based on all 1225 randomised patients who received any dose of study drug during the study treatment period

Subgroup analysis

- The consistency of OS results in important subgroups was examined based on the primary population. The subgroups were defined by demographic (e.g., age and sex) and baseline prognostic characteristics (e.g., PD-L1 status and subgrouping, ECOG performance status, prior lines of chemotherapy, histology, smoking history)

Handling of missing data and censoring methods

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

Table 21: Summary of analysis methods for efficacy parameters

Endpoint	Definition	Censoring	Methodology
OS	Time from the date of randomisation to the date of death due to any cause	Date patient last known to be alive or at date of randomisation plus 1 day for those w/o post-BL information	Kaplan-Meier methodology, logrank test, and Cox regression, stratified for PP ITT population and PDL-1 status
PFS per RECIST v1.1	Interval between date of randomisation and date of first documented PD per RECIST v1.1 or death	Last tumour assessment for those w/o PD and alive or at date of randomisation plus 1 day for those w/o post-BL assessments	Kaplan-Meier methodology, Cox regression, stratified for PP ITT population and TC1/2/3 or IC1/2/3 subgroup, and unstratified for all other subgroups
ORR per RECIST v1.1	Proportion of patients achieving confirmed best response of CR or PR per RECIST v1.1	Patients without any post baseline tumour assessments were considered non responders	Clopper-Pearson methods for 95% CI of response rates and Mantel-Haenszel test for difference in rates
DOR	Interval between first documented objective response (CR or PR) and first documented PD or death	Date of last tumour measurement	Kaplan-Meier methodology, stratified for PP ITT population and TC1/2/3 or IC1/2/3 subgroup, and unstratified for all other subgroups

POPLAR

The following analyses of POPLAR have taken place:

- Interim analysis (clinical cut-off 30th January 2015)
- Primary analysis (clinical cut-off 8th May 2015)

- Updated efficacy analysis (clinical cut-off 1st December 2015)

Determination of sample size for POPLAR

POPLAR was designed to provide an initial assessment of the efficacy and safety of atezolizumab, with the primary purpose being the estimation of the OS and PFS hazard ratios in the overall population and the PD-L1 immunohistochemistry (IHC) 2/3 subset. The study was designed to enrol a minimum of approximately 54 PD-L1 IHC 2/3 patients, with a maximum of 300 total patients enrolled in the case that the PD-L1 IHC 2/3 prevalence is lower than 18%. The study was expected to enrol 285 total patients and 55 PD-L1 IHC 2/3 patients; these numbers were used for the statistical calculations described below (F. Hoffmann-La Roche Ltd, 2013).

POPLAR analysis populations

Randomised population (ITT)

- Population for efficacy analyses includes all randomised patients, regardless of PD-L1 expression and whether they received any study drug.
- In the efficacy analyses using the intention-to-treat (ITT) population, patients were grouped according to the treatment arm to which they were assigned

Safety population

- The primary safety analyses were based on all randomised patients who received any dose of study drug during the study treatment period
- Patients who were randomised to the study but who did not receive any study drug were not included in the safety population

Subgroup analysis

- The consistency of overall survival results in important subgroups was examined based on the ITT population. The subgroups were defined by demographic (e.g., age and sex) and baseline prognostic characteristics (e.g., PD-L1 expression subsets, ECOG performance status, prior lines of chemotherapy, histology, smoking history)

Handling of missing data and censoring methods

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

Table 22: Summary of analysis methods for efficacy parameters (POPLAR)

Endpoint	Definition	Censoring	Methodology
OS	Time from the date of randomisation to the date of death due to any cause	Date patient last known to be alive or at date of randomisation plus 1 day for those w/o post-baseline information	Kaplan-Meier methodology and stratified log-rank test for ITT, unstratified log-rank test for biomarker subsets, Cox regression, stratified for ITT and unstratified for biomarker subsets
PFS per RECIST v1.1	Interval between date of randomisation and date of first documented PD per RECIST v1.1 or death	Last tumour assessment for those w/o PD and alive or at date of randomisation plus 1 day for those w/o post-baseline assessments	Kaplan-Meier methodology, Cox regression, stratified for ITT and unstratified for biomarker subsets
ORR per RECIST v1.1	Proportion of patients achieving confirmed best response of CR or PR per RECIST v1.1	n/a	Clopper-Pearson methods for 95% CI of response rates and Mantel-Haenszel test for difference in rates
DOR	Interval between first documented objective response (CR or PR) and first documented PD or death	Date of last tumour measurement	Kaplan-Meier methodology

Primary hypothesis for both POPLAR and OAK

The primary efficacy endpoint for both trials was duration (in months) of OS. The null and alternative hypotheses for OS analysis were phrased in terms of the survival functions $S_A(t)$ and $S_B(t)$ in Arm A (atezolizumab) and Arm B (docetaxel), respectively:

H_0: $S_A(t) = S_B(t)$ versus H_1: $S_A(t) \neq S_B(t)$

Kaplan-Meier methodology was used to estimate the median OS for each treatment arm and to construct survival curves for the visual description of the difference between the treatment arms. The hazard ratio was estimated in the ITT population using a stratified Cox regression model with the same stratification variables used in the stratified log-rank test, including 95% confidence intervals (CIs). An unstratified hazard ratio was also estimated for the ITT population and the PD-L1 selected subsets.

Assumptions for POPLAR

The power and 95% CIs for OS and PFS in the ITT population are based on the following assumptions:

- Event times are exponentially distributed;
- Median PFS in the control arm is 3 months;
- Median OS in the control arm is 8 months, and;
- Patients are enrolled over 8 months.

Patients were followed until approximately 180 patient deaths in the ITT population occurred.

Assumptions for OAK

Study design assumptions in OAK were based on results from POPLAR, suggesting that a fully powered study for OS evaluation in an ITT population was possible with fewer than 1225 patients. Therefore, the primary OS analysis in OAK was conducted on the PP of the first 850 randomised patients at the primary analysis time.

Estimates of the number of events required to demonstrate efficacy with regard to OS were based on the following assumptions:

- Event times exponentially distributed
- A 7.5% 24-month dropout rate assumed for both treatment arms
- Greater than 95% power for the primary analysis of OS in the ITT
- Median survival of 10 months in the docetaxel arm
- 65% prevalence rate for TC1/2/3 or IC1/2/3

4.5 Participant flow in the relevant randomised controlled trials

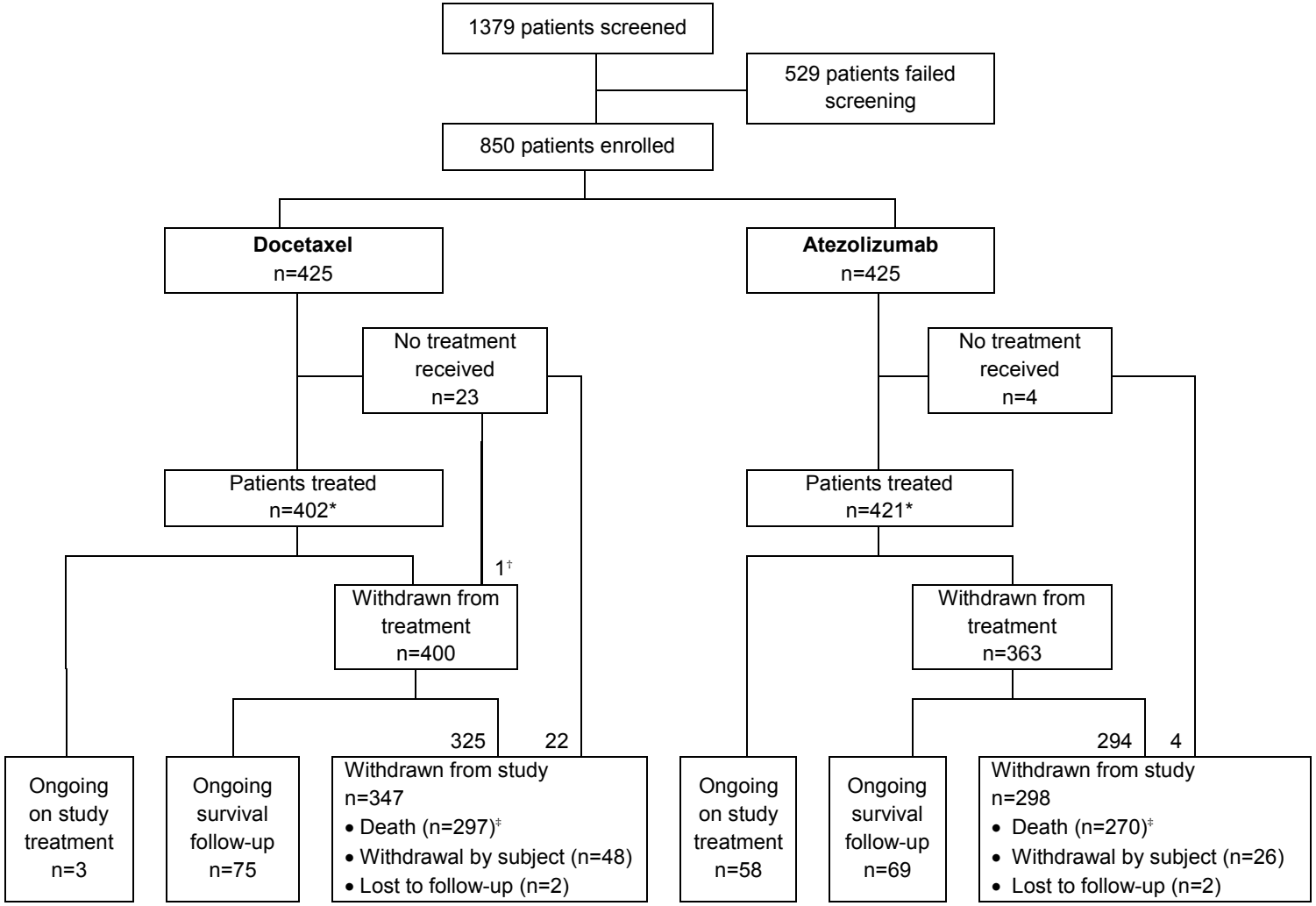
OAK

Primary population: For the PP, a total of 850 patients were randomised; 425 patients to the docetaxel arm and 425 patients to the atezolizumab arm.

Overall, 3.2% of patients did not receive any study treatment (5.4% in the docetaxel arm vs. 0.9% in the atezolizumab arm). For these patients, the most common reason for not receiving any study treatment on the docetaxel arm was consent withdrawal by patient (4.5%) and on the atezolizumab arm was death (0.5%).

The median duration of survival follow-up was similar between the arms: 21.3 months in the docetaxel arm (range 0.0–26.9+; + denotes a censored value) and 21.4 months in the atezolizumab arm (range 0.1–27.1). The minimum follow-up time at the time of the clinical cut-off date was 19 months (duration from last patient randomised date to clinical cut-off date) (Figure 6).

Figure 6: Patient disposition in OAK (primary population)



*One patient randomised to docetaxel received atezolizumab
†One patient withdrew from treatment before receiving any dose of study drug, but did not withdraw from the study at the time of the clinical cut-off date
‡Two additional deaths (1 docetaxel, 1 atezolizumab) were collected from public record for a total of 298 deaths in the docetaxel arm and 271 deaths in the atezolizumab arm. These two patients are captured in the study discontinuation eCRF as "withdrawal by patient", but were included as deaths (i.e., not censored) in the efficacy analyses.

Among safety-evaluable patients in the PP, a higher proportion of patients discontinued docetaxel compared with atezolizumab (99.3% vs 83.9%). The majority of patients in both arms discontinued study treatment due to progressive disease (64.6% docetaxel vs 72.5% atezolizumab). More patients in the docetaxel arm compared with the atezolizumab arm discontinued treatment due to withdrawal of consent (10.0% vs 2.1%). In addition, more patients in the docetaxel arm (19.7%) compared with the atezolizumab arm (8.5%) discontinued treatment due to AEs.

Table 23: Reasons for treatment discontinuation in OAK

n (%)	Atezolizumab n=422 (actual)	Docetaxel n=401 (actual)	All patients N=823 (actual)
Withdrawn from treatment	354 (83.9)	398 (99.3)	752 (91.4)
Adverse event	36 (8.5)	79 (19.7)	115 (14.0)
Progressive disease	306 (72.5)	259 (64.6)	565 (68.7)
Physician decision	2 (0.5)	19 (4.7)	21 (2.6)
Withdrawal by subject	9 (2.1)	40 (10.0)	49 (6.0)
Other	1 (0.2)	1 (0.2)	2 (0.2)

Source:(F. Hoffmann-La Roche Ltd, 2016b)

Patient demographics and baseline characteristics (OAK)

As with POPLAR, the study population for OAK comprised predominantly white (70%) males (61%) with a median age of 64 years (range 33.0–85.0 years) and an ECOG performance of 1 (63%). The majority of patients had a history of tobacco use; 67% were previous smokers and 15% were current smokers.

The demographic characteristics were generally well balanced between the treatment arms.

Table 24: Patient demographics and baseline characteristics in OAK (ITT population)

	Atezolizumab n=425	Docetaxel n=425
Median age, years (range)	63.0 (33.0–82.0)	64.0 (34.0-85.0)
Age group, n (%) <65 ≥65	 235 (55) 190 (45)	 218 (51) 207 (49)
Male, n (%)	261 (61)	259 (61)

Race, n (%)		
Caucasian	302 (71)	296 (70)
Asian	85 (20)	95 (22)
Black or African American	5 (1)	11(3)
Other	13 (3)	9 (2)
Unknown	20 (5)	14 (3)
Mean weight at baseline, kg (SD)	72.89 (17.79)	70.61 (16.08)
Tobacco use history, n (%)		
Never	84 (20)	72 (17)
Current	59 (14)	67 (16)
Previous	282 (66)	286 (67)
ECOG PS, n (%)		
0	155 (36)	160 (38)
1	270 (64)	265 (62)
Pathology/histology, n (%)		
Non-squamous	313 (74)	315 (74)
Squamous	112 (26)	110 (26)
Number of prior therapies, n (%)		
1	320 (75)	320 (75)
2	105 (25)	105 (25)
Current disease status, n (%)		
Locally advanced	29 (7)	19 (5)
Metastatic disease	396 (93	406 (95)
Mean months from initial diagnosis to randomisation (SD)	21.04 (21.45)	20.06 (23.0)
Number of metastatic sites at enrolment, mean (SD)	2.89 (1.43)	2.97 (1.32)
Confirmed metastases at enrolment, n (%)		
Liver	83 (20)	94 (22)
Bone	135 (32)	133 (31)
Brain	38 (9)	47 (11)
Lung	386 (91)	391 (92)
Pleural effusion	84 (20)	96 (23)
Lymph nodes	277 (65)	291 (66)
EGFR mutation		
Positive	42(10)	43 (10)
Negative	318 (75)	310 (73)
Unknown	65 (15)	72 (17)
EML4-ALK translocation		
Positive	2 (<1)	0
Negative	223 (52)	201 (47)
Unknown	200 (47)	224 (53)
KRAS mutation		
Positive	26 (6)	33 (8)
Negative	99 (23)	104 (24)
Unknown	300 (71)	288 (68)
TC3 or IC3, n (%)	72 (16.9)	65 (15.3)
TC2/3 or IC2/3, n (%)	129 (30.4)	136 (32.0)
TC1/2/3 or IC1/2/3, n (%)	241 (56.7)	222 (52.2)

ECOG, Eastern Cooperative Oncology Group performance score; SD, standard deviation
Source:(Rittmeyer et al., 2016, F. Hoffmann-La Roche Ltd, 2016b)

POPLAR

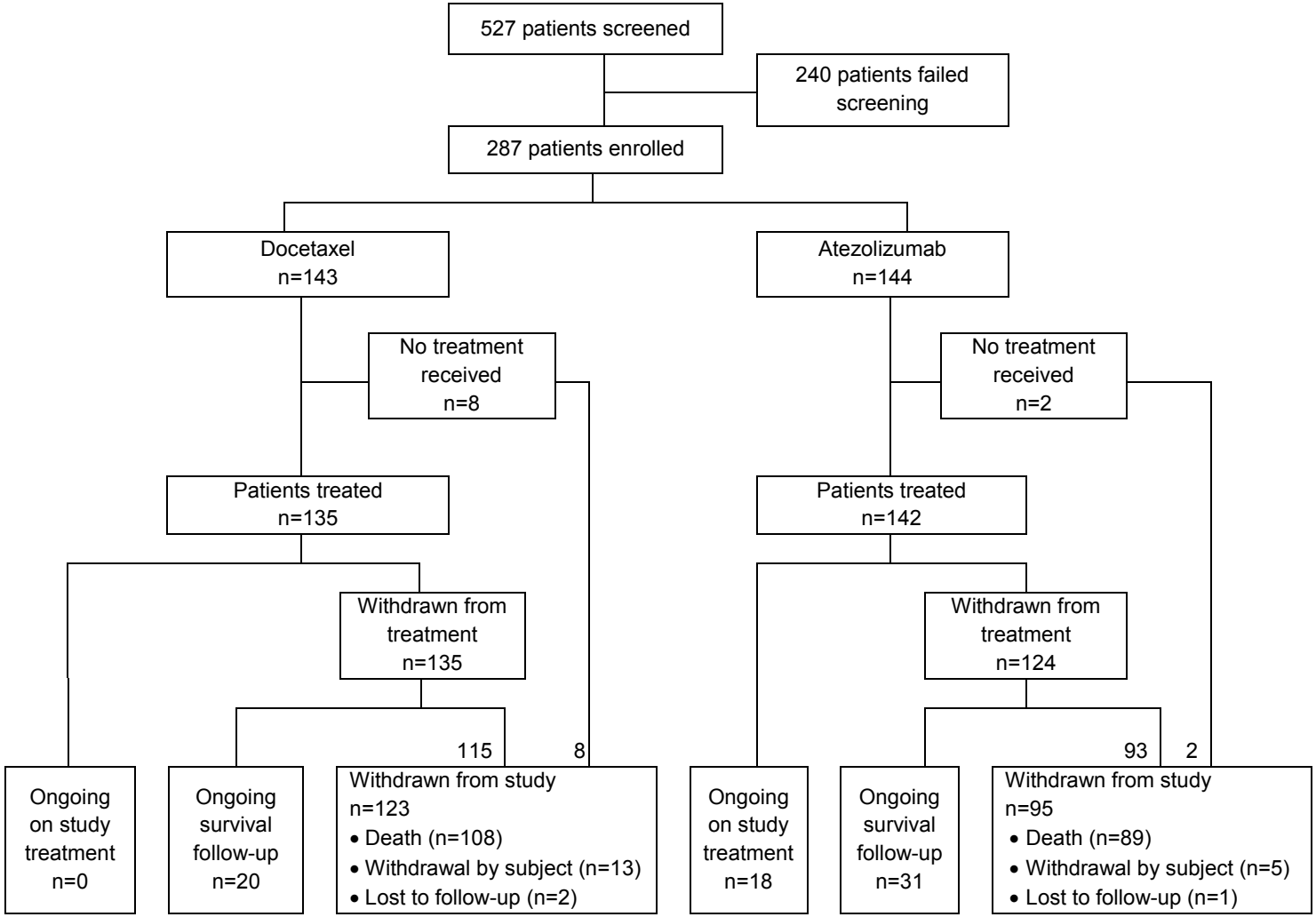
A total of 287 patients were randomised; 143 patients to the docetaxel arm and 144 patients to the atezolizumab arm. Overall, ten patients (eight in the docetaxel arm and two in the atezolizumab arm) did not receive any study treatment.

Primary analysis: The median duration of follow up for the primary analysis was similar across the arms: 15.7 months in the docetaxel arm (range 0.1–18.7) and 14.8 months in the atezolizumab arm (range 0.2–19.6). The minimum follow up time at the time of the clinical cut-off date was 13.3 months. One patient (0.7%) in the docetaxel arm and 24 patients (16.7%) in the atezolizumab arm were still on treatment. A further 36 patients (25.2%) in the docetaxel arm and 36 patients (25.0%) in the atezolizumab arm were alive and in the survival follow-up period. 93 patients (65.0%) in the docetaxel arm and 78 patients (54.2%) in the atezolizumab arm had died.(F. Hoffmann-La Roche Ltd, 2015a, Fehrenbacher et al., 2016)

At the time of the primary analysis, the proportion of patients who had withdrawn from the study was higher in the docetaxel arm (74.1%) compared with the atezolizumab arm (58.3%), which was mainly driven by a higher incidence of death in the docetaxel arm (65.0% vs. 54.2%). One patient in each arm was lost to follow-up.

Updated analysis: An updated analysis of OS and DOR was performed with a clinical cut-off of 1st December 2015, providing an additional 7 months of follow-up (a total of minimum follow-up of 20 months) (Figure 7).

Figure 7: Patient disposition in POPLAR (updated analysis)



All patients discontinued docetaxel compared with 87.3% of patients receiving atezolizumab at the time of the updated analysis. The majority of patients in both arms discontinued study treatment due to progressive disease (63.7% vs. 75.4%). More patients experienced AEs leading to study drug discontinuation in the docetaxel arm (23.0% vs 9.2%).

Table 25: Reasons for treatment discontinuation in POPLAR (updated analysis)

n (%)	Atezolizumab n=142	Docetaxel n=135	All patients N=277
Withdrawn from treatment	124 (87.3)	135 (100)	259 (93.5)
Death	2 (1.4)	1 (0.7)	3 (1.1)
Adverse event	13 (9.2)	31 (23.0)	44 (15.9)
Progressive disease	107 (75.4)	86 (63.7)	193 (69.7)
Physician decision	0	10 (7.4)	10 (3.6)
Withdrawal by subject	2 (1.4)	7 (5.2)	9 (3.2)

Source:(F. Hoffmann-La Roche Ltd, 2016a)

Patient demographics and baseline characteristics (POPLAR)

The study population comprised predominantly white (78.7%) males (58.9%) with a median age of 62 years (range 36–84 years) and an ECOG performance of 1 (68.0%). The majority of patients had a history of tobacco use; 64.5% were previous smokers and 16.0% were current smokers.

The demographic characteristics were generally well balanced between the treatment arms except for a higher proportion of men in the atezolizumab arm (64.6 vs 53.1%) (Table 26).

Table 26: Patient demographics and baseline characteristics in POPLAR (ITT population)

	Atezolizumab n=144	Docetaxel n=143
Median age, years	62.0	62.0
Age group, n (%)		
<65	87 (60.4)	87 (60.8)
≥65	57 (39.6)	56 (39.2)
Male, n (%)	93 (64.6)	76 (53.1)
Race, n (%)		
Caucasian	110 (76.4)	116 (81.1)
Asian	23 (16.0)	13 (9.1)
Black or African American	3 (2.1)	4 (2.8)
American Indian or Alaska Native	0	1 (0.7)
Native Hawaiian or other Pacific Islander	2(1.4)	0
Other	4 (2.8)	4 (2.8)
Unknown	2 (1.4)	5 (3.5)

Mean weight at baseline, kg (SD)	n=141 73.98 (16.56)	n=133 75.95 (20.17)
Tobacco use history, n (%)		
Never	27 (18.8)	29 (20.3)
Current	25 (17.4)	21 (14.7)
Previous	92 (63.9)	93 (65.0)
ECOG PS, n (%)	n=142	n=142
0	46 (32.4)	45 (31.7)
1	96 (67.6)	97 (68.3)
Pathology/histology, n (%)		
Non-squamous	95 (66.0)	95 (66.4)
Squamous	49 (34.0)	48 (33.6)
Number of prior therapies, n (%)		
1	93 (64.6)	96 (67.1)
2	51 (35.4)	47 (32.9)
Current disease status, n (%)		
Locally advanced	8 (5.6)	5 (3.5)
Metastatic disease	136 (94.4)	138 (96.5)
Mean months from initial diagnosis to randomisation (SD)	16.96 (15.52)	20.27 (19.66)
Number of metastatic sites at enrolment, mean (SD)	2.97 (1.38)	3.1 (1.39)
Confirmed metastases at enrolment, n (%)		
Liver	33 (22.9)	33 (23.1)
Bone	35 (24.3)	46 (32.2)
Brain	8 (5.6)	15 (10.5)
Lung	132 (91.7)	125 (87.4)
Pleural effusion	41 (28.5)	27 (18.9)
EGFR mutation	n=83	n=83
T790M	1 (1.2)	0
Positive	10 (12.0)	8 (9.6)
EML4-ALK mutation	n=61	n=58
Positive	0	3 (5.2)
KRAS mutation	n=42	n=30
Positive	14 (33.3)	13 (43.3)
TC3 or IC3, n (%)	24 (16.7)	23 (16.1)
TC2/3 or IC2/3, n (%)	50 (34.7)	55 (38.5)
TC1/2/3 or IC1/2/3, n (%)	93 (64.6)	102 (71.3)

ECOG, Eastern Cooperative Oncology Group performance score; SD, standard deviation
Source:(F. Hoffmann-La Roche Ltd, 2015a, Fehrenbacher et al., 2016)

4.6 Quality assessment of the relevant randomised controlled trials

Critical appraisal of the included RCTs was performed using the format provided in the NICE submission template which adhered to the Centre for Reviews and Dissemination (CRD), University of York guidance (CRD 2008). A summary is presented below.

Table 27: Quality assessment of the identified RCT

Study Question	Grade (Yes/No/ Not Clear/N/A)	
	NCT02008227 (OAK)	NCT01903993 (POPLAR)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	N/A (open label study)	N/A (open label study)
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	n/a (open label study)	n/a (open label study)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	N/A (full data available)	N/A (full data available)
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

4.7 Clinical effectiveness results of the relevant randomised controlled trials

OAK

The data discussed in this section will be taken from the primary analysis (clinical cut-off 7th July 2016) in which a total of 850 patients were randomised; 425 patients to the docetaxel arm and 425 patients to the atezolizumab arm (i.e. the primary population) (Rittmeyer et al., 2016, F. Hoffmann-La Roche Ltd, 2016b).

Co-primary endpoint

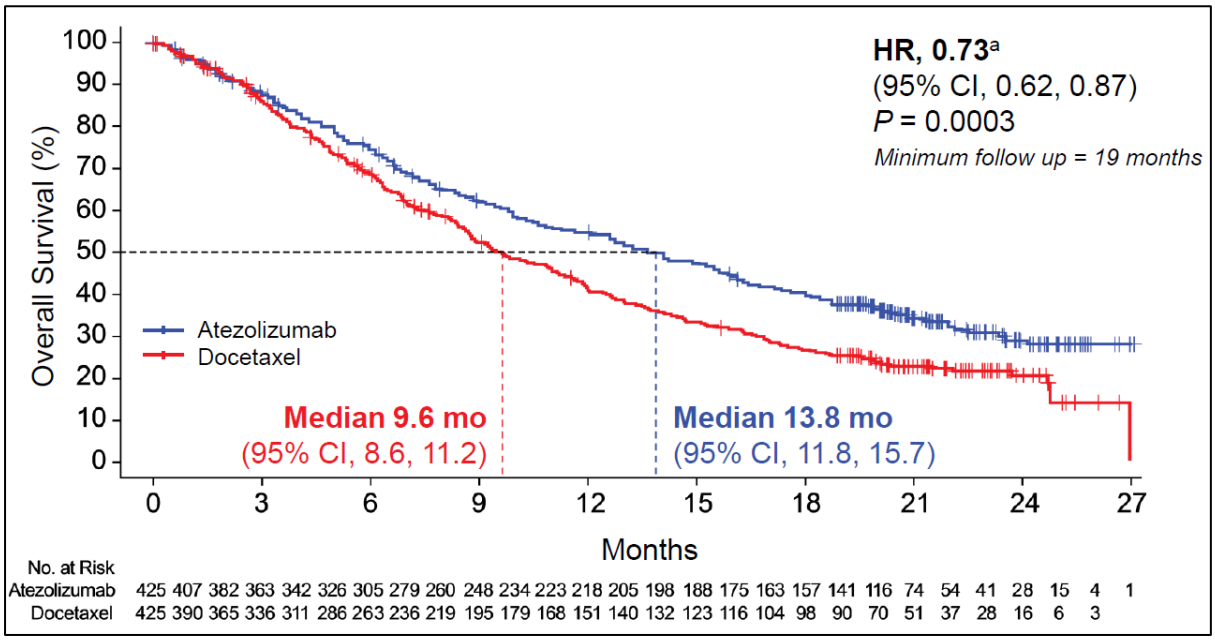
Overall survival

The OAK study met its co-primary endpoints; treatment with atezolizumab was associated with a statistically significant and clinically meaningful improvement in OS, compared with docetaxel in the ITT population (HR 0.73, 95% CI: 062, 0.87; p=0.0003), and in patients with

≥1 % PD-L1 expression (TC1/2/3 or IC1/2/3) (HR 0.74, 95% CI: 0.58, 0.93; p=0.0102). At the time of the primary analysis, and a minimum follow up of 19 months, 569 patients had died among the 850 randomised (70.1% event/patient ratio). The Kaplan-Meier curves separate at approximately 3 months, and separation was maintained thereafter. The median overall survival in the ITT population was 9.6 months (95% CI: 8.6, 11.2) in the docetaxel arm and 13.8 months (95% CI: 11.8, 15.7) in the atezolizumab arm (Figure 8).

The proportion of patients alive at 12 months was 55% and 41% in the atezolizumab and docetaxel arms respectively. At 18 months, the proportion of survivors was 40% in the atezolizumab arm and 27% with docetaxel.

Figure 8: OAK, Kaplan-Meier plot of OS, stratified analysis (ITT)



Source:(Rittmeyer et al., 2016, F. Hoffmann-La Roche Ltd, 2016b)
[a]Stratified HR

Atezolizumab showed significant improvement in OS for people regardless of PD-L1 status, with a similar effect observed in patients with no measurable PD-L1 expression (TC0/IC0) to that seen in the ITT population (HR 0.75, 95% CI:0.59, 0.96; p=0.0205).

Crossover from the docetaxel arm to the atezolizumab arm was not originally permitted in OAK, however this was subsequently allowed following analysis of the primary population (n=850). Five percent of patients randomised to atezolizumab, and 17% of patients in the docetaxel arm, went on to receive subsequent cancer immunotherapies, predominantly nivolumab (Table 28).

Table 28: Subsequent therapies in OAK

Treatment, %	Atezolizumab n=425	Docetaxel n=425
Any non-protocol therapy	206 (48.5)	192 (45.2)
Chemotherapy	176 (41.4)	131 (30.8)
Targeted therapy	63 (14.8)	66 (15.5)
Immunotherapy	19 (4.5)	73 (17.2)
Nivolumab	16 (3.8)	58 (13.6)

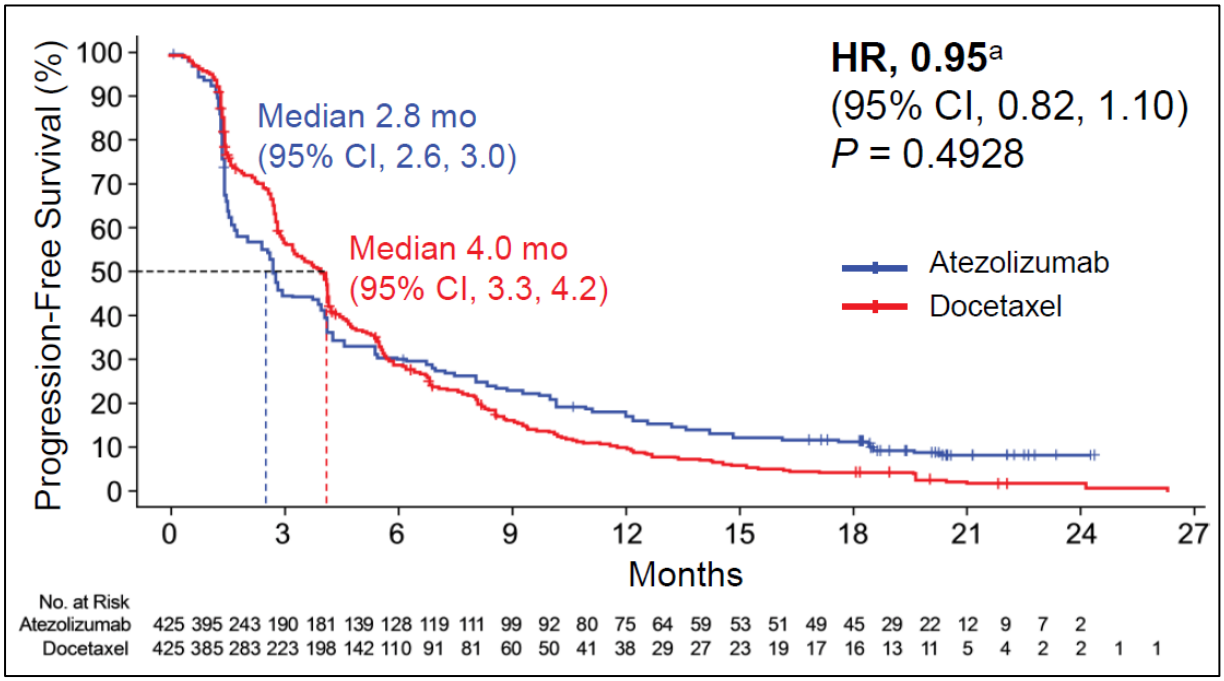
Source:(Barlesi F et al., 2016, F. Hoffmann-La Roche Ltd, 2016b)

Secondary endpoints

Investigator-assessed PFS per RECIST v1.1

Consistent with the known profiles and mechanism of action of immunotherapies, there was no statistically significant difference in PFS between atezolizumab and docetaxel in the primary analysis of OAK. The median duration of PFS in the ITT population was 2.8 months (95% CI: 2.6, 3.0) in the atezolizumab arm and 4.0 months (95% CI: 3.3, 4.2) in the docetaxel arm (HR=0.95, 95% CI: 0.82, 1.10) (Figure 9).

Figure 9: OAK, KM plot of PFS per RECIST v 1.1 (ITT population)



Source:(Barlesi F et al., 2016, F. Hoffmann-La Roche Ltd, 2016b, Rittmeyer et al., 2016)
[a]Stratified HR

ORR per RECIST v1.1

The proportion of patients with a confirmed response per RECIST v1.1 was similar in both arms: 13.6% (95% CI: 10.53, 17.28) in the docetaxel arm and 13.4% (95% CI: 10.32, 17.02) in the atezolizumab arm.

Table 29: Summary of ORR

	Atezolizumab n=425	Docetaxel n=425
Responders, n (%) (95% CI)	58 (13.6) (10.53, 17.28)	57 (13.4) (10.32, 17.02)
Complete response, n (%) (95% CI)	6 (1.4) (0.52, 3.05)	1 (0.2) (0.01, 1.30)
Partial response, n (%) (95% CI)	52 (12.2) (9.27, 15.73)	56 (13.2) (10.11, 16.77)
Stable disease, n (%) (95% CI)	150 (35.3) (30.75, 40.05)	177 (41.6) (36.92, 46.50)
Progressive disease, n (%) (95% CI)	187 (44.0) (39.22, 48.86)	117 (27.5) (23.33, 32.04)

CI, confidence interval
Source:(F. Hoffmann-La Roche Ltd, 2016b, Rittmeyer et al., 2016)

Duration of response

The median DOR among responders in OAK was more than doubled in the atezolizumab arm (16.3 months, 95% CI: 10.0, NE) compared with the docetaxel arm (6.2 months, 95% CI: 4.9, 7.6) in the ITT population (HR 0.34, 95% CI: 0.21, 0.55), with 52% of atezolizumab responses ongoing versus 18% in the docetaxel arm at the time of the clinical cut-off date.

Table 30: OAK, duration of response in the ITT population

	Atezolizumab n=58	Docetaxel n=57
Patients without event, n (%)	30 (51.7)	10 (17.5)
Median duration of response, months (95% CI)	16.3 (10.0, NE)	6.2 (4.9, 7.6)
Unstratified HR (95% CI)	0.34 (0.21, 0.55)	

CI, confidence interval; HR, hazard ratio; NE, not estimated
Source:(F. Hoffmann-La Roche Ltd, 2016b, Rittmeyer et al., 2016)

Patient-reported outcomes: EORTC QLQ-C30, EORTC QLQ-LC13, and Time-to-deterioration of lung cancer symptoms

Completion rates for both arms were consistently high over the course of treatment. The average global health status and functioning scores (i.e. physical, role, social, emotional, and cognitive) as measured by the EORTC QLQ-C30 did not show clinically meaningful deterioration over time for both treatment arms, suggesting maintained HRQoL and patient-reported functioning for patients remaining on treatment.

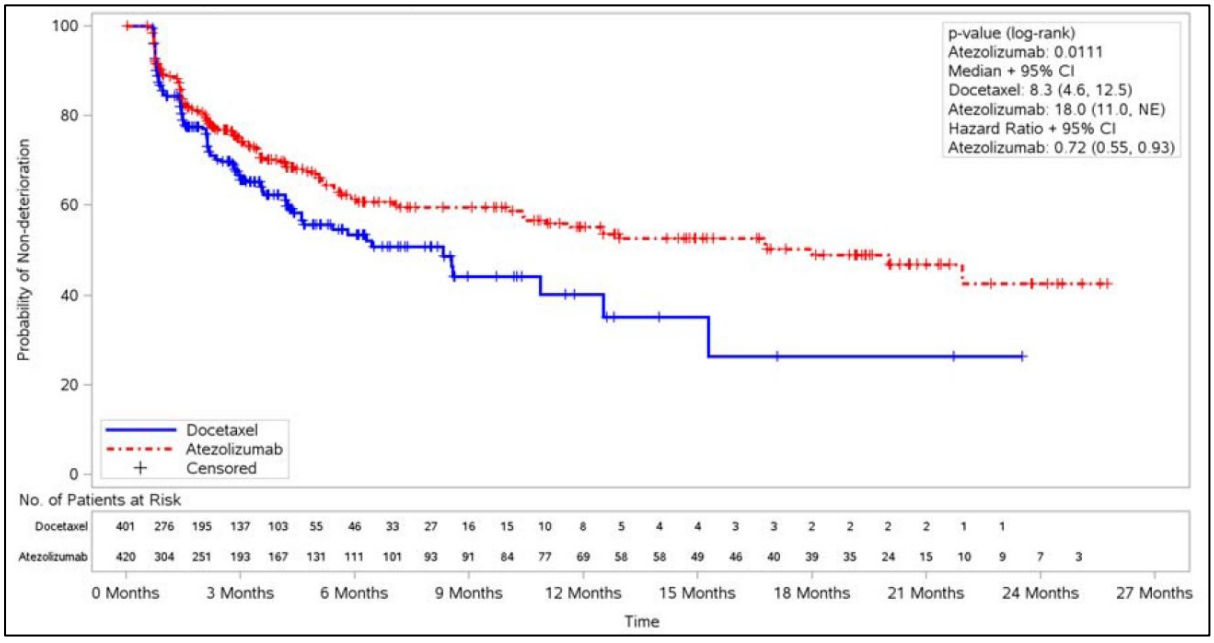
Patients in the atezolizumab arm did not show clinically meaningful worsening in commonly reported cancer treatment-related symptoms (i.e. fatigue, nausea/vomiting, diarrhoea, constipation, alopecia, peripheral neuropathy, and sore mouth) as compared to patients in

the docetaxel arm who demonstrated clinically meaningful worsening in alopecia and peripheral neuropathy throughout treatment.

Patients in the atezolizumab arm demonstrated prolonged time until the deterioration of patient-reported chest pain as compared with docetaxel (HR 0.72, 95% CI: 0.55, 0.93). The median time to clinically meaningful deterioration in chest pain severity was 8.3 months in the docetaxel arm versus 18.0 months in the atezolizumab arm. These findings coincide with supportive analyses which were conducted to summarise the severity and change of chest pain at multiple time points to further understand the observed time-to-deterioration benefit of atezolizumab in the chest pain symptom score.

Patients in both arms experienced minimal chest pain at baseline: 60.6% of patients in the docetaxel arm and 57.7% of patients in the atezolizumab arm reported no chest pain at baseline, with similar proportions in each subsequent category (i.e. not at all, a little, quite a bit, very much). At the time of radiographic disease progression (PD) per RECIST criteria v1.1, the proportion of asymptomatic patients (i.e., with severity level of “not at all”) decreased in the docetaxel arm (54.2%), and increased in the atezolizumab arm (66.4%). A total of 11.4% of patients in the atezolizumab arm experienced clinically meaningful worsening in chest pain severity (≥10 point increase from baseline) at the time of radiographic disease progression per RECIST criteria v1.1, compared with 25.4% of patients in the docetaxel arm.

Figure 10: Time to deterioration of chest pain (primary population)



Source:(F. Hoffmann-La Roche Ltd, 2016b)

Further information on the patient-reported outcomes in OAK, including EQ-5D, will be discussed in section 5.4 of this submission.

POPLAR

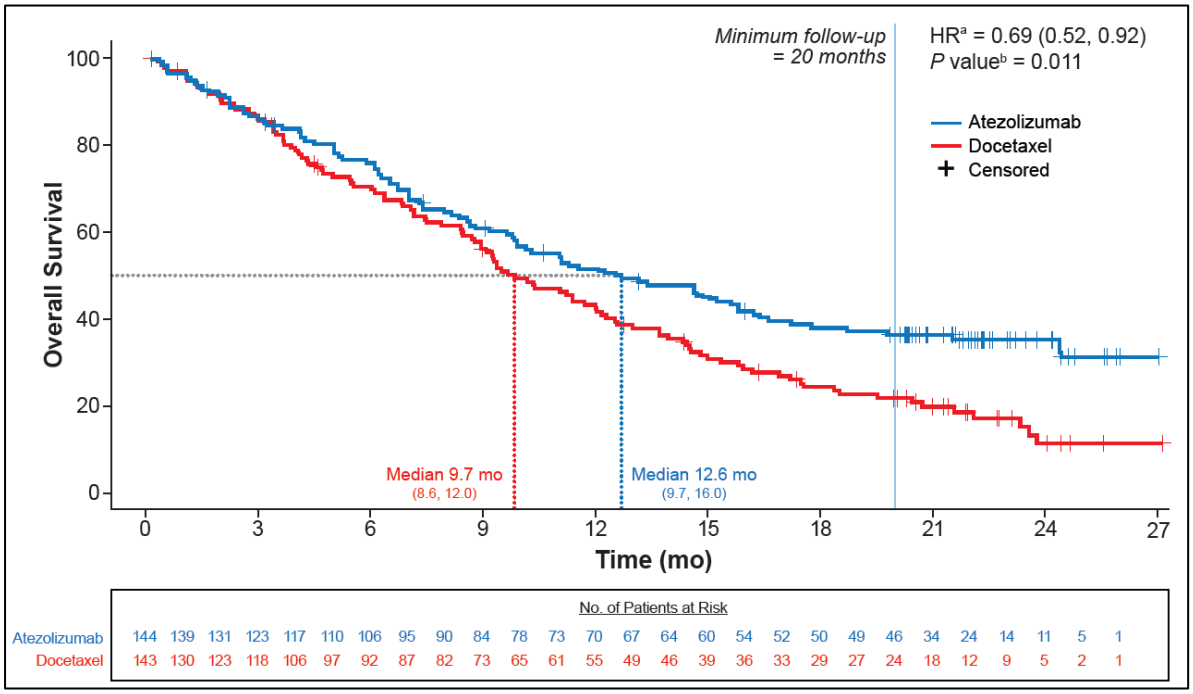
The data discussed in this section will be taken, where available, from the updated analysis (clinical cut-off 1st December 2015) (Smith et al., 2016), although the primary and interim analyses results (clinical cut-off 8th May 2015 and 30th January 2015 respectively)(Fehrenbacher et al., 2016, F. Hoffmann-La Roche Ltd, 2015a) will also be presented for comparative purposes.

Primary endpoint

Overall survival

At the time of the updated analyses (December 2015), 200 patients had died among the 287 randomised (70% event/patient ratio). Treatment with atezolizumab was associated with a clinically meaningful and statistically significant prolongation in OS compared with docetaxel; HR 0.69, 95% CI: 052, 0.92; p=0.011. The Kaplan-Meier curves showed a separation from approximately 3 months that was maintained with further increased separation beginning at approximately 9 months (Figure 11). The median overall survival in the ITT population was 9.7 months (95% CI 8.6, 12.0) in the docetaxel arm and 12.6 months (95% CI: 9.7, 16.0) in the atezolizumab arm.

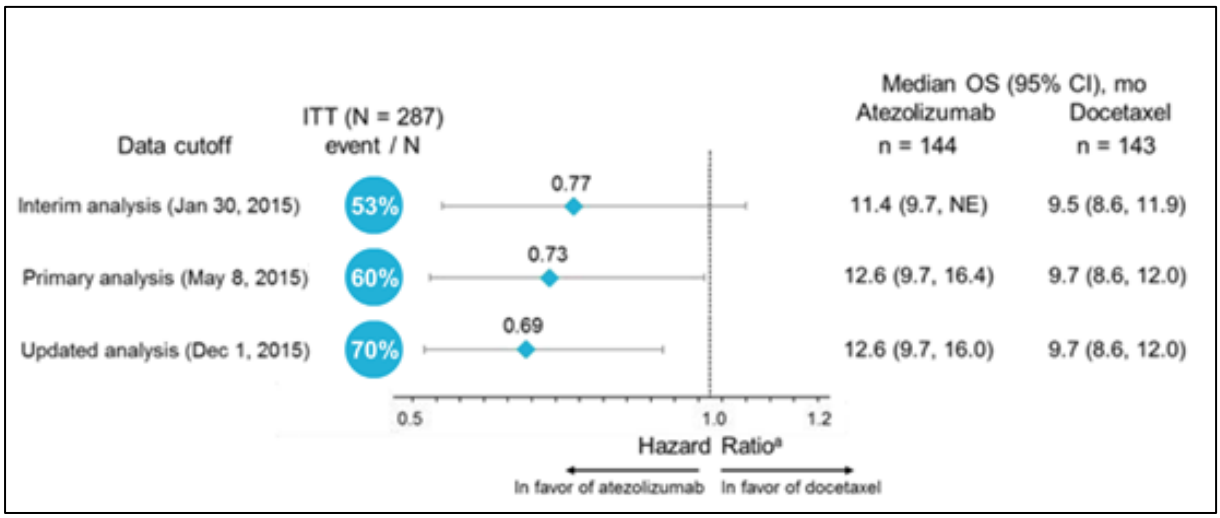
Figure 11: POPLAR, Kaplan-Meier plot of OS, stratified analysis (ITT, cut-off 1st December 2015)



Source: (Smith et al., 2016)

This extended follow up in POPLAR reveals further separation late in OS curves and increased benefit with atezolizumab versus docetaxel compared with earlier analyses as shown in Figure 10.

Figure 12: OS in POPLAR with increasing data maturity



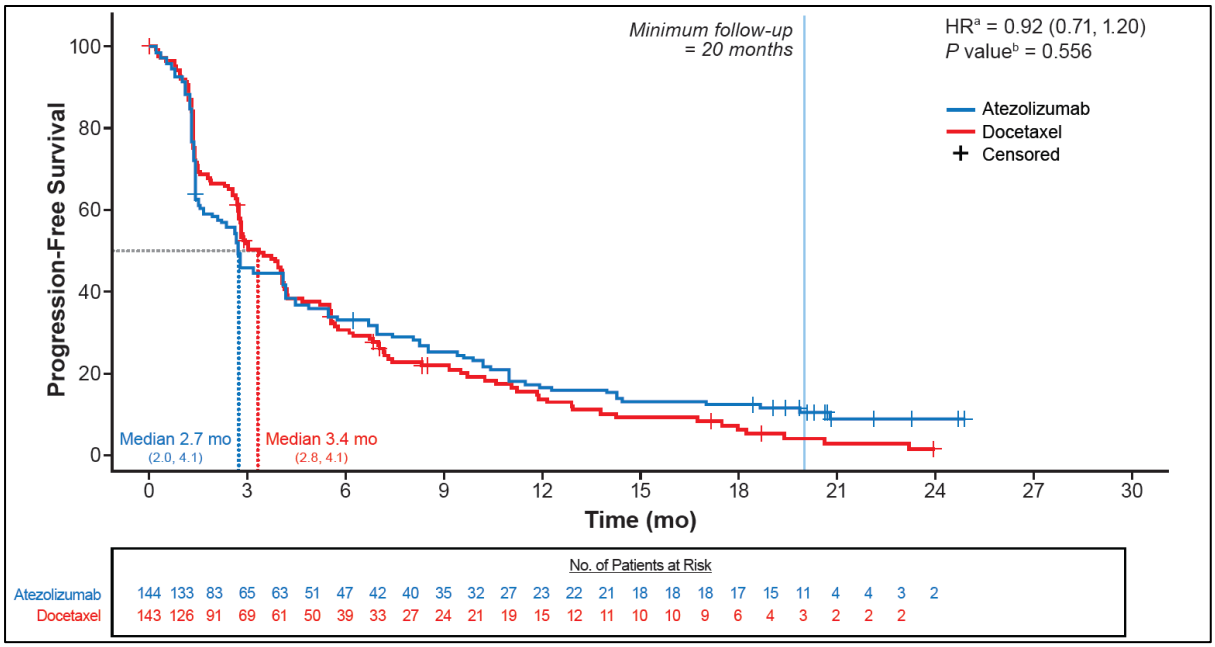
[a]Stratified HR

Secondary endpoints

PFS per RECIST v1.1

The median PFS in the ITT population was similar between the arms: 3.4 months (95% CI: 2.8, 4.1) in the docetaxel arm and 2.7 months (95% CI: 2.0, 4.1) in the atezolizumab arm (HR=0.92, 95% CI: 0.71, 1.20). No clear or persistent separation of the KM curves was observed early in the curves though late separation can be seen reflecting the prolonged responses seen in some atezolizumab recipients (Smith et al., 2016).

Figure 13: POPLAR, KM plot of PFS per RECIST v 1.1 (ITT population)



This result is consistent with that seen in the primary analysis, in which the median duration of PFS was 3.0 months (95% CI: 2.8, 4.1) in the docetaxel arm and 2.7 months (95% CI: 2.0, 4.1) in the atezolizumab arm (HR=0.94, 95%CI: 0.72, 1.23) (Fehrenbacher et al., 2016).

ORR per RECIST v1.1

The proportion of patients with a confirmed response per RECIST v1.1 was similar in both arms: 14.7% (95% CI: 9.3, 21.6) in the docetaxel arm and 15.3% (95% CI: 9.8, 22.2) in the atezolizumab arm. One patient in the atezolizumab arm achieved a complete response, and a similar proportion of patients had a partial response (14.7% vs. 14.6%).

These results did not significantly change as compared to the primary analysis; 14.7% (95% CI: 9.33, 21.57) of patients in the docetaxel arm and 14.6% (95% CI: 9.26, 21.42) in the atezolizumab arm had a confirmed response per RECIST v1.1. One patient in the atezolizumab arm achieved a complete response, and a similar proportion of patients had a

partial response (14.7% vs. 13.9%) or stable disease (35.0% vs. 37.5%) (Fehrenbacher et al., 2016, F. Hoffmann-La Roche Ltd, 2015a).

Duration of response

Among responders, the median DOR was more than doubled in the atezolizumab arm (18.6 months, 95% CI: 11.6, NE) compared with the docetaxel arm (7.2 months, 95% CI: 5.6, 12.5) (HR 0.32, 95% CI: 0.15, 0.70), with 11 of 22 (50%) of atezolizumab responses ongoing (Smith et al., 2016).

Table 31: Duration of response in the ITT population

	Atezolizumab n=22	Docetaxel n=21
Responders with ongoing response, n (%)	11 (50)	3 (14)
Median duration of response, months (95% CI)	18.6 (11.6, NE)	7.2 (5.6, 12.5)
HR (95% CI)	0.32 (0.15, 0.70)	

CI, confidence interval; HR, hazard ratio; NE, not estimated

The updated analysis of the DOR in the ITT population revealed an increase in the median DOR for atezolizumab responders from 14.3 months (95% CI: 11.6, NE) in the primary analysis, with no change for docetaxel responders.

Patient-reported outcomes: EORTC QLQ-C30, EORTC QLQ-LC13, and time-to-deterioration of lung cancer symptoms

Global health status/quality of life, functioning, and lung cancer symptoms (cough, dyspnoea, chest pain, arm/shoulder pain) were assessed by the EORTC QLQ-C30/LC13.

Patients in the atezolizumab arm did not demonstrate clinically meaningful change (improvement or decline) on any of the subscales assessed, while patients on the docetaxel arm had a meaningful increase in alopecia. There was no difference between the arms on time-to-deterioration of lung cancer symptoms.

4.8 Subgroup analysis

OAK

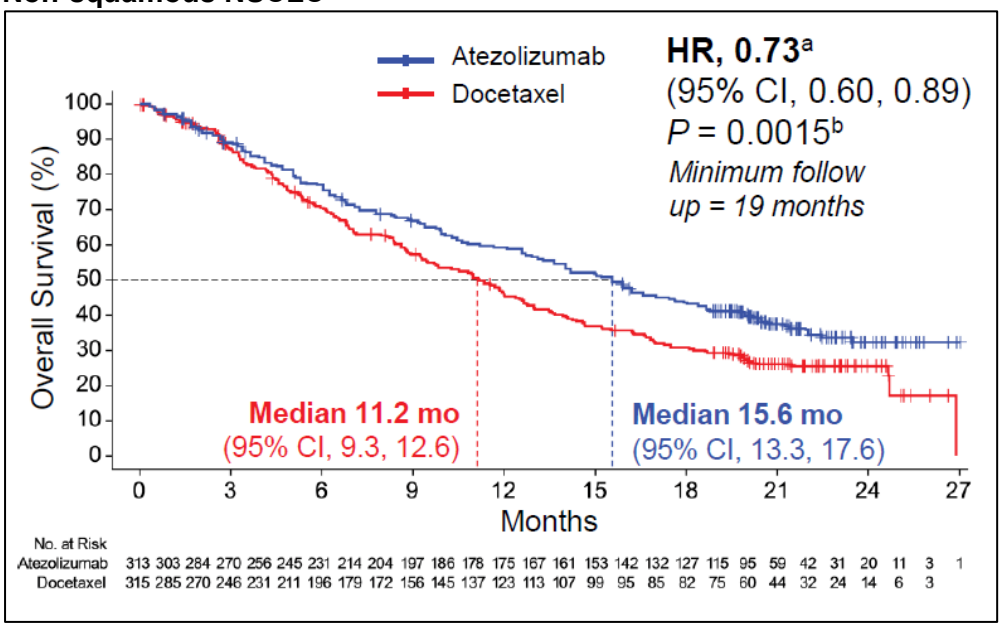
Overall survival in histology subgroups

Improved survival with atezolizumab was observed regardless of histology, although a longer median overall survival was observed in atezolizumab-treated patients with

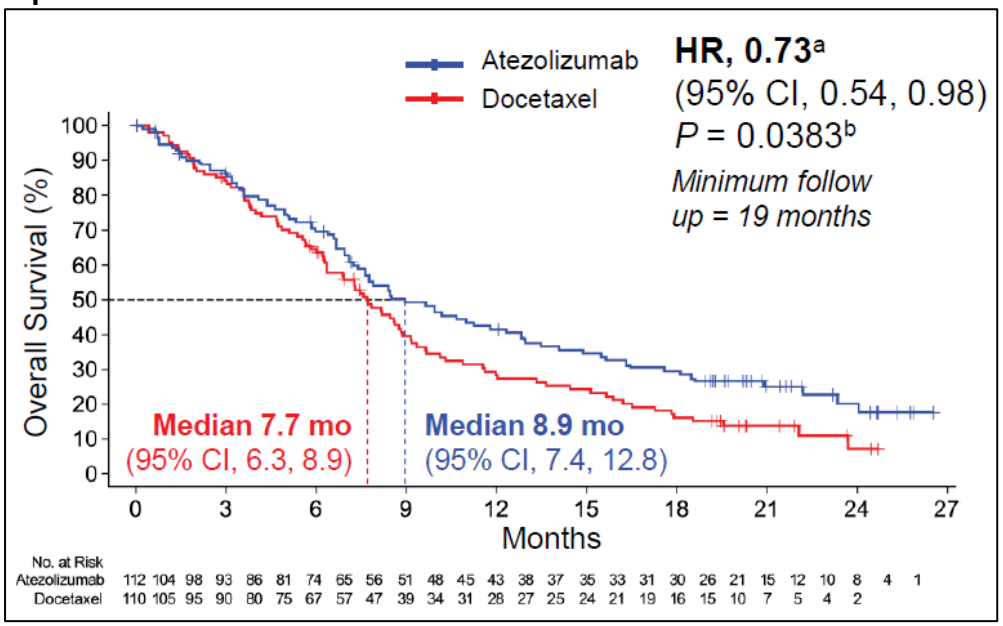
non-squamous NSCLC (15.6 months, compared with 8.9 months in squamous NSCLC), reflecting the inherently worse prognosis of patients with squamous cancers. Please see section 3.1 for an overview of non-squamous and squamous histologies.

Figure 14: OAK, OS in histology subgroups

Non-squamous NSCLC



Squamous NSCLC

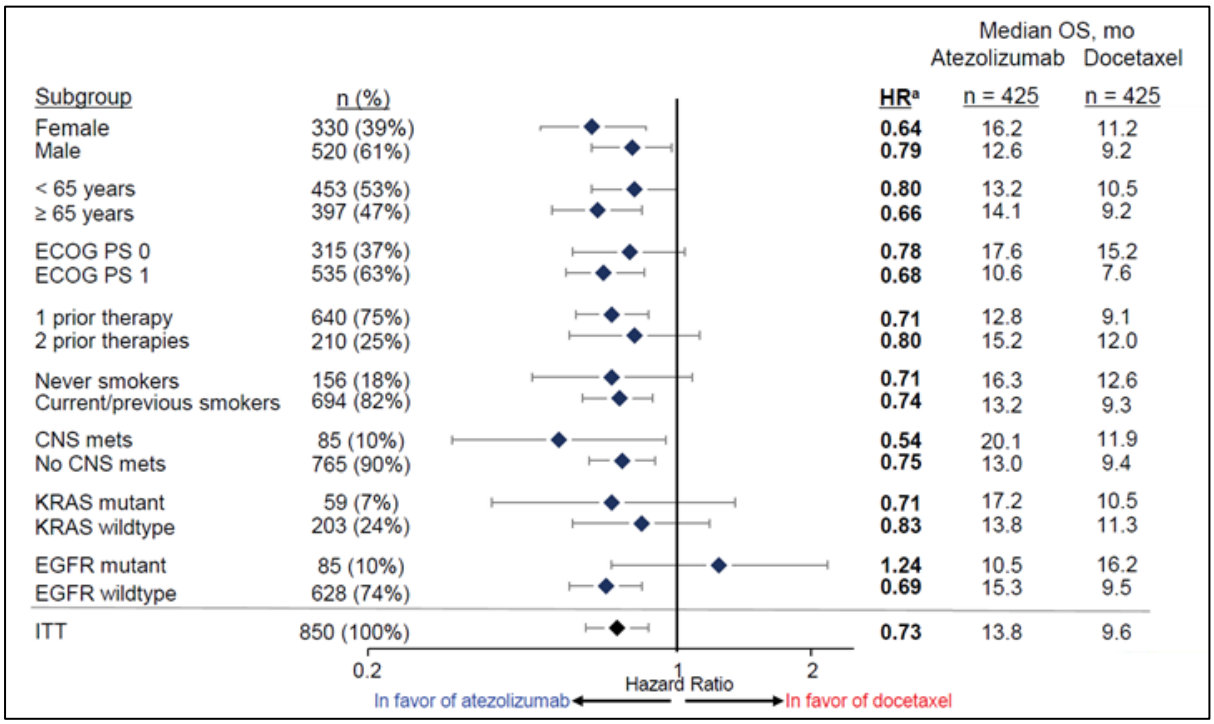


[a]Unstratified HRs
[b]P values for descriptive purposes only
Source:(Barlesi F et al., 2016, F. Hoffmann-La Roche Ltd, 2016b, Rittmeyer et al., 2016)

Overall survival by baseline characteristics

The improvement in OS with atezolizumab compared with docetaxel was consistent across other baseline characteristics, including patients with CNS metastases.

Figure 15: OAK, OS by baseline characteristics



[a]Stratified HR for ITT, unstratified for subgroups
Source:(Barlesi F et al., 2016, F. Hoffmann-La Roche Ltd, 2016b, Rittmeyer et al., 2016)

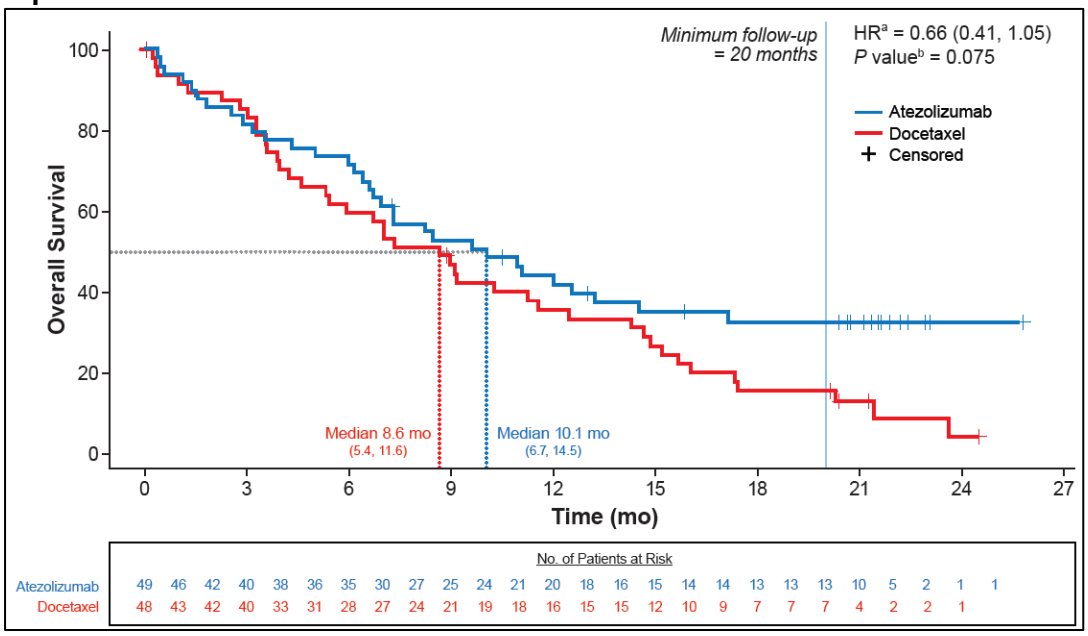
POPLAR

Overall survival in histology subgroups

Survival curves for squamous and non-squamous NSCLC showed a continuous separation over time (Figure 16), with a more pronounced improvement in HR over time in the squamous subgroup (Figure 17).

Figure 16: POPLAR, OS in histology subgroups (updated analysis)

Squamous NSCLC



Non-squamous NSCLC

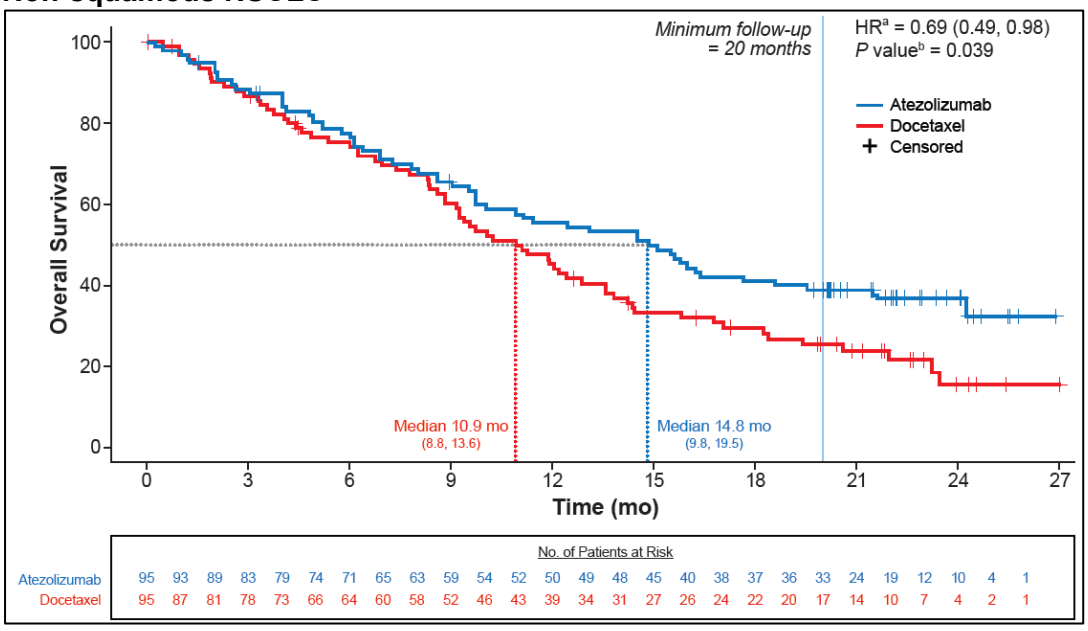
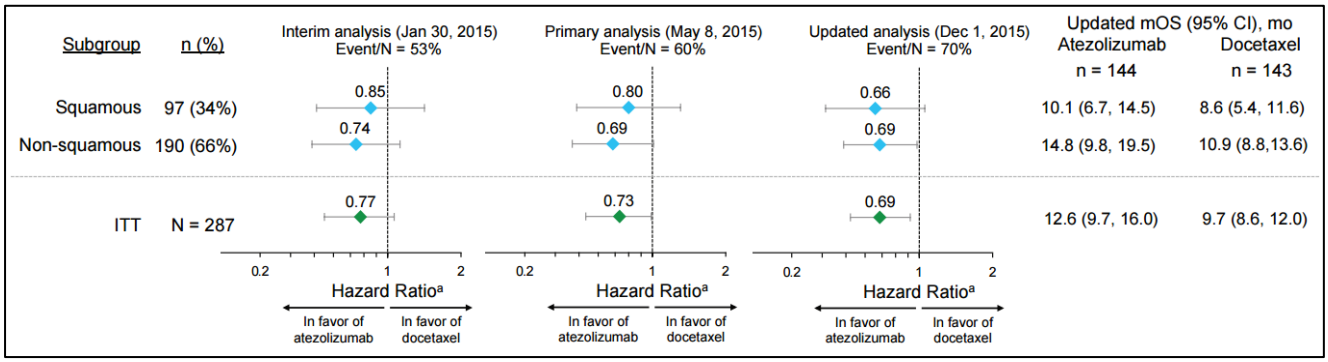


Figure 17: POPLAR, HRs over time in histology subgroups

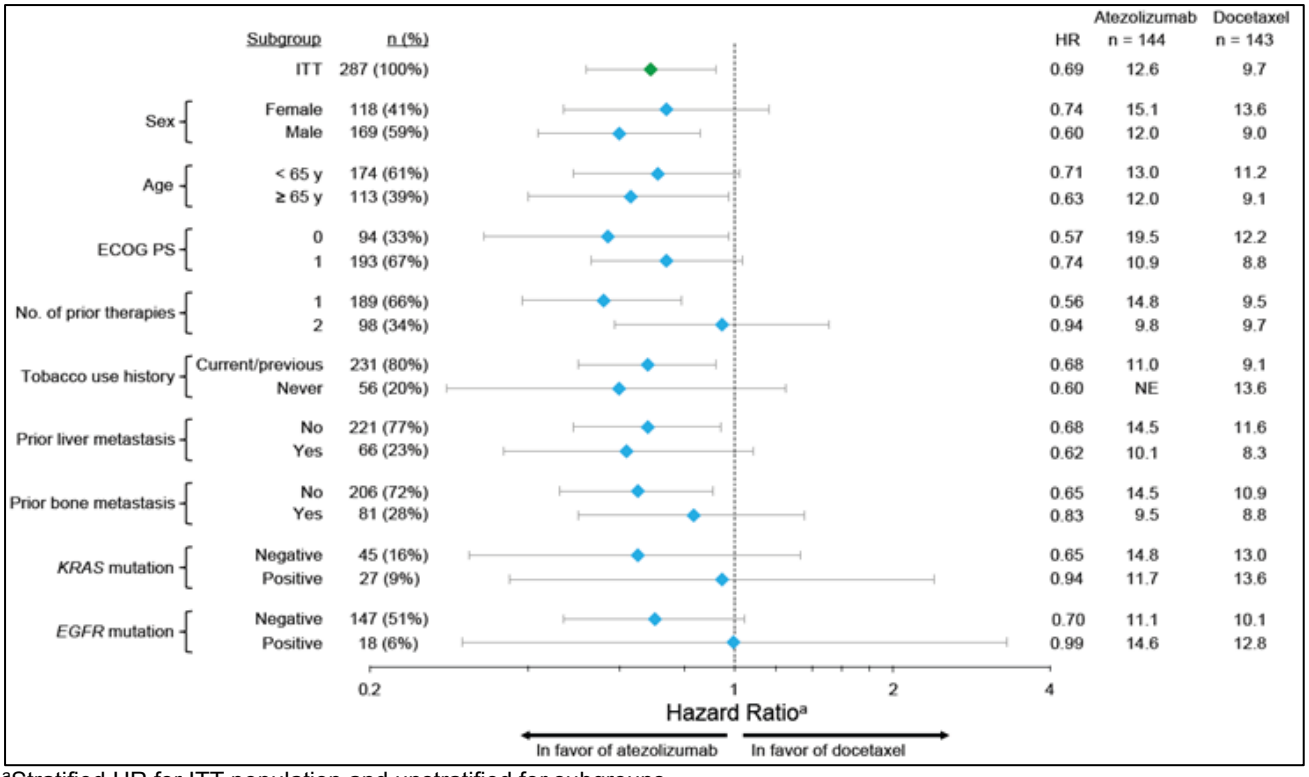


[a]Stratified HR; Source:(Smith et al., 2016)

Overall survival by baseline characteristics

An improvement in OS with atezolizumab compared with docetaxel was generally seen across baseline characteristics (Figure 18).

Figure 18: POPLAR, OS by baseline characteristics (updated analysis)



[a]Stratified HR for ITT population and unstratified for subgroups
EGFR T790M subgroup not included because no patients in the docetaxel arm were known to have this mutation. mOS for atezolizumab arm patient (n=1) was 16.0 months.
EML4 ALK mutation subgroup not included because none of the atezolizumab arm patients were known to have this genetic rearrangement.
Source:(Smith et al., 2016)

4.9 Meta-analysis

The evidence source for atezolizumab in metastatic NSCLC is principally made up of two clinical trials: one phase III study (OAK), and one phase II study (POPLAR). Given an indirect treatment comparison was required to compare atezolizumab to comparators of interest, and both clinical trials were to be included in this analysis, a meta-analysis was not considered necessary.

4.10 Indirect and mixed treatment comparisons

Summary of indirect treatment comparison

The comparative efficacy and safety of atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy has been studied in two randomised clinical trials; an open-label Phase II study (POPLAR, GO28753, NCT01903993), and an open-label Phase III study (OAK, GO28915, NCT02008227), both as compared to docetaxel. Therefore, an ITC was required in order to compare to other relevant comparators:

1. Studies for comparators were identified through SLR
2. The ITC was conducted to support pricing and reimbursement submissions across all markets, and included comparators not listed in the final scope; results presented below are restricted to the comparators considered relevant to the UK
3. Traditional NMA approaches were identified as unsuitable, due to violation of the proportional hazards assumption, and a fractional polynomial framework was employed (which does not rely on the proportional hazards assumption)
4. Simpler first order models were chosen within the fractional polynomial framework: For OS, the model with p1=0 (Weibull) was the best fit by DIC and by visual inspection of curve fit. For PFS, the model with p1=1 (Gompertz) was the best fit by DIC and visual inspection
5. For OS, the fixed effects model had the lowest DIC, although the differences were small (less than 2 points). For PFS, the random effects model had the lowest DIC, but again the differences were small (less than 5 points). Hence, simpler fixed model results are presented throughout the results section
6. Results of OS were statistically significantly in favour of atezolizumab vs both comparators of interest
7. Results of the PFS indicated atezolizumab was comparable to docetaxel and nintedanib (plus docetaxel). This is consistent with the demonstrated efficacy profile of immunotherapies, and reinforces that the traditional methods of measuring radiographical progression of tumours are not considered appropriate for this group of treatment options.

Search strategy

As described in section 4.1, a systematic search of the literature was undertaken in June 2016 to identify phase II-IV RCTs investigating the efficacy and safety of pharmacological interventions for second- and further-line treatment for locally advanced/metastatic NSCLC. For full details of the strategy, please refer to Section 4.1.

Study selection

The final scope for this appraisal includes docetaxel, nintedanib (plus docetaxel), nivolumab, pembrolizumab and best supportive care (BSC). The OAK and POPLAR studies include a direct comparison to docetaxel, but do not compare to other comparators of interest. Thus an indirect treatment comparison (ITC) is required to appraise the clinical- and cost-effectiveness of atezolizumab to other comparators. Considering the comparators listed in the final scope:

- Pembrolizumab has conducted all trials in, and has a marketing authorisation (MA) for, PD-L1 positive NSCLC patients. The tools utilised for pembrolizumab and atezolizumab to assess PD-L1 expression differ significantly, both in how expression is measured (pembrolizumab: TC only; atezolizumab: TC and IC), but importantly also in which patients are considered positive expressors. Hence, not only are the populations for atezolizumab and pembrolizumab not matched by MA and trial design, but even through utilising a diagnostic test, the eligible patient populations are not equivalent. By including results for pembrolizumab from only PD-L1 positive NSCLC patients within the analysis, there is a risk the relative clinical benefits of pembrolizumab are overestimated, and therefore would not be a true reflection of the comparative efficacy versus atezolizumab (in the all-comer population which is under consideration). Coupled with its recent approval by NICE (TAG issued 11th January 2017; implying it is unlikely to represent a standard of care at time the time of submission), pembrolizumab is not considered to be a relevant comparator, hence has been excluded from the results.
- Nivolumab has received a negative recommendation in its Appraisal Consultation Document (ACD) from NICE, and cannot be considered standard of care: nivolumab has therefore also been excluded from the results.
- BSC has been excluded from the analysis. It is considered that patients who are eligible for treatment with atezolizumab would be considered fit enough for other treatment, hence BSC is not an appropriate comparator. This assumption was validated with clinical experts (see Executive Summary), and was also deemed

appropriate by NICE and the Evidence Review Group (ERG) in the appraisal of pembrolizumab (National Institute for Health and Care Excellence, 2017).

The ITC was conducted to support pricing and reimbursement submissions across all countries, and also included comparators not listed in the final scope (afatinib; dacomitinib; erlotinib; gefitinib; paclitaxel; pemetrexed). The methods and search results of this broader ITC are described below, with the final efficacy comparison results focused on those comparators considered relevant to this appraisal: docetaxel and nintedanib (plus docetaxel).

Nintedanib (plus docetaxel) is licensed (and recommended by NICE) only for those patients with adenocarcinoma histology, which is not consistent with the anticipated marketing authorisation for atezolizumab. The pivotal trial supporting the licence of nintedanib (plus docetaxel) (LUME-Lung 1) was, however, conducted in a broader population of all second-line NSCLC patients. In order to conduct a like-with-like comparison versus atezolizumab in its anticipated licence, the "total population" from the nintedanib (plus docetaxel) trial was compared to the atezolizumab ITT population[4]. Consistent with the favourable prognosis seen in patients with non-squamous vs squamous forms of NSCLC[5] in other trial programmes (Kawase et al., 2012), the OAK and POPLAR studies demonstrated improved outcomes in the subgroup of patients with non-squamous NSCLC (Figure 14, Figure 16). Therefore, the impact of this approach is not anticipated to significantly affect overall results.

As described in section 4.1, a total of 184 unique studies were identified from the SLR, reporting data on pharmacological treatments used as 2nd and further line treatments for patients with locally advanced/metastatic NSCLC.

The ITC considered studies investigating compartors of interest irrespective of treatment line to ensure capture of all relevant data.

Based on input from clinical experts (see Executive Summary), it was decided not to include studies that compared investigational interventions and interventions that have not been yet labeled/approved for the treatment in NSCLC in the US and Europe. This reduced the evidence base to a total of 49 RCTs: 47 RCTs reporting evidence for 2nd and 3rd line treatments, one RCT for 2nd line and one RCT for 2nd and further line treatments to be evaluated for inclusion in the NMA. Finally, consistent with the final scope, and based on further expert input, erlotinib combination arms were also excluded, reducing the evidence base to 19 RCTs, reporting 16 active treatments.

[4] Although a similar scenario has been described for the comparison vs. pembrolizumab, the KEYNOTE-010 study did not include a negative-expressor (i.e. all-comer) population.
[5] Adenocarcinoma makes up at least 85% of all non-squamous histologies (see section 3.1 & 4.8)

All 49 studies evaluated for inclusion are detailed in Table 32, including a description of rationale for exclusion. The 19 studies included in the network are highlighted in the same table.

Figure 19: Study selection flow chart for NMA

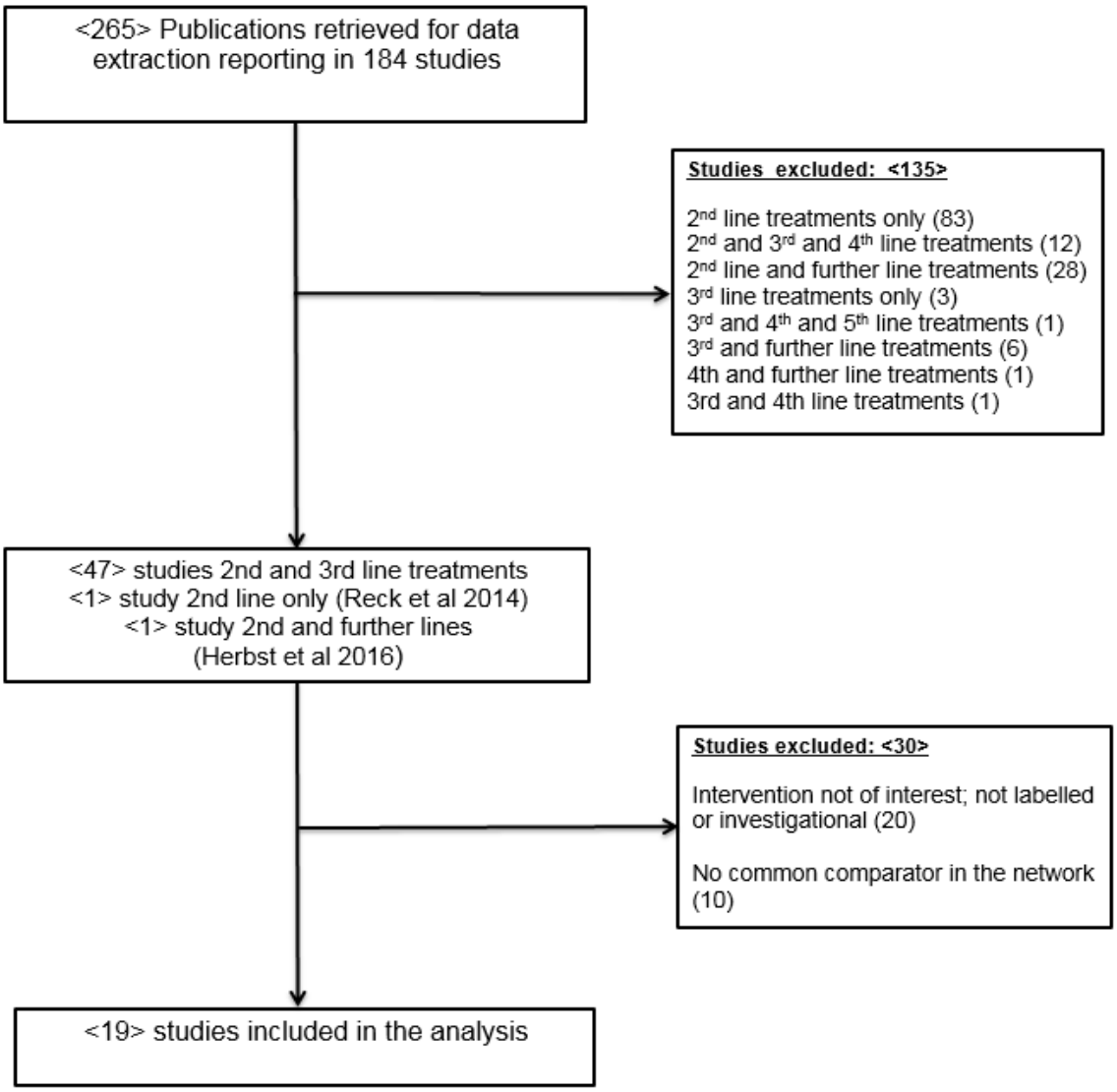


Table 32: Studies evaluated for inclusion

Trial name	Intervention	Type of therapy	In/Excluded criterion (network)	In/Excluded criterion (results)
Azuma 2014 (ATTENTION trial)	Tivantinib + Erlotinib	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Placebo + Erlotinib			
Bergqvist 2014 (NCT01561456)	AXL1717	Targeted therapy	Not labelled or investigational	Not in final scope
	Paclitaxel	Chemotherapy		
Borghaei 2016 (CheckMate 057, NCT01673867)	Nivolumab 3 mg/kg	PD-1/PD-L1 inhibitor	Included	Not considered relevant to this appraisal
	Docetaxel 75 mg/m²	Chemotherapy		

Trial name	Intervention	Type of therapy	In/Excluded criterion (network)	In/Excluded criterion (results)
Brahmer 2015 (Checkmate 017, NCT01642204)	Nivolumab 3 mg/kg	PD-1/PD-L1 inhibitor	Included	Not considered relevant to this appraisal
	Docetaxel 75 mg/m²	Chemotherapy		
Carter 2013	Selumetinib and erlotinib in KRAS mutant (KRAS Mut 2)	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Selumetinib KRAS mutant (KRAS Mut 1)			
	Erlotinib Wild type KRAS (WT KRAS 1)			
Chu 2014	Paclitaxel (175 mg/m^2) + cisplatin (60 mg/m^2)	Chemotherapy	Not connected to the network	Not in final scope
	Azithromycin (500 mg) + paclitaxel (175 mg/m^2) + cisplatin (60 mg/m^2)			
Esteban-Gonzalez 2003	Docetaxel 36 mg/m^2	Chemotherapy	Included	Not in final scope
	Paclitaxel			
Fukuoka 2003	Gefitinib 250 mg/d	Targeted therapy	Included	Not in final scope
	Gefitinib 500 mg/d			
Georgoulias 2005	Irinotecan 110 and 100 mg/m^2 + cisplatin 80 mg/m^2	Chemotherapy	Not connected to network	Not in final scope
	Cisplatin 80 mg/m^2			
Groen 2013 (NCT00265317)	Sunitinib + Erlotinib	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Placebo + Erlotinib			
Hainsworth 2010	AZD6244	Targeted therapy	Not labelled or investigational	Not in final scope
	Pemetrexed	Chemotherapy		
Halmos 2015 (NCT00660816)	Pemetrexed 500 mg/m^2 or docetaxel 75/m^2	Chemotherapy	Not connected to the network	Not in final scope
	Pemetrexed 500 mg/m^2 or docetaxel 75/m^2 + Erlotinib 100-150 mg (days 2-15 of each treatment cycle)	Targeted therapy + chemotherapy		
Heist 2014 (NCT00630110)	NPI-2358 + docetaxel (30 cohort) 75 mg/m^2	Targeted therapy + chemotherapy	Not labelled or investigational	Not in final scope
	Docetaxel (30 cohort) 75 mg/m^2	Chemotherapy		
	NPI-2358 + docetaxel (20 cohort) 75 mg/m^2	Targeted therapy + chemotherapy		
	Docetaxel (20 cohort) 75 mg/m^2	Chemotherapy		
Herbst 2016*	Pembrolizumab 2 mg/kg	PD-1/PD-L1 inhibitor	Included in scenario analysis	Not considered relevant to this appraisal
	Docetaxel 75 mg/m(2) every 3 weeks	Chemotherapy		
Janne 2007	CI-1033 50 mg	Targeted	Not connected to	Not in final scope

Trial name	Intervention	Type of therapy	In/Excluded criterion (network)	In/Excluded criterion (results)
	(Canertinib)	therapy	network	
	CI-1033 150 mg (Canertinib)			
	CI-1033 450 mg (Canertinib)			
Janne 2013	Selumetinib + docetaxel 75mg/m^2	Targeted therapy + chemotherapy	Not connected to network	Not in final scope
	Placebo + docetaxel 75mg/m^2	Chemotherapy		
Kapoor 2015	Gefitinib 150mg daily every 3 weeks	Targeted therapy	Included	Not in final scope
	Docetaxel 75mg/m^2 every 3 weeks	Chemotherapy		
Karampeazis 2013 (HORG, NCT00440414)	Pemetrexed 500mg	Chemotherapy	Included	Not in final scope
	Erlotinib 150mg	Targeted therapy		
Kawaguchi 2014 (DELTA, UMIN000002314)	Erlotinib 150 mg/day	Targeted therapy	Included	Not in final scope
	Docetaxel 60 mg/m^2 every 3 weeks	Chemotherapy		
Kelly 2012	Erlotinib	Targeted therapy	Not labelled or investigational	Not in final scope
	Pralatrexate			
Kim 2008 (INTEREST, NCT00076388)	Gefitinib 250mg/day	Targeted therapy	Included	Not in final scope
	Docetaxel 75 mg/m^2	Chemotherapy		
Kim 2016	Pemetrexed (500 mg/m^2 on day 1 of every 21-day cycle)	Chemotherapy	Included	Not in final scope
	Gefitinib (250 mg once daily)	Targeted therapy		
Kiura 2008	Vandetanib (100 mg/day)	Targeted therapy	Not connected to network	Not in final scope
	Vandetanib (200 mg/day)			
	Vandetanib (300 mg/day)			
Levy 2014	PX-866 + Docetaxel 75 mg/m^2	Targeted therapy	Not labelled or investigational	Not in final scope
	Docetaxel 75 mg/m^2	Chemotherapy		
Li 2015	Pemetrexed 500 mg/m^2 + cyclophosphamide 20 mg/kg	Chemotherapy	Not labelled or investigational	Not in final scope
	Pemetrexed 500 mg/m^2			
Maitland 2014 (NCT00203931)	Cetuximab (Arm A)	Targeted therapy	Not connected to network	Not in final scope
	Cetuximab + Pemetrexed (Arm B)	Targeted therapy + Chemotherapy		
Maruyama 2008 (V-15-32)	Docetaxel 60 mg/m^2	Chemotherapy	Included	Not in final scope
	Gefitinib 250mg	Targeted therapy		
Miller 2012 (LUX-Lung 1, NCT00656136)	Afatinib + best supportive care	Targeted therapy	Included	Not in final scope
	Placebo + best supportive care			

Trial name	Intervention	Type of therapy	In/Excluded criterion (network)	In/Excluded criterion (results)
Moran 2014	Erlotinib (150 mg daily)	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Erlotinib (150 mg daily) + dalotuzumab (10 mg/kg wk)			
Murakami 2014 (UMIN000001098)	Docetaxel 60 mg/m^2 Zoledronic acid every 3 weeks	Chemotherapy	Not labelled or investigational	Not in final scope
	Docetaxel 60 mg/m^2 every 3 weeks			
Natale 2009 (6474IL/0003)	Gefitinib	Targeted therapy	Not labelled or investigational	Not in final scope
	Vandetanib (ZD6474)			
Neal 2015 (NCT01708954)	Erlotinib	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Cabozantinib			
	Erlotinib + Cabozantinib			
OAK study (NCT02008227)	Atezolizumab	PD-1/PD-L1 inhibitor	Included	**Included**
	Docetaxel 75mg/m^2	Chemotherapy		
Ohe 2008	Pemetrexed 500mg/m^2	Chemotherapy	Included	Not in final scope
	Pemetrexed 1000mg/m^2			
Oton 2014	Efatutazone (0.5 mg) + Erlotinib (150 mg)	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Erlotinib (150 mg)			
Parikh 2011	Talactoferrin (1.5 g in 15 mL phosphate-based buffer twice a day) + standard supportive care	Immunotherapy	Not labelled or investigational	Not in final scope
	Placebo (15 mL phosphate-based buffer twice a day) + standard supportive care			
POPLAR (NCT01903993)	Atezolizumab	PD-1/PD-L1 inhibitor	Included	**Included**
	Docetaxel 75 mg/m^2	Chemotherapy		
Ramalingam 2011	Erlotinib (150 mg/d) + Placebo	Targeted therapy	Not labelled or investigational	Not in final scope
	Erlotinib (150 mg/d) + R1507 (9 mg/kg/week)			
	Erlotinib (150 mg/d) + R1507 (16mg/kg every 3 weeks)			
Ramalingam 2012 (NCT00769067)	Dacomitinib 45 mg QD	Targeted therapy	Included	Not in final scope
	Erlotinib 150 mg QD			
Ramalingam 2014 (ARCHER 1009)	Dacomitinib + PBO	Targeted therapy	Included	Not in final scope
	Erlotinib + PBO			
Reck 2011	Nintedanib (BIBF 1120) b.i.d. 250 mg	Targeted therapy	Not connected to the network	Not connected to the network
	Nintedanib (BIBF 1120) b.i.d. 150 mg			

Trial name	Intervention	Type of therapy	In/Excluded criterion (network)	In/Excluded criterion (results)
Reck 2014* (LUME-Lung 1)	Docetaxel 75 mg/m^2 + Nintedanib 200 mg BID	Targeted therapy+ chemotherapy	Included in scenario analysis	**Included**
	Docetaxel 75 mg/m^2 + placebo	Chemotherapy		
Scagliotti 2013 (MARQUEE, NCT01244191)	Tivantinib + Erlotinib	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Placebo + Erlotinib			
Sebastian 2010	BI 2536 (day 1) 200 mg	Targeted therapy	Not connected to network	Not in final scope
	BI 2536 (day 1-3) 50/60 mg			
Spigel 2011	Erlotinib	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Erlotinib + Sorafenib			
Spigel 2013 (NCT00854308)	Onartuzumab + Erlotinib	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Placebo + Erlotinib			
Spigel 2014 (METLung trial, NCT01456325)	Onartuzumab + Erlotinib	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Erlotinib + placebo			
Stephenson 2014 (NCT00732810)	Dinaciclib 50mg/m^2	Targeted therapy	Erlotinib combination not of interest	Not in final scope
	Erlotinib 150mg			
	Erlotinib 150mg --> Dinaciclib 50mg/m^2			
Thatcher 2005 (ISEL)	Gefitinib 250 mg/day	Targeted therapy		Not in final scope

Analysis methods

Outcome measures of particular interest were OS (time to event) and PFS (time to event). These are consistent with the appraisal scope, and either PFS or OS was the primary efficacy endpoint for all included studies. OS and PFS are reported in the network meta-analysis (NMA) results below. Other non-time-to-event measures included were OS at 12 months, ORR, and treatment-related adverse events (TRAEs).

As discussed above, nintedanib (plus docetaxel) is licensed and recommended only for those patients with adenocarcinoma histology, which is not consistent with the appraisal scope, or anticipated marketing authorisation for atezolizumab. Therefore, a like-with-like comparison between the “total population” from the nintedanib (plus docetaxel) trial and the atezolizumab ITT population was conducted.

The full trial patient characteristics of the included studies are detailed in Appendix 4.

Network meta-analysis methodology

The NMA was conducted under a Bayesian framework.

For binary outcomes (ORR, TRAE and 12 month OS), standard NMA approaches using both random effects (RE) and fixed effects (FE) models were explored. As binary outcomes do not generate parameter inputs for the economic model, methodology and results for these outcomes are not further described below, but can be found in Appendix 4. For the key outcomes of interest – time-to-event outcomes of PFS and OS – fractional polynomial (FP) models are used.

Unlike the standard and hierarchical NMA approaches, FP models do not rely on the proportional hazards (PH) assumption.

Prior immunotherapy appraisals in melanoma (National Institute for Health and Care Excellence, 2015aj, National Institute for Health and Care Excellence, 2016cg) and NSCLC (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2016d), (National Institute for Health and Care Excellence, 2017) for pembrolizumab and nivolumab have determined the proportional hazards assumption (Chen, 2013) is unlikely to hold when comparing these therapies to traditional chemotherapies for time-to-event outcomes. This assumption was ratified upon the visual inspection of the diagnostic plots of the log cumulative hazard for PFS and OS over the log of time for the OAK arms to test the PH assumption (Figure 20, Figure 21). Based on the log cumulative hazard plots, it was determined the PH assumption does not hold as the curves cross each other, and hence the FP model is considered the most appropriate approach.

Figure 20: OS log-cumulative hazard plot

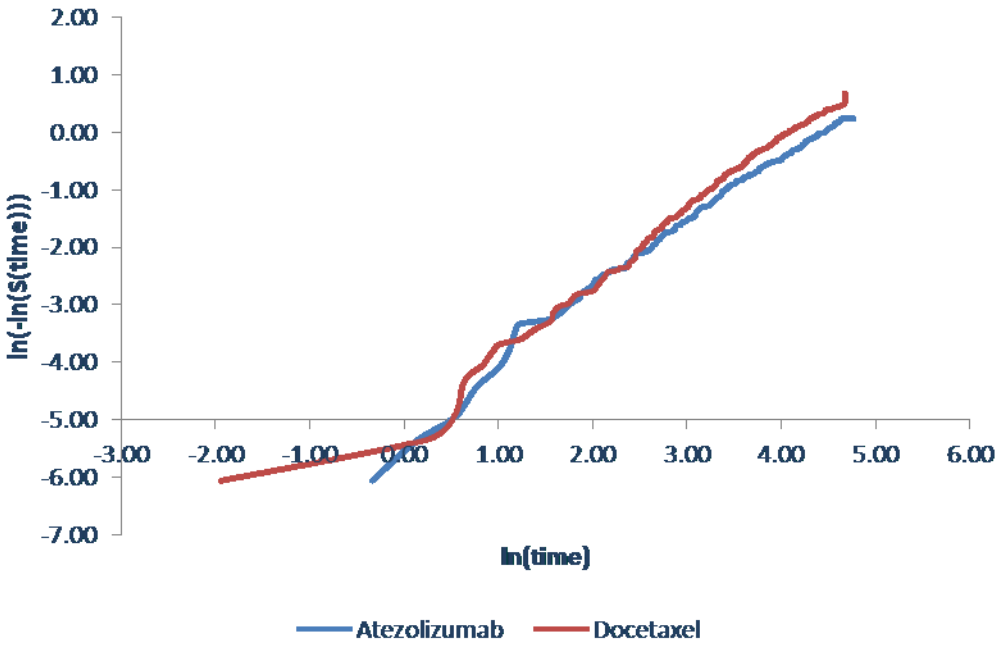
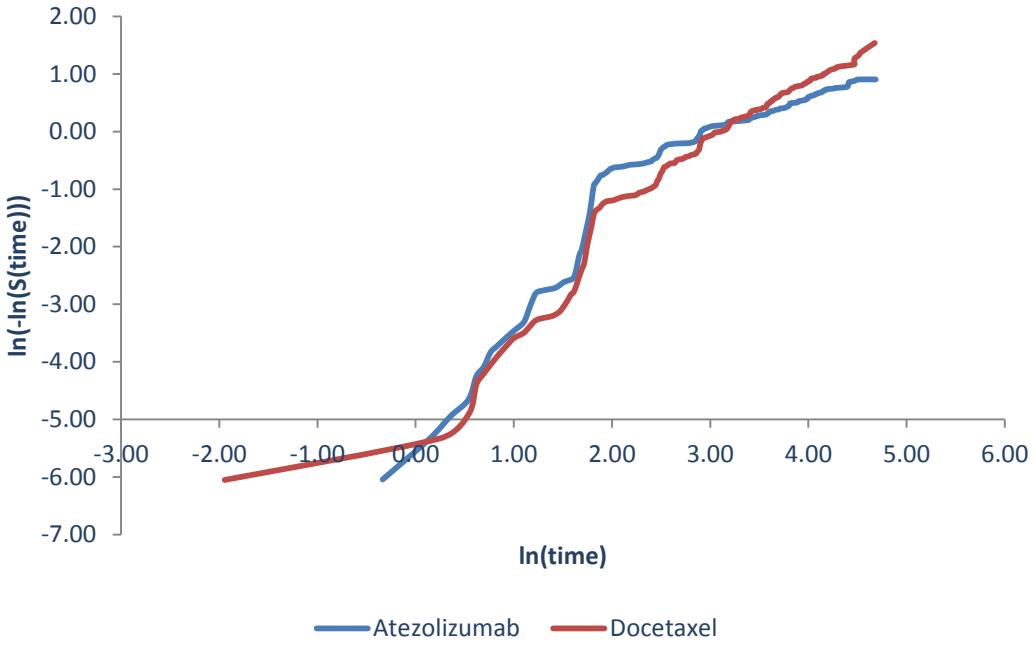


Figure 21: PFS log-cumulative hazard plot



For time-to-event outcomes FE FP models were first fit, with RE models subsequently fit if the data allowed. Five models were considered in the FE framework:

- First order FPs with exponent P1 = 0 (equivalent to Weibull model), and P1 = 1 (equivalent to Gompertz model);
- Second order FPs with exponents P1, P2 in (0, 1), i.e. P1=P2=0; P1=0, P2=1; and P1=P2=1.

The FP models used covered a broad range of hazard ratio shapes including constant, monotonically increasing, monotonically decreasing, U-shaped, and inverted-U-shaped hazard ratio curves. This was considered broad enough for the present data and did not, therefore, include higher order polynomials or additional exponents (P1, P2).

For most studies, digitalised KM curves were divided into monthly time intervals, with extracted survival proportions from each time interval used to calculate patients at risk at the beginning of the time interval, and incident number of deaths. For the OAK and POPLAR trials of atezolizumab, individual patient data were available to calculate these quantities. Binomial likelihood distribution derived event probability from the underlying hazard function given by a fractional polynomial, for each time interval (Jansen, 2011).

For the FP NMA, uninformative priors were used as per equation 9 of (Jansen, 2011) (see Figure 22): multivariate normal with zero mean and covariance and 10,000 variance for d and μ parameters; uniform (0,2) for σ.

Figure 22: Equation 9 of Jansen 2011

$$\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix} \sim Normal\left(\begin{pmatrix}0\\0\\0\end{pmatrix}, T_{\mu}\right) \quad T_{\mu} = \begin{pmatrix}10^4 & 0 & 0\\ 0 & 10^4 & 0\\ 0 & 0 & 10^4\end{pmatrix}$$

$$\begin{pmatrix}d_{0Ak}\\ d_{1Ak}\\ d_{2Ak}\end{pmatrix} \sim Normal\left(\begin{pmatrix}0\\0\\0\end{pmatrix}, T_{d}\right) \quad T_{d} = \begin{pmatrix}10^4 & 0 & 0\\ 0 & 10^4 & 0\\ 0 & 0 & 10^4\end{pmatrix}$$

$$\Sigma \sim Wishart(\Omega, 3) \qquad \Omega = \begin{pmatrix}10^2 & 0 & 0\\ 0 & 10^2 & 0\\ 0 & 0 & 10^2\end{pmatrix}$$

Programming language can be found in Appendix 4.

Model selection

The Deviance Information Criteria (DIC) assessed the heterogeneity of the included studies. This is consistent with the recommendations of NICE Decision Support Unit (DSU) (Dias, 2013) for networks of this size.

DIC allowed for a comparison of the goodness-of-fit of competing FP models: FE models with different sets of exponents, and FE and RE models with the same set of exponents. Differences in DIC of less than 5 points were not considered meaningful (Dias, 2013).

Due to the complexity of the FP models, a staggered approach to model selection was taken. This is in contrast to the general preference given to RE models.

FE versions of the models with different sets of exponents were initially fit. Model fit was assessed, with the RE version of the best performing FE model fit, as per the priors in section 4.10.3.2 (as per Figure 22). The models were then compared again in terms of DIC and the best performing model was reported as base case. Preference was given to simpler models if there was little to choose between them.

To avoid over-fitting, posterior correlation between parameters were explored – models with excessive posterior correlation indicates over-fitting. The ability of the models to be used for extrapolations and comparisons of estimates against observed KM curves was also considered.

First and second order FPs with exponents p1, p2 from the set (0,1) were fit using fixed effects models to choose the set of exponents for the final model. Based on smallest DIC alone, the second order models, specifically p1=p2=0, appeared to be the best fit for all analyses. However, upon viewing the fitted curves from the second order models, there was a survival “plateau” for some treatments, where the curves flattened and a proportion of patients did not experience the event during the time horizon. In some cases this proportion

was substantial and led to expected survivals and long term survival rates that were unrealistic for patients with NSCLC. This appears to be due to slope parameters that are too negative, with the hazard approaching zero before all patients have had time to experience the event. This leads to very large hazard ratios at later time points for some treatment comparisons.

In addition, a strong correlation between the posterior distributions of parameters within a treatment was noted. There was a strong negative correlation (approx. -0.7 to -0.9) between d0 (intercept) and d1 (slope) for both first and second order models. For second order models, there was also strong negative correlation (approx. -0.9 to -1) between d1 and d2 and strong positive correlation (approx. 0.5 to 0.8) between d0 and d2. Excessive correlation may be a sign of over-fitting leading to unstable parameter estimates.

Therefore, the simpler first order models were chosen. The first order model with lowest DIC is presented in the base case analysis.

For OS, the model with p1=0 (Weibull) was the best fit by DIC (see Table 33) and by viewing fitted curves. The FE model had the lowest DIC, although the differences were small (less than 2 points), indicating no evidence of substantial heterogeneity.

Table 33: DIC for all fixed effects models: OS

Model	p1	p2	Notes	DIC	pD	Deviance
1st order, fixed	0	NA	Weibull	4106.134*	59.58930	4046.133
1st order, fixed	1	NA	Gompertz	4170.862	59.52014	4111.170
2nd order, fixed	0	0		3844.632	90.13611	3754.623
2nd order, fixed	0	1		3880.134	89.37459	3790.585
2nd order, fixed	1	1		3952.492	91.31607	3860.920

*Random effects model DIC: 4106.535

For PFS, the model with p1=1 (Gompertz) was the best fit by DIC (see Table 34). The random effects model had the lowest DIC, but again the differences were small (less than 5 points), indicating no evidence of substantial heterogeneity. Hence, consistent with the approach stated above, simpler fixed models results are presented throughout the results.

Table 34: Deviance Information Criteria for all fixed effects models: PFS

Model	p1	p2	Notes	DIC	pD	Deviance
1st order, fixed	0	NA	Weibull	3934.154	45.09746	3888.831
1st order, fixed	1	NA	Gompertz	3925.829*	45.45058	3880.056
2nd order, fixed	0	0		3009.775	68.64979	2941.185
2nd order, fixed	0	1		3333.022	68.17952	3264.803
2nd order, fixed	1	1		3599.188	68.50818	3530.471

*Random effects model DIC: 3921.603

Analyses were run with 200,000 iterations of which 50,000 were discarded as burn in, and a thinning parameter of 100, with 2 chains. There was some degree of autocorrelation for some parameters, but no evidence that the models had not converged.

A 5 year time horizon for OS and 2.5 year time horizon for PFS was used for presenting the FP NMA time-dependent outputs (expected survivals, survivor functions and hazard ratios over time).

Figure 23: OS network (FP NMA)

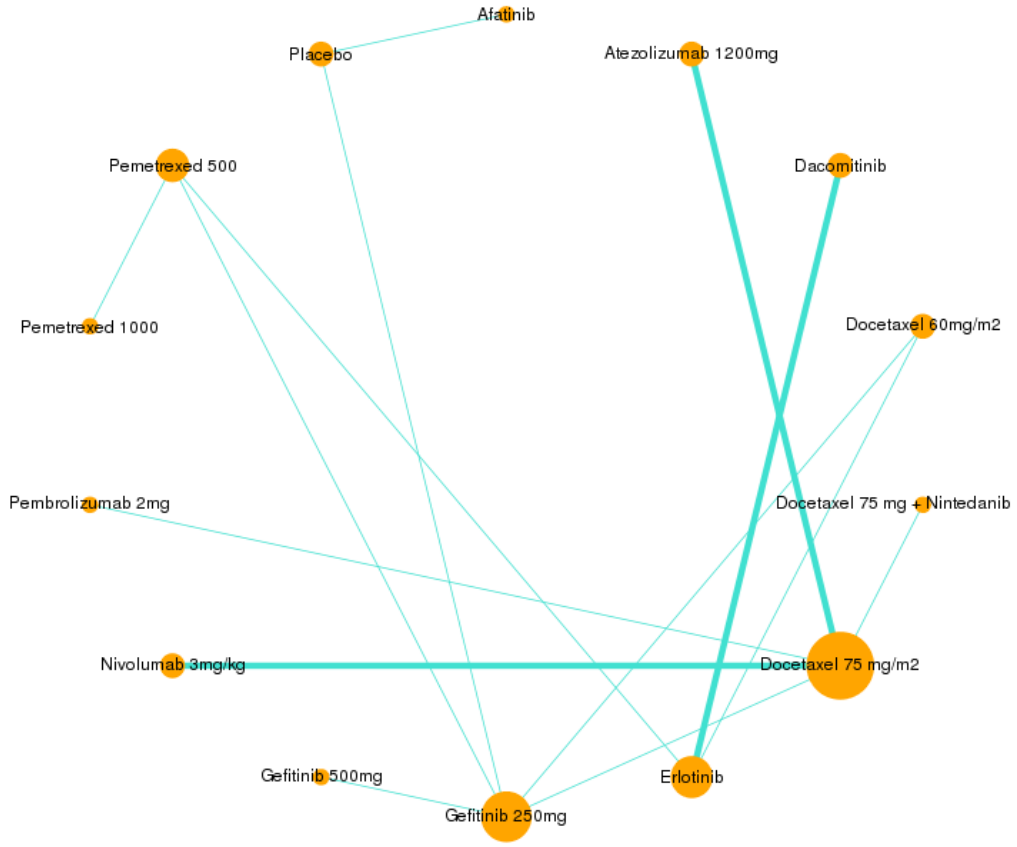


Table 35: Included studies and treatments in OS network (FP NMA)

Study	Reference treatment	Comparator
Borghaei 2016 (CheckMate 057, NCT01673867)	Nivolumab 3mg/kg	Docetaxel 75 mg/m^2
Brahmer 2015 (CheckMate 017, NCT01642004)	Nivolumab 3mg/kg	Docetaxel 75 mg/m^2
Fukuoka 2003 (IDEAL1)	Gefitinib 500mg	Gefitinib 250mg
Herbst 2015 (KEYNOTE 010)	Pembrolizumab 2mg	Docetaxel 75 mg/m^2
Karampeazis 2013 (HORG, NCT00440414)	Pemetrexed 500	Erlotinib
Kawaguchi 2014 (DELTA, UMIN000002314)	Erlotinib	Docetaxel 60 mg/m^2
Kim 2008 (INTEREST, NCT00076388)	Gefitinib 250mg	Docetaxel 75 mg/m^2

Kim 2016 (NCT01783834)	Pemetrexed 500	Gefitinib 250mg
Maruyama 2008 (V-15-32)	Gefitinib 250mg	Docetaxel 60 mg/m^2
Miller 2012 (LUX-Lung 1, NCT00656136)	Placebo	Afatinib
Ohe 2008	Pemetrexed 500	Pemetrexed 1000
Ramalingam 2012 (NCT00769067)	Erlotinib	Dacomitinib
Ramalingam 2014 (ARCHER 1009, NCT01360554)	Erlotinib	Dacomitinib
Reck 2014 (LUME-Lung 1, NCT00805194)	Docetaxel 75 mg/m^2	Docetaxel 75 mg + Nintedanib 200mg
Thatcher 2005 (ISEL)	Placebo	Gefitinib 250mg
POPLAR IPD	Docetaxel 75 mg/m^2	Atezolizumab 1200mg
OAK IPD	Docetaxel 75 mg/m^2	Atezolizumab 1200mg

Figure 24: PFS network (FP NMA)

Table 36: Included studies and treatments in PFS network (FP NMA)

Study	Reference treatment	Comparator
Borghaei 2016 (CheckMate 057, NCT01673867)	Nivolumab 3mg/kg	Docetaxel 75 mg/m^2
Brahmer 2015 (CheckMate 017, NCT01642004)	Nivolumab 3mg/kg	Docetaxel 75 mg/m^2
Fukuoka 2003 (IDEAL1)	Gefitinib 500mg	Gefitinib 250mg
Herbst 2015 (KEYNOTE 010)	Pembrolizumab 2mg	Docetaxel 75 mg/m^2
Kawaguchi 2014 (DELTA, UMIN000002314)	Erlotinib	Docetaxel 60 mg/m^2
Kim 2008 (INTEREST, NCT00076388)	Gefitinib 250mg	Docetaxel 75 mg/m^2
Kim 2016 (NCT01783834)	Pemetrexed 500	Gefitinib 250mg
Maruyama 2008 (V-15-32)	Gefitinib 250mg	Docetaxel 60 mg/m^2
Ramalingam 2012 (NCT00769067)	Erlotinib	Dacomitinib
Ramalingam 2014 (ARCHER 1009, NCT01360554)	Erlotinib	Dacomitinib
Reck 2014 (LUME-Lung 1, NCT00805194)	Docetaxel 75 mg/m^2	Docetaxel 75 mg + Nintedanib 200mg
POPLAR IPD	Docetaxel 75 mg/m^2	Atezolizumab 1200mg
OAK IPD	Docetaxel 75 mg/m^2	Atezolizumab 1200mg

Results of the NMA

For each endpoint, a forest plot of the relative difference in expected survival (in months) for atezolizumab versus competing interventions is provided. The plots represent the summary measure by a vertical mark (point estimate). The associated credible intervals are the lateral tips of the point estimates. A dashed vertical line of no effect is also included at 0 for no difference in expected survival. In addition to the graphical representation of the results, all pairwise comparisons are presented in separate tables (cross-tabulations).

As the ORR, TRAEs and 12 month OS results of the standard NMA are not incorporated into the economic model, the results are not discussed in this section.

Overall survival time-to-event

Results for OS are from fixed effects 1st order p1=0 (Weibull) models with a time horizon of 5 years for expected survival differences.

The fractional polynomial equations are (t is time in months):

- 1st order: log hazard = beta0 + beta1 (t^p1)
- 2nd order: log hazard = beta0 + beta1 (t^p1) + beta2 (t^p2)

with t^0 = log t.

If p1=p2=p the model becomes a repeated powers model:

- log hazard = beta0 + beta1 (t^p) + beta2 (t^p) log t

The OS FP equation coefficients can be found in Table 37.

Table 37: FP equation parameters: Overall survival (FE FP model, first order p1=0)

	beta0 posterior median (95% CrI)	beta1 posterior median (95% CrI)
Docetaxel 75 mg + Nintedanib 200 mg	-2.994 (-3.496, -2.499)	0.165 (-0.078, 0.407)
Docetaxel 75 mg/m²	-2.951 (-3.364, -2.562)	0.180 (-0.027, 0.398)
Atezolizumab 1200 mg	-2.987 (-3.521, -2.481)	0.012 (-0.240, 0.274)

Table 38: FP equation parameters: OS (FE FP model, first order p1=0), reference treatment = placebo

	d0 posterior median (95% CrI)	d1 posterior median (95% CrI)
Placebo	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)
Docetaxel 75 mg + Nintedanib 200 mg	-0.139 (-0.587, 0.328)	-0.088 (-0.340, 0.160)
Docetaxel 75 mg/m²	-0.095 (-0.446, 0.248)	-0.072 (-0.279, 0.139)
Atezolizumab 1200 mg	-0.131 (-0.616, 0.365)	-0.239 (-0.490, 0.022)

The treatment contrasts d are related to the beta parameters in the fractional polynomial equations via beta = baseline + d; Treatment contrasts versus non-reference treatments are simple linear combinations of the contrasts versus reference treatment.

Atezolizumab showed (statistically significant) favourable expected overall survival time (measured in months) compared to all competing interventions (Figure 25, Table 39): Cells highlighted in green showed statistically significant better results for atezolizumab, cells in orange show comparable results. The resulting hazard ratios over time are shown in Figure 26.

Figure 25: Forest plot of atezolizumab vs intervention of expected survival difference (months) – Overall survival

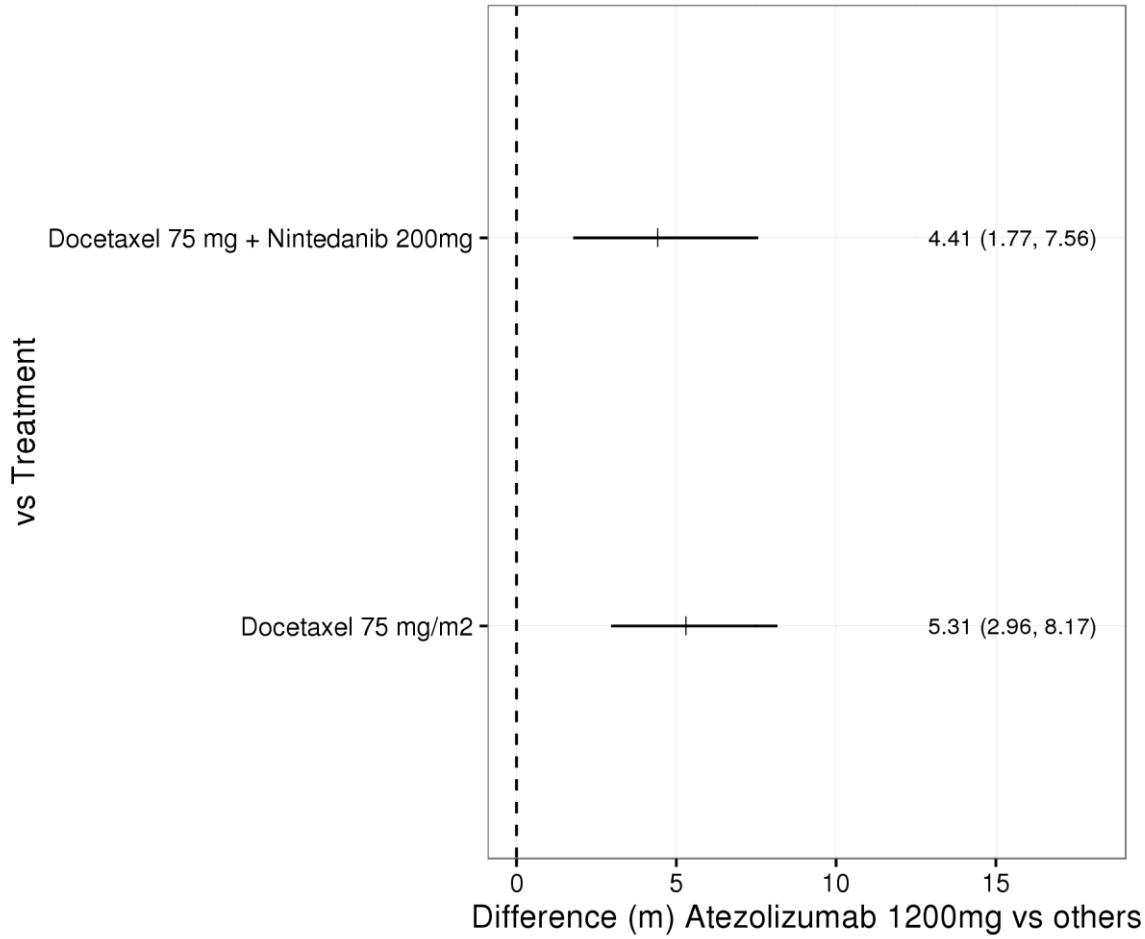
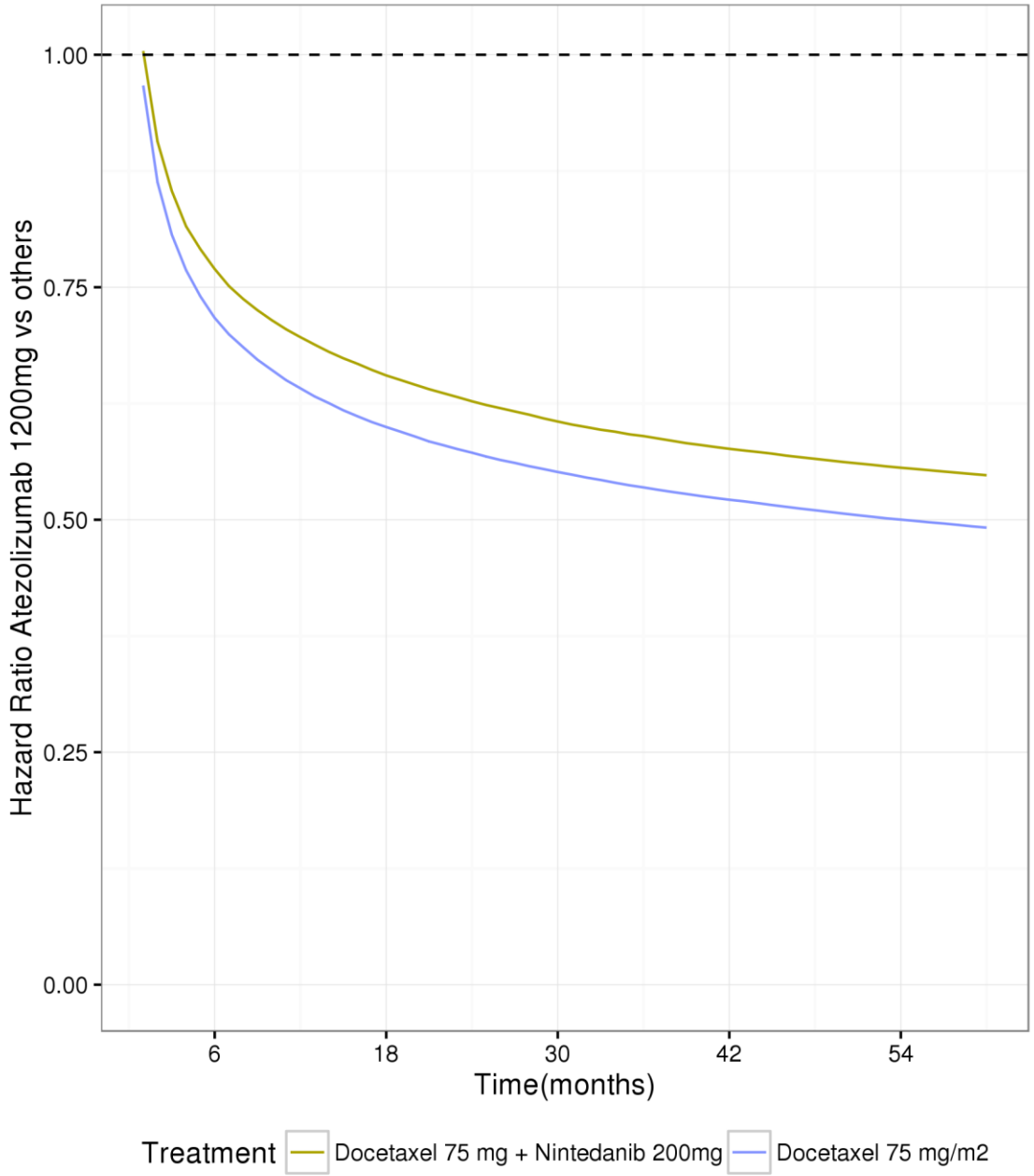


Table 39: Cross-tabulations of expected survival difference (months) and 95% CrIs (FP approach)

	Docetaxel 75 mg + Nintedanib 200 mg	**Docetaxel 75 mg/m^2**
Docetaxel 75 mg/m^2	-0.85 (-2.41, 0.42)	-
Atezolizumab 1200 mg	4.41 (1.77, 7.56)	5.31 (2.96, 8.17)

Figure 26: OS hazard ratios over time; Atezolizumab 1200mg vs comparators (FP approach)



Progression free survival time-to-event

PFS results are from fixed effects 1st order p1=1 (Gompertz), 2.5 year time horizon.

The fractional polynomial equations are (t is time in months):

- 1st order: log hazard = beta0 + beta1 (t^p1)
- 2nd order: log hazard = beta0 + beta1 (t^p1) + beta2 (t^p2)

with t^0 = log t.

If p1=p2=p the model becomes a repeated powers model:

- log hazard = beta0 + beta1 (t^p) + beta2 (t^p) log t

The overall survival fractional polynomial equation coefficients can be found in Table 40.

Table 40: FP equation parameters: PFS (FE FP model, first order p1=1)

	beta0 posterior median (95% CrI)	beta1 posterior median (95% CrI)
Docetaxel 75 mg/m^2	-1.723 (-1.839, -1.614)	0.037 (0.017, 0.056)
Docetaxel 75 mg + Nintedanib 200 mg	-2.024 (-2.265, -1.788)	0.053 (-0.001, 0.103)
Atezolizumab 1200 mg	-1.394 (-1.547, -1.240)	-0.047 (-0.072, -0.021)

Table 41: FP treatment contrast parameters: PFS (FE FP model, first order p1=1), reference treatment=docetaxel 75 mg/m^2

	d0 posterior median (95% CrI)	d1 posterior median (95% CrI)
Docetaxel 75 mg/m^2	0.000 (0.000, 0.000)	0.000 (0.000, 0.000)
Docetaxel 75 mg + Nintedanib 200 mg	-0.297 (-0.554, -0.044)	0.017 (-0.045, 0.074)
Atezolizumab 1200 mg	0.326 (0.152, 0.514)	-0.083 (-0.109, -0.058)

Atezolizumab showed comparable results to competing interventions: See Figure 27 and Table 42. For the cross-tabulation of all pairwise treatment comparisons, cells highlighted in orange show the comparable results. The resulting hazard ratios over time are shown in Figure 28.

Figure 27: Forest-plot of atezolizumab vs intervention of expected PFS difference (months) (FP approach)

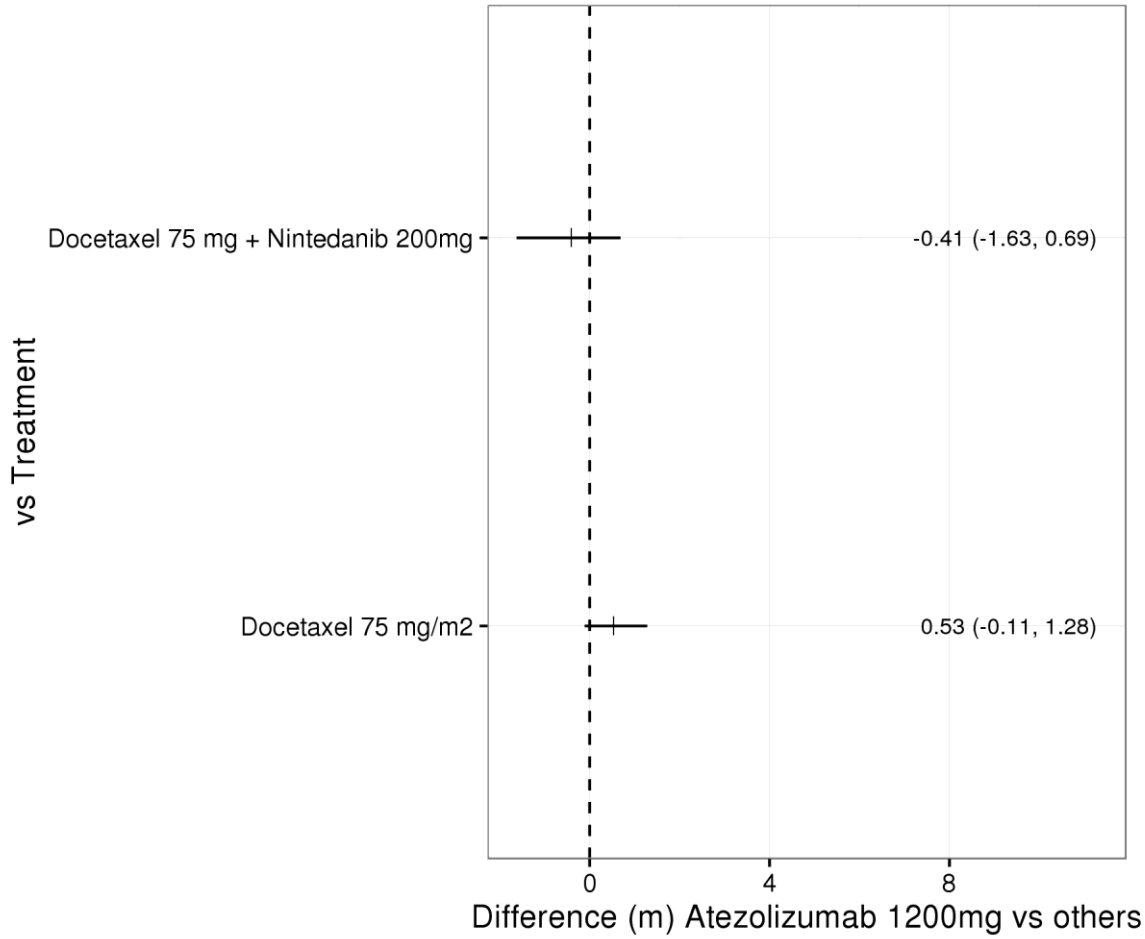
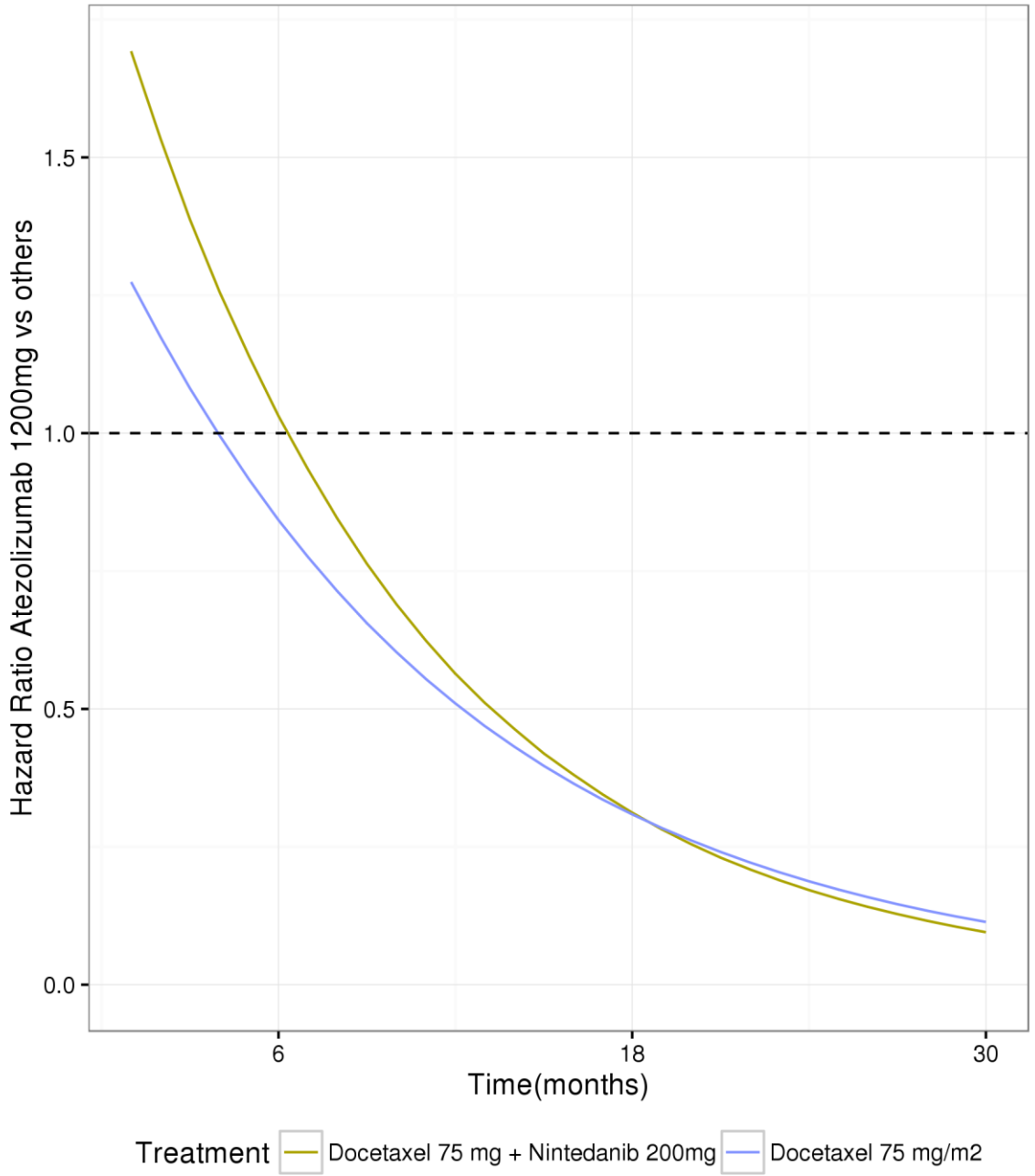


Table 42: Cross-tabulations of expected PFS difference (months) and 95% CIs (FP approach)

	Docetaxel 75 mg/m^2	**Docetaxel 75 mg + Nintedanib 200 mg**
Docetaxel 75 mg + Nintedanib 200 mg	0.93 (0.22, 1.87)	-
Atezolizumab 1200 mg	0.53 (-0.11, 1.28)	-0.41 (-1.63, 0.69)

Figure 28: PFS hazard ratios over time; Atezolizumab 1200mg vs comparators (FP approach)



The progression-free survival NMA results are supportive of the arguments already discussed regarding the traditional methods of monitoring cancer progression. It has been demonstrated that the traditional criteria of “progression-free” and “progressed disease” in cancer treatment are not well suited to the appraisal of immunotherapies. This is reflected in the proposed label, whereby treatment beyond progression is specified given patients continue to receive clinical benefit from treatment beyond the traditional RECIST criteria radiologically confirmed progression, as seen in the atezolizumab clinical trials.

Limitations

The analysis used aggregate level data (extracted Kaplan-Meier curves) for all interventions, with the exception of for atezolizumab, where patient level data from the OAK and POPLAR studies were available. Patient-level analyses have the advantage that no (conservative) assumption has to be made regarding the censoring process. Furthermore, patient-level network meta-analyses have greater power to estimate meta-regression models thereby reducing inconsistency and providing the opportunity to explore differences in effect among subgroups. However, obtaining patient-level data for all RCTs in the network was not possible.

As data were only reported from the studies over a relatively short time period, there were some concerns with the reliability of extrapolating the modelled results over a longer time horizon. Therefore estimated quantities such as expected overall survival, expected progression free survival, hazard ratios and survivor functions over time are only presented for a restricted period of 5 years for OS and 2.5 years for PFS. Mean survivals over an extended lifetime horizon are likely to be longer for all treatments, but these are difficult to estimate reliably without additional follow up in the trials.

The FP NMA was only conducted for OS and PFS, however it has been demonstrated that the traditional PFS criteria in cancer treatment are not well suited to the appraisal of immunotherapies. Rather, time-to-treatment discontinuation would have been a more informative endpoint to measure.

Finally, there are limitations with regards to the comparison versus nintedanib (plus docetaxel):

- The nintedanib (plus docetaxel) trial included in the analysis was not a 2nd and 3rd line study, therefore it is possible that it is not comparable to the other studies in the network if line of therapy is an effect modifier, and there is no clear way to determine if this is a confounding factor.
- Nintedanib (plus docetaxel) is licensed (and recommended by NICE) only for those patients with adenocarcinoma histology, however the comparison undertaken was versus the unlicensed "total population" from the LUME-Lung-1 trial. This was to allow for a like-with-like comparison versus atezolizumab in its anticipated licence. Consistent with the favourable prognosis seen in patients with non-squamous vs. squamous forms of NSCLC[6] in other trial programmes, the OAK and POPLAR studies demonstrated improved outcomes in the subgroup of patients with non-

[6] Adenocarcinoma makes up at least 85% of all non-squamous histologies (see section 3.1 & 4.8)

squamous NSCLC (Figure 14, Figure 16). Therefore, the impact of this approach is not anticipated to significantly affect overall results.

Assessment of heterogeneity was conducted by comparing DIC statistics, as recommended by the NICE DSU (Dias, 2013). In terms of fixed versus random effects models, for OS, the fixed effects model had the lowest DIC, although the differences were small (less than 2 points). For PFS, the random effects model had the lowest DIC, but again the differences were small (less than 5 points), indicating no evidence of substantial heterogeneity. Hence simpler fixed models results were utilised.

4.11 Non-randomised and non-controlled evidence

There is limited evidence from non-randomised and non-controlled sources that supplements the RCT data from POPLAR and OAK. The clinical development programme of atezolizumab in NSCLC included two single arm Phase II studies, BIRCH (study GO28754) and FIR (study GO28625). However, BIRCH and FIR will not be discussed during this submission as these studies enrolled PD-L1 positive patients only and are therefore not relevant to the anticipated indication of atezolizumab.

4.12 Adverse reactions

Given the larger patient population, the majority of the data reported in this section will be taken from the Phase III OAK study. However,

Table 43 below confirms there were no major differences between the safety profile of atezolizumab in POPLAR and OAK. Overall, atezolizumab was well tolerated in both studies, with a favourable safety profile versus docetaxel. Less than 10% of patients stopped atezolizumab treatment because of adverse events compared with 1 in 5 of those receiving docetaxel.

The safety analyses from OAK reported in this section are based on all randomised patients who received a dose of study drug during the study treatment period (N=1225). In total, 38 patients who did not receive any study drug were excluded from the safety evaluable population: 33 patients from the docetaxel arm and 5 patients from the atezolizumab arm, resulting in a total of 1187 patients.

Table 43: Overview of the safety profile of atezolizumab compared with docetaxel in POPLAR and OAK

n (%)	OAK		POPLAR	
	Atezolizumab n=609	Docetaxel n=578	Atezolizumab n=142	Docetaxel n=135
Total patients with at least one event	573 (94)	555 (96)	136 (96)	130 (96)
Treatment related AEs	390 (64)	496 (86)	95 (67)	119 (88)
Grade 3–4 AEs	227 (37)	310 (54)	57 (40)	71 (53)
Treatment related Grade 3–4 AEs	90 (15)	247 (43)	16 (11)	52 (39)
Grade 5 AEs	10 (2)	14 (2)	6 (4)	5 (4)
Treatment related deaths	0 (0)	1 (0.2)	1 (1)	3 (2)
Serious AEs	194 (32)	181 (31)	50 (35)	46 (34)
AEs leading to withdrawal from treatment	46 (8)	108 (19)	11 (8)	30 (22)
AE leading to dose modification/interruption	152 (25)	210 (36)	34 (24)	44 (33)

AEs, adverse events
Source:(Fehrenbacher et al., 2016, F. Hoffmann-La Roche Ltd, 2016b, Rittmeyer et al., 2016)

Exposure to atezolizumab in OAK

The median duration of treatment (2.1 months docetaxel vs 3.4 months atezolizumab), as well as the median number of cycles (4 vs 6), was higher with atezolizumab compared with docetaxel. The median dose intensity was identical (97.7%) in both treatment arms. Notably more patients in the atezolizumab arm received at least 6 months (11.2% vs 33.2%) and 12 months (2.4% vs 20.5%) of treatment, as compared to docetaxel.

Table 44: Study drug exposure in OAK

	Atezolizumab n=609	Docetaxel n=578
Median treatment duration, months (range)	3.4 (0–26)	2.1 (0–23)
Treatment duration, n (%)		
0–≤3 months	294 (48)	351 (61)
>3–≤6 months	113 (19)	162 (28)
>6–≤12 months	77 (13)	51 (9)
>12 months	125 (21)	14 (2.4)
Median number of doses (range)	6.0 (1–38)	4.0 (1–30)
Missed doses, n (%)		
No missed dose	573 (94)	538 (93)
At least one missed dose	36 (6)	40 (7)
At least two missed doses	1 (<1)	1 (<1)
At least three missed doses	0	1 (<1)

Source:(F. Hoffmann-La Roche Ltd, 2016b)

All grade adverse events in OAK

The majority of patients in both arms (96.0% docetaxel vs 94.1% atezolizumab) reported at least one AE (any grade). This is expected given the highly symptomatic nature of advanced

lung cancer. AEs reported by at least 20% of patients in either treatment arm are shown below by preferred term.

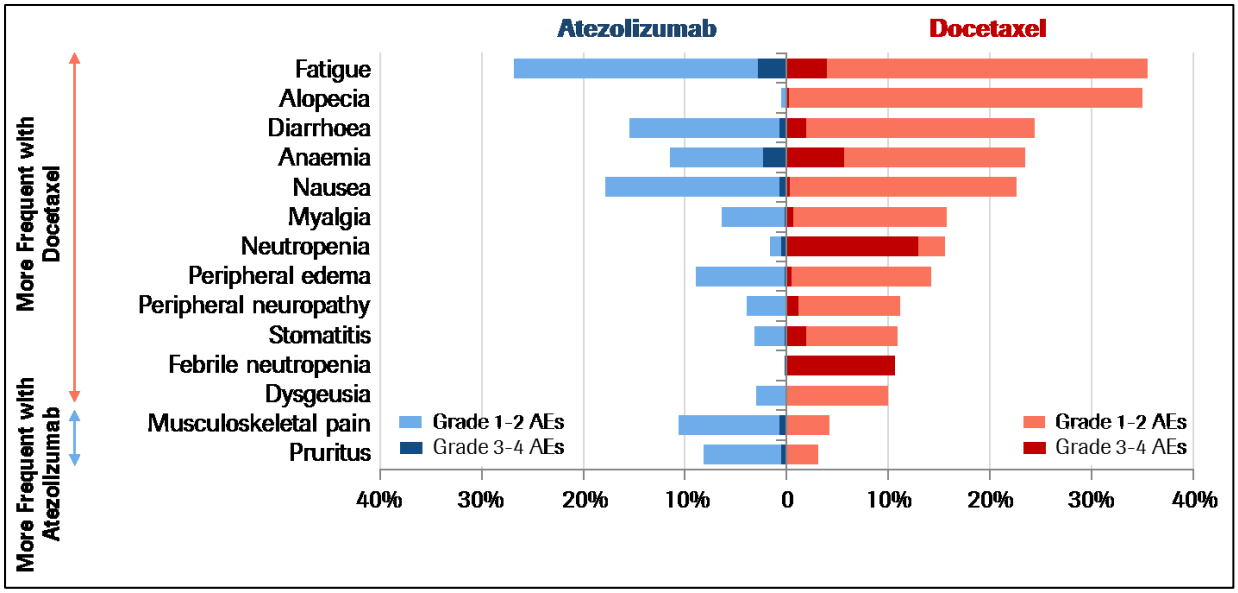
Table 45: Adverse events reported in ≥20% of patients

Number of patients with at least one event, (%)	Atezolizumab n=609	Docetaxel n=578
Gastrointestinal disorders	172 (28)	219 (38)
Nausea	108 (18)	131 (23)
Diarrhoea	94 (15)	141 (24)
General disorders and admin site conditions	163 (27)	205 (36)
Fatigue	163 (27)	205 (36)
Metabolism and nutrition disorders	143 (24)	136 (24)
Decreased appetite	143 (24)	136 (24)
Respiratory, thoracic and mediastinal disorders	141 (23)	105 (18)
Cough	141 (23)	105 (18)
Blood and lymphatic system disorders	70 (12)	136 (24)
Anaemia	70 (12)	136 (24)
Skin and subcutaneous tissue disorders	3 (0.5)	202 (35)
Alopecia	3 (0.5)	202 (35)

Source:(F. Hoffmann-La Roche Ltd, 2016b)

Patients in the atezolizumab arm did not experience any AEs (grade-independent) with an incidence that was ≥10% higher compared with docetaxel. AEs reported in a higher proportion of patients in the atezolizumab arm (≥5% difference [any grade] compared with docetaxel arm) were musculoskeletal pain (10.5% vs 4.3%) and pruritus (8.2% vs 3.1%) (Figure 29).

Figure 29: OAK, all cause adverse events, any grade (≥5% difference between arms)



Source:(Rittmeyer et al., 2016)

Among 64 patients (10.5%) in the atezolizumab arm who reported 75 events of musculoskeletal pain, the majority (94%) experienced Grade 1 or 2 events with the

remaining 4 patients reporting Grade 3 events. Ten of the 64 patients (15.6%) had events considered by the investigator to be related to atezolizumab treatment. There was one serious Grade 3 event of musculoskeletal pain reported, which was considered by the investigator as unrelated to atezolizumab treatment. No patient discontinued atezolizumab due to musculoskeletal pain.

Among 50 patients (8.2%) in the atezolizumab arm who reported 76 events of pruritus, the majority (94%) experienced Grade 1 or 2 events with the remaining 3 patients (6%) reporting Grade 3 events. The majority (76%) had events that were considered by the investigator to be related to atezolizumab treatment. One patient reported a serious Grade 3 event of pruritus, which was considered by the investigator as unrelated to atezolizumab treatment. No patient discontinued atezolizumab treatment due to pruritus.

Treatment-related adverse events

The proportion of patients who reported at least one AE (any grade) considered by the investigator to have a reasonable suspected causal relationship to study treatment was higher in the docetaxel arm (85.8%) compared with the atezolizumab arm (64.0%).

Table 46: Treatment-related adverse events reported in ≥10% patients (any grade)

MedDRA preferred term, n (%)	Atezolizumab n=609	Docetaxel n=578
Alopecia	3 (0.5)	198 (34)
Fatigue	87 (14)	177 (31)
Decreased appetite	52 (9)	116 (20)
Anaemia	24 (4)	114 (20)
Nausea	53 (9)	112 (19)
Diarrhoea	47 (8)	109 (19)
Asthenia	51 (8)	96 (17)
Neutropenia	7 (1)	85 (15)
Myalgia	21 (3)	81 (14)
Febrile neutropenia	0	61 (11)
Stomatitis	13 (2)	59 (10)
Neuropathy peripheral	6 (1)	58 (10)

Source:(F. Hoffmann-La Roche Ltd, 2016b)

A higher proportion of patients in the docetaxel arm experienced treatment-related Grade 3 or 4 AEs compared with patients in the atezolizumab arm (42.7% vs 14.8%). In the docetaxel arm, ≥10% of patients experienced each of the following Grade 3–4 events: fatigue, asthenia, nausea, diarrhoea, stomatitis, alopecia, anaemia, neutropenia, febrile neutropenia, peripheral neuropathy, decreased appetite, and myalgia; whereas one Grade 3–4 event (fatigue) was reported in ≥10% of patients in the atezolizumab arm.

Serious adverse events

A similar proportion of patients in both treatment arms reported serious adverse events (SAEs): 31.3% docetaxel and 31.9% atezolizumab. Four SAEs were reported in ≥2% of patients in either treatment arm: pneumonia, dyspnoea, pleural effusion, and febrile neutropenia.

Patients in the atezolizumab arm did not experience any SAE with an incidence that was ≥2% higher compared with docetaxel. SAEs reported in a higher proportion of patients in the docetaxel arm (≥2% difference compared with atezolizumab arm) were pneumonia (5.4% vs 3.3%) and febrile neutropenia (6.4% vs 0% patients); these are both common adverse drug reactions (ADRs) for docetaxel.

The proportion of patients experiencing SAEs considered by the investigator to have a reasonable suspected causal relationship to study treatment was higher in the docetaxel arm (17.6%) compared with the atezolizumab arm (10.3%).

Table 47: Treatment-related SAEs reported in ≥2 patients

MedDRA preferred term, n (%)	Atezolizumab n=609	Docetaxel n=578
Total number of patients with at least one event	63 (10.3)	102 (17.6)
Febrile neutropenia	0	36 (6.2)
Pneumonia	2 (0.3)	11 (1.9)
Diarrhoea	0	6 (1.0)
Pyrexia	3 (0.5)	5 (0.9)
Neutrophil count decreased	0	5 (0.9)
Anaemia	0	4 (0.7)
Pleural effusion	1 (0.2)	3 (0.5)
Vomiting	0	3 (0.5)
Dehydration	0	3 (0.5)
Neutropenia	0	3 (0.5)
Lung infection	0	3 (0.5)
Colitis	1 (0.2)	2 (0.3)
Acute kidney injury	1 (0.2)	2 (0.3)
Lower respiratory tract infection	0	2 (0.3)
Neutropenic sepsis	0	2 (0.3)
Urinary tract infection	0	2 (0.3)
Asthenia	0	2 (0.3)
Syncope	0	2 (0.3)
Pneumonitis	6 (1.0)	1 (0.2)
Hypersensitivity	3 (0.5)	0
Meningitis	3 (0.5)	0
Sepsis	2 (0.3)	0
Guillain-Barre syndrome	2 (0.3)	0
Hepatitis	2 (0.3)	0

Source:(F. Hoffmann-La Roche Ltd, 2016b)

Adverse events of special interest

Overall, protocol-defined adverse events of special interest (AESIs-focused on AEs that might represent autoimmune mediated events) of any grade were reported for 132 patients (22.8%) in the docetaxel arm and 184 patients (30.2%) in the atezolizumab arm (Table 20). AESIs were observed at a higher frequency for dermatologic, hepatic, and endocrine events in the atezolizumab arm compared with the docetaxel arm, which is consistent with the atezolizumab mechanism of action. In the docetaxel arm, neurologic AESIs were observed at a high frequency, with the most frequently reported event being peripheral neuropathy, which is a common adverse drug reaction for docetaxel. Across the study arms, the majority of patients with AESIs experienced events of Grade 1 or 2, 3.5% had a Grade 3 AESI, 0.3% had a Grade 4 AESI, and no patient reported a Grade 5 AESI.

Table 48: Summary of AESI

AESI, MedDRA preferred term	Atezolizumab n=609	Docetaxel n=578
Any adverse event, n (%)	184 (30.2)	132 (22.8)
Grade 1	87 (14.3)	82 (14.2)
Grade 2	66 (10.8)	36 (6.2)
Grade 3	28 (4.6)	14 (2.4)
Grade 4	3 (0.5)	0
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source:(F. Hoffmann-La Roche Ltd, 2016b)

Fatal adverse events

At the time of the clinical cut-off, a higher proportion of patients in the docetaxel arm (69.6%; 402/578) compared with the atezolizumab arm (62.9%; 383/609) had died. In both treatment arms, the majority of deaths occurred more than 30 days after the last dose of study drug (89.6% vs 83.8%).

Regardless of time window, the most common cause of death was progressive disease (PD) in both treatment arms. PD accounted for 93.5% (376/402) of deaths in the docetaxel arm and 93.2% (357/383) of deaths in the atezolizumab arm.

Among all deaths that occurred within 30 days of last study drug dose, a greater proportion of patients in the docetaxel arm compared with the atezolizumab arm died due to AEs rather than PD (33.3% [14/42] vs 16.1% [10/62]).

Table 49: Deaths and causes of death

	Atezolizumab n=609	Docetaxel n=578
All deaths, n	383	402
≤30 days from last study drug administration, n (%)	62 (16.2)	42 (10.4)
Adverse event	10 (16.1)	14 (33.3)
Progressive disease	51 (82.3)	28 (66.7)
Other	1 (1.6)	0
>30 days from last study drug administration	321 (83.8)	360 (89.6)
Adverse event	15 (4.7)	10 (2.8)
Progressive disease	306 (95.3)	348 (96.7)
Other	0	2 (0.6)

Source:(F. Hoffmann-La Roche Ltd, 2016b)

4.12.3 Overview of the safety of the technology in relation to the decision problem

The safety data from OAK are consistent with the known safety profile of atezolizumab, with no new safety signals observed. Atezolizumab was well tolerated, with a favourable safety profile compared with docetaxel. Specifically, atezolizumab treated patients had fewer Grade 3 or 4 AEs (especially for those deemed related to study treatment per the investigator); AEs leading to treatment discontinuation; and AEs leading to dose modifications or interruptions which can be interpreted as those that are dangerous or intolerable to the patient. Patients in the atezolizumab arm did not experience any AEs (grade-independent) with an incidence that was ≥10% higher compared with docetaxel. Patients in the docetaxel arm compared with the atezolizumab arm showed higher frequencies (≥5% difference) of known common docetaxel toxicities, such as alopecia, stomatitis, myalgia, fatigue, nausea, diarrhoea, neutropenia, and peripheral neuropathy, some of which can be clinically important when

high-grade (e.g., infections associated with severe or prolonged neutropenia) and even at low grade can be expected to impact on the enjoyment of everyday life. Events of pneumonia and febrile neutropenia reported as SAEs were observed at higher frequencies (≥2% difference) in patients in the docetaxel arm compared with the atezolizumab arm.

Only two AE preferred terms, musculoskeletal pain and pruritus, were reported with a higher incidence (≥5%) in patients receiving atezolizumab than docetaxel after adjustment for exposure. They were seen in 10.5% vs 4.3% and 8.2% vs 3.1% of patients, respectively with the majority of cases of mild-moderate severity and less than 1% of patients experiencing either event at Grade 3

The incidence of fatal AEs was low in both arms, and no grade 5 immune-mediated AEs or AESIs were observed.

The lower incidence of AEs of atezolizumab was seen despite longer treatment duration driven by the greater efficacy of atezolizumab.

4.13 Interpretation of clinical effectiveness and safety evidence

As discussed in Section 3.1, there remains an unmet need for new treatments that improve survival for patients with locally advanced or metastatic NSCLC without causing significant toxicity or a deterioration in quality of life, particularly in those patients who are not eligible for targeted therapies and those relapsing after first-line chemotherapy.

Evidence for the efficacy and safety of atezolizumab in patients with locally advanced or metastatic NSCLC whose disease has progressed on or after treatment with platinum-based chemotherapy, regardless of PD-L1 expression level, is available from two clinical studies; an open-label Phase III study (OAK) and an open-label Phase II study (POPLAR). Both OAK and POPLAR compared atezolizumab against docetaxel, which is regarded as the standard of care for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy. The OAK study is the largest Phase III trial of a PD-L1 directed antibody in previously treated NSCLC patients (see Table 16) and confirms the findings of the controlled Phase II POPLAR study.

Summary of clinical efficacy

The OAK study met its co-primary endpoints by demonstrating a statistically significant and clinically meaningful improvement in OS in both the ITT and PD-L1-positive subgroup (TC1/2/3 or IC1/2/3), compared with docetaxel; HR: 0.73 (95% CI: 0.62, 0.87) and 0.74 (95% CI: 0.58, 0.93), respectively. The Kaplan-Meier curves in Figure 8 demonstrate an early

separation of the curves for atezolizumab and docetaxel, which do not cross for the duration of the study.

The clinical efficacy demonstrated in the ITT population for both OAK and POPLAR was not dependent on PD-L1 expression; both studies demonstrated clinical activity in patients with negative PD-L1 expression (TC0 and IC0), with a statistically significant benefit observed in OAK (HR 0.75, 95% CI: 0.59, 0.96) similar to that seen in unselected patients

This benefit in OS was observed in all important clinical subgroups in OAK, including patients with CNS metastases. Furthermore, improvements in OS were seen with atezolizumab compared with docetaxel regardless of histology, with statistically significant and clinically meaningful benefits in both non-squamous and squamous NSCLC; HR 0.73 (95% CI: 0.60, 0.89) and 0.73 (95% CI: 0.54, 0.98), respectively.

Underpinning the improvement in OS seen in patients treated with atezolizumab are very prolonged anti-tumour responses that are much more durable than those seen after conventional cytotoxic chemotherapy. In OAK, the median DOR was 16.3 months compared with just 6.2 months for docetaxel. Moreover, with 52% of atezolizumab responders ongoing versus 18% in the docetaxel arm at the time of the clinical cut-off date, this disparity is likely to grow as the data matures, as it did in POPLAR. Overall, this suggests an enduring benefit of atezolizumab in some patients of the sort that has characterised successful immunotherapy in other diseases, notably melanoma (Eggermont et al., 2016).

Interestingly in neither OAK nor POPLAR was there a statistically significant difference in PFS. Discordance between PFS and OS is another finding shared with other recent developments in immunotherapy (Brahmer et al., 2015, Fehrenbacher et al., 2016, Herbst et al., 2016). While PFS is an appropriate endpoint to assess the activity of agents that are likely to elicit rapid control of tumour growth, it may be less suitable for therapies where tumour control may develop over time, especially when data are immature and the full impact of a minority of prolonged responders cannot be discerned. This apparent discordance between PFS and OS may also be due, in part, to an initial increase in tumour volume from increased immune infiltration, delayed anti-tumour activity, or anti-tumour immune activation beyond progression that might be sustained by continued treatment (Wolchok et al., 2009).

Summary of safety

Atezolizumab was well tolerated in both POPLAR and OAK, with no new safety signals identified. The safety profile was distinct from that of docetaxel, with lower rates of drug

discontinuations due to adverse events, Grade 3–4 adverse events, and adverse events common to chemotherapy, including nausea and peripheral neuropathy; most atezolizumab adverse events were low grade, implying limited impact on patient well-being. Potential immune-mediated adverse events, such as increased aspartate aminotransferase, colitis and hepatitis occurred at low frequency in the atezolizumab arm and were generally manageable and reversible.

Strengths and limitations of clinical evidence

The study populations in both OAK and POPLAR are largely reflective of the NSCLC population in the UK. Both studies recruited patients from the UK (31 patients from 8 centres and 11 patients from 4 centres for OAK and POPLAR, respectively, Table 16) indicating that both trial populations, and therefore results of these trials, will reflect UK practice. Furthermore, feedback from clinical experts confirms that the baseline characteristics of patients enrolled into both studies are reflective of the population seen in UK clinical practice.

Atezolizumab is compared against a relevant active comparator in OAK and POPLAR as docetaxel is regarded as the standard of care for patients who progress following first-line chemotherapy. Furthermore, OAK and POPLAR were designed to capture endpoints which are relevant to UK clinical practice and that address the unmet medical need for this patient population, in particular overall survival, overall response rate and duration of response.

A key strength of the POPLAR and OAK studies is that patients were enrolled irrespective of PD-L1 status, which was assessed on both tumour cells and tumour infiltrating immune cells. As discussed above, atezolizumab demonstrates a consistent efficacy and safety profile regardless of PD-L1 expression level in OAK and POPLAR, corroborating the findings from early Phase I studies.

There is a lack of clinical efficacy comparing against nintedanib (plus docetaxel). Whilst a direct comparison versus docetaxel was possible through the OAK trial, an indirect treatment comparison was required to compare atezolizumab to nintedanib (plus docetaxel). Nintedanib (plus docetaxel) is licensed and recommended by NICE only for those patients with adenocarcinoma histology, which is not consistent with the anticipated marketing authorisation for atezolizumab. As such, in order to conduct a like-with-like comparison versus atezolizumab in the anticipated licence, the “total population” from the nintedanib (plus docetaxel) trial was compared to the atezolizumab ITT population. Consistent with the favourable prognosis seen in patients with non-squamous v. squamous forms of NSCLC in

other trial programmes, the OAK and POPLAR studies demonstrated improved outcomes in the subgroup of patients with non-squamous NSCLC. Therefore, the impact of this approach is not anticipated to significantly affect overall results.

Standard NMA methodology was deemed inappropriate upon violation of the proportional hazards assumption. Rather, fractional polynomial models were utilised, which measures the varying hazard ratios over time. A method considered more appropriate for the appraisal of immunotherapies. The economic analyses in Section 5.2 demonstrates that using the first order fractional polynomial results in a linear increase in log-HRs over time, as the HR from the tail of the observed data continue (moderately) in the same direction for the extrapolated tail. Whilst the approach taken for this analysis was robust and appropriate for the data set, fractional polynomial models add a degree of complexity to the comparison of atezolizumab versus the standards of care at present in the UK.

In conclusion, the data show that atezolizumab provides a significant and clinically meaningful survival benefit in previously treated patients with locally advanced or metastatic NSCLC, regardless of PD-L1 expression, with dramatically increased response duration and a favourable safety profile compared with docetaxel.

End-of-life criteria

Due to the limited treatment options second-line and beyond for locally metastatic or advanced NSCLC, patients are anticipated to have a short duration of survival. Atezolizumab meets end of life criteria, as highlighted below.

Table 50: End-of-life criteria

<table>
<tr><th>Criterion</th><th>Data available</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>Yes – median survival for Stage IIIb and Stage IV NSCLC is 7.5 months and 3.4 months, respectively (Section 3.4) (Beckett P et al., 2013)</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>Yes – in OAK, atezolizumab was associated with a statistically significant improvement in OS compared with docetaxel in the ITT population (HR 0.73, 95% CI: 062, 0.87, Figure 8).
The median overall survival in the ITT population was 9.6 months (95% CI: 8.6, 11.2) in the docetaxel arm and 13.8 months (95% CI: 11.8, 15.7) in the atezolizumab arm (Section 4.7) (Rittmeyer et al., 2016)

Mean OS results are >3 months for atezolizumab as compared to all comparators, and median OS results are >3 months for atezolizumab when compared to docetaxel when taking results from the economic analysis as shown in the table below (Section 5.7):
<table>
<tr><td></td><td>Mean (mo)</td><td>Median (mo)</td></tr>
<tr><td>Atezolizumab</td><td>31.1</td><td>13.3</td></tr>
<tr><td>Docetaxel</td><td>14.1</td><td>9.8</td></tr>
<tr><td>Nintedanib+docetaxel</td><td>16.4</td><td>10.6</td></tr>
</table>
</td></tr>
<tr><td>The treatment is licensed or otherwise indicated for small patient populations</td><td>The total eligible treatment population for atezolizumab in 2018 is estimated to be [redacted]. However, incorporating Roche market share assumptions, it is predicted that [redacted] patients would be eligible for treatment (Section 6.1)</td></tr>
</table>

4.14 Ongoing studies

OAK was initially designed to enrol 850 patients, and the sample size was later increased to enrol up to 1,300 patients to provide sufficient power for an OS comparison in patients with high PD-L1 expression (TC3 or IC3, assuming a prevalence of approximately 20%); the final enrolment was 1225.

[redacted]

There is one additional ongoing study for atezolizumab in second-line NSCLC. This is a Phase III, multicentre, open-label, randomised, controlled study to evaluate the efficacy and safety of atezolizumab compared with docetaxel in Asian patients (currently recruiting patients in China and South Korea) with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen. No data from this study is expected to become available within the next 12 months (Clinical Trials.Gov).

5. Cost effectiveness

Summary of cost effectiveness

- Cost-utility analyses were conducted to compare atezolizumab to the key comparators of interest: docetaxel, and nintedanib (plus docetaxel)
- A three-state partitioned survival model was built and included the health-states “on treatment”, “off treatment” and death. The time horizon is 25 years, which captures all relevant costs and benefits
- Clinical benefits were derived from the OAK study, and the indirect treatment comparison (ITC) for comparators, and extrapolated to the 25 year time horizon
- For both PFS and time to treatment discontinuation extrapolation, Kaplan-Meier with a gamma tail was used
- For OS extrapolation, a mix-cure rate was used, with the cure-log-logistic distribution. The mixture cure model accounts for the decrease in cancer-related mortality-risk over time by estimating overall mortality risk at a given point in time by combining the cancer-related and background mortality risk. The weight assigned to the background mortality is referred to as the “cured fraction” (not to be interpreted as a clinical ‘cure’ from cancer, but the proportion of patients for whom the risk of death attributable to cancer is equivalent to the risk of death from other causes)
- Upon validation with all atezolizumab trials and UK-real world evidence, an OS cure fraction of 2% was used
- Benefits are expressed in QALYs. Utility values were derived from EQ-5D data collected in the OAK trial
- Atezolizumab provided a life-year and QALY gain over all comparators
- The resulting ICERs (without PAS) are:
    - £72,356 versus docetaxel
    - £56,076 versus nintedanib (plus docetaxel)
- The resulting ICERs (with PAS) are:
    - [redacted] versus docetaxel
    - [redacted] versus nintedanib (plus docetaxel)

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

A SLR was performed to identify cost-effectiveness evidence for atezolizumab for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy. The aim of the systematic review was to identify the economic evidence (EE) from all lines of metastatic NSCLC (mNSCLC) therapy to support the development of cost-effectiveness models for atezolizumab.

The searches were performed on 4th September 2016. Hand searches were also performed on 21st November 2016, including: Google Scholar, HTA agency websites (NICE, SMC, AWMSG, PBAC, CADTH, INESSS, pCODR and HAS), Cost-Effectiveness Analysis Registry, Research Papers in Economics (RePEc website), conferences for last 1-2 years (ISPOR US and EU, HTAi, SMDM), and bibliographic reference lists of included papers and of relevant systematic reviews of economic evaluations. For further details, please see Appendix 5.

Table 51: Data sources for the economic systematic review

Database	Platform	Date span of search	Date searched
Embase	Embase.com www.embase.com	From database inception (1974) to 3-Sep-2016 (updated daily)	04-Sep-2016
Medline	Embase.com www.embase.com	From database inception (1966) to 3-Sep-2016 (updated daily)	04-Sep-2016
Medline InProcess & e-publications ahead of print	PubMed search interface: http://www.ncbi.nlm.nih.gov/pubmed/	From database inception to 17-Nov-2016	04-Sep-2016 initially & weekly alerts received to cut-off date of 18-Nov-2016
NHS EED	Cochrane library http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception to 31st March 2015 (database closed)	04-Sep-2016
HTAD	Cochrane library http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception to July 2016 (updated monthly)	04-Sep-2016

To determine which studies were eligible, inclusion and exclusion criteria were applied when evaluating the literature search results.

Details of the search strategy for the SLR are provided in Appendix 5.

Figure 30 depicts the PRISMA flow for the SLR. A total of 73 articles were included in the systematic review, representing 55 unique studies or submissions. A summary of the rationale for exclusion of studies can be found in Appendix 6.

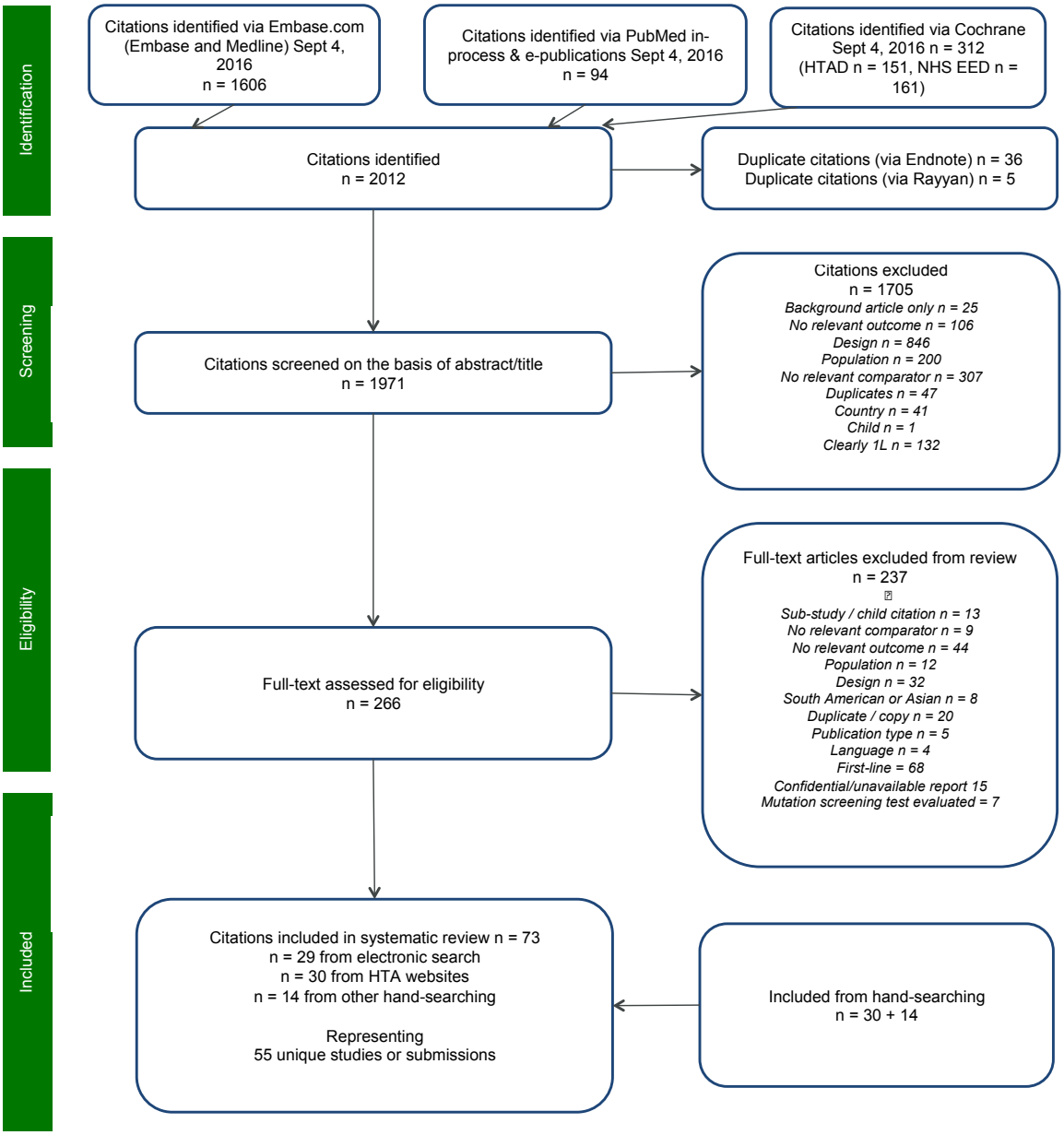
Table 52: Inclusion and Exclusion Criteria for Economic Evaluation Systematic Literature Review

Characteristic	Inclusion criteria	Exclusion criteria & code
Population	• Adult patients (16 years+) • Locally advanced or metastatic NSCLC, second/subsequent line	e1/e2 pop: population not of interest, e.g. • In vitro data • Animal data • Mixed adult/child population or child population • Mixed disease populations without mNSCLC data reported separately • Not disease of interest • 1L metastatic NSCLC data (tx-naïve or maintenance 1L tx will be excluded but tagged* • Non-metastatic population settings • Treatment or prevention for/of a secondary condition rather than for mNSCLC itself (e.g. of VTE or anaemia)
Interventions / comparators	• Licensed and unlicensed pharmacological interventions used in the second/subsequent line within the metastatic setting, compared to each other or to placebo or standard of care. • Companion tests + pharmacological agent, if the objective is to assess the pharmacological agent primarily (tagged)	e1/e2 comp: • Non-pharmacological treatments • Companion test evaluations • Companion test + pharmacological agent, where the objective is to assess the companion test primarily (tagged) • Service delivery evaluations • Supplements for anaemia • Imaging e.g. NeoSPECT, PET • Biopsy methods • Screening studies/bronchoscopy, thoracoscopy • Stereotactic radiotherapy • Radiofrequency ablation • Chemoradiotherapy • Surgery • Palliative endobronchial therapies (e.g. brachytherapy, stenting, photodynamic therapy, laser, electrocautery, cryotherapy, debulking, external beam radiotherapy) • Pharmacological therapy vs. surgery or radiotherapy or chemoradiotherapy
Outcomes	• Evaluation includes both costs *and* effectiveness/utility measures (need not necessarily report an ICER)	e1/e2 outcome: • No outcome of interest

	• Sub-outcomes of interest are: cost components, health states, interim/proxy efficacy measures, safety endpoints	• Cost study only • Effects but not costs • Neither costs nor effects evaluated • Cost-of-illness studies of key interest will be tagged*
Study design	• EEs (CEA, CUA) • EEs alongside a clinical trial • Health technology assessments	e1/e2 design: • Study design not of interest • Pilot studies, MEAs, Case reports, BIA, Review articles, COI, WTP studies, MCDA, Social cost value analysis • SRs/NMAs** • CBA, CMA, CCA studies will be excluded but tagged*
Country	EMEA countries#, USA, Canada, Australia and New Zealand	S. American or Asian countries
Perspective	Payer, societal	Unclear perspective
Time horizon	Unlimited	N/A
Date limits	Unlimited	N/A
Child citation	Citation linked to another paper but with unique data	e1/e2 child: • child citation or sub-study with no unique data, determined at 1st or 2nd pass
Duplicate citation		e1 dup: duplicate/copy
Publication type		e1 pub: publication type not of interest e.g. editorials, commentaries, letters, notes, press articles, unless relevant data has been published in a letter, for example, that does not appear elsewhere in the literature. Confidential reports where unable to use report, or Hayes Inc. reports requiring purchase
Language	• English or French** • Any foreign language paper with an English abstract will be included if sufficient information is present in the English abstract to ensure the eligibility criteria are met	e1 lang: Full text in language other than English or French with no English abstract or no abstract. Or insufficient information in English language abstract of foreign language full paper to assess eligibility

**Whilst planned in the protocol, no language restriction was placed on the search string. Only 4 articles were excluded at second pass on the basis of language; all of which would have otherwise been excluded through other criteria. Hence, such a restriction did not impact the results of the SLR

Figure 30: PRISMA flow chart



5.1.2 Description of studies

The full SLR was conducted from a global perspective (excluding Asia and South America), to support the HTA process for countries beyond just the UK. From the total included studies, the subset most relevant to the decision problem of this appraisal, meeting the NICE reference case and being relevant to decision-making in the UK have been extracted and reported in Table 53.

There was one abstract without a corresponding full publication (Zhou et al., 2015), two full papers (Lewis G, 2010, Holmes et al., 2004) and 8 HTA submissions. With the exception of

the abstract where it was not reported (Zhou Z et al. 2015) and Holmes J, et al. 2004, where there was no discounting (2 year time horizon), all the models used 3.5% discounting of costs and effects. Holmes J et al. 2004 justifed not applying any discounting by indicating that the resource use and benefits from treatment with docetaxel were fairly immediate compared to other interventions, such as screening programmes.

Model types include Markov, semi-Markov, decision-tree and partitioned survival models. Time horizon ranged from 2-20 years. Use of the half-cycle correction was not widely reported, but, all of the more recent UK submissions have used a half-cycle correction.

Only one study evaluated the cost-effectiveness of an immunotherapy treatment for NSCLC; however, this was for a restricted population (non-squamous NSCLC) and conducted from the Scottish perspective.

It is acknowledged that three critical cost-utility studies derived from ongoing HTA assessments (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2016d), (National Institute for Health and Care Excellence, 2017) were not available for full inclusion in the SLR (on-going at time of review). Nevertheless, a summary of these studies has been included from the data that was available in Table 54. Please note, one of the three appraisals (pembrolizumab) has since been published as of 11th January 2017.

Please refer to Appendix 7 for the Drummond checklist-quality assessment for each of the UK-relevent cost-effectiveness studies.

Table 53: Summary list of published UK cost-utility and cost-effectiveness studies

Study	Cost year	Summary of model	Population	Cost results (GBP £)	Health outcome results (QALYs, unless otherwise stated)	Base-case ICER (GBP £/QALY (unless otherwise stated) or dominant)
Holmes 2004 UK FP (Holmes et al., 2004)	2000/2001	Model type and number of health states not reported, 2 yr time horizon, UK NHS perspective, cycle length not reported	Stage IV NSCLC pts in 2L after prior cisplatin or carboplatin who had not been treated previously with taxanes	DOC GBP £4432 BSC GBP £0 (assigned)	DOC 8.89 mths BSC 5.16 mths DOC vs BSC 3.82 mths (0.3197 LYG)	DOC vs BSC £13,863/LYG Using 95% CI for no. of tx cycles (which changes DOC cost, admin cost and co-drug cost): ICER GBP £10,985/LYG, £16,738/LYG Using median no. of tx cycles (median DOC tx cost, median admin costs, and co-drug costs): ICER GBP £11,505/LYG
Lewis 2010 UK FP (Lewis G, 2010)	2009	Health state transition model, 3 health states (PF, PD, death), 2 yr time horizon, UK NHS/PSS perspective, 1 mth cycle length, used half cycle correction	2LL Previously treated stage IIIb/IV NSCLC	ERL £13,730 DOC £13,956	ERL 0.238 DOC 0.206	ERL dominant vs DOC
SMC 1180 NIV 2016 Scotland HTA submission (Scottish Medicines Consortium, 2016)	NR	Partitioned survival model, 3 health states (PF, PD, death), lifetime (20 yrs) time horizon, NHS Scotland perspective, cycle length and use of half cycle correction not reported	Pts with locally advanced or metastatic non-squamous NSCLC after prior CHEMO in adults. Sub-group analyses for PD-L1 expression	Incremental NIV vs DOC £36,830	Incremental NIV vs DOC 0.73	NIV vs DOC £50,565/QALY NIV vs NIN+DOC £56,092/QALY 2-yr stopping rule NIV vs DOC £27,027/QALY NIV vs NIN+DOC £25,116/QALY

TA124 PEM 2007 UK HTA submission (National Institute for Health and Care Excellence, 2007)	2007	Markov model, 4 health states (Response, SDis, PD, death), 3 yr time horizon, UK NHS/PSS perspective, 3 wk cycle length	2L Locally advanced or metastatic (Stage IIIb/IV) squamous NSCLC after failure of previous tx Sub-group analyses for ECOG PS	PEM £8,906 DOC £7,532 BSC £5,527 *ERG corrected analyses* PEM £14,220 DOC £10,622 BSC £5,533	PEM 0.49 DOC 0.42 BSC 0.29 *ERG corrected analyses* PEM 0.4396 DOC 0.4366 BSC 0.2862	PEM vs DOC £18,672/QALY PEM vs BSC £16,458/QALY *ERG corrected analyses* Assuming equal survival PEM vs DOC £458,333/QALY Incorporating additional corrections for assumptions and parameters that do not appear clinically and / or economically justified PEM vs DOC £1,185,164/QALY PEM vs BSC £59,431/QALY
TA296 CRZ UK HTA submission (later updated to TA422) (National Institute for Health and Care Excellence, 2016c)	2011/12	Semi-Markov model, 3 health states (PF, PD, death), 15 yr time horizon, NHS/PSS perspective, 30 day cycle length, used half cycle correction	2L ALK+ advanced or metastatic previously treated NSCLC	CRZ £54,149 DOC £13,922 BSC £6,021	CRZ 1.949 DOC 0.981 BSC 0.592	CRZ vs DOC £41,544/QALY CRZ vs BSC £35,455/QALY
TA310 AFA 2013 UK HTA submission * (National Institute for Health and Care Excellence, 2014)	2012	PSurv model, 3 health states (PF, PD, death), 10 yr time horizon, UK NHS perspective, 1 mth cycle length, used half cycle correction	TKI-naive pts with locally advanced or metastatic NSCLC with EGFR M +ve 1L mainly, but also considered 2L if patients have had prior CHEMO while waiting for mutation test	NR (commercial in confidence)	AFA 1.594 ERL 1.423 GEF 2.291	AFA vs ERL £10,076/QALY AFA vs GEF £17,933/QALY Note: in view of issues with manufacturer's model, ERG did not consider it appropriate to conduct any exploratory analyses

TA347 NIN 2014 UK HTA submission (National Institute for Health and Care Excellence, 2015n)	2012/13	Markov model, 3 health states (PF, PD, death), 15 yr time horizon, UK NHS/PSS (though only included NHS costs in model), 3 wks cycle length, used half cycle correction	2L Locally advanced and/or metastatic, stage IIIb/IV or recurrent NSCLC with adenocarcinoma histology who failed after 1L CHEMO	NR (commercial in confidence)	NR (commercial in confidence)	Revised manufacturer estimate, incorporating PAS NIN+DOC vs DOC £46,580/QALY Exploratory ERG analyses for OS NIN+DOC vs DOC £566,804/QALY
TA374 ERL and GEF 2015 UK HTA submission (Greenhalgh et al., 2015), (National Institute for Health and Care Excellence, 2015a)	2011/13	*ROCHE model* PSurv model, 3 health states (PF, PD, death), 6 yr time horizon, UK NHS/PSS perspective, 1 wk cycle length	2L Same as pts recruited to BR.21 trial, ≥18 years, ECOG PS score 0-3 and who had documented pathological evidence of NSCLC Sub-group analyses for EGFR M –ve population	ERL £13,522 BSC £5,993	ERL 0.579 BSC 0.432	ERL vs BSC £51,036/QALY
TA374 ERL and GEF 2015 UK HTA submission (Greenhalgh et al., 2015), (National Institute for Health and Care Excellence, 2015a)	2011/12	*ERG model* Decision tree, 3 health states (PF, PD, death), 5 yr time horizon, UK NHS/PSS perspective, cycle length not reported, used half cycle correction	2L Stage III or IV NSCLC, good PS and for whom curative tx is not an option, with 3 distinct populations of pts who exhibit EGFR-activating mutations (EGFR M +ve); pts who do not	*EGFR M +ve* NR *EGFR M –ve* ERL £14,049 DOC £13,504 *EGFR unknown* ERL £14,446.38	*EGFR M +ve* NR *EGFR M –ve* ERL 0.4863 DOC 0.5930 *EGFR unknown* ERL 0.4484 BSC 0.3452	*EGFR M +ve* information available did not allow any formal decision modelling to be undertaken. *EGFR M -ve* DOC dominates ERL *EGFR unknown* ERL vs BSC £61,161.81/QALY [Comparison not possible for ERL

			exhibit EGFR-activating mutations (EGFR M -ve); pts with EGFR mutation status unknown (EGFR unknown) Sub-group analysis for EGFR M -ve (or EGFR wild-type) from trial BR.21	BSC £8,132.79		vs GEF]
TA395 CER 2015 UK HTA submission (National Institute for Health and Care Excellence, 2016a)	2014	Markov model, 3 health states (PF, PD, death), 10 yr time horizon, UK NHS/PSS perspective, 1 mth cycle length	3L ALK+ advanced NSCLC previously treated with CRZ	*Novartis model:* CER £59,155 BSC £7,203 ERG exploratory analyses BC: CER £70,620 BSC £7,339	*Novartis model:* CER 1.08 BSC 0.25 ERG exploratory analyses BC: CER 1.06 BSC 0.27	*Novartis model:* CER vs BSC £62,456/QALY ERG exploratory analyses BC: CER vs BSC £79,528/QALY
TA403 RAM 2016 UK HTA submission ** (National Institute for Health and Care Excellence, 2016ch)	2013/14	PSurv model, 3 health states (PF, PP, death), 15 yr time horizon, UK NHS perspective, 21 days cycle length, used half cycle correction	2L Locally advanced or metastatic NSCLC progressed after platinum-based CHEMO Sub-group analyses for non-squamous population	*Eli Lilly model*: RAM+DOC £35,283 DOC £10,995 ERG corrected model: RAM+DOC £38,609 DOC £12,448	*Eli Lilly model*: RAM+DOC 0.816 DOC 0.692	*Eli Lilly model*: RAM+DOC vs DOC £194,919/QALY ERG corrected model: RAM+DOC vs DOC £175,000/QALY

Zhou 2015 UK AB (Zhou et al., 2015)	NR	Decision tree, 3 health states (PF, PD, death), time horizon NR, UK NHS/PSS perspective, cycle length NR	2L Locally advanced or metastatic (Stage IIIb/IV) previously treated ALK+ NSCLC	CER £80,445	CER 2.69	CER vs CRZ £30,536/QALY CER vs DOC £44,847/QALY CER vs PEM £38,966/QALY

Abbreviations: 1L, First-line; 2L, Second-line; AFA, Afatinib; ALK, Anaplastic Lymphoma Kinase; BC, Base Case; BSC, Best Supportive Care; CER, Ceritinib (oral); CRZ, Crizotinib (oral); DOC, Docetaxel (i.v.); ECOG, Eastern Cooperative Oncology Group; EGFR, Epidermal Growth Factor Receptor; ERG, Evidence Review Group; ERL, Erlotinib (oral); GEF, Gefitinib; HTA, Health Technology Assessment; ICER, Incremental Cost-Effectiveness Ratio; LYG, Life Years Gained; M -ve, Mutation Negative; M +ve, Mutation Positive; mth, Month; NHS, National Health Service; NIN, Nintedanib (oral); , Nivolumab (i.v.); NR, Not Reported; NSCLC, Non-small Cell Lung Cancer; PAS, Patient Access Scheme; PD, Progressive Disease; PEM, Pemetrexed (i.v.); PF, Progression Free; PP, Post-Progression; PS, Performance-status; PSS, Personal Social Services; PSurv, Partitioned Survival; Pt, Patient; QALY, Quality-Adjusted Life Year; RAM, Ramucirumab (i.v.); wk, Week; yr, Year;
* The final scope of TA310 included both first line and second-line settings. Consideration could be given as to whether to include this study or not.
** RAM+DOC i.v. vs DOC i.v. or ERL oral or NIN oral +DOC i.v. (adenocarcinoma histology) or NIV i.v. (squamous histology) or CRZ oral (ALK+)

Table 54: Summary of ongoing (as of 21st November 2016) relevant NICE technology appraisals in-progress

Submission	Cost year	Summary of model	Population	Cost results (GBP £)	Health outcome results (QALYs, unless otherwise stated)	Base-case ICER (GBP £/QALY, unless otherwise stated, or dominant)
ID900 NIV UK NICE HTA * (National Institute for Health and Care Excellence, 2016d)	NR	Markov model, 3 health states (Pre-progression, Post-Progression, Death), lifetime (20 yr) time horizon, UK NHS/PSS perspective, cycle length 1 wk	Previously treated locally advanced or metastatic non-squamous NSCLC	Total costs NR NIV: £31,960 (course of 12.6 doses)	NR	Company's BC including PAS: NIV vs DOC <£50,000 NIV vs BSC not provided Using Committee's preferred assumptions: NIV vs DOC >£80,000 (including PAS) NIV vs DOC >£50,000 (including PAS and 2-yr stopping rule) NIV vs NIN+DOC >£150,000 (including PAS) NIV vs NIN+DOC >£150,000 (including PAS & 2-yr stopping

						rule)
ID811 NIV UK NICE HTA (National Institute for Health and Care Excellence, 2016ar)	NR	Model type NR, 3 health states (PF, PD, Death), further model details NR	Previously treated locally advanced or metastatic squamous NSCLC	Total costs NR	NR	Company's revised BC including PAS: NIV vs DOC: £66,100 ERG model including PAS and Committee's preferred assumptions: NIV vs DOC: £73,500
PEMB UK NICE HTA ** (National Institute for Health and Care Excellence, 2017)		Markov model, partitioned survival method, 3 health states (Pre-progression, Post-Progression, Death), lifetime (30 yr) time horizon, UK NHS/PSS perspective, cycle length 1 wk	PD-L1-positive NSCLC after platinum-based chemotherapy	Total costs NR	NR	Final preferred models: PEMB vs : £46,148 to £65,200 without stopping rule

Abbreviations: BC, basecase; DOC, docetaxel; ICER, Incremental Cost-Effectiveness Ratio; NHS, National Health Service; NIN, nintedanib; NIV, nivolumab; NR, Not Reported; NSCLC, Non-Small Cell Lung Cancer; PAS, Patient Access Scheme; PEMB, pembrolizumab; PSS, Personal Social Services; QALY, Quality Adjusted Life Year; UK, United Kingdom; wk, week; yr, year

* Exact ICERs were commercial in confidence and not reported in the documentation available

** Since hand-searching performed this technology appraisal has been completed and was published 11-Jan-2017, TA428 https://www.nice.org.uk/guidance/ta428 in which PEMB was recommended: 'Pembrolizumab is recommended as an option for treating locally advanced or metastatic PD-L1 positive non-small-cell lung cancer in adults who have had at least one chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]-positive tumour), only if pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression,' and the company provides the agreed PAS. Most likely ICERs from company model £61,954 to £44,490 (without stopping rule) and Committee considered that ICER was <£50,000 with 2 yr stopping rule

5.2 De novo analysis

5.2.1 Patient population

The de novo analysis will assess use of atezolizumab for treating locally advanced or metastatic NSCLC after prior chemotherapy. This population is consistent with both the appraisal scope, decision problem, Marketing Authorisation, and the study population of GO28915 [OAK].

5.2.2 Model structure

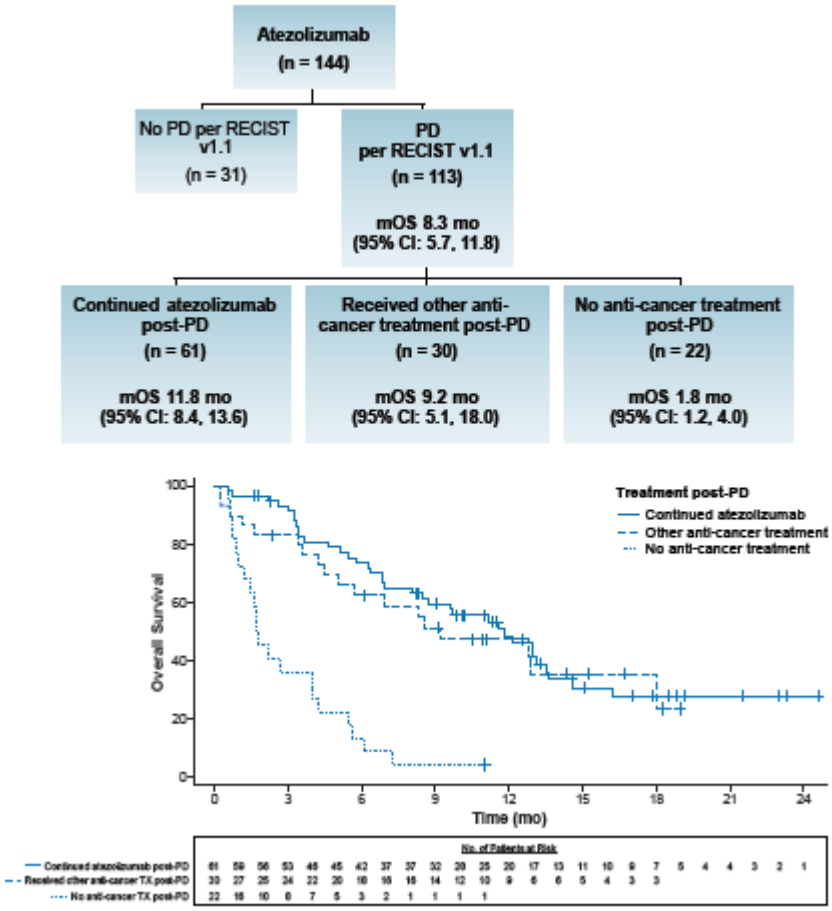
The economic evaluation was developed in Microsoft Excel and is is an Area-Under-the-Curve (AUC; or 'partitioned survival') model. The model is composed of 3-mutually exclusive health states: "on treatment", "off treatment" and Death (Figure 32).

The model structure is a slight adaptation on that seen in previous economic evaluations submitted to NICE in this indication, which have historically utilised a "progression-free-survival", "progressed disease", "death" health state structure (National Institute for Health and Care Excellence, 2015a), (National Institute for Health and Care Excellence, 2015n), (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2016d),(National Institute for Health and Care Excellence, 2017). It has been demonstrated that the traditional modelling methods in cancer treatment (as above) are not well suited to the appraisal of immunotherapies. On this basis, a new approach which was considered better suited to circumstances where treatment beyond progression is common – i.e. with patients continuing to receive clinical benefit from treatment, as seen in the atezolizumab clinical trials (Figure 31) (Mazieres J, 2016).

An "on treatment", "off treatment" health state structure was the most appropriate structure for atezolizumab. The only exception to this structure is for the comparators:

- Nintedanib (plus docetaxel): treatment duration, supportive care costs and utilities are all determined through the traditional PFS/PD/Death model structure, due to the restricted data available for this comparator, and;
- Docetaxel supportive care costs.

Figure 31: Overall Survival Post-PD in Atezolizumab Arm Patients by Follow-Up Treatment Received - POPLAR



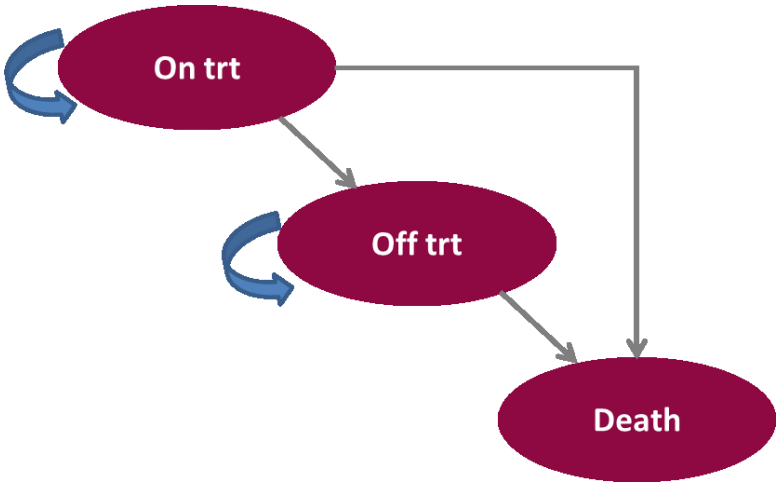
The health economic model was developed to compare the cost-effectiveness of atezolizumab versus docetaxel (and relevant comparators) in patients with locally advanced or metastatic NSCLC who have progressed during or following prior chemotherapy. Nintedanib (plus docetaxel) is also included within the base case cost-effectiveness analysis, incorporated through the mixed treatment comparison (or NMA) as described in Section 4.10. These comparators represent the current standard of care in the second-line setting in the UK for all locally advanced or metastatic NSCLC patients, and are the treatments most likely to be displaced from UK clinical practice following the introduction of atezolizumab.

The model inputs (efficacy, safety and tolerability) were based on the results of the phase III OAK trial, and the NMA outlined in Section 4.10. Results are reported in terms of cost per life years gained and costs per 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 “on treatment” and “off treatment” at discrete time points. The three health states in the model represent the primary stages of disease in locally advanced or metastatic

NSCLC treated with immunotherapies. The “on treatment” health state occupancy is modelled using time-to-treatment discontinuation (TTD). This means that drug costs and utility benefit are based on actual treatment duration, and patients who are treated beyond radiological progression (due to continuing benefit from treatment), go on to accrue utility benefit, and costs, for this period.

Figure 32: Area under the curve model structure



All patients start in the “on treatment” health state. They remain in this health state until they discontinue treatment (transition into “off treatment” health state) or they experience death. Following treatment discontinuation, patients remain in the “off treatment” health state until death, incurring the costs of follow-up treatment. In the event of death the patient will enter the absorbing health state of Death. Patients cannot transition to an improved health state (back to “on treatment”); a restriction that is consistent with prevailing clinical practice with immunotherapies, and previous economic modelling in NSCLC (National Institute for Health and Care Excellence, 2015a), (National Institute for Health and Care Excellence, 2015n), (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2017), (National Institute for Health and Care Excellence, 2016d).

Due to the structural form of the model, patient’s transitions between the health states are not explicitly modelled. The number 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 TTD and OS survival curves from OAK, with the proportion of patients in the “off treatment” health state assumed to be the difference between the two. The partitioned survival approach allows for modelling of OS and TTD based on study-observed events, which is expected to accurately reflect disease progression and the long-term expected survival profile of patients treated with atezoluzumab. However, the primary limitation of this approach is that the transitions are not explicitly modelled, therefore the model structure is rigid and does not allow exploratory or

sensitivity analysis to be explored by changing the transition probability between different health states.

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.

All patients are treated until loss of clinical benefit, which may be beyond progression, consistent with the OAK protocol. Treatment costs include costs of drug acquisition, administration and monitoring. Routine 'weekly supportive care' costs are implemented as health state costs. Finally, adverse event (AE) costs have been applied for the duration of time in which patients were considered to be on treatment, given AEs are likely to occur for the entire time patients are exposed to the study medications. As such, weekly rate of adverse event is calculated by using number of AE occurrence divided by the total time (weeks) at risk which is the sum of time on treatment for each patient in the trial. The costs associated with adverse events management were therefore multiplied by the rate of adverse event and then summed to calculate total cost of adverse event by treatment arm (ITT population in OAK). These costs were applied to each weekly model cycle as long as the patients are on treatment.

The economic model uses a time horizon of 25 years, which was considered to be appropriate as the lifetime of patients with locally advanced or metastatic NSCLC taking into account typical age at diagnosis and advanced nature of disease. This ensures all benefits and costs accrued by patients are captured, and is consistent with the anticipated survival based on the economic model, with only 1% patients still alive at 25 years for atezolizumab, and 0% patients alive for the docetaxel and nintedanib (plus docetaxel) comparators. Finally, this is consistent with the range of time horizons presented in previous NICE STAs in this disease area (nivolumab: 20 years; pembrolizumab: 30 years), and was validated by expert clinical opinion (see Executive Summary) (National Institute for Health and Care Excellence, 2017),(National Institute for Health and Care Excellence, 2016d),(National Institute for Health and Care Excellence, 2016ar).

The model has been designed to use a weekly cycle, with the proportion of patients in each health state calculated every 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, half-cycle correction was applied to each time interval in the Markov trace sheets of the model. This is also consistent with previous NICE STAs in this disease area (National Institute for Health and Care Excellence, 2015a), (National Institute for Health and Care Excellence, 2015n), (National Institute for Health and Care Excellence,

2016ar), (National Institute for Health and Care Excellence, 2017), (National Institute for Health and Care Excellence, 2016d).

5.2.3 Features of the de novo analysis

Table 55: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	25 years	Adequate to capture all costs and benefits for patients with NSCLC, treated with an immunotherapy
Were health effects measured in QALYs; if not, what was used?	Yes, measured in QALYs	In line with the NICE 'Guide to the Methods of Health Technology Appraisals 2013'
Discount of 3.5% for utilities and costs	Yes	In line with the NICE 'Guide to the Methods of Health Technology Appraisals 2013'
Perspective (NHS/PSS)	UK NHS	In line with the NICE 'Guide to the Methods of Health Technology Appraisals 2013'
PSS, personal social services; QALYs, quality-adjusted life years		

5.2.4 Intervention technology and comparators

The final scope includes the following treatments as relevant comparators to atezolizumab in locally advanced or metastatic NSCLC: docetaxel, nintedanib (plus docetaxel), nivolumab, pembrolizumab, and best supportive care.

Considering these proposed comparators:

- Pembrolizumab has conducted all trials in, and has a marketing authorisation for, PD-L1 positive NSCLC patients. The tools utilised for pembrolizumab and atezolizumab to assess PD-L1 expression differ significantly, both in how expression is measured (pembrolizumab: TC only; atezolizumab: TC and IC), but importantly also in which patients are considered positive expressors. Hence, not only are the populations for atezolizumab and pembrolizumab not matched by MA and trial design, but even through utilising a diagnostic test, the eligible patient populations are not equivalent. By including results for pembrolizumab from only PD-L1 positive NSCLC patients within the analysis, there is a risk the relative clinical benefits of pembrolizumab are overestimated, and therefore would not be a true reflection of the comparative efficacy versus atezolizumab (in the all-comer population which is under consideration). Coupled with its recent approval by NICE (TAG issued 11th January

2017; implying it is unlikely to represent a standard of care at time the time of submission), pembrolizumab is not considered to be a relevant comparator, hence has been excluded from the results.

- Nivolumab has received a negative recommendation in its Appraisal Consultation Document (ACD) from NICE, and cannot be considered standard of care: nivolumab has therefore also been excluded from the results
- BSC has been excluded from the analysis. It is considered that patients who are eligible for treatment with atezolizumab would be considered fit enough for other treatment, hence BSC is not an appropriate comparator. This assumption was validated with clinical experts (see Executive Summary), and was also deemed appropriate by NICE and the ERG in the appraisal of pembrolizumab (National Institute for Health and Care Excellence, 2017).

Hence, the comparators assessed in the economic model include docetaxel, and nintedanib (plus docetaxel). The docetaxel comparison is driven from direct evidence obtained in the OAK trial; the nintedanib (plus docetacel) comparison is incorporated through the mixed treatment comparison (or NMA) as described in Section 4.10.

As described in the NMA methods (section 4.10), nintedanib (plus docetaxel) is licensed (and recommended by NICE) only for those patients with adenocarcinoma histology, which is not consistent with the anticipated marketing authorisation for atezolizumab. The pivotal trial supporting the licence of nintedanib (plus docetaxel) (LUME-Lung 1) was, however, conducted in a broader population of all 2L NSCLC patients. In order to conduct a like-with-like comparison versus atezolizumab in its anticipated licence, the "total population" from the nintedanib (plus docetaxel) trial was compared to the atezolizumab ITT population[7]. Consistent with the favorable prognosis seen in patients with non-squamous vs. squamous forms of NSCLC[8] in other trial programmes (Kawase et al., 2012), the OAK and POPLAR studies demonstrated improved outcomes in the subgroup of patients with non-squamous NSCLC (Figure 14, Figure 16). Therefore, the impact of this approach is not anticipated to significantly affect overall results.

As part of the base case analysis, planned dose (based on average BSA within OAK) with vial sharing is assumed. This dosing selection is aligned with the marketing authorisations of all treatments compared in the model, and also allows for a conservative approach to the

[7] Although a similar scenario has been described for the comparison vs. pembrolizumab, the KEYNOTE-010 study did not include a negative-expressor (i.e. all-comer) population.
[8] Adenocarcinoma makes up at least 85% of all non-squamous histologies (see section 3.1 & 4.8)

costing of comparators: accounting for any vial sharing which may happen in clinical practice.

However, other options are available in the model, including:

- Actual average dose per administration as recorded in the OAK trial (average amount per population)
- Planned dose based on individual patient characteristics (based on OAK)

Within each of these three scenarios, a further option has also been provided to choose between the inclusion or exclusion of vial sharing for the calculation of the number of vials used. This option is only applicable to docetaxel as atezolizumab is given in a fixed dose (one vial of atezolizumab per administration) and nintedanib is an oral treatment.

All dosing options detailed above are explored as part of the sensitivity analysis. However, the impact on the results is minimal.

No treatment discontinuation rule has been applied for atezolizumab: based on the OAK trial and marketing authorisation, patients receive therapy until loss of clinical benefit. However, in line with clinical practice, a treatment cap for docetaxel (only) has been included for both the docetaxel, and nintedanib (plus docetaxel) comparisons. The base case analysis incorporates this cap at 6 cycles (18 weeks), in line with clinical expert opinion (see Executive Summary), and other recent submissions in NSCLC (National Institute for Health and Care Excellence, 2016ar),(National Institute for Health and Care Excellence, 2016d),(National Institute for Health and Care Excellence, 2017).

5.3 Clinical parameters and variables

5.3.1 Incorporation of clinical data into the economic model

The primary data source for the economic model was the data derived from the pivotal OAK clinical trial. OAK was a phase III study comparing atezolizumab to docetaxel. Therefore this study is the data source for the intervention, clinical outcomes (OS, PFS), adverse events, treatment dose and duration of treatment. An indirect treatment comparison was conducted and used to allow comparison to nintedanib (plus docetaxel), as discussed in previous sections.

The follow-up period in OAK was shorter than the time horizon of the economic model (25 years to represent a lifetime horizon), hence extrapolation of OS, PFS and TTD from OAK was required.

NICE DSU guidance (Latimer, 2013) was followed to identify base case parametric survival models for OS, PFS and TTD.

Firstly, the proportional hazards (PH) assumption was tested. The PH assumption states that the hazard in one group (arm A) is a constant proportion of the hazard in the other group (arm B). This proportion is the hazard ratio. That is, although the hazard may vary with time, the ratio of the hazard rates is constant. A diagnostic plot of the log cumulative hazard for PFS, OS and TTD over the log of time for the OAK arms was visually inspected to test the PH assumption (Figure 33, Figure 34, Figure 35). Based on the log cumulative hazard plots, it was determined that the PH assumption does not hold as the curves cross each other. This was then further confirmed when assessing the linear relationship between scaled Schoenfield residuals and time (Grambsch P; Therneau T, 1994) (Figure 36 and Figure 37, Schoenfield residuals for PFS not shown as curves clearly cross).

Given rejection of the PH assumption, the next recommendation from the NICE DSU is to explore separate parameterisations for each comparator arm. However, this appraisal has taken an alternative approach by conducting fractional polynomial network meta-analyses (section 4.10). As part of this, the atezolizumab KM data is parameterised, and an extrapolation fit to the data based on best fit and clinical plausibility. Comparator curves are then constructed using the atezolizumab curve as a reference, applying the time dependant (i.e. non proportional) hazard ratios. As such, the fractional polynomials framework removes the need for separate parameterisations for each comparator.

Finally, as per NICE DSU guidance, all parametric models were assessd against the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for fit to the observed data. Extrapolated portions of the curves were also visually inspected to help identify the most plausible survival model. The chosen base case models are a balance between the statistical fit, visual inspection, and validated in terms of clinical plausibility in both the short- and long-term.

Whilst the base case analysis utilises results from the fractional polynomials NMA approach, an alternative approach is explored within the sensitivity analysis which relies on docetaxel data from the OAK study, with separate survival parameterisations fit to the comparator arms.

Figure 33: OS log-cumulative hazard plot

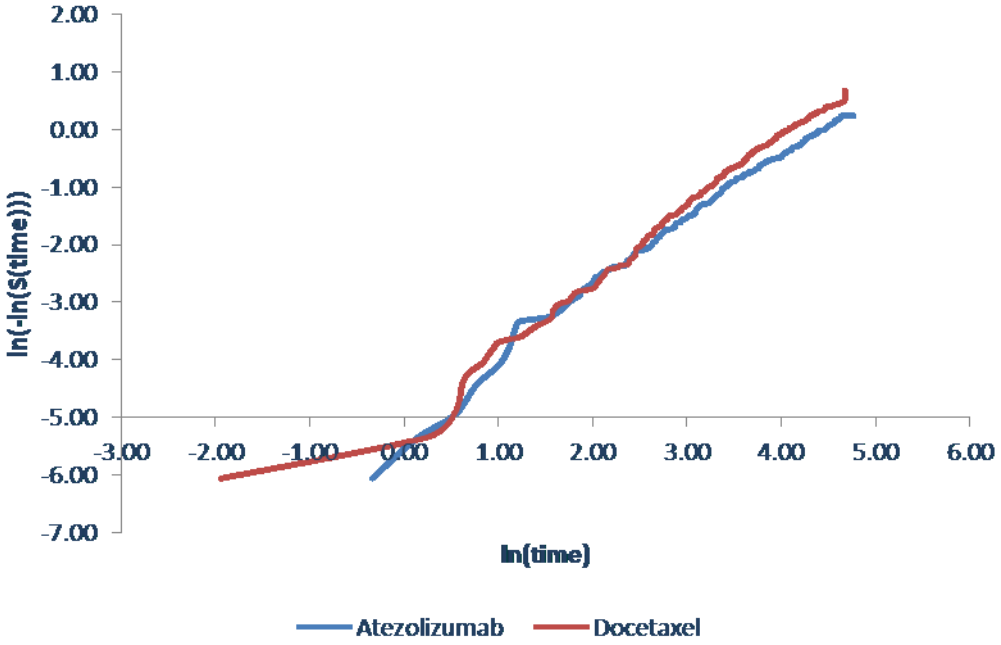


Figure 34: PFS log-cumulative hazard plot

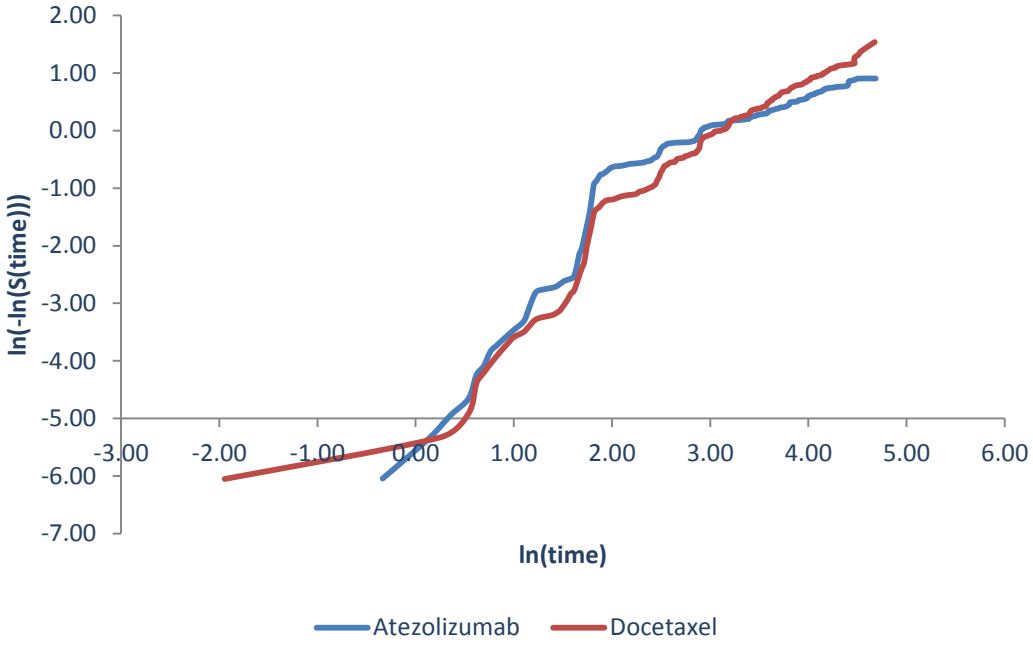


Figure 35: TTD log-cumulative hazard plot

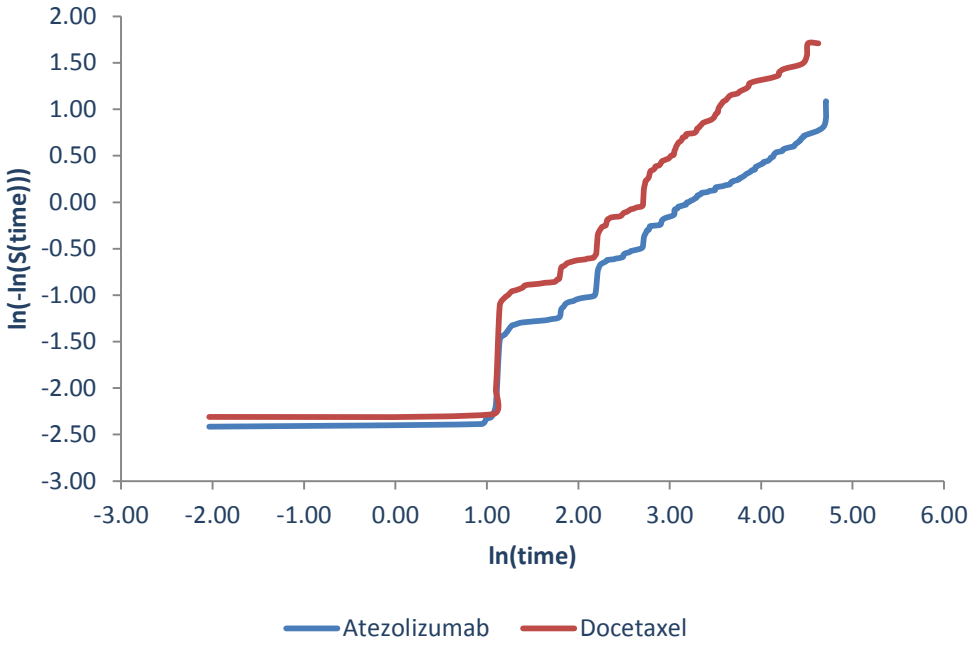


Figure 36: Schoenfield residuals: TTD

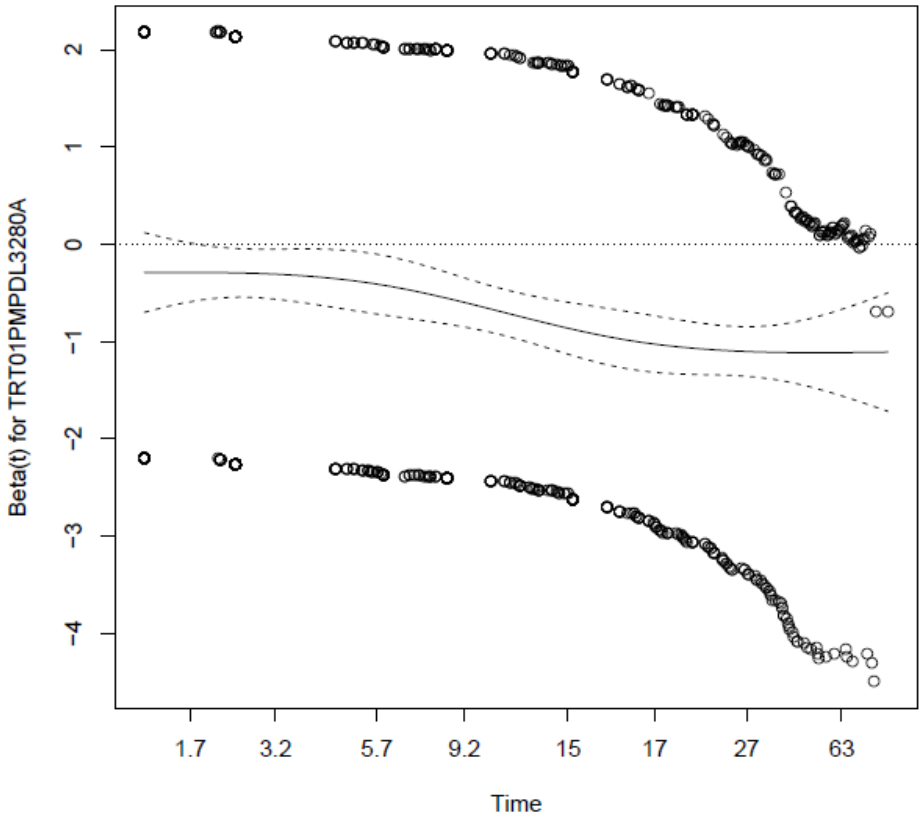
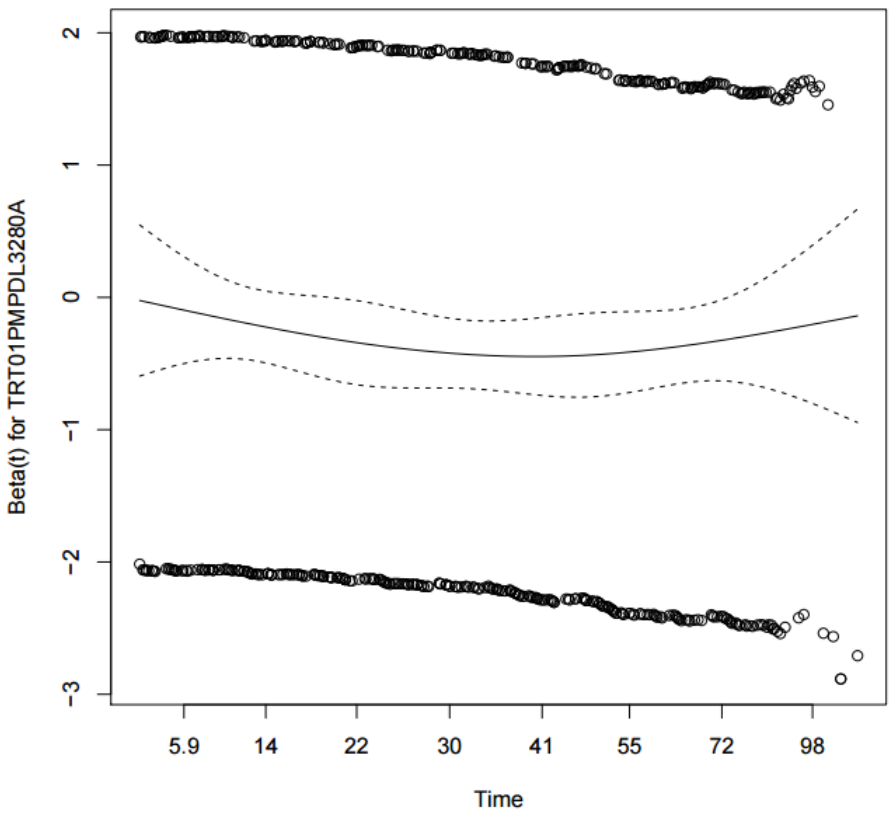


Figure 37: Schoenfield residuals: OS



5.3.2 TTD extrapolation

Atezolizumab

TTD is calculated as the difference between the times where the patient received the first dose, to receiving the last dose of atezolizumab (or docetaxel).

To determine which extrapolation was the most appropriate fit to the observed data, alternative distributions were mapped to the observed KM data from the trial through paramaterisation. The following candidate distributions were assessed for goodness of fit using AIC, BIC and visual assessment: Exponential, Weibull, Log-normal, Gamma, Log-logistic, and Gompertz. Based on the AIC and BIC statistics (Table 56), the Gamma distribution was considered the most appropriate functional form. However, visual inspection shows that, whilst this distribution is the best fit amongst the traditional parametric curves, it was not visually an optimal fit (see Figure 38). This was also true for the Weibull distribution (second best fit in terms of AIC/BIC – see Figure 39). This suggested a more complex fitting curve was most appropriate. Hence, KM data, with extrapolated tails were assessed.

The OAK trial has a relatively large sample size (n=425 for both the atezolizumab and docetaxel arms) and therefore the unadjusted KM data provide a robust representation of

the relative efficacy between atezolizumab and docetaxel. In addition, there is precedent from recent NICE appraisals for use of unadjusted trial KM data followed by extrapolation (National Institute for Health and Care Excellence, 2015n), (National Institute for Health and Care Excellence, 2016d), (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2017).

To reduce the uncertainty in the long term extrapolation, the starting point at which the parametric distribution is applied is based on consideration of the proportion of patients at risk using the OAK data. According to the Pocock criteria, the threshold used to implement the parameterised tail of KM data should not be greater than 20% (or less than 10%) of patients still at risk, and a mid-point of 15% was selected. (Pocock et al., 2002) Based on visual inspection, and in-line with the AIC/BIC best statistical fit, the KM with Gamma tail was utilised in the base case analysis (see Figure 40). Visual fits for all other extrapolations can be found in Appendix 8.

To assess the impact of the uncertainty regarding the most appropriate point to apply the Gamma tail, sensitivity analyses were conducted utilising the 10% and 20% at-risk threshold for atezolizumab. In addition, sensitivity analyses were conducted on all other plausible extrapolation methods. The only exception was for Gompertz: a sensitivity analysis could not be run because the model did not converge.

Table 56: Summary of goodness of fit for TTD

Parametric distribution	AIC	BIC
Exponential	3087.36 (4)	3096.79 (3)
Weibull	3010.19 (2)	3024.33 (2)
Log-normal	3155.71 (6)	3168.85 (6)
Gamma	**3008.68 (1)**	**3022.82 (1)**
Log-logistic	3084.20 (3)	3098.34 (4)
Gompertz	3089.36 (5)	3103.50 (5)

Comparators

TTD for docetaxel was similarly taken from the OAK trial. As seen in the KM data (Figure 40), few patients were still at risk on the docetaxel arm at the OAK study data cut. Therefore a ‘1% at risk’ starting point for the extrapolation was applied to the docataxel arm (corresponding to 17% at risk for atezolizumab).

TTD data were not available for nintedanib (plus docetaxel), therefore in order to extrapolate the treatment effect, results of the fractional polynomial NMA using PFS as a proxy were incorporated into the economic model. The NMA has been previously described in section 4.10.9.

The nintedanib (plus docetaxel) comparator curve is constructed using the atezolizumab extrapolation, and applying the time-dependant log HRs over the span of the extrapolation (see Figure 41).

Figure 38: Parametric and KM estimates for TTD: Gamma distribution

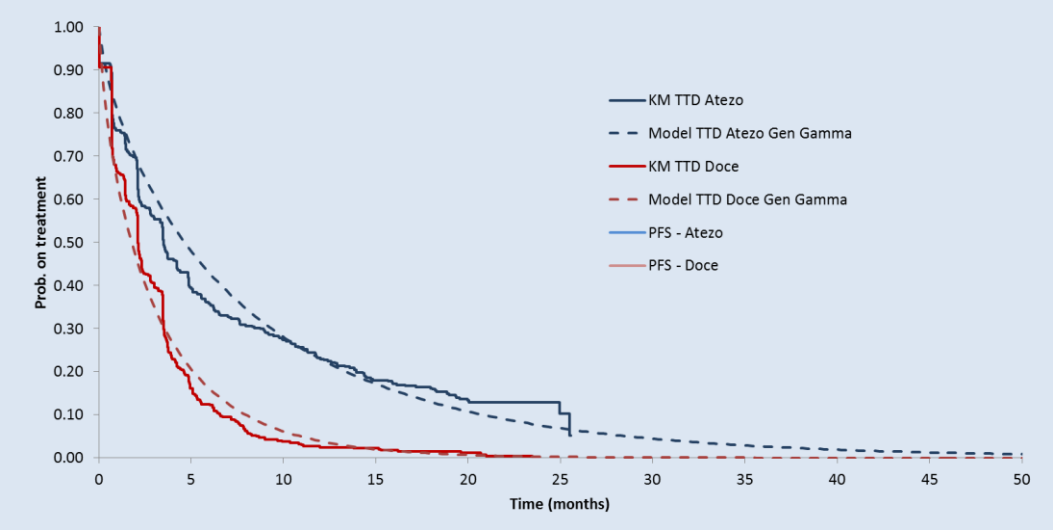


Figure 39: Parametric and KM estimates for TTD: Weibull distribution

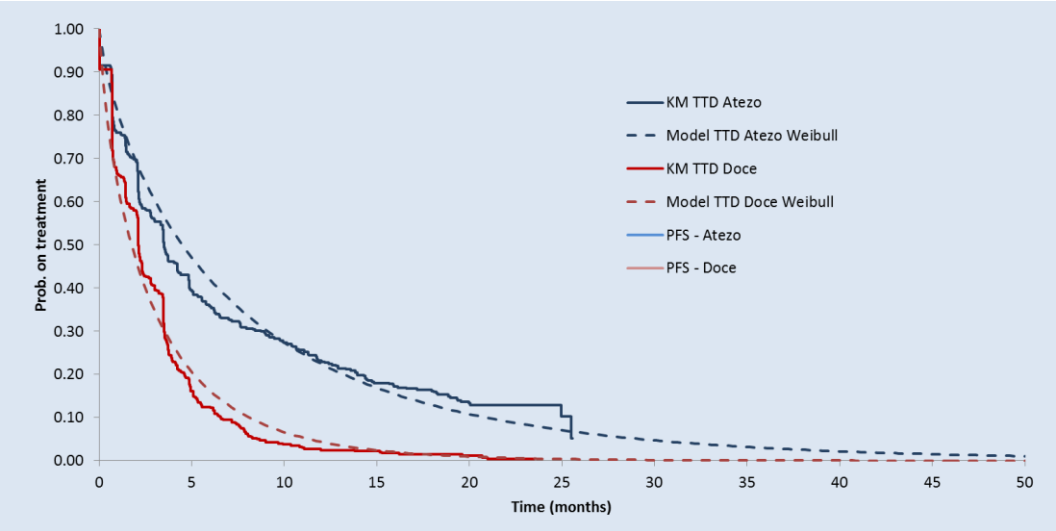


Figure 40: Parametric and KM estimates for TTD: Atezolizumab base case

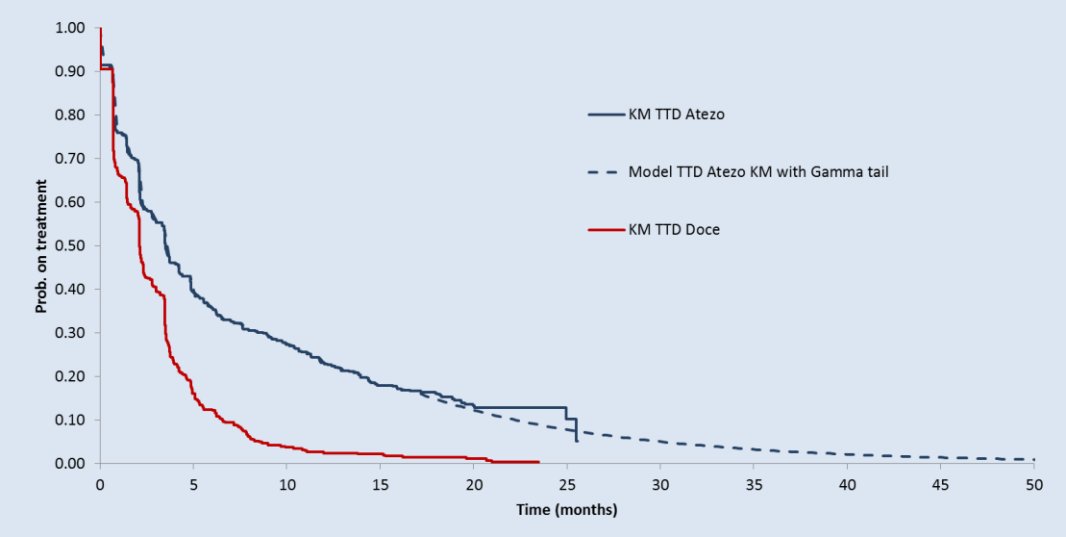
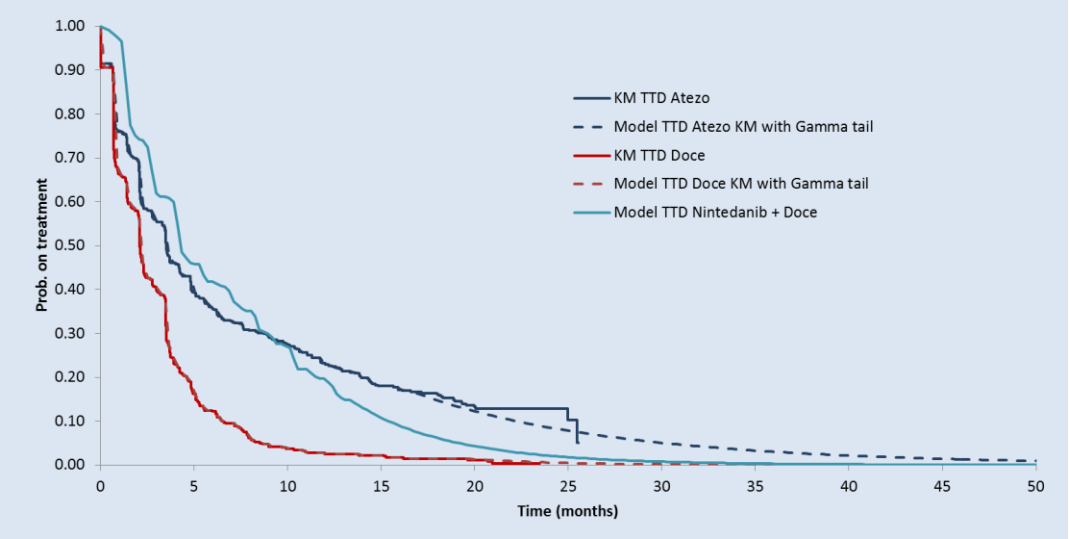


Figure 41: Parametric and KM estimates for TTD: all comparators



5.3.3 PFS extrapolation

Atezolizumab

Similar to the approach taken to incorporate TTD in to the economic model, alternative distributions were mapped to the observed KM PFS data from the trial. Paramaterisation was used to define the most appropriate functional form for fit to the observed data, with candidate curves checked for clinical pleausibility through visual inspection.

The AIC and BIC goodness of fit can be found in Table 57. Based on the AIC and BIC statistics, the Gamma distribution was considered the most appropriate functional form. However, similar to TTD, visual inspection identified that full parameterisation of PFS data

did not fit the observed data particularly well (see Figure 42). This was also true for the log-normal (second best fit by AIC/BIC, see Figure 43), hence use of KMs with parametric tails were considered. Visual fits for all other extrapolations can be found in Appendix 8.

Using the same rationale outlined above for TTD, the KM with Gamma tail applied upon 15% at risk for atezolizumab was utilised in the base case analysis (see Figure 44).

Table 57: Summary of goodness of fit for PFS

Parametric distribution	AIC	BIC
Exponential	2519.13 (4)	2528.62 (4)
Weibull	2521.13 (5)	2535.37 (5)
Log-normal	2373.27 (2)	2387.50 (2)
Gamma	**2361.98 (1)**	**2380.96 (1)**
Log-logistic	2384.88 (3)	2399.12 (3)
Gompertz	2521.13 (6)	2535.37 (6)

Comparators

The FP NMA was conducted on all comparators for the PFS and OS time-to events. Hence, a similar approach to TTD is taken for PFS, with the exception of utilising the FP NMA results, as opposed to OAK data for the docetaxel extrapolation.

Results of the fractional polynomial NMA were incorporated into the economic model in order to generate the extrapolation for the comparators. Comparator curves are constructed using the atezolizumab extrapolation, and applying the time-dependant log HRs over the span of the extrapolation (see Figure 45).

As explained in section 5.2.2, the model structure does not rely on PFS to a significant degree: the exceptions being for the comparison with nintedanib (plus docetaxel) where TTD data are not available (PFS used as a proxy), and supportive care costs in the docetaxel comparison.

As a result, the impact of alternative extrapolations for PFS is minimal, although explored as part of the sensistivity analysis. Again, the Gompertz model did not converge, and a sensitivity analysis could not be run.

Figure 42: Parametric and KM estimates for PFS: Gamma distribution

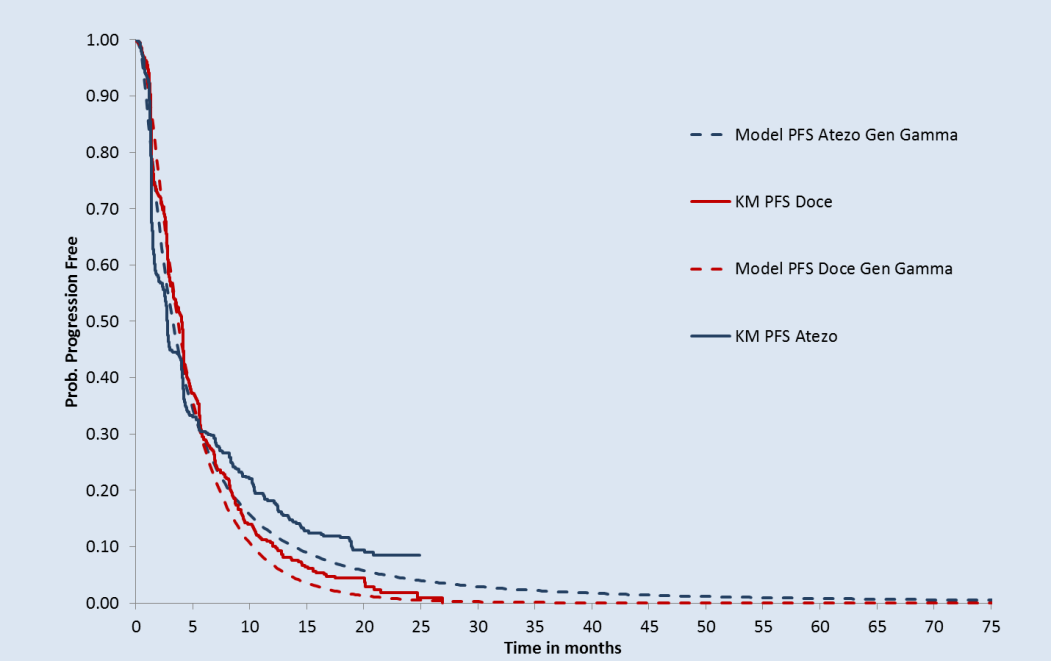


Figure 43: Parametric and KM estimates for PFS: Log-normal distribution

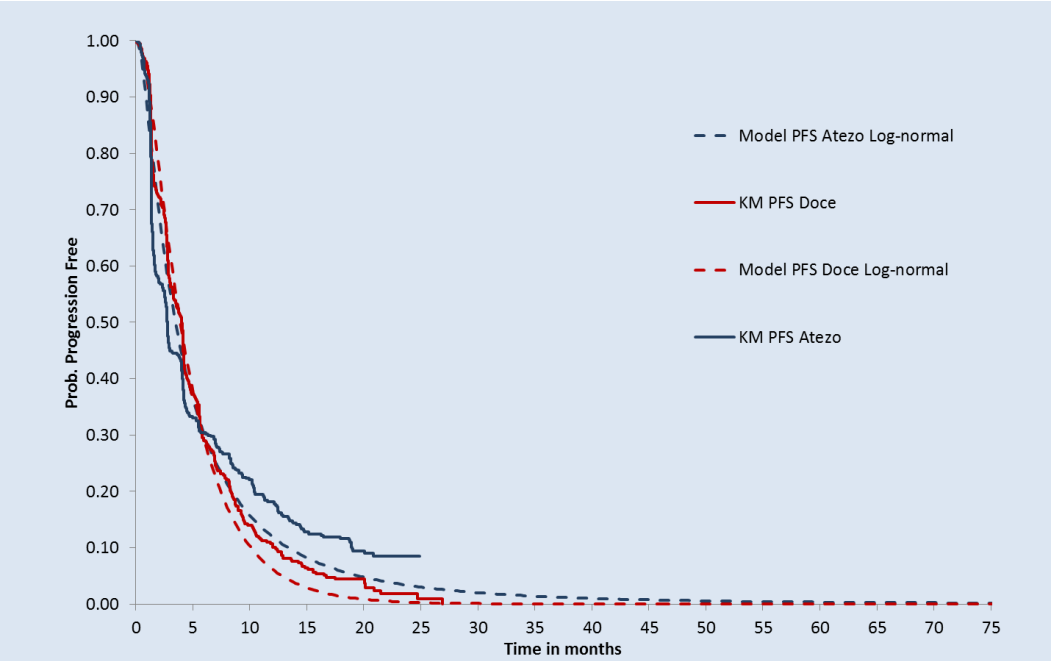


Figure 44: Parametric and KM estimates for PFS: Atezolizumab base case

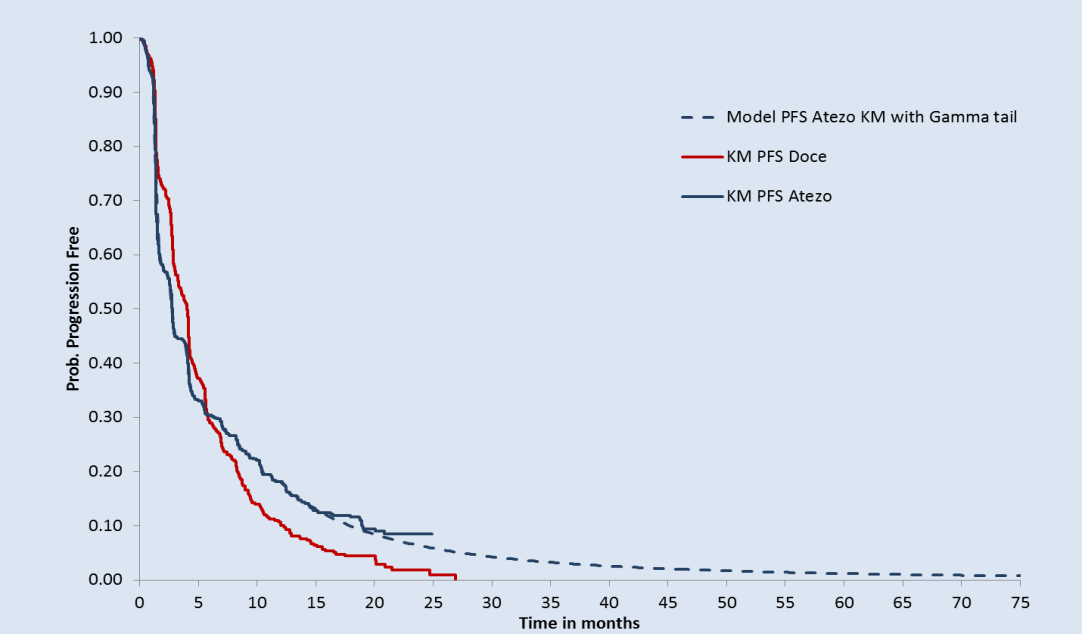
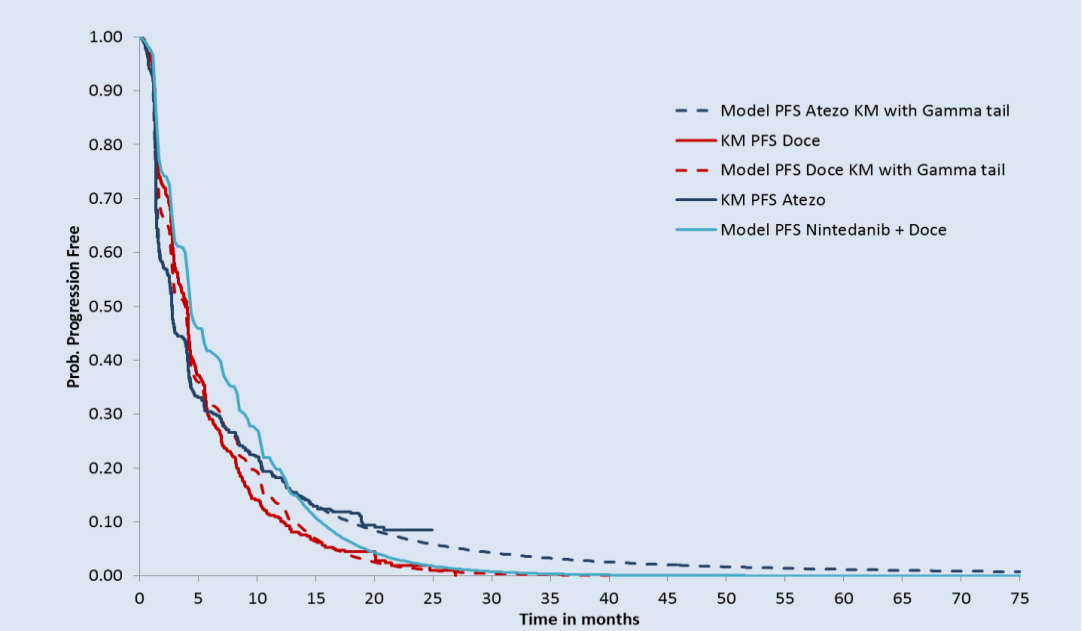


Figure 45: Parametric and KM estimates for PFS: all comparators



5.3.4 OS extrapolation

Experience with immunotherapy agents has increased over the last few years, with indications in melanoma, lung cancer and renal cancer in the last 18 months. Data available for immunotherapy agents suggest the risk of death for patients treated with these drugs declines over time, and it is plausible that some patients experience sustained response, and survival, over time. Clinical experts (see Executive Summary) all assented the expectation is long term survival will be possible for some NSCLC patients, given the

mechanism of action of atezolizumab. This is supportive of recent NICE appraisals which have also concluded that whilst the magnitude of effect is unknown, a long term benefit can be witnessed in the overall survival tails of immunotherapies (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2016d), (National Institute for Health and Care Excellence, 2017).

Long term evidence is not available from clinical trials, and with relatively immature data from the OAK study - use of traditional parametric survival analysis which relies on the observed data for atezolizumab will fail to account for this change in mortality rate and 'flattening' of the tail of the survival curve.

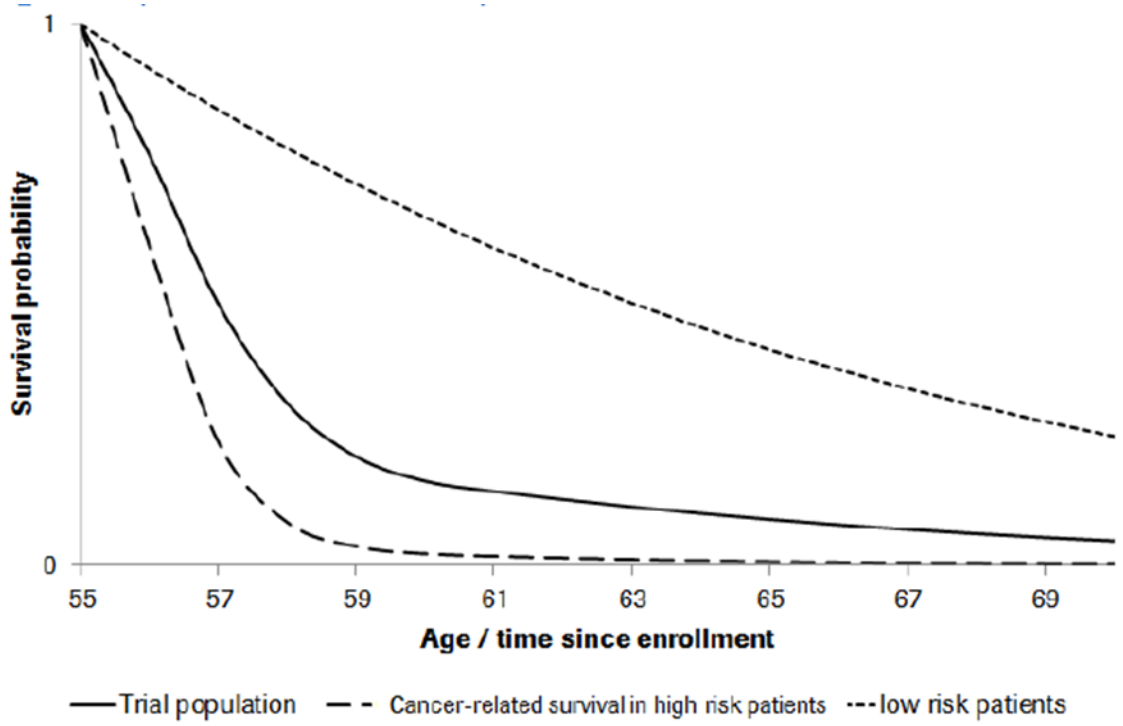
Various methods have been utilised in previous immunotherapy appraisals, with NICE assessments highlighting both strengths and weaknesses to the approaches. An important consideration is the clinical plausibility of the resulting extrapolated survival curve.

Mix-cure rate model

The OS estimates for this analysis were modelled using the mixture cure-rate methodology, as previously described in appraisal TA414, October 2016 (National Institute for Health and Care Excellence, 2016b).

The mixture model accounts for the decrease in cancer-related mortality-risk over time. Statistically, this decrease in the cancer-related mortality-risk is accounted for by an estimation of the overall mortality risk at a given point in time, as a mixture between the cancer-related and background mortality risk. The estimation uses a dataset including the observed survival times in the OAK trial and the background mortality risks from life-tables. The weight assigned to the background mortality is referred to as the "cured fraction". However this 'cure rate fraction', should not be interpreted as a clinical 'cure' from cancer. Rather, the proportion of patients for whom their disease is stable, and the risk of death attributable to cancer, is equivalent to the risk of death from other causes. This can be interpreted as a proportion of patients whom are as likely to die of non-cancer causes as from cancer. These two populations (those with low risk of cancer related death, and those with high risk of cancer related death) are combined to produce an average survival for the whole population, illustrated in Figure 46 below.

Figure 46: Stylised illustration of cause-specific survival rates



The trial population survival is expressed as S(t), and incorporates the patients at high risk of cancer-related death [$S_c(t)$], and the patients at low risk [$S^b(t)$]. The 'cure fraction' is expressed as π.

$$S(t) = S^b(t)\pi + (1-\pi)S^b(t)S_c(t)$$

In order to ascertain the 'cure fraction', long term survival data for NSCLC patients is required, with this often being provided by registry data.

In addition, expert clinical opinion was sought to validate the plausibility of the long-term survival outputs from the economic model (see Executive Summary). Based on their experience and knowledge of immunotherapies, unanimous opinion suggested that an overall survival rate of approximately 10% of patients treated with atezolizumab at 5 years would not be implausible. This is supported by the recent appraisal for pembrolizumab (National Institute for Health and Care Excellence, 2017), where under the Committees preferred assumptions, the resulting 5-year OS estimate was 10.4% (and was specifically acknowledged in the FAD). In addition, similar assumptions were made for the nivolumab appraisals (National Institute for Health and Care Excellence, 2016ar),(National Institute for Health and Care Excellence, 2016d) although these figures have not yet been validated by the Appraisal Committee.

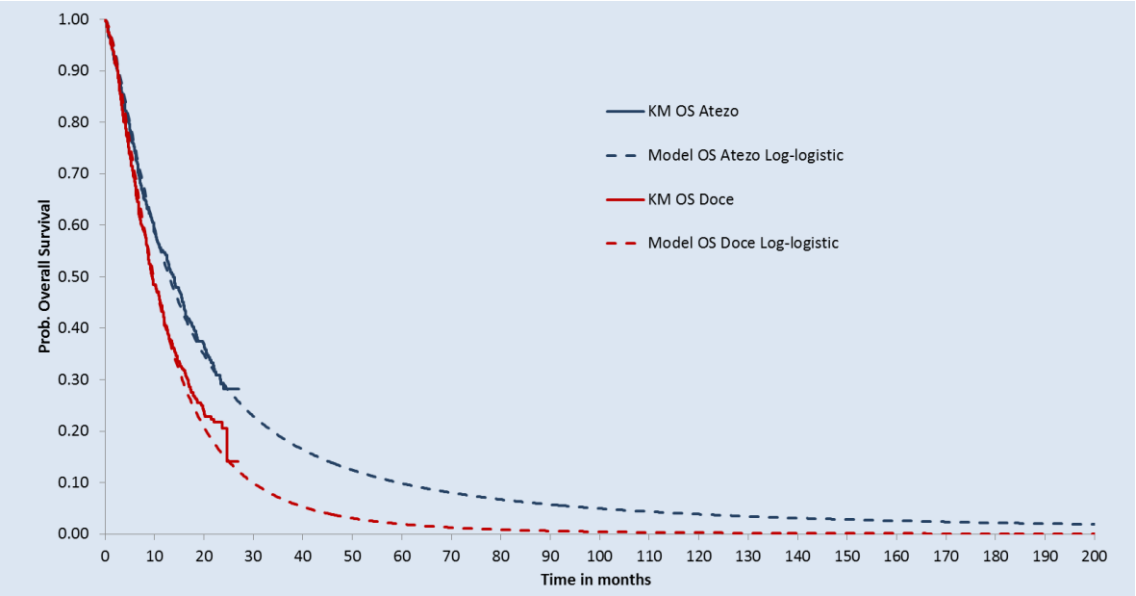
Firstly, the Exponential, Weibull, LogLogistic, LogNormal, Gompertz, Gamma and Generalized Gamma parametric models were fit to the OAK data: AIC and BIC statistics can be found in Table 58.

Table 58: Summary of goodness of fit for OS

Parametric distribution	AIC	BIC
Exponential	2266.50 (4)	2275.99 (4)
Weibull	2259.07 (3)	2273.30 (3)
Log-normal	2270.53 (6)	2284.77 (6)
Gamma	2252.36 (2)	2271.35 (2)
Log-logistic	**2251.90 (1)**	**2266.14 (1)**
Gompertz	2267.34 (5)	2281.58 (5)

According to visual fit and the AIC and BIC criterion, the log-logistic function was the most appropriate fit (Figure 47). This extrapolation was validated with external experts (see Executive Summary), and considered the appropriate distribution for the data available.

Figure 47: Parametric and KM estimates for OS: Log-logistic distribution



The cure function was then applied to the log logistic function based on the evidence from clinical trials, RWE and clinical expert opinion.

To identify an appropriate cure fraction, data for atezolizumab (OAK, POPLAR) were initially considered. However, as the longest follow up available was 2 years from the OAK ITT population, real-world evidence was required to assess overall survival beyond this point.

From the recent NICE appraisals of pembrolizumab and nivolumab (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2016d), (National Institute for Health and Care Excellence, 2017) the Committees and ERGs have deemed The National Lung Cancer Audit (NLCA) the most appropriate source for registry data.

The National Lung Cancer Audit (NLCA) monitors the care delivered for people diagnosed with lung cancer and mesothelioma in England, Wales and Scotland, and provides up to 5 years OS data in England for Stage IIIB and Stage IV NSCLC

Survival estimates are, therefore representative of UK clinical practice and applicable to this economic assessment. Two survival curves were assessed: survival by stage of disease (Figure 48), and survival by stage with/without chemotherapy (Figure 49) (Beckett P et al., 2013). Each graph was digitised using DigitizeIt, with the aim of obtaining a survival probability by year, to support long term survival estimates.

Figure 48: NLCA survival by stage of NSCLC

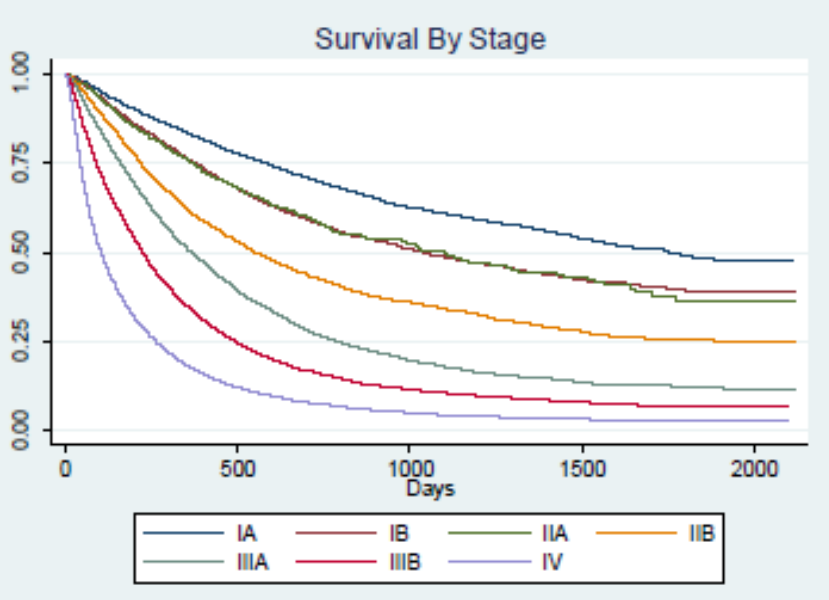
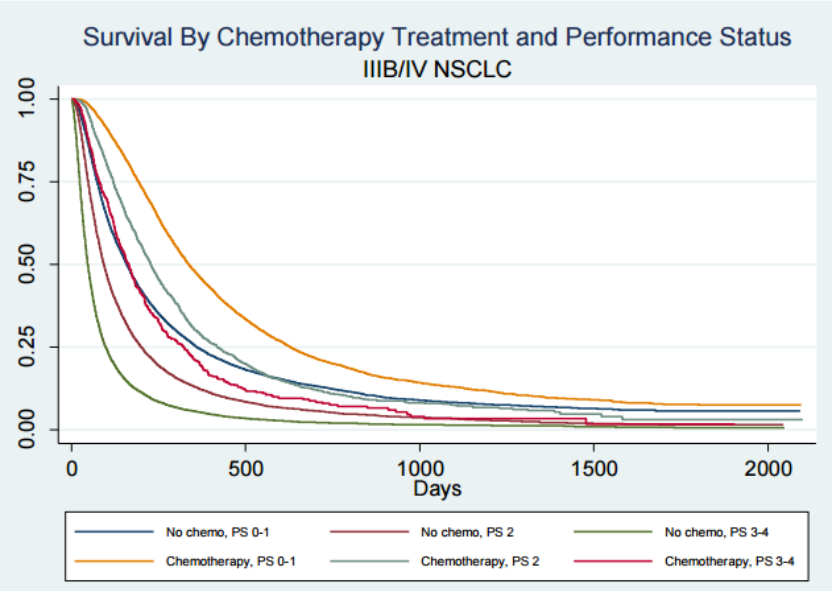


Figure 49: NLCA survival by chemotherapy treatment and performance status of NSCLC



Based on the comparable survival estimates (see Table 59), a 'cure fraction' of 2% is applied for the extrapolation of atezolizumab, indicating that for 2% of patients (for whom their disease is stable), the risk of death attributable to cancer, is equivalent to the risk of death from other causes. In other words, 2% of patients are as likely to die of non-cancer causes as from cancer. Alternative proportions for the cure fraction are explored in scenario analyses.

Table 59: Overall survival estimates: extrapolation validation

Data source	Curve	Proportion alive						
		6 months	1 year	1.5 years	2 years	3 years	5 years	10 years
Mixed-cure 2% **	Atezolizumab OS	72%	55%	41%	32%	21%	12%	6%
	Docetaxel OS	71%	45%	29%	19%	9%	2%	0%
OAK (ITT)	Atezolizumab OS	74.9%	54.7%	40%	29.2%*	NA	NA	NA
	Docetaxel OS	68.7%	41.1%	26.9%	20.6%*	NA	NA	NA
POPLAR (ITT)	Atezolizumab OS	75.4%	51.6%	38.1%	NA	NA	NA	NA
	Docetaxel OS	69.1%	41.9%	24.5%	NA	NA	NA	NA
NLCA *** (OS Stage IIIB/IV; PS0-1 with chemotx)	Treatment not specified	77%	47%	30%	20%	13%	7%	NA
NLCA *** (OS stage IV)	Treatment not specified	33%	17%	10%	7%	4%	2%	NA

* Based on censored data beyond minimum follow-up (28 patients alive in atezolizumab arm, 16 patients alive in docetaxel arm); NA: not available
** 2% cure fraction is applied to atezolizumab only
*** Survival data provided are based on data from 135,390 patients submitted to the NLCA from trusts in England (2006-2010 inclusive). The document does not provide specific numbers or proportion of patients by stage, performance status or therapy for the period covered (2006-2010).

As with PFS, the comparator curves are constructed using the atezolizumab extrapolation, and applying the time-dependant log HRs over the span of the extrapolation.

The resulting parametric curves are demonstrated in Figure 50 and Figure 51.

For visual fits of the alternative extrapolations, please see Appendix 8.

Figure 50: Parametric and KM estimates for OS: atezolizumab vs docetaxel

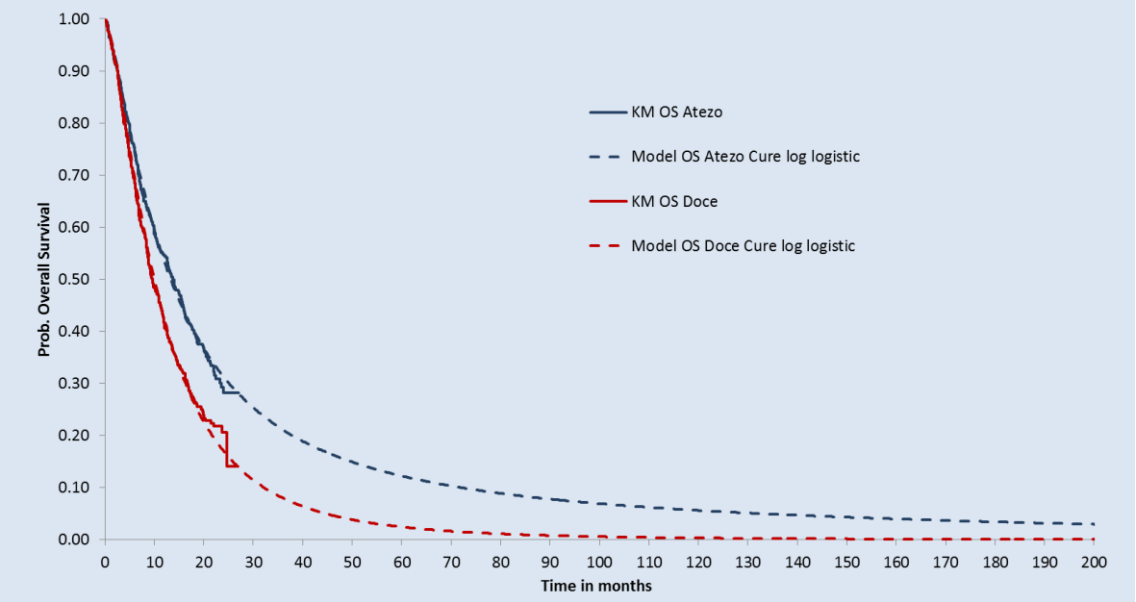
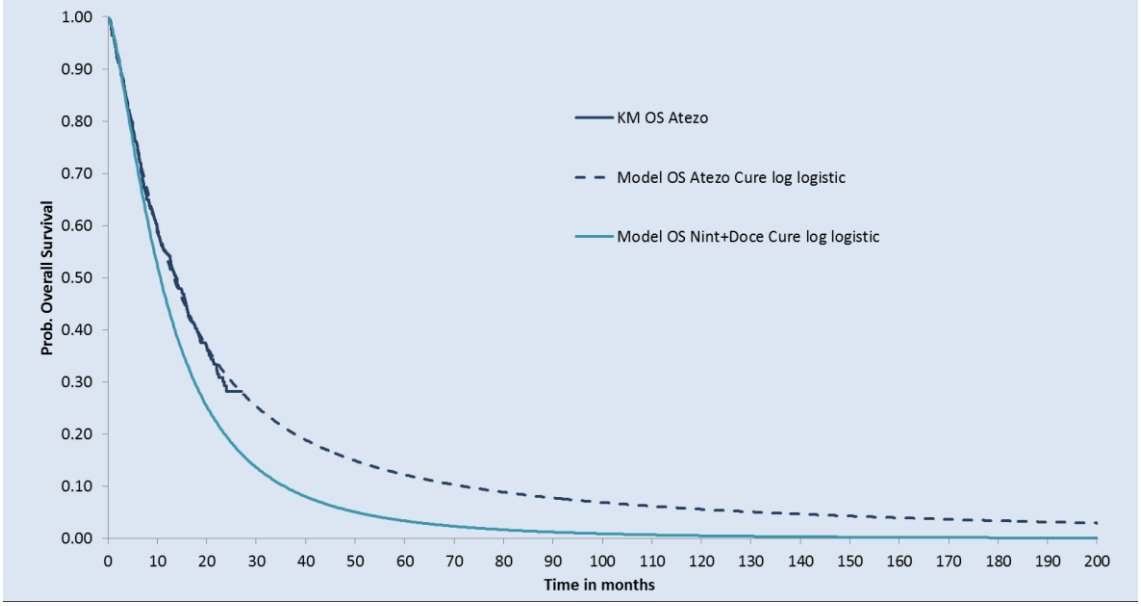


Figure 51: Parametric and KM estimates for OS: atezolizumab vs nintedanib (plus docetaxel)



Using the first order fractional polynomial, the log-HRs increase linearly over time, as the HR from the tail of the observed data continue in the same direction for the extrapolated tail. This HR continues at a rate, and to a value, that was not considered implausible. However,

to explore the sensitivity on this, scenario analyses have been incorporated capping the hazard ratios at different points in time. The impact on the results is minimal.

Finally, sensitivity analyses were also conducted on all other plausible extrapolations, as well as different cure-fractions for the log-logistic extrapolation. Again, the Gompertz model did not converge, and a sensitivity analysis could not be run.

Adjusting for treatment switching

Crossover from the docetaxel arm to the atezolizumab arm was not permitted for the primary population in OAK. However, 5% of patients randomised to atezolizumab, and 17% of patients in the docetaxel arm, went on to receive subsequent cancer immunotherapies, predominantly nivolumab (Table 28).

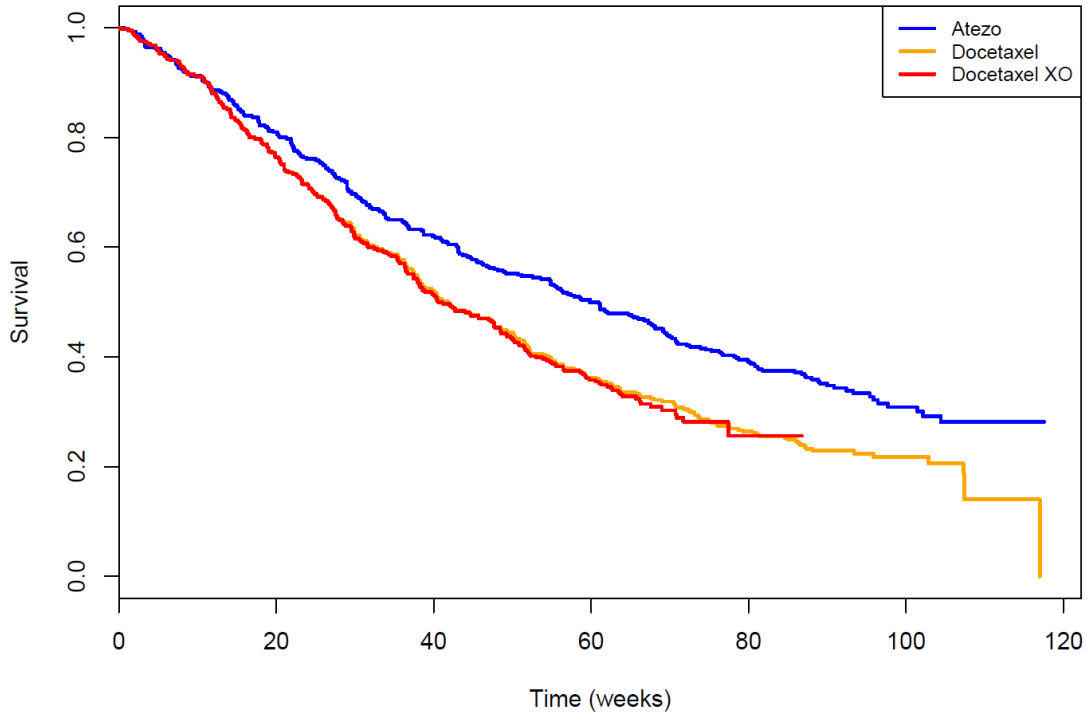
As such, the OS treatment effect estimate of the docetaxel arm was assessed to determine if adjustment was required to correct for any bias induced by treatment switch.

Similar to the pembrolizumab appraisal (National Institute for Health and Care Excellence, 2017), and in-line with the NICE DSU guidance (Latimer, 2014), the Rank Preserving Structural Failure Time (RPSFT) method was used to assess the impact of cross-over on OS estimates.

The KM estimates of crossover adjusted OS in OAK can be seen in Figure 52. Based on the results, crossover was considered to only make a marginal impact, hence was excluded from the economic model. By not adjusting for treatment switching, the current ICER estimates versus docetaxel should be considered as conservative.

This is also true for the nintedanib (plus docetaxel) comparison. Within the LUME-Lung 1 trial, treatment switching was balanced across all populations of patients (Reck et al., 2014) and therefore an adjustment was not required. Given the common docetaxel arm links to the nintedanib (plus docetaxel) comparison from LUME-Lung 1, it stands that the artificial inflation of docetaxel efficacy also applied to nintedanib (plus docetaxel). Therefore, the current ICER estimates versus nintedanib (plus docetaxel) should also be considered as conservative.

Figure 52: KM estimates of crossover (RPSFT) adjusted OS in OAK (ITT primary population; 7 Jul 2016 data cut)



XO: Docetaxel OS estimate accounting for treatment switching

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality of life data from clinical trials

Health-related quality of life was evaluated in the OAK trial using the EuroQoL EQ-5D-3L[9], QLQ-C30 and QLQ-LC13. All HRQoL utilities incorporated in the cost-effectiveness model and described in the following section were derived from this trial. Evaluation of HRQoL using EQ-5D directly from patients is consistent with the NICE reference case, hence is used as the base case analysis.

The EQ-5D questionnaire was administered and completed on Cycle 1, Day 1 (prior to any health care interaction), on Day 1 of each subsequent cycle, and at the treatment discontinuation visit (within 30 days after the last treatment dose). The assessments were required prior to administration of study drug and prior to any other study assessment(s) to ensure that the validity of the instruments was not compromised. In addition, for the atezolizumab arm, the EQ-5D-3L was also collected at 6, 12, and 24 weeks following disease progression via telephone interview performed by trained site staff and in compliance with best practices and recommendations by EuroQol. Study personnel recorded

[9] Time trade-off (TTO) technique used to develop the UK scoring functions

patient responses on a paper copy of the EQ-5D-3L during the telephone interview as record of source documentation.

Three approaches were considered to capture utilities within the model:

1. Estimation of utilities based on health states:

The most commonly seen approach to estimate utilities in oncology economic modelling is through traditional health states of “progression free” and “progressed disease”. The movement between these two health states is triggered by a relative change in tumour size, as measured by the RECIST 1.0 criteria. As discussed in section 5.2.2, treatment with atezolizumab is maintained until loss of clinical benefit, based on data from the OAK study and anticipated marketing authorisation. Often, this is beyond the radiological “progression”, which itself is an asymptomatic change in status. As such, use of a traditional approach (i.e. a utility for “progressed disease”) would underestimate the utility experienced by a patient still receiving benefit from treatment.

Therefore, an alternative approach of “on treatment” and “off treatment” health states was considered. The methodology behind this approach remains: patients experience a higher utility associated with “on treatment” given they are still experiencing clinical benefit. This utility then decreases once a patient discontinues treatment, on the basis there is no longer any clinical benefit. However, clinical expert feedback (see Executive Summary) indicated this approach does not capture the full utility of patients, of note, as HRQoL deteriorates as a patient moves towards death.

2. Estimation of utilities based on time to death

Based on clinical expert feedback, a time until death approach was assessed. This approach reflects the known decline in cancer patients’ quality of life during the terminal phase of the disease. The approach has been previously used in the estimation of HRQoL in NSCLC patients receiving palliative radiotherapy (van den Hout et al., 2006) and in advanced melanoma patients (Batty AJ et al., 2011, Batty AJ et al., 2012, Hatswell et al., 2014). Time to death was demonstrated as more relevant than progression-based utilities since by considering more health states it offers a better HRQoL data fit (Batty AJ et al., 2011, Batty AJ et al., 2012, Hatswell et al., 2014).

Based on OAK EQ-5D data, time to death was categorized into the following groups:

- ≤ 5 weeks before death
- 5 and ≤ 15 weeks before death
- 15 and ≤ 30 weeks before death

- >30 weeks before death

EQ-5D scores collected within each time category were used to estimate mean utility associated with that category. The EQ-5D utility scores were estimated per treatment arm, and pooled for both arms.

Whilst considered a robust approach to capturing HRQoL as a patient nears death, it was considered limited in capturing the additional differentiation in QoL experienced in different health states.

3. Combination approach: estimation of utilities based on health states and time to death

The base case uses a proximity to death approach, as outlined above, combined with the health state utility approach. Given patients experience both health-state related disutility, and end-of-life disutility, the two options can be considered complementary, and therefore combining is the most appropriate approach to use.

Table 60 details the utility values in the base case.

Table 60: Summary of health states utility values – reference case

	On treatment	Off treatment
≤ 5 weeks before death	0.39	0.35
> 5 and ≤ 15 weeks before death	0.61	0.43
> 15 and ≤ 30 weeks before death	0.71	0.58
> 30 weeks before death	0.77	0.68

The impact of alternative approaches on the model results have also been considered, and presented in the sensitivity analyses: OAK utility data for “on treatment” and “off treatment”, without any time-til- death approach incorporated; Nafees 2008 published utility data, and Chouaid 2013 published utility data are all explored.

5.4.2 Health-related quality of life studies

A SLR was performed to identify Health Related Quality of Life (HRQoL) evidence for metastatic NSCLC. This included patient/caregiver generic preference-based utility values (EQ-5D, EQ-5D-5L, HUI, SF-6D, AQOL, 15D, QWB, multi-attribute utility) relating to mNSCLC health states; disutilities or decrements for progressive disease or AEs; or directly

elicited utility scores (SG, TTO, EQVAS), suitable for use in an economic model for a HTA submission or to inform the atezolizumab model.

The searches were performed on 7th September 2016, and a date limit was applied on each database (Table 61). Manual searches were also performed on 5th December 2016, with the same date acting as the cut off. The search strategies for each database, as well as the manual search details are provided in Appendix 9.

Table 61: QoL SLR electronic database sources

Database	Platform	Date span of search	Date searched
Embase	Embase.com www.embase.com	From database inception (1974) to 6-Sep-2016 (updated daily)	07-Sep-2016
Medline	Embase.com www.embase.com	From database inception (1966) to 6-Sep-2016 (updated daily)	07-Sep-2016
Medline InProcess & e-publications ahead of print	PubMed search interface: http://www.ncbi.nlm.nih.gov/pubmed/	From database inception to 17-Nov-2016	07-Sep-2016 initially & weekly alerts received to cut-off date of 18-Nov-2016
CDSR	Cochrane library http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception to August 31st 2016 (September issue, updated monthly)	07-Sep-2016
DARE	Cochrane library http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception to 31st March 2015 (database closed)	07-Sep-2016
CENTRAL	Cochrane library http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception to July 31st 2016 (August issue, updated monthly)	07-Sep-2016
NHS EED	Cochrane library http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception to 31st March 2015 (database closed)	07-Sep-2016
HTAD	Cochrane library http://onlinelibrary.wiley.com/cochranelibrary/search/	From database inception to July 2016 issue (updated monthly)	07-Sep-2016

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; HTAD, Health Technology Assessment Database; NHS EED, National Health Service Economic Evaluation Database

Abstracts were screened by one reviewer and a 50% sample checked by a second reviewer. In the instance of borderline cases remaining these were accepted into second pass. Full papers were reviewed by one reviewer and a 50% sample quality check conducted by a second researcher. Discrepancies were discussed and resolved. If a paper remained borderline a third appropriate reviewer adjudicated. European foreign language papers were screened by appropriate linguists.

To identify disutilities or utility decrements relevant to the experience of patients with NSCLC, a broader population is allowed for in the string, including those associated with lung cancer; and with progressive disease in advanced/metastatic cancer. A broad search was also included to identify adverse event disutilities including:

- Disutilities associated with AEs associated with cancer treatment
- Disutilities associated with the most common sites of metastasis from the lung (bone, respiratory system, nervous, adrenal gland and liver
- Disutilities associated with specific grade III-IV AEs known to occur with treatments used in the field
- Disutilities of particular interest, including: neutropenia, infection, sepsis, fatigue, lethargy, nausea, vomiting, ulcers, stomatitis, GI disturbance, diarrhoea, visual disturbance, hearing loss, hair loss, psychological/self-esteem changes.

The utility filter is adapted from Arber et al., 2015 for searches in the platform Embase.com.

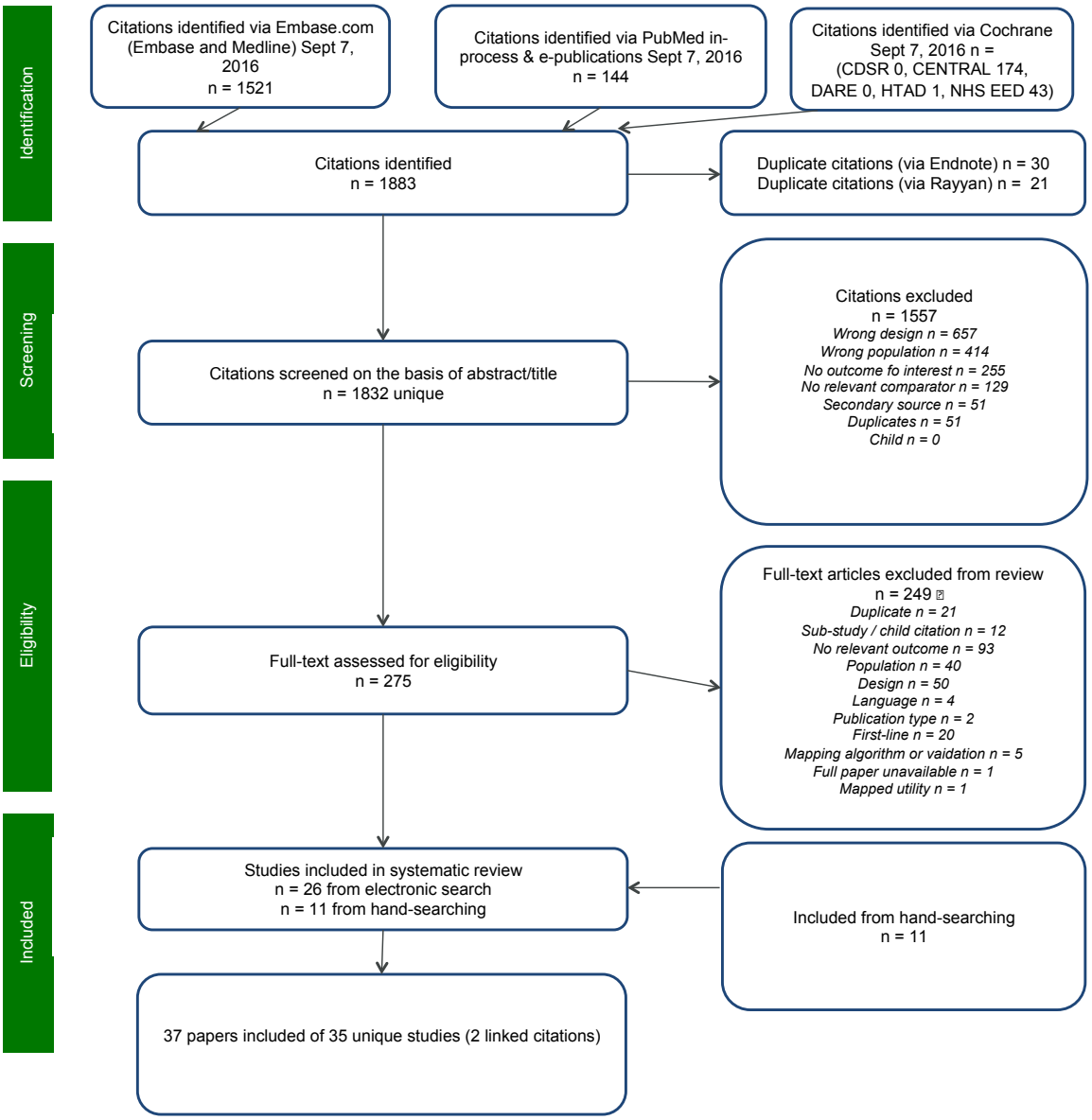
The search strings have no date restriction, nor language restriction.

Eligibility criteria for the SLR are detailed in Appendix 9.

The electronic database searches identified 1883 citations (1521 from Medline/Embase, 144 from Medline InProcess/e-publications, and 218 from the Cochrane Library databases). After system duplicate removal (51 citations – 20 via Endnote de-duplification and 21 via Rayyan) and abstract screening (1557 exclusions), 275 papers were screened at second pass and 248 citations excluded with rationale. An additional 11 citations (Bradbury PA et al., 2008, Chang C et al., 2016, Chen et al., 2011, Dansk V et al., 2016, Handorf et al., 2012, Huang M et al., 2016, Langley et al., 2013, Lloyd et al., 2008, Lloyd et al., 2005, Tabberer et al., Westwood et al., 2014) were included following hand-searching.

The PRISMA flow chart for the systematic review is shown in Figure 53.

Figure 53: Flow-chart for published articles



A total of 37 articles were included in the SLR.

Of these 37, 21 reported EQ-5D index scores (Bradbury PA et al., 2008, Dansk V et al., 2016, Huang M et al., 2016, Langley et al., 2013), (Tabberer et al.), (Yalcin Balcik and Sahin, 2016), (Blackhall et al., 2014), (Chevalier et al.), (Chouaid et al., 2013), (Griebsch et al., 2014), (Grutters et al., 2010), (Hirsh et al., 2013), (Iyer et al., 2013), (Jang et al., 2010), (Novello et al., 2015), (Brahmer et al., 2015)}, (Schuette et al., 2012), (Stewart et al., 2015), (Trippoli et al., 2001), (Yang et al., 2014), (Yokoyama et al., 2013), and 2 directly-elicited SG or TTO from patients (Lloyd et al., 2008, Grunberg et al., 2009). One non-RCT study provided utilities from another preference-based instrument: AQOL (Manser et al., 2006), one provided SF12 (Linnet et al., 2015) data and two summarised EQ-5D VAS (Rudell et al.,

2016), (Schwartzberg et al.).The latter 3 studies were retained in the dataset because they provided data not available from other (preferred) types of utility. Finally, 8 studies used general public valuations of vignettes with directly-elicited SG or TTO (Chang C et al., 2016, Chen et al., 2011, Lloyd et al., 2008, Lloyd et al., 2005, Doyle et al., 2008), (Matza et al., 2014), (Nafees et al., 2016), (Nafees et al., 2008). It should be noted that the Nafees et al. 2008 utilities are general public valuations using directly-elicited SG. Although not formally meeting the NICE reference case, the Nafees et al. 2008 utilities have been extensively used in cost-utility analyses and NICE submissions in NSCLC.

Although second and subsequent line (2L+) data was of primary interest, where an included paper also reported 1L data this was extracted for comparative purposes. Further, 1L data for AEs from Nafees et al. 2016 (Nafees et al., 2016) were extracted to identify the next most appropriate AE distutilities, if data were not available from the 2L setting.

Appendices 9 and 10 summarises the output of the SLR, including the utilities and disutilities most appropriate as options for use in the atezolizumab model.

To be appropriate for CEA, utilities should be estimated from a reasonable sample size and a measure of dispersion should be available. Quality indicators should also be reported to be able to assess how robust the estimate is and whether it might be prone to bias.

Of the studies most closely matched to the atezolizumab population providing main health state data, all studies provided a measure of dispersion, but the sample size varied from 17 for PD (Chevalier et al.), (Chouaid et al., 2013)) and 44-46 for PF((Chevalier et al.), (Chouaid et al., 2013), through 100 for Nafees et al. 2008((Nafees et al., 2008)) to a larger sample for Huang et al. 2016 (Huang M et al., 2016): in this study 560 patients were enrolled in total globally though the exact sample size for PF and PD health states was not reported.

Studies contributing data for AEs were generally of a reasonable sample size. Less robust estimates were from Handorf et al. 2012 (Handorf et al., 2012) (by virtue of being expert opinion estimates), Yokoyama et al.'s average disutility for SREs in bone metastasis (n=9 only) (Yokoyama et al., 2013), Lloyd et al.'s patient TTO sample for anaemia disutilites by Hb level (n=26) and Westwood et al.'s treatment mode disutilities (i.v. and oral) where the sample size is not known (Westwood et al., 2014).

Of the studies reporting utilities for main health states (e.g. PF, PD), those most closely matching the population enrolled in the atezolizumab phase III clinical trial populations are the 2L studies of Chevalier et al. 2013 (Chevalier et al.), Chouaid et al. 2013 (Chouaid et al., 2013), Huang et al. 2016 (10) (although PDL1+) and Nafees et al. 2008 (Nafees et al.,

2008). In particular, the study of Huang et al. 2016 specifies that patients are post-platinum therapy. Also providing a similar population (2L+) are Griebsch et al. 2014 (Griebsch et al., 2014) (Lux Lung 1 data only), Schwarzberg et al. 2015 (Schwartzberg et al.) and Stewart et al. 2015 (Stewart et al., 2015).

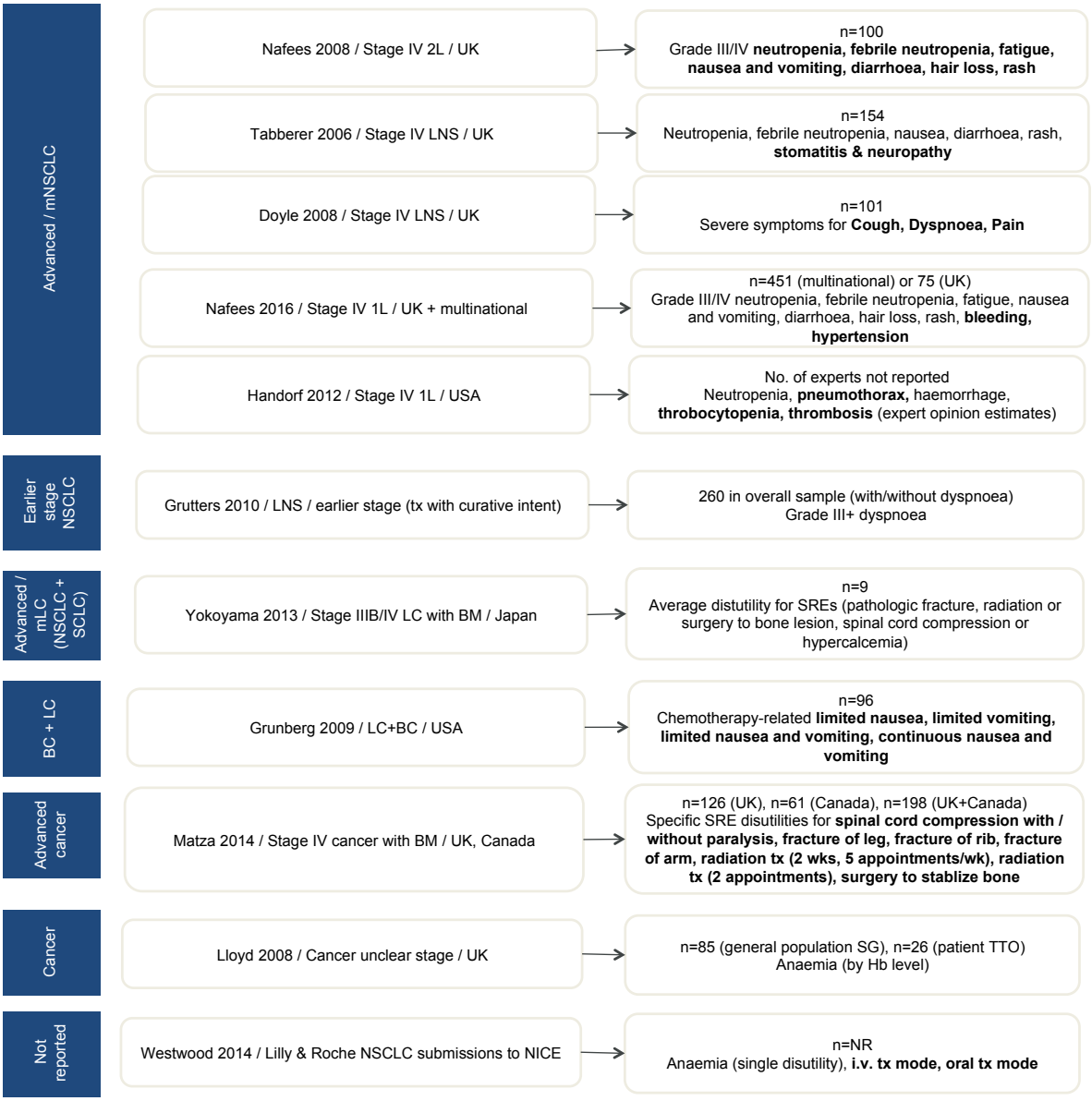
Docetaxel-specific utilities are available from Blackhall et al. 2014 (Blackhall et al., 2014) (crizotinib, pemetrexed, docetaxel) - 2L after progression on platinum-based 1L therapy - and Chen et al. 2010 (Docetaxel, pemetrexed, erlotinib, best supportive care) - docetaxel as 2L advanced NSCLC treatment.

Of the studies reporting AE health state (dis)utilities, Figure 54 illustrates which studies better match the atezolizumab trial population of advanced/metastatic NSCLC in the 2L setting. Matching populations are at the top of the figure, with broader, less well matching, populations, towards the bottom. Health states in bold indicate the best available (from a population perspective) utility data.

In summary, the literature most consistent with the utilities obtained in the OAK trial and the methodology used in the atezolizumab base case analysis is Huange et al. 2016, where time-to-death utilities, and health state based utilities were reported for patients on pembrolizumab or docetaxel. The time intervals used were >360 days, 180-360 days, 90-180 days, 30-90 days and <30 days. For comparative purposes, the phase III 'OAK' trial utilities, which also relate to health states at certain timepoints before death, for patients on atezolzumab or docetaxel, used slightly different time categories from those of Huang et al. In the OAK trial the intervals were >210 days, 105-210 days, 35-105 days and <35 days. There was no timepoint equivalent to the >360 days timepoint of Huang et al. Comparing the utilities at equivalent timepoints obtained from pembrolizumab or docetaxel vs. those obtained from atezolizumab or docetaxel, respectively, the utilities are seen to be very similar: 0.73 vs. 0.77, 0.69 vs. 0.71, 0.60 vs. 0.61 and 0.40 vs. 0.39.

Progression-free/stable disease health state utilities for 2L advanced/metastatic NSCLC recommended for use in cost-effectiveness analyses ranged from 0.74-0.76 for patient-derived EQ-5D to 0.653 for general population-derived SG. Progressive disease utilities in this population ranged from 0.59 to 0.69 from patient-derived EQ-5D. Disutilities for progression from a stable state were -0.056 or -0.065, or -0.1798 by general population-derived SG. Again, these utilities are similar to those obtained from atezolizumab or docetaxel in OAK.

Figure 54: Populations of studies reporting adverse event health state (dis)utilities



5.4.3 Adverse reactions

There are two approaches that could be taken regarding the inclusion of AE impacts on HRQoL:

1. The assumption that any disutility has already been incorporated in to the base case health state utilities through 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.

Following the guidance received in recent technology appraisals (National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d, National Institute for Health and Care Excellence, 2017), the economic model includes the quality of life decrement of all grade 3-5 AEs, which occurred in ≥2% of patients in either treatment arm of the OAK trial (see section 5.5.3).

The disutility per episode for each of the included AEs was sourced from literature. This was then cross-checked and aligned with the ERG and committee-accepted available evidence from other recent technology appraisals (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2016d). The resulting disutilities are shown in Table 62.

Disutilities are applied to each treatment arm whilst patients are still receiving treatment. As per the SmPCs, this is until loss of clinical benefit for atezolizumab, and until progressed disease for nintedanib (plus docetaxel). Conversely, in line with clinical practice, disutilities associated with adverse events due to docetaxel treatment are no longer applied once treatment is discontinued after 6 cycles, or 18 weeks.

Table 62: Disutilities of adverse events

Adverse Event	Disutility	Source
Anaemia	-0.07346	(Nafees et al., 2008)
Fatigue	-0.07346	(Nafees et al., 2008)
Febrile Neutropenia	-0.09002	(Nafees et al., 2008)
Neutropenia	-0.08973	(Nafees et al., 2008)
Leukopenia	-0.08973	Assumed equal to Neutropenia (National Institute for Health and Care Excellence, 2016ar),(National Institute for Health and Care Excellence, 2016d)
Neutropenic sepsis	-0.09002	Assumed equivalent to Febrile Neutropenia
Neutrophil count decreased	0	Assumption (National Institute for Health and Care Excellence, 2016ar),(National Institute for Health and Care Excellence, 2016d)
Pneumonia	-0.008	(Marti et al., 2013)
Respiratory Tract Infection	-0.096	Assumption adapted from Hunter 2015 (Hunter, 2015)
White blood cell count decreased	-0.05	(National Institute for Health and Care Excellence, 2015n)

5.4.4 Health-related quality-of-life data used in cost-effectiveness analysis

EQ-5D analyses based on OAK data showed that as a patient moves towards death, HRQoL decreased over time. In addition, OAK data showed differences in quality of life dependent on whether a patient was on treatment, or off treatment. To capture HRQoL as appropriately as possible, utilities were divided in to categories reflecting the time to death (see Section 5.4.1) and applied in addition to the on treatment and off treatment health states. This approach was validated with UK clinicians (see Executive Summary) and considered representative of real-world QoL for NSCLC patients. Sensitivity analyses were conducted on different methods to capture HRQoL, such as utilising published literature, however it was considered OAK-based utility data was the most appropriate to use in the base case.

The utility is applied to the model consistently over time, based on the time until death, and health state a patient is in. Due to the differing levels of utility (see section 5.4.1), HRQoL is not assumed constant over time, rather utility decreases over time as a patient moves closer to the death health state, in addition to when a patient discontinues treatment.

Table 63: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Base case: by progression status and time-to-death (weeks)				
On treatment				
≤ 5 weeks before death	0.39	(0.24-0.55)	5.4 p.164	OAK reported EQ-5D utilities in line with NICE reference case. Use of progression-based and time to death utilities since approaches are complementary
5 and ≤ 15 weeks before death	0.61	(0.53-0.68)	5.4 p.164	
15 and ≤ 30 weeks before death	0.71	(0.69-0.74)	5.4 p.164	
>30 weeks before death	0.77	(0.75-0.78)	5.4 p.164	
Off treatment				
≤ 5 weeks before death	0.35	(0.27-0.44)	5.4 p.164	
5 and ≤ 15 weeks before death	0.43	(0.37-0.49)	5.4 p.164	
15 and ≤ 30 weeks before death	0.58	(0.55-0.61)	5.4 p.164	
>30 weeks before death	0.68	(0.66-0.71)	5.4 p.164	
Adverse event disutilities				
Anaemia	-0.07346	NR	5.4 p.171	Implementation of adverse event

Fatigue	-0.07346	NR	5.4 p.171	disutilities consistent with recent appraisals. (National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d, National Institute for Health and Care Excellence, 2017)
Febrile Neutropenia	-0.09002	NR	5.4 p.171	
Leukopenia	-0.08973	NR	5.4 p.171	
Neutropenia	-0.08973	NR	5.4 p.171	
Neutropenic sepsis	-0.09002	NR	5.4 p.171	
Neutrophil count decreased	0	NR	5.4 p.171	
Pneumonia	-0.008	NR	5.4 p.171	
Respiratory Tract Infection	-0.096	NR	5.4 p.171	
White blood cell count decreased	-0.05	NR	5.4 p.171	

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

A review of the recent NICE appraisals in NSCLC was undertaken. Given two SLRs were undertaken in 2015 and 2016 for nivolumab (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2016d) and pembrolizumab (National Institute for Health and Care Excellence, 2017), both of which were considered robust and accurate by the ERGs and Committees, it was decided not to undertake an additional review. Instead, the costs and resource use considered in the model are derived from figures and values considered to be appropriate from either the nivolumab or pembrolizumab appraisals.

The costs incorporated in the model include drug and administration costs related to the intervention and comparator; drug acquisition costs for subsequent treatment; monitoring costs; costs associated with managing and treating adverse events; and terminal care costs. Health resource use data is also applied. Since there are no NHS reference costs or payment-by results (PbR) tariffs for costing atezolizumab, an assumption was made that the administration of atezolizumab is equal to that of nivolumab and pembrolizumab: NHS reference Cost code SB12Z (simple chemotherapy). This costing was deemed appropriate by both ERGs and committees in the appraisal of these treatments.

All figures were tested with clinical experts and deemed appropriate to use (see Executive Summary).

5.5.2 Intervention and comparators' costs and resource use

5.5.2.1 Drug acquisition costs

Drug acquisition cost used in the model by pack/vial size and by dose for the initial treatments are presented in Table 64 and Table 65.

- Atezolizumab: as per the anticipated licence, the model uses a fixed dose of 1,200 mg concentrate solution for infusion, administered over 60 minutes for the first infusion, and if well tolerated, as a 30 minute infusion every three weeks (Q3W) thereafter. Please refer to the SmPC in Appendix 1. The list price of a vial is £3807.69.

- Docetaxel: the model assumes a dose of 75kg/m^2, administered per cycle (European Medicines Agency, 2012). Prices for docetaxel vary considerably between the BNF (list price) and eMIT (Drugs and pharmaceutical electronic market information database): in order to generate a conservative estimate, the model uses the lowest cost option.
  The weighted average BSA for men and women from the OAK trial was utilised to estimate the average cost per dose of docetaxel per patient. As a conservative estimate, full vial sharing is assumed for the administration of docetaxel. As per clinical practice in England, the model incorporates a maximum treatment duration of 18 weeks, or 6 cycles of docetaxel. This is consistent with other recent appraisals in NSCLC (National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d, National Institute for Health and Care Excellence, 2017).

- Nintedanib: administered orally as 200mg twice daily in a soft capsule (European Medicines Agency, 2015). The list price is presented, and incorporated in to the model. However, there is a patient access scheme (PAS) in place for nintedanib, but the level of discount is unknown.
  Following the feedback provided by the ERG for the nintedanib NICE submission (National Institute for Health and Care Excellence, 2015n); in clinical practice tablets are dispensed to patients at the time of docetaxel administration in blister packs sufficient to self-treat until the date of the next docetaxel dose (i.e. for days 2 to 21 of

each cycle). Any missing doses are unlikely to affect the dispensing pattern. Therefore, missed doses will not alter the amount and cost of the product dispensed.

It is assumed that patients on the standard dose of 200mg twice per day use the 30-day pack of 100 mg capsules (120 pills) and patients on the reduced dose of 150mg twice per day use the 30-day pack of 150 capsules (60 pills). As both packs cost the same (£2,151.10), the daily cost per patient is the same. Therefore only the 100mg pack is incorporated in to the model.

Table 64: Drug acquisition costs

Drug	Vial/pack concentration	Vial/pack volume	Dose per vial/pack	Cost per vial/pack	Source
Atezolizumab (list)	1200mg/ml	20 ml	1200 mg	£3807.69	UK list price
Docetaxel	20 mg/ml	7 ml	140 mg	£17.77	eMIT
	20 mg/ml	1 ml	20 mg	£4.92	
Nintedanib (list price)	100 mg	120	12000	£2151.10	BNF
	150 mg	60	9000	£2151.10	

Table 65: Drug cost per treatment cycle

Drug	Total dose per administration	No. of vials/pack	Method of administration	Total drug cost per cycle
Atezolizumab (list price)	1,200 mg	1 x 1200 mg Q3W	IV;no vial sharing	£3807.69
Docetaxel	75mg/m^2 * BSA = 135.75 mg	1 x 7ml vial Q3W	IV; vial sharing	£34.39
Nintedanib (list price)	100mg	200 mg twice daily Days 2 to 21 of a standard 21 day docetaxel treatment cycle	Oral	£1434.07

Drug acquisition costs – subsequent treatments

The economic model includes costs of subsequent treatment for patients who have progressed.

At 25 months follow up, approximately 13% of patients were still on treatment with atezolizumab[10]. Therefore, we do not have a complete data set of post-discontinuation

[10] Subject to censoring

threapies (distribution of treatments, time on subsequent treatment). As such, so as not to bias the analysis by giving a falsly low subsequent treatment cost to atezolizumab, an average has been taken by pooling the arms.

The average cost of subsequent treatment was calculated by weighing the distribution of subsequent treatments received amongst all patients (as per the OAK trial: atezolizumab and docetaxel arms), the unit cost of each subsequent treatment, and the average duration of treatment. This one off cost is then applied to every patient as they discontinue, regardless of whether they are discontinuing from atezolizumab, docetaxel or nintedanib (plus docetaxel).

As per the OAK trial, 45% of all patients (regardless of treatment arm within the economic analyses) have been assumed to receive subsequent pharmacological treatment, and 55% of patients went on to receive radiotherapy.

One amendment was made to the distribution of subsequent therapy: Within the OAK trial it was noted approximately 4.5% of the atezolizumab arm, and 17.2% of the docetaxel arm who had progressed on to subsequent pharmacological treatments received another immunotherapy. Upon consultation with clinical experts (see Executive Summary), it was deemed unlikely that in clinical practice patients would receive a subsequent immunotherapy after discontinuation of atezolizumab. Given the costs of subsequent therapy are pooled across treatment arms, this proportion was removed from the analysis. However, this presents a limitation within the economic model given the large disparity of patients who went on to receive an immunotherapy between the treatment arms: In effect, by removing this, the economic model underestimates the costs associated with docetaxel treatment. In parallel, whilst no adjustments for treatment switching have been implemented, the efficacy associated with docetaxel is overestimated.

Table 66 and Table 67 detail the drug acquisition costs, dose and frequency of administration for all pharmacological subsequent treatments. Table 68 details the radiotherapy costs for all other patients.

The average time on subsequent pharmacotherapy treatment was 13.596 weeks, and the average cost £1,987.06. The average number of doses per patient undertaking subsequent radiotherapy was 20.58; and the average cost £1,353.08. In total, this equated to a post discontinuation cost of £3,340.14.

A scenario will be run whereby 100% of patients receive subsequent pharmacological treatment, and 0% receive radiotherapy as it is unclear whether radiotherapy is used frequently as a third line treatment in clinical practice.

However, results are not sensitive to this cost, with an approximately 3-fold change in cost equating to a less than £50 difference in the ICER.

Table 66: Drug acquisition costs (subsequent treatments)

Drug	Dose/vial concentration	Pack size/vial volume	Cost per pack/vial	Source
Docetaxel	10mg/ml	1ml	£4.92	eMIT
		4ml	£12.47	
		7ml	£17.77	
		8ml	£34.83	
Carboplatin	10mg/ml	5ml	£3.57	eMIT
		15ml	£7.62	
		45ml	£19.06	
Gemcitabine	200mg/vial	200mg	£3.52	eMIT
	1,000mg/vial	1,000mg	£30.89	
Erlotinib	150mg	30 tablets	£1631.53	DMD
Pemetrexed	1mg/ml	100ml	£144.00	DMD
		500ml	£720.00	
Vinorelbine	10mg/ml	1ml	£5.04	eMIT
		5ml	£18.24	

Table 67: Drug acquisition costs per week (subsequent treatments)

Drug	Total dose required per administration	Dose required	Drug cost per cycle	Drug cost per week (including admin cost)
Docetaxel	75 mg/m^2	-	£34.33	£67.26
Carboplatin	400 mg/m^2	723	£53.55	£55.22
Gemcitabine	1,000 mg/m^2	1,808	£105.60	£68.24
Erlotinib	150 mg	150	£54.38	£1,552.07
Pemetrexed	500 mg/m^2	904	£1,440.00	£535.78
Vinorelbine	28 mg/m^2	45	£25.20	£192.54

Table 68: Radiotherapy costs

Radiotherapy preparation	Cost	Source
SC47Z: Preparation for simple radiotherapy with imaging and simple calculation (Outpatient)	£283.06	NHS reference costs 2015-16
SC22Z: Deliver a fraction of treatment on a megavoltage machine (Outpatient)	£105.77	NHS reference costs 2015-16

Table 69: Subsequent therapy distribution

Description		Value
Proportion undertaking any pharmacological subsequent treatments		45%
Proportion undertaking radiotherapy as a subsequent treatments		55%
Mean doses per patient of radiotherapy		20.58
Distribution of pharmacological treatments	Docetaxel	14.91%
	Carboplatin	8.74%
	Gemcitabine	7.71%
	Erlotinib	5.53%
	Pemetrexed	4.88%
	Vinorelbine	5.14%
Time on subsequent treatment	Docetaxel	11.64 weeks
	Carboplatin	13.05 weeks
	Gemcitabine	17.48 weeks
	Erlotinib	10.80 weeks
	Pemetrexed	16.49 weeks
	Vinorelbine	12.11 weeks

5.5.2.2 Administration costs

The costs of administration utilised in the economic model for atezolizumab and comparators are shown in Table 70. As per the nivolumab and pembrolizumab appraisals in NSCLC (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2016d), (National Institute for Health and Care Excellence, 2017), the cost associated with administering atezolizumab is assumed to be that of a simple chemotherapy (as described in the NHS reference costs).

As nintedanib is taken orally, an additional administration cost of pharmacist time is applied whilst patients are also receiving docetaxel. However, once docetaxel is discontinued and patients continue treatment on nintedanib monotherapy (after a maximum 6 cycles), only the administration cost of pharmacist time associated with nintedanib is applied.

An additional data source was located detailing National tariffs for alternative chemotherapy regimens (Health and Social Care Information Centre, 2016). Within this, nintedanib delivery

was costed at £183.50 [Healthcare Resource Group (HRG) code: SB11Z; Deliver Exclusively Oral Chemotherapy]. However, this cost was considered high for an oral therapy, therefore is only included as a sensitivity analysis.

Table 70: Drug administration costs

Drug	Type of administration		NHS reference code	Cost per administration	Source
Atezolizumab	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient Setting	SB12Z (outpatient)	£198.94	NHS reference costs 2015-16
Docetaxel	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB12Z (outpatient)	£198.94	NHS reference costs 2015-16
Nintedanib (pre-docetaxel discontinuation) – base case	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB12Z (outpatient)	£198.94	NHS reference costs 2015-16
	12 minutes pharmacist time every 30 days	Hospital pharmacist (band 6); radiographer cost per working hour		£46 per hour = £9.20 per administration	PSSRU 2016 (13)
Nintedanib (post-docetaxel discontinuation) – base case	12 minutes pharmacist time every 30 days	Hospital pharmacist (band 6); radiographer cost per working hour		£46 per hour = £9.20 per administration	PSSRU 2016 (13)
Nintedanib (pre-docetaxel discontinuation) – scenario analysis	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB12Z (outpatient)	£198.94	NHS reference costs 2015-16
	Deliver Exclusively Oral Chemotherapy	Outpatient setting	SB11Z	£183.50	NHS reference costs 2015-16
Nintedanib (post-docetaxel discontinuation) – scenario analysis	Deliver Exclusively Oral Chemotherapy	Outpatient setting	SB11Z	£183.50	NHS reference costs 2015-16

5.5.2.3 Monitoring and disease management costs

Disease management costs are applied for both “on treatment”, and “off treatment” health states. The unit costs of resource use are consistent over cycle lengths, however the frequency of resource consumption per cycle varies between the health states. The types of resource and frequency of use are derived from previous technology appraisals and validated by UK clinicians (see Executive Summary).

Table 71 details the cost of monitoring a patient whilst on treatment. This is applied to the “on treatment” health state for all treatment arms.

Table 71: Monitoring costs

Type of monitoring	No. required per 3 weeks	Unit cost	Cost per 3 weeks	Source
WF01A: Non-Admitted Face to Face Attendance, Medical Oncology	1	£162.84	£162.84	NHS reference costs 2015-16

Table 72 details the resource use for “on treatment” health state and Table 73 describes the resource use in “off treatment”. Unit costs are details in Table 74. The total cost per week in the “on treatment” health state is £128.25, and the total cost per week in “off treatment” is £120.12.

Table 72: Resource use for “on treatment” health state

Resource	No. required per 3 weeks	% of patient requiring resource	Unit cost	Cost per 3 weeks	Source
Routine GP visit (at surgery)	0.63	100%	£45.68	£28.78	(National Institute for Health and Care Excellence, 2015a, National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d, National Institute for Health and Care Excellence, 2017) The values were updated following clinician validation
Oncologist	0.8	100%	£167.08	£133.66	(National Institute for Health and Care Excellence, 2015n, National Institute for Health and Care Excellence, 2017) The values were updated following clinician validation

Full blood test	1	100%	£3.10	£3.10	(National Institute for Health and Care Excellence, 2015n, National Institute for Health and Care Excellence, 2017)
Liver function test	1	100%	£1.18	£1.18	(National Institute for Health and Care Excellence, 2015n, National Institute for Health and Care Excellence, 2017)
Renal function test (with electrolytes)	1	100%	£1.18	£1.18	(National Institute for Health and Care Excellence, 2015n, National Institute for Health and Care Excellence, 2017)
CT scan (thorax or abdominal)	0.28	100%	£118.53	£33.19	(National Institute for Health and Care Excellence, 2015n, National Institute for Health and Care Excellence, 2017)
Palliative care	2	100%	£91.83	£183.66	(National Institute for Health and Care Excellence, 2015n, National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)
Total cost per week)	£128.25 per week				

Table 73: Resource use for "off treatment" health state

Resource	No. required per 3 weeks	% of patient requiring resource	Unit cost	Cost per 3 weeks	Source
Routine GP visit (at surgery)	1	100%	£45.68	£45.68	(National Institute for Health and Care Excellence, 2015a, National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)
Routine GP visit (at patient's home)	0.25	100%	£67.16	£16.79	(National Institute for Health and Care Excellence, 2015a, National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d) The values were updated following clinician validation
Palliative care (days)	2	100%	£91.83	£183.66	(National Institute for Health and Care Excellence, 2015n, National Institute for

					Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)
Oncologist	0.46	100%	£167.08	£76.86	(National Institute for Health and Care Excellence, 2015n, National Institute for Health and Care Excellence, 2017)
Full blood test	1	100%	£3.10	£3.10	(National Institute for Health and Care Excellence, 2015n), (National Institute for Health and Care Excellence, 2017)
Liver function test	0.46	100%	£1.18	£0.54	(National Institute for Health and Care Excellence, 2015n, National Institute for Health and Care Excellence, 2017)
Renal function test (with electrolytes)	0.46	100%	£1.18	£0.54	(National Institute for Health and Care Excellence, 2015n), (National Institute for Health and Care Excellence, 2017)
CT scan (thorax or abdominal)	0.28	100%	£118.53	£33.19	(National Institute for Health and Care Excellence, 2015n, National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d, National Institute for Health and Care Excellence, 2017)
Total cost per week)	£120.12 per week				

Table 74: Unit costs (on and off treatment health states)

Resource	Unit cost	Source
Routine GP visit (patient's home)	£67.16	PSSRU 2016 10.3c: Per patient contact lasting 17.2 minutes, including direct care staff costs, with qualification costs
Routine GP visit (surgery)	£45.68	PSSRU 2016 10.8b: Per patient contact lasting 11.7 minutes, including direct care staff costs, with qualification costs
Palliative care (day case)	£91.83	NHS reference costs (2015-16) N21AF: Specialist Nursing, Palliative/Respite Care, Adult, Face to face
CT scan	£118.53	NHS reference costs (2015-16)

		RD22Z: Computerised Tomography Scan of one area, with pre and post contrast
X-ray	£37.30	NHS reference costs (2015-16) Diagnostic imaging (code: 812), unit cost (weighted average of consultant-led and non-consultant-led appointments)
Oncologist visit	£167.08	NHS reference costs (2015-16) Medical oncology (code: 370), consultant-led appointment
Full blood test	£3.10	NHS reference costs (2015-16) DAPS05: direct access pathology; haematology
Liver function test	£1.18	NHS reference costs (2015-16) DAPS04: direct access pathology; clinical biochemistry
Renal function test (with electrolytes)	£1.18	NHS reference costs (2015-16) DAPS04: direct access pathology; clinical biochemistry

An end of life/terminal care cost is applied to patients who enter the death state as a one off cost, in line with the erlotinib and gefitinib MA, nivolumab and pembrolizumab appraisals (National Institute for Health and Care Excellence, 2015a), (National Institute for Health and Care Excellence, 2016ar), (National Institute for Health and Care Excellence, 2016d), (National Institute for Health and Care Excellence, 2017). 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. Resource use and costs are shown in Table 75 and Table 76. The total cost of end of life is £3,679.37.

Table 75: Resource use for terminal care/end of life

Resource	Number required	Reference	% of patients in each setting	Source
Hospitalisation admission (+excess bed days)	1 (+0.84 excess bed days)	(National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d, National Institute for Health and Care Excellence, 2017)	55.8%	(National Institute for Health and Care Excellence, 2015a, National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)
Macmillan Nurse (home setting)	50	Marie Curie Cancer Care	27.3%	
Hospice care	1.00	(National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d, National Institute	16.9%	

		for Health and Care Excellence, 2017)		

Table 76: Resource costs for terminal care

Resource	Unit cost	Reference	Weighted unit cost	Total cost of care in each setting
Hospitalisation admission (+excess bed days)	£4051.39 (+ £211.03 for 0.84 excess bed days) =£4,262.42	NHS reference costs 2015-16 (Department of Health 2016) Respiratory Neoplasms without intervention, with CC score 13+ (currency code DZ17S), Non-elective inpatient stay – long stay	£2,378.43	£2,378.43
Macmillan Nurse (home setting)	£29.33 Assumed 2/3 of the cost of a community nurse: £44 per working hour, based on average salary of £31,902 equating to Band 6.	(National Institute for Health and Care Excellence, 2015a, National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d); PSSRU 2016 (10.1)	£8.01	£400.50
Hospice care	£5,328.03 Assumed 25% increase on hospitalisation setting)	(National Institute for Health and Care Excellence, 2015a, National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)	£900.44	£900.44
Total cost				£3,679.37

5.5.3 Adverse event unit costs and resource use

There are three analysis populations defined in the OAK CSR:

- The first 850 randomised patients (primary population ITT). Of the primary population, 425 were randomised to docetaxel and 425 to atezolizumab, respectively;
- The ITT population including all 1,225 randomised patients;
- The safety evaluable population of 1,187 patients who received any dose of study drug at the primary analysis time (safety evaluable population). In total, 38 patients

who did not receive any study drug and were excluded from the safety evaluable population.

The efficacy data presented in the CE model are based on the primary analysis of OAK (clinical cutoff date: 7 July 2016), occurring after 569 death events were observed in the first 850 randomised patients (primary population ITT). It was considered appropriate to align the efficacy and safety populations for the CE model, rather than analyse two different populations, particularly as the drug costs in the model are based on dosing assumptions and time to treatment discontinuation for the first 850 randomised patients. Therefore the safety analyses in the CE model are also based on the first 850 randomised patients who received any dose of study drug at the primary analysis time (n=823). Note that this is different to the safety evaluable population presented in the OAK CSR, and the clinical sections of this submission.

All grade ≥3 treatment related AEs with an incidence of ≥2% in either the docetaxel or atezolizumab arms of the OAK trial (primary population ITT who received any dose) are included in the base case analyses (see Table 77). Two exceptions have been made to this general rule: Firstly, one grade 5 AE was experienced. Given the severity of this AE, this has been included despite a low incidence. In addition, neutropenic sepsis has also been included. This is because the definitions of neutropenic sepsis and febrile neutropenia frequenty overlap, and expert clinical opinion suggests they are interchangeable (see Executive Summary). Therefore, given the rate of febrile neutropenia, it was considered important to include.

Based on this list of AEs, the corresponding rates for nintedanib (plus docetaxel) were sourced directly from the LUME-Lung-1 trial.

The weekly rate of occurrence for each AE is implemented in the model through the overall probability of any patient experiencing the event in any given cycle (see Table 78). This is calculated by using number of AE occurrence divided by the total time (weeks) at risk which is the sum of time on treatment for each patient in the trial. The probability of any patient experiencing the event is then multipled by the average managament costs of the AE to obtain an adverse event cost per patient per week.

The costs of treating AEs are per episode. Where possible, the National Schedule of Reference Costs (2015/16) (Department of Health) were used to cost AEs. Where there were gaps in the data, costs were sourced from prior NICE submissions in NSCLC and inflated to the appropriate costing year (seeTable 79). Assumptions around the costs of treating each adverse event were validated by UK clinicians.

A scenario analysis was run incorporating the costs and rates of AEs based on a real world evidence study conducted by Roche in 2016 (Talbot T et al., 2017b, Talbot T et al., 2017a). Details of these costs are reported in Table 80.

Table 77: Adverse Event rates included in the economic model

Adverse event	Grade	Rate: atezolizumab (%)	Rate: docetaxel (%)
Anaemia	3	0.5	4
Fatigue	3	1.7	3.7
Febrile Neutropenia	3+4	0	9.9
Leukopenia	3+4	0	3.4
Neutropenia	3+4	0.4	15.4
Neutropenic Sepsis	4	0	0.5
Neutrophil Count Decreased	3+4	0	11.7
Pneumonia	3	0.5	2.2
Respiratory Tract Infection	3+5	0.2	0.4
White Blood Cell Count Decreased	3+4	0	3.9

Table 78: Adverse events as included in economic model

	Atezolizumab			Docetaxel			Nintedanib + Docetaxel		
Adverse Event	**Occurrence of AE**	**N patients with AE**	**Probability of event**	**Occurrence of AE**	**N patients with AE**	**Probability of event**	**Occurrence of AE**	**N patients with AE**	**Probability of event**
Anaemia	6	2	0.0005	17	16	0.0032	7	NR	0.0007
Fatigue	7	7	0.0006	17	15	0.0032	37	NR	0.0038
Febrile Neutropenia	0	0	0	44	40	0.0082	46	NR	0.0048
Leukopenia	0	0	0	16	14	0.0030	19	NR	0.0020
Neutropenia	2	2	0.0002	70	62	0.0129	79	NR	0.0082
Neutropenic Sepsis	0	0	0	2	2	0.0004	0	NR	0.0000
Neutrophil Count Decreased	0	0	0	125	47	0.0230	209	NR	0.0214
Pneumonia	2	2	0.0002	10	9	0.0019	0	NR	0.0000
Respiratory Tract Infection	1	1	0.0001	2	2	0.0004	0	NR	0.0000
White Blood Cell Count Decreased	0	0	0	23	16	0.0043	107	NR	0.0110

Table 79: Adverse event costs

	Erlotinib & Gefitinib TA374 (National Institute for Health and Care Excellence, 2015a)	Nivolumab ID900, ID811 (National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)	Nintedanib TA347 (National Institute for Health and Care Excellence, 2015n)	Pembrolizumab ID840 (National Institute for Health and Care Excellence, 2017)	HRG 2015-16 (Department of Health)	**Unit cost used in the atezolizumab model**	Source
NHS ref costs used in submission	2011/12	2013/14	2012/13	2013/14		**2014/15**	
PSSRU HCHS Pay & prices index	282.5	290.5	287.3	290.5	297	**297**	
Unit used to inflate to 2015-2016 using PSSRU	1.05133	1.02238	1.03376	1.02238	1	**1**	Curtis and Burns (2016)
Anaemia		978	2610.66	2610.66	1313.09	**£1313.09**	HRG 2015/16 (SA04H [Iron Deficiency Anaemia with CC Score 10-13])
Fatigue	2317.2	3015.13	2610.66	2317.2	NA	**£3082.59**	(National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)
Febrile Neutropenia	7331.78	5489.94	2339	7331.78	NA	**£5612.78**	(National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)

Neutropenic Sepsis	7331.78	5489.94	2339	7331.78	NA	**£5612.78**	(National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)
Leukopenia		354.72			NA	**£362.66**	(National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)
Neutropenia	179.83	354.72	560.08	179.83	NA	**£362.66**	(National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)
Neutrophil Count Decreased		0		179.83	NA	**0**	(National Institute for Health and Care Excellence, 2016ar, National Institute for Health and Care Excellence, 2016d)
Pneumonia		1822.85			1888.36	**£2783.99**	HRG 2014/15 (DZ11T (Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9))
Respiratory Tract Infection					3734.417	**£3515.13**	HRG 2014/15 (DZ27P (Respiratory Failure with Single Intervention, with CC Score 11+))

White Blood Cell Count Decreased		423	560.08	560.08	NA	**£432.47**	Nivolumab (ID900, ID811)

Table 80: Adverse event sensitivity analysis

Adverse event	n(%) of patients experiencing AE	Mean NHS cost for managing a patient with event (£)
Using ANC ≤1.0 x 10^9/L or ≤0.5 x 10^9/L definition for neutropenia diagnosis		
Confirmed *or* suspected NS episode	21 (17.4%)	£2,545.19
Neutropenia without sepsis	13 (10.7%)	£323.48
Other haematological events		
Anaemia	38 (31.4%)	£78.35

Adverse event costs are applied to each treatment arm whilst patients are still receiving treatment. As per the SmPCs, this is until loss of clinical benefit for atezolizumab, and until progressed disease or unacceptable toxicity for docetaxel, and nintedanib (plus docetaxel). Conversely, in line with clinical practice, costs associated with adverse events due to docetaxel are no longer applied once treatment is discontinued after 6 cycles, or 18 weeks.

5.6 Summary of base-case de novo analysis inputs and assumptions

Table 81 summarises all variables applied in the economic model.

Table 81: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General parameters			
Discount rate (costs)	3.5%	Fixed	5.2.2
Discount rate (efficacy)	3.5%	Fixed	5.2.2
Time horizon	25 years	Fixed	5.2.2
Patient age	63 years	Fixed	4.5
Baseline body weight	72 kg	Fixed	4.5
Baseline height	167 cm	Fixed	NR
BSA	1.81m²	Fixed	5.2.4
Health state utilities			
On treatment			
≤ 5 weeks before death	0.39	0.24-0.55; Normal	5.4.1
> 5 and ≤ 15 weeks before death	0.61	0.53-0.68; Normal	5.4.1
> 15 and ≤ 30 weeks before death	0.71	0.69-0.74; Normal	5.4.1
> 30 weeks before death	0.77	0.75-0.78; Normal	5.4.1
Off treatment			
≤ 5 weeks before death	0.35	0.27-0.44; Normal	5.4.1
> 5 and ≤ 15 weeks before death	0.43	0.37-0.49; Normal	5.4.1
> 15 and ≤ 30 weeks before death	0.58	0.55-0.61; Normal	5.4.1
> 30 weeks before	0.68	0.66-0.71; Normal	5.4.1

death			
Adverse event disutilities			
Anaemia	-0.07346	SE: 0.02; Normal	5.4.3
Fatigue	-0.07346	SE: 0.02; Normal	5.4.3
Febrile Neutropenia	-0.09002	SE: 0.02; Normal	5.4.3
Leukopenia	-0.08973	SE: 0.02; Normal	5.4.3
Neutropenia	-0.08973	SE: 0.02; Normal	5.4.3
Neutropenic sepsis	-0.09002	SE: 0.02; Normal	5.4.3
Neutrophil count decreased	0	SE: 0.00; Normal	5.4.3
Pneumonia	-0.008	SE: 0.00; Normal	5.4.3
Respiratory Tract Infection	-0.096	SE: 0.02; Normal	5.4.3
White blood cell count decreased	-0.05	SE: 0.01; Normal	5.4.3
Parametric curves			
TTD atezolizumab	KM + Gamma tail	Multivariate normal distribution	5.3.2
TTD comparators	KM + Gamma tail	Multivariate normal distribution	5.3.2
PFS atezolizumab	KM + Gamma tail	Multivariate normal distribution	5.3.3
PFS comparators	KM + Gamma tail	Multivariate normal distribution	5.3.3
OS atezolizumab	Mixed cure rate model & log logistic	Multivariate normal distribution	5.3.4
OS comparators	Mixed cure rate model & log logistic	Multivariate normal distribution	5.3.4
Treatment costs			
Atezolizumab (list)	£3807.69	Fixed	5.5.2
Docetaxel	Table 64, Table 65	Fixed	5.5.2
Nintedanib	Table 64, Table 65	Fixed	5.5.2
Administration atezolizumab	£198.94	Fixed	5.5.2
Administration docetaxel	£198.94	Fixed	5.5.2
Administration nintedanib	Table 70	Fixed	5.5.2
Subsequent treatment			
Pharmacological therapy cost	Table 66	Fixed	5.5.2
Radiotherapy cost	Table 68	Gamma distribution	5.5.2
Subsequent treatment distribution	Table 69	Beta distribution	5.5.2
Time on subsequent treatment	Table 69	Gamma distribution	5.5.2
Adverse event management costs			
Atezolizumab	£1313.09	Lognormal distribution	5.5.3
Docetaxel	£3082.59	Lognormal distribution	5.5.3
Nintedanib + Docetaxel	£5612.78	Lognormal distribution	5.5.3
Anaemia	£5612.78	Lognormal distribution	5.5.3

Fatigue	£362.66	Lognormal distribution	5.5.3
Febrile Neutropenia	£362.66	Lognormal distribution	5.5.3
Leukopenia	0	Lognormal distribution	5.5.3
Neutropenia	£2783.99	Lognormal distribution	5.5.3
Neutropenic sepsis	£3515.13	Lognormal distribution	5.5.3
Neutrophil count decreased	£432.47	Lognormal distribution	5.5.3
Health state costs			
On treatment monitoring cost	162.84	Lognormal distribution	5.5.2
On treatment/PFS	£282.96	Lognormal distribution	5.5.2
Off treatment/PD	£128.25	Lognormal distribution	5.5.2
Terminal care	£3679	Lognormal distribution	5.5.2

The key assumptions used in the economic model are reported in Table 82.

Table 82: Key assumptions used in economic model

Parameter	Base-case assumption	Justification
Comparator	Docetaxel Nintedanib + Docetaxel	Based on UK clinical practice and consistent with OAK data
Time horizon	25 years	Life-time equivalent consistent with NICE reference case
Clinical efficacy and safety	Efficacy and safety results for atezolizumab seen in the OAK study are transferable to UK population	The OAK study included UK patients. Expert clinical advice suggests the outcomes seen from the study are expected in UK patients given the similarity of patient characteristics between the trial and real-world, and the inclusion of UK sites and patients in OAK (Table 16)
ITC: Nintedanib + Docetaxel	The "total population" cohort from the LUME-Lung-1 study for nintedanib (plus docetaxel) provides a representative evidence base to assess the relative efficacy of this regimen vs. atezolizumab	Nintedanib (plus docetaxel) is licensed (and recommended by NICE) only for those patients with adenocarcinoma histology. The ITC compares the "total population" from LUME-Lung-1 to the atezolizumab ITT population (its anticipated licence), allowing a like-with-like comparison. Consistent with the favourable prognosis seen in patients with non-squamous vs. squamous forms of NSCLC[11] in other trial programmes (Kawase et al., 2012), the OAK and POPLAR studies demonstrated improved outcomes in the subgroup of patients with non-

[11] Adenocarcinoma makes up at least 85% of all non-squamous histologies (see section 3.1 & 4.8)

		squamous NSCLC (Figure 14, Figure 16). Therefore, the impact of this approach is not anticipated to significantly affect overall results.
Survival: OS	2% cure rate, log-logistic	Choice of extrapolation technique was based on statistical goodness-of-fit, clinical plausibility and validation with RWE
Survival: PFS	KM with Gamma tail	Choice of extrapolation technique was based on statistical and visual goodness-of-fit and clinical plausibility
Survival: TTD	KM with Gamma tail	Choice of extrapolation technique was based on statistical and visual goodness-of-fit and clinical plausibility
Treatment duration	Atezolizumab treatment duration is based on time on treatment results of the OAK study	OAK results suggest patients in 2L continue to received treatment (and benefit from treatment) beyond progression
	Treatment duration for docetaxel capped at 18 weeks	In clinical practice, docetaxel is subject to a cap of 6 cycles
	Treatment duration for nintedanib (plus docetaxel) is based on PFS	Treatment duration results are not available for nintedanib (plus docetaxel), and as treatment is until progression, PFS is a suitable surrogate.
End of life cost	Based on previous NICE TAs	Applied as a one off cost for all patients who die to take into consideration the added expense of terminal care
HRQoL	Based on EQ5D data collected in OAK. Utility values are allocated by time to death and by health state to adequately capture quality of life. Utilities are not, however differentiated by treatment arm	EQ5D from OAK is consistent with NICE recommendations. Clinical opinion suggests HRQoL is not appropriately captured solely through the use of progression-based health states for atezolizumab due to the atypical responses. Clinical opinion also suggests there is a decline in HRQoL as a patient moves towards death: as confirmed by the OAK data. In sensitivity analyses, the impact of considering alternative approaches was considered.
Safety	Grade 3 or higher severity adverse events experienced by ≥ 2% of patients in OAK are included in the analysis	Conservative approach

	The incidence of AEs from OAK trial was assumed to reflect that observed in practice	RWE supports assumption
	The safety data included in the CE model was based on the primary population of OAK (first 850 randomised patients). This provides a representative evidence base to assess the relative safety of atezolizumab	It was considered appropriate to align the efficacy and safety populations for the CE model, rather than analyse two different populations, particularly as the drug costs in the model are based on dosing assumptions and time to treatment discontinuation for the first 850 randomised patients.
Subsequent treatment	Treatment type and duration of therapy based on pooled arms of OAK	Given the incomplete data set for atezolizumab, arms were pooled to ensure costs were not underestimated for atezolizumab. Resulting average cost is applied as a one-off cost for all patients moving out of the "on treatment" health state for all comparators included in the model to take into account any treatment costs following second-line therapy.
	3rd line immunotherapy removed upon clinical opinion	It would not be standard practice to treat with another immunotherapy after atezolizumab treatment failure. However, the cost of subsequent immunotherapy treatment has also been removed from the docetaxel arm, where 3rd line immunotherapy treatment would be the standard of care, and was used at a greater incidence in the OAK study (17% versus 4%). As such, the model underestimates the total cost of the treatment pathway with docetaxel 2L, whilst including the treatment benefit.
Resource use	As per section 5.5.5	Assumptions based on prior appraisals, and feedback received from ERG appraisal reviews.

5.7 Base-case results

5.7.1 Base-case incremental cost effectiveness analysis results

Base-case results of the economic model are presented below.

Atezolizumab provided a QALY gain of 1.47, and a life-year gain of 2.22, at a total drug cost of £44,784, and total overall cost of £73,911 at list price. In contrast, docetaxel provides a QALY gain of 0.73, and a life-year gain of 1.19, at a total cost of £19,941; and nintedanib (plus docetaxel) provides a QALY gain of 0.83, and a life-year gain of 1.31, at a total cost of £37,702 at list price.

As such, the atezolizumab resulting ICER versus docetaxel is £72,356, and versus nintedanib (plus docetaxel) is £56,076. The equivalent ICERs incorporating the proposed PAS for atezolizumab are [redacted] vs. docetaxel, and [redacted] vs. nintedanib (plus docetaxel).

However, nintedanib is associated with a PAS, at an unknown level of discount; therefore the analysis could not be conducted at the with-PAS price level. Instead, this is explored in the sensitivity analyses below.

See Table 83 for a summary of the base case results.

The ICER associated with the nintedanib (plus docetaxel) versus docetaxel comparison should be interpreted with caution. This is an artefeact of the data used for nintedanib (plus docetaxel) (total population as opposed to adenocarcinoma population). However, as this is an assessment of atezolizumab, and based on the rationale and assumptions set out in section 5.2, this is not anticipated to have a major bearing on the results.

Table 83: Base-case results (list prices)

				Versus Docetaxel				Versus N+D			
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	£19,941	1.19	0.73	-	-	-	-	-	-	-	-
Nintedanib + Docetaxel	£37,702	1.31	0.83	£17,761	0.13	0.10	Ext. dominated	-	-	-	-
Atezolizumab	£73,911	2.22	1.47	£53,970	1.04	0.75	£72,356.07	£36,209	0.91	0.65	£56,076.16

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Note: numbers may not sum due to rounding

Table 84: Base-case results (with-PAS)

				Versus Docetaxel				Versus N+D			
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	£19,941	1.19	0.73	-	-	-	-	-	-	-	-
Nintedanib + Docetaxel	£37,702	1.31	0.83	£17,761	0.13	0.10	Ext. dominated	-	-	-	-
Atezolizumab	[redacted]	2.22	1.47	[redacted]	1.04	0.75	[redacted]	[redacted]	0.91	0.65	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Note: numbers may not sum due to rounding

5.7.2 Clinical outcomes from the model

As described in section 5.3, the primary data source for the economic model was the data derived from the pivotal OAK clinical trial. However, the follow-up period in OAK was shorter than the time horizon of the economic model (25 years to represent a lifetime horizon); therefore extrapolation of OS, PFS and TTD from OAK was required for the area-under-the-curve (AUC) partitioned survival approach. This was particularly critical when considering the expectation of durable responses in a significant proportion of patients receiving atezolizumab, as demonstrated by immunotherapies in the metastatic setting of other indications. Whilst the methodology followed to conduct this was considered robust, any extrapolation is associated with uncertainty.

A comparison of results from the model to observed data from the OAK and POPLAR studies allow some assessment of the accuracy of the modelled survival. Results for PFS and OS from the model are compared to trial data in Table 85. Generally, the model is accurate in both PFS and OS estimation, supporting the approach taken in the extrapolations. Additionally the extrapolated 5 and 10 year OS results for atezolizumab were validated by clinical experts as being clinically plausible (Table 87). In addition, the docetaxel extrapolation was cross-checked against the NLCA registry dataset (available up to 5 years), and also deemed reflective of clinical practice (Table 88).

Table 85: Summary of model results compared with observed clinical data: atezolizumab

	Model	OAK	POPLAR
Median PFS (months)	2.76	2.8	2.7
Median OS (months)	13.34	13.8	12.6
12-month OS	54%	55%	51.6%
18-month OS	39.7%	40%	38.1%

Table 86: Summary of model results compared with observed clinical data: docetaxel

	Model	OAK	POPLAR
Median PFS (months)	3.96	4.0	3.0
Median OS (months)	9.84	9.6	9.7
12-month OS	42%	41%	41.9%
18-month OS	25.9%	27%	24.5%

Table 87: Comparison of modelled and expert opinion results for OS: atezolizumab

	5 year OS	10 year OS	20 year OS	25 year OS
Expert clinical advice*	10%	7.5%	2%	NR
Model: atezolizumab	12%	5.6%	2.2%	1.4%

*Clinicians emphasised that predicting survival for atezolizumab patients would be difficult without more data, but provided an estimated approximation of the OS rates that might be seen

Table 88: Comparison of modelled and NLCA registry data for OS: docetaxel

	2 year OS	3 year OS	5 year OS
NLCA (OS Stage IIIB/IV; PS0-1 with chemotherapy)	20%	13%	7%
NLCA (OS stage IV)	7%	4%	2%
Model: Docetaxel	17%	8%	2%

The movement of patients through the model health states over time are illustrated below.

From these figures it can be seen patients spend a greater amount of time in the "on treatment" health state, and experience longer OS when receiving atezolizumab, as compared to comparator.

Figure 55: Markov trace for on/off treatment health states over time: atezolizumab

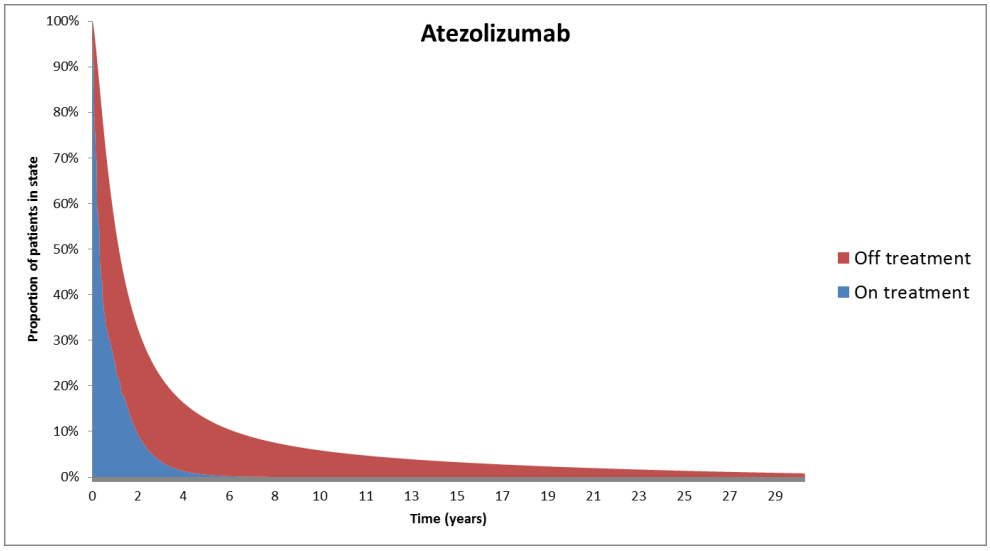


Figure 56: Markov trace for on/off treatment health states over time: docetaxel

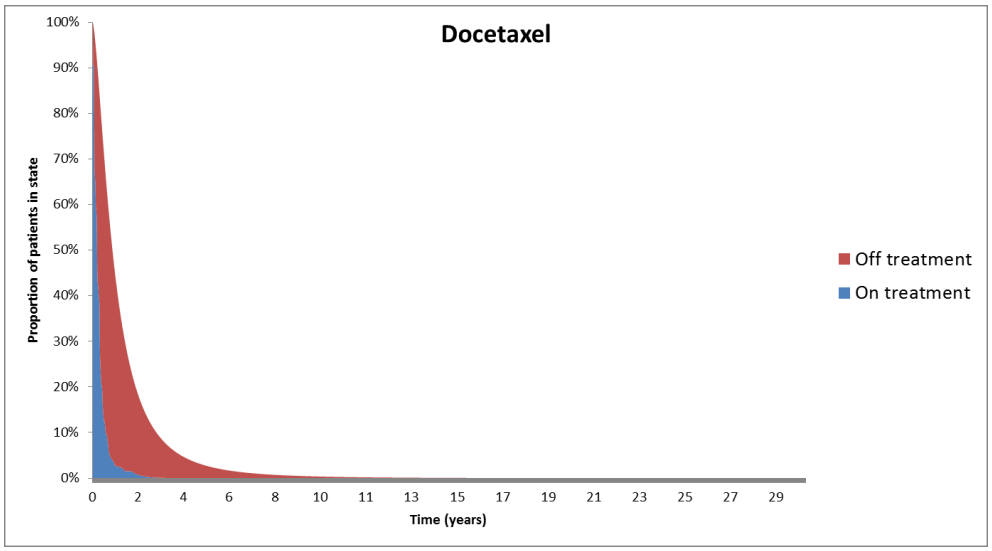
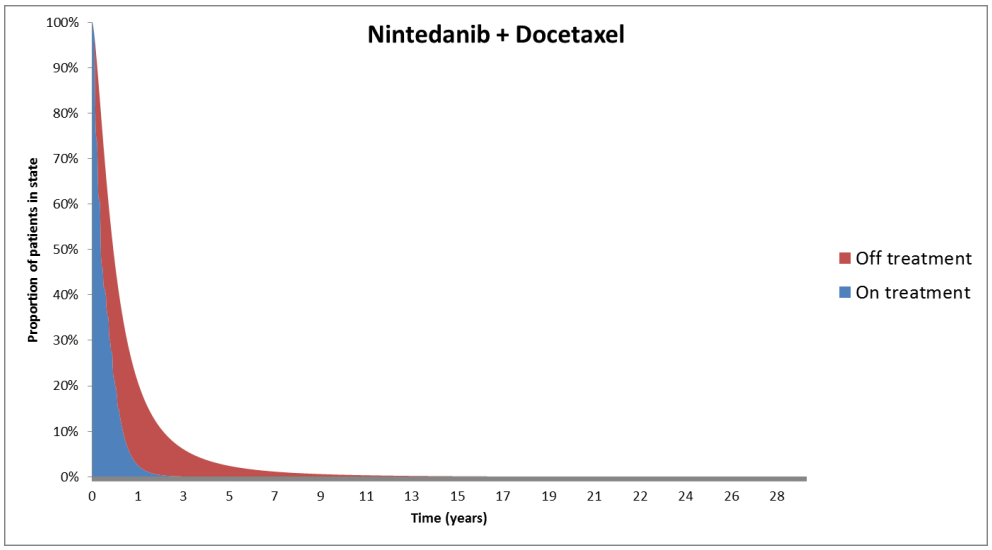
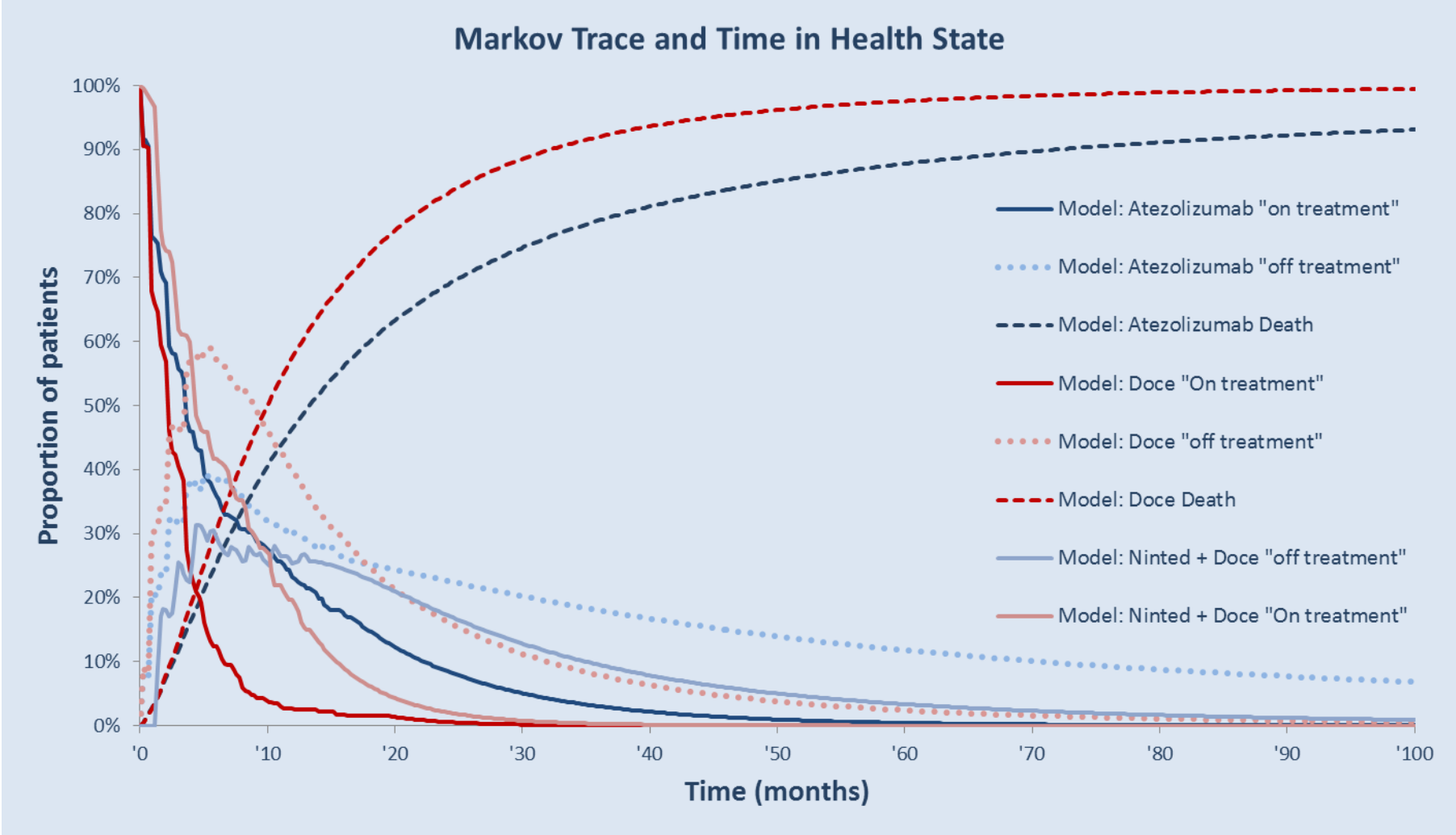


Figure 57: Markov trace for health states over time: nintedanib + docetaxel (PFS used as a proxy)



The aggregated result for on/off treatment health states for the comparisons is shown below.

Figure 58: Markov trace: on/off treatment: combined results for all comparators



PFS used as a proxy for nintedanib plus docetaxel “on treatment”

5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

The QALY gain disaggregated by health states allows exploration of which health state is driving QALY gain. Table 89 and Table 90 show the results for the comparison to docetaxel and nintedanib (plus docetaxel), respectively.

In all comparators, the majority of incremental QALY gain for atezolizumab is achieved when patients are in the "off treatment" health state. These results are as expected, given the substantial survival gain anticipated with immunotherapy treatments compared with PFS gains (see Section 4.13).

Table 89: Summary of QALY gain by health state: comparison to docetaxel

Health state	QALYs: Atezolizumab	QALYs: Docetaxel	Increment	% absolute increment QALYs
On treatment	0.47	0.18	0.29	38.31%
Off treatment	1.00	0.55	0.46	61.34%
Adverse events	0.00	0.00	0.00	0.35%
Total	1.47	0.73	0.75	100.00%

Note: numbers may not sum due to rounding

Table 90: Summary of QALY gain by health state: comparison to nintedanib + docetaxel

Health state	QALYs: Atezolizumab	QALYs: Nintedanib + docetaxel	Increment	% absolute increment QALYs
On treatment	0.47	0.40	0.007	10.60%
Off treatment	1.00	0.45	0.56	86.43%
Adverse events	0.00	-0.02	-0.02	2.97%
Total	1.47	0.83	0.65	100.00%

Note: numbers may not sum due to rounding
PFS used as a proxy for nintedanib (plus docetaxel) "on treatment"

A breakdown of the difference in costs can be found below. Cost is disaggregated by health state and resource use for all comparators. For the with-PAS cost breakdown, please see the confidential PAS appendix.

Table 91: Disaggregated costs: comparison to docetaxel

		Atezolizumab	Docetaxel	Increment	% absolute increment
Mean costs in PFS/On treatment	Treatment cost	£44,784	£124	£44,660	80.26%
	Drug administration	£2,340	£718	£1,622	2.91%
	Adverse events	£109	£761	-£652	1.17%
	Supportive care	£9,696	£6,790	£2,907	5.22%
Total costs in PFS/On treatment		£56,929	£8,393	£48,536	89.57%

Mean costs in PD/Off treatment	Supportive care	£10,490	£4,872	£5,618	10.10%
	Subsequent therapy cost	£3,123	£3,153	-£30	0.05%
Total costs in PD/Off treatment		£13,613	£8,025	£5,588	10.15%
Terminal care cost		£3,369	£3,523	-£154	0.28%
Total costs		**£73,911**	**£19,941**	**£53,970**	100%

Note: numbers may not sum due to rounding

Table 92: Disaggregated costs: comparison to nintedanib + docetaxel

		Atezolizumab	**Nintedanib + Docetaxel**	**Increment**	**% absolute increment**
Mean costs in PFS/On treatment	Treatment cost	£44,784	£14,912	£29,872	75.38%
	Drug administration	£2,340	£1,049	£1,291	3.26%
	Adverse events	£109	£1,435	-£1,326	3.35%
	Supportive care	£9,696	£8,474	£1,223	3.09%
Total costs in PFS/On treatment		£56,929	£25,870	£31,059	85.07%
Mean costs in PD/Off treatment	Supportive care	£10,490	£4,957	£5,533	13.96%
	Subsequent therapy cost	£3,123	£3,310	-£187	0.47%
Total costs in PD/Off treatment		£13,613	£8,267	£5,346	14.44%
Terminal care cost		£3,369	£3,566	-£196	0.49%
Total costs		£73,911	£37,702	**£36,209**	**100%**

Note: numbers may not sum due to rounding

5.8 Sensitivity analyses

5.8.1 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 section 5.6.

Results of the PSA compared to deterministic results are presented in Table 93. The scatterplot in Figure 59 shows the iterations and the cost effectiveness acceptability curve is shown in Figure 60.

The analyses below are based on the proposed list price of atezolizumab. Please see the confidential PAS appendix for PSA results incorporating the atezolizumab PAS.

Table 93: PSA results compared to base-case (without PAS)

	Costs		QALYs		ICERs (vs. docetaxel)		ICERs (vs. N+D)	
	Base case	PSA	Base case	PSA	Base case	PSA	Base case	PSA
Docetaxel	£19,941	£20,880	0.73	0.74	-	-	-	-
Nintedanib + docetaxel	£37,702	£38,676	0.83	0.84	Ext. dominated	Ext. dominated	-	-
Atezolizumab	£73,911	£73,033	1.47	1.47	£72,356	£73,934	£56,076	£57,777

Figure 59: Scatterplot of PSA results for cost effectiveness plane

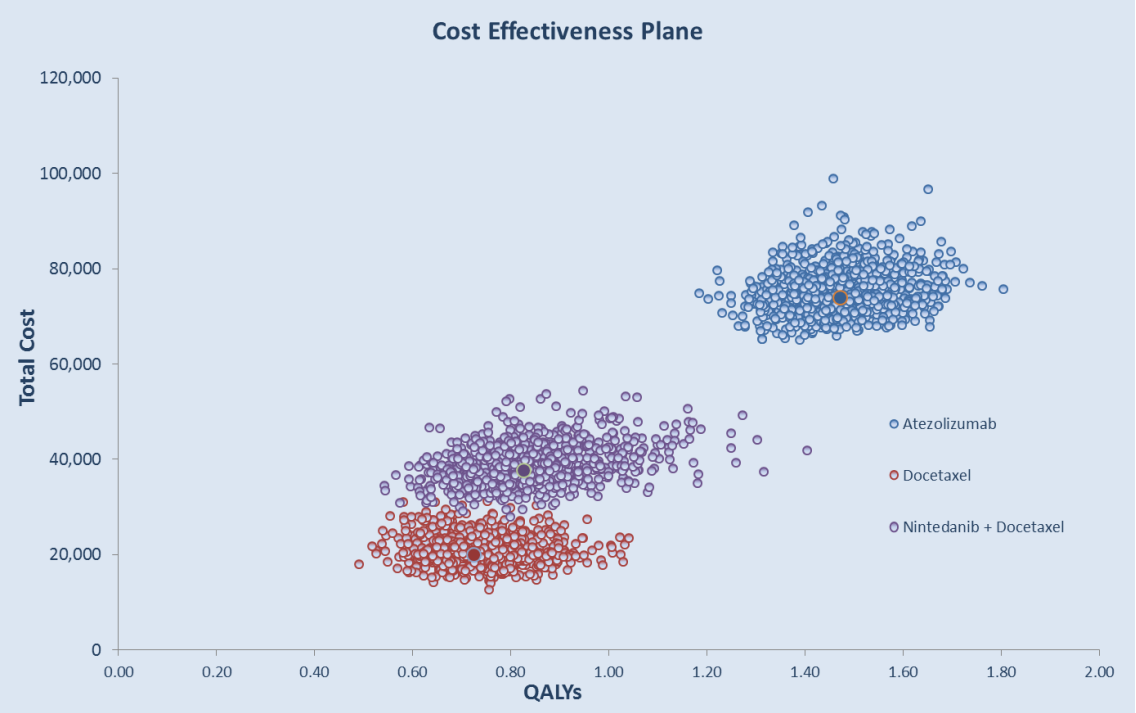
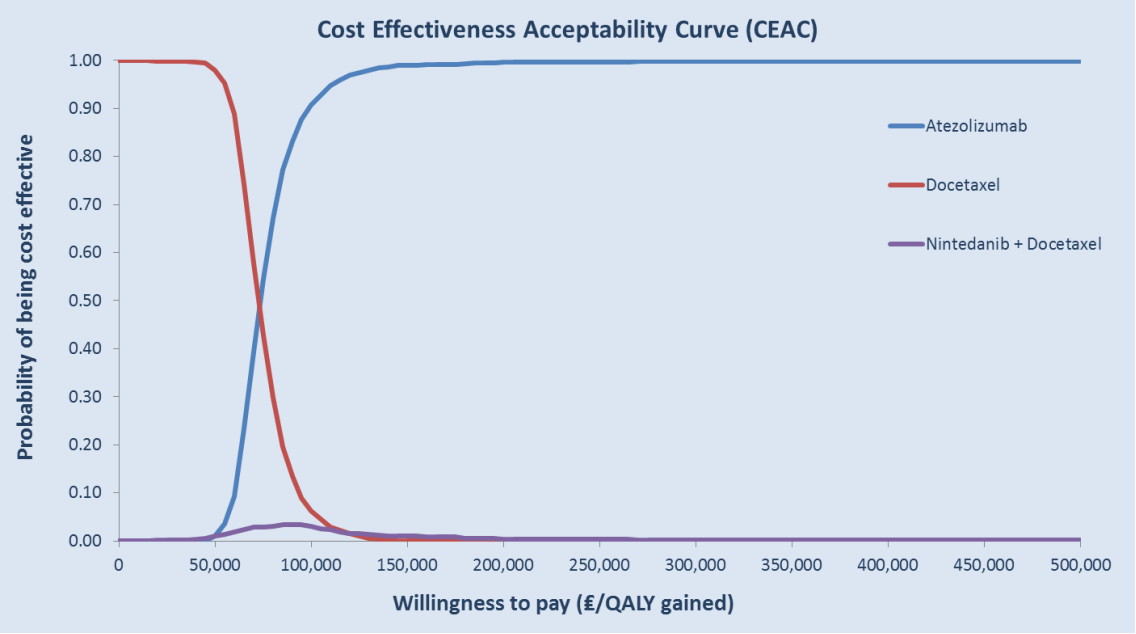


Figure 60: Cost-effectiveness acceptability curve



5.8.2 Deterministic sensitivity analysis

The choice of parameters to include in univariate analysis was considered a-priori, and further informed by the results in section 5.7, with focus on the parameters providing greatest impact on the percentage increment in costs or QALYs, thus 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 94 below. Generally, the base case value of parameters were varied across a +/- 50% range. The exception to this general approach was for drug costs, whereby only a small increase on list price was used as the higher value, with a greater reduction implemented for the lower value: this analysis was of particular use for the comparison to nintedanib (plus docetaxel), where the value of the nintedanib PAS is unknown. Instead, up to a 75% discount to the list price is explored. Results of the analyses using atezolizumab list price are displayed in Figure 61 and Figure 62.

These results are further explored and discussed in 5.8.3, scenario analysis below.

For the results of the deterministic senstivity analysis with-PAS, please see the confidential PAS appendix.

Table 94: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value
Cure fraction	2%	0%	5%
Monthly cost of atezolizumab	£5,500	[redacted]	+10%
Discount effects	3.5%	1.5%	6%
Discount costs	3.5%	1.5%	6%
Supportive costs, on treatment, atezolizumab	£282.96	-50%	+50%
Supportive costs, off treatment, atezolizumab	£128.25	-50%	+50%
Supportive costs, on treatment, docetaxel	£282.96	-50%	+50%
Supportive costs, off treatment, docetaxel	£128.25	-50%	+50%
Supportive costs, on treatment, nintedanib+docetaxel	£282.96	-50%	+50%
Supportive costs, off treatment, nintedanib+docetaxel	£128.25	-50%	+50%
Weekly AE cost, docetaxel	£75.87	-50%	+50%
Weekly AE cost, nintedanib+docetaxel	£47.93	-50%	+50%

Figure 61: Comparison to docetaxel univariate sensitivity analysis (without-PAS)

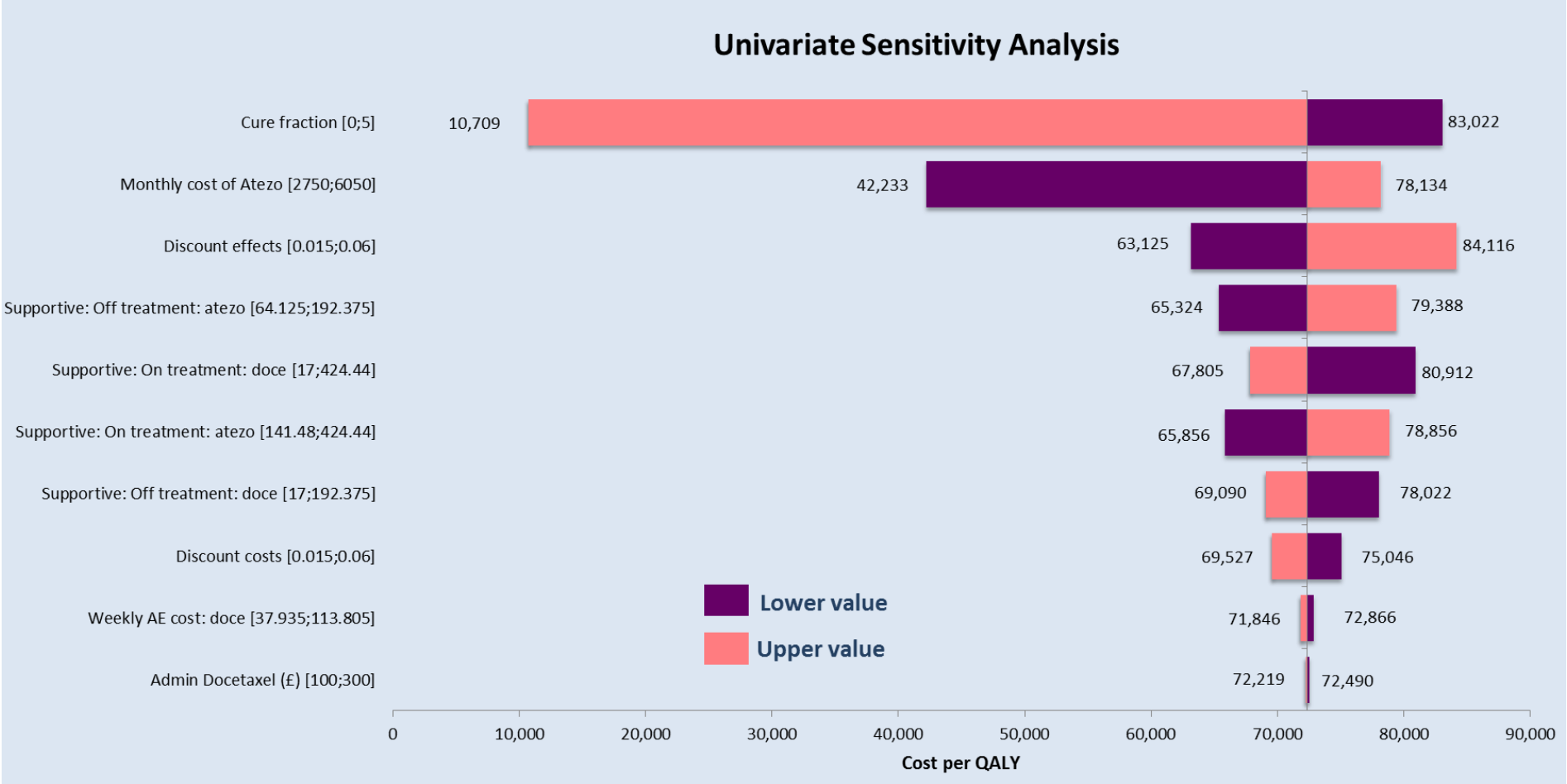
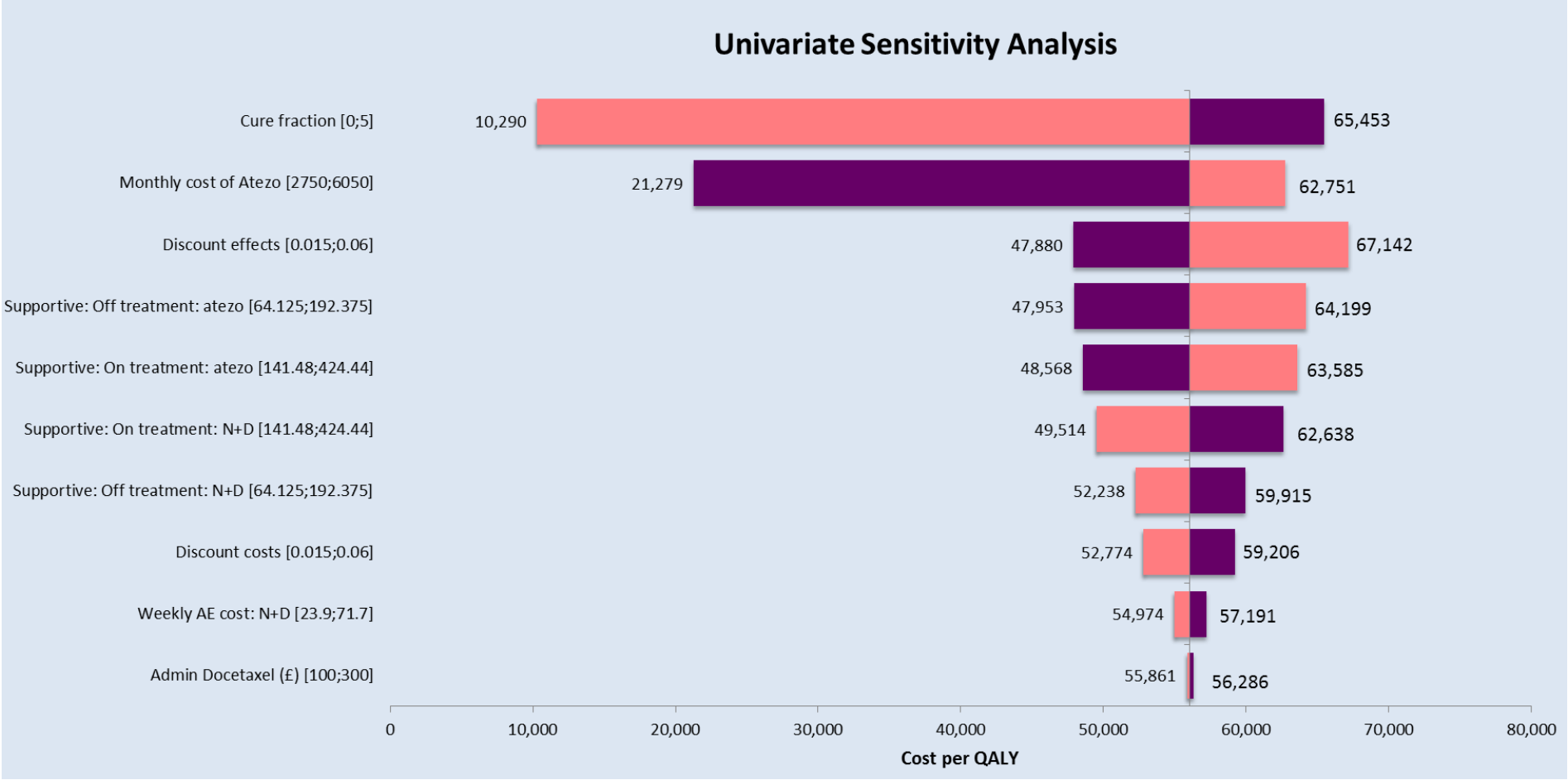


Figure 62: Comparison to nintedanib + docetaxel univariate sensitivity analysis (without-PAS)



5.8.3 Scenario analysis

Scenario analyses were conducted to assess uncertainty around structural assumptions of the model. Without-PAS results are shown in Table 95 (for with-PAS, please see the confidential PAS appendix) for the following scenarios exploring parameter changes:

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions.

- Alternative utilities:
    - On/Off treatment only
    - Published literature
        - Chouaid 2013
        - Nafees 2008
- Alternative OS Extrapolations
    - Traditional parameterisations
    - KM + tail only for the next best fitting curve
- Alternative OS mixed cure fraction
- Alternative PFS Extrapolations
    - Traditional parameterisations
    - KM + tail only for the next best fitting curve
- Alternative TTD Extrapolations
    - Traditional parameterisations
    - KM + tail only for the next best fitting curve
- Alternative treatment durations
- Alternative NMA approach (standard NMA)
- Alternative vial share assumptions
- Alternative nintedanib (plus docetaxel) administration costs
- Post-discontinuation therapy cost: 0% radiotherapy, 100% pharmacological therapy
- Use of Roche Febrile Neutropenia RWD: rates and costs
- Incorporation of an OS HR cap
    - 24 months (trial follow up)
    - 36 months
    - 48 months

Table 95: Results from scenario analyses: atezolizumab vs. docetaxel (without PAS)

		Atezolizumab			Docetaxel			Atezo vs. doce
	Description	**Total LYs**	**Total QALYs**	**Total costs**	**Total LYs**	**Total QALYs**	**Total costs**	**ICER**
OS distribution	**Cure log logistic Base Case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£19,941**	**£72,356**
	Exponential	1.56	1.02	£69,566	1.09	0.66	£19,262	£138,689
	Weibull	1.48	0.96	£69,031	1.07	0.64	£19,131	£155,326
	Log-normal	1.95	1.28	£72,113	1.14	0.69	£19,642	£89,257
	Gen Gamma	1.60	1.04	£69,816	1.08	0.65	£19,228	£129,030
	Log-logistic	1.98	1.31	£72,335	1.14	0.69	£19,622	£85,744
	Gompertz	1.48	0.96	£69,021	1.07	0.64	£19,143	£156,450
	KM with Gamma tail	1.61	1.05	£69,908	1.09	0.66	£19,280	£127,861
	KM with log-logistic tail	1.98	1.31	£72,335	1.14	0.69	£19,622	£85,744
	Piecewise exponential	1.54	1.00	£69,440	1.07	0.65	£19,174	£140,231
PFS distribution*	**KM with Gamma tail Base case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£19,941**	**£72,356**
	Exponential	2.22	1.47	£73,911	1.19	0.73	£20,043	£72,219
	Weibull	2.22	1.47	£73,911	1.19	0.73	£20,043	£72,219
	Log-normal	2.22	1.47	£73,911	1.19	0.73	£19,550	£72,880
	Gen Gamma	2.22	1.47	£73,911	1.19	0.73	£19,537	£72,897
	Log-logistic	2.22	1.47	£73,911	1.19	0.73	£19,352	£73,146
	Gompertz	2.22	1.47	£73,911	1.19	0.73	£19,647	£72,750
	KM with log-normal tail	2.22	1.47	£73,911	1.19	0.73	£19,882	£72,436

	Piecewise exponential	2.22	1.47	£73,911	1.19	0.73	£19,923	£72,380
TTD distribution	**KM with Gamma tail Base case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£19,941**	**£72,356**
	Exponential	2.22	1.47	£72,515	1.19	0.72	£19,955	£70,531
	Weibull	2.22	1.47	£74,901	1.19	0.73	£19,711	£73,940
	Log-normal	2.22	1.50	£97,288	1.19	0.75	£19,641	£104,153
	Gen Gamma	2.22	1.47	£74,794	1.19	0.73	£19,711	£73,747
	Log-logistic	2.22	1.50	£98,845	1.19	0.76	£19,797	£106,502
	Gompertz	2.22	1.47	£72,515	1.19	0.72	£19,955	£70,531
	KM with Weibulll tail	2.22	1.47	£74,835	1.19	0.73	£19,941	£73,502
	Piecewise exponential	2.22	1.47	£77,139	1.19	0.73	£19,940	£76,398
Treatment duration	**Actual treatment duration Base case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£19,941**	**£72,356**
	Until progression	2.22	1.47	£69,548	1.19	0.74	£20,478	£68,029
Dosing scenarios	**Planned dose w. vial sharing Base case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£19,941**	**£72,356**
	Planned dose wo. vial sharing	2.22	1.47	£73,911	1.19	0.73	£19,941	£72,356
	Actual dose wo. vial sharing	2.22	1.47	£73,911	1.19	0.73	£19,941	£72,356
	Actual dose w. vial sharing	2.22	1.47	£73,918	1.19	0.73	£19,940	£72,366

	Planned ind. dose wo. vial sharing	2.22	1.47	£73,909	1.19	0.73	£19,922	£72,378
	Planned ind. dose w. vial sharing	2.22	1.47	£73,909	1.19	0.73	£19,922	£72,378
Utility scenarios	**OAK (proximity to death) Base case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£19,941**	**£72,356**
	OAK (On/Off treatment)	2.22	1.50	£73,911	1.19	0.78	£19,941	£75,246
	Nafees et al., 2008	2.22	1.16	£73,911	1.19	0.64	£19,941	£103,681
	Chouaid et al., 2013	2.22	1.38	£73,911	1.19	0.76	£19,941	£86,621
NMA scenarios	**Frac. Poly Base case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£19,941**	**£72,356**
	OAK Doc arm	2.22	1.47	£73,911	1.19	0.73	£20,094	£72,181
Time horizon (years)	**25 Base case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£19,941**	**£72,356**
	10	1.97	1.30	£72,082	1.18	0.72	£19,895	£90,500
	15	2.11	1.39	£73,093	1.19	0.72	£19,933	£79,494
	20	2.18	1.44	£73,624	1.19	0.73	£19,940	£74,693
	30	2.25	1.49	£74,061	1.19	0.73	£19,941	£71,212
TTD KM proportion at risk (%)	**15 Base case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£19,941**	**£72,356**
	10	2.22	1.47	£74,884	1.19	0.73	£19,941	£73,549
	20	2.22	1.47	£72,720	1.19	0.73	£19,941	£70,892
PFS KM proportion at risk (%)	**15 Base case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£20,028**	**£72,356**
	10	2.22	1.47	£73,911	1.19	0.73	£19,908	£72,239
	20	2.22	1.47	£73,911	1.19	0.73	£19,890	£72,424
Cure fraction (%)	**2 Base case**	**2.22**	**1.47**	**£73,911**	**1.19**	**0.73**	**£19,941**	**£72,356**
	0	2.07	1.36	£72,885	1.19	0.73	£19,941	£83,022

	1	2.14	1.42	£73,395	1.19	0.73	£19,941	£77,301
	3	2.30	1.53	£74,433	1.19	0.73	£19,941	£68,039
	4	2.39	1.58	£74,961	1.19	0.73	£19,941	£64,237
	5	2.47	1.64	£75,495	1.19	0.73	£19,941	£60,863
OS HR cap	24 months (trial follow up)	2.22	1.47	£73,911	1.19	0.73	£19,943	£72,377
	36 months	2.22	1.47	£73,911	1.19	0.73	£19,941	£72,353
	48 months	2.22	1.47	£73,911	1.19	0.73	£19,941	£72,356
Roche RWD study	Rates and costs of AEs	2.22	1.47	£73,890	1.19	0.73	£19,944	£72,324
Post-discontinuation therapy cost	0% radiotherapy, 100% pharmacological therapy	2.22	1.47	£74,917	1.19	0.73	£20,956	£72,343
Alternative nintedanib administration costs	£183.50: Deliver Exclusively Oral Chemotherapy (SB11Z)	2.22	1.47	£73,911	1.19	0.73	£19,941	£72,356

* Model structured on “on treatment” and “off treatment” for both atezolizumab and docetaxel. PFS is not a driver, therefore minimal impact on results.

Table 96: Results from scenario analyses: atezolizumab vs. nintedanib+docetaxel (without PAS)

		Atezolizumab			Nintedanib+Docetaxel			Atezo vs. N+D
	Description	**Total LYs**	**Total QALYs**	**Total costs**	**Total LYs**	**Total QALYs**	**Total costs**	**ICER**
OS distribution	**Cure log logistic Base case**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**
	Exponential	1.56	1.02	£69,566	1.18	0.73	£36,752	£114,068
	Weibull	1.48	0.96	£69,031	1.15	0.71	£36,583	£128,932

	Log-normal	1.95	1.28	£72,113	1.26	0.79	£37,368	£70,512
	Gen Gamma	1.60	1.04	£69,816	1.17	0.73	£36,765	£104,719
	Log-logistic	1.98	1.31	£72,335	1.26	0.79	£37,339	£67,331
	KM with Gamma tail	1.61	1.05	£69,908	1.18	0.73	£36,810	£103,888
	KM with log-logistic curve	1.98	1.31	£72,335	1.26	0.79	37,339	£67,331
	Piecewise exponential	1.54	1.00	£69,440	1.16	0.72	£36,671	£115,189
PFS distribution*	**KM with Gamma tail Base case**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**
	Exponential	2.22	1.47	£73,911	1.31	0.82	£37,226	£56,722
	Weibull	2.22	1.47	£73,911	1.31	0.82	£37,227	£56,721
	Log-normal	2.22	1.47	£73,911	1.31	0.82	£35,047	£59,725
	Gen Gamma	2.22	1.47	£73,911	1.31	0.82	£35,206	£59,506
	Log-logistic	2.22	1.47	£73,911	1.31	0.82	£34,175	£60,916
	KM with Log-normal tail	2.22	1.47	£73,911	1.31	0.82	£37,267	£56,683
	Piecewise exponential	2.22	1.47	£73,911	1.31	0.83	£37,555	£56,282
TTD distribution	**KM with Gamma tail Base case**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**
	Exponential	2.22	1.47	£72,515	1.31	0.83	£37,702	£54,025
	Weibull	2.22	1.47	£74,901	1.31	0.83	£37,702	£57,500
	Log-normal	2.22	1.50	£97,288	1.31	0.83	£37,702	£88,760
	Gen Gamma	2.22	1.47	£74,794	1.31	0.83	£37,702	£57,340
	Log-logistic	2.22	1.50	£98,845	1.31	0.83	£37,702	£90,855
	KM with Weibulll tail	2.22	1.47	£74,835	1.31	0.83	£37,702	£57,414

	Piecewise exponential	2.22	1.47	£77,139	1.31	0.83	£37,702	£60,727
Treatment duration	**Actual treatment duration Base case**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**
	Until progression	2.22	1.47	£69,548	1.31	0.83	£37,702	£49,743
Dosing scenarios	**Planned dose w. vial sharing Base case**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**
	Planned dose wo. vial sharing	2.22	1.47	£73,911	1.31	0.83	£37,703	£56,076
	Actual dose wo. vial sharing	2.22	1.47	£73,911	1.31	0.83	£37,703	£56,076
	Actual dose w. vial sharing	2.22	1.47	£73,918	1.31	0.83	£37,702	£56,087
	Planned ind. dose wo. vial sharing	2.22	1.47	£73,909	1.31	0.83	£37,678	£56,110
	Planned ind. dose w. vial sharing	2.22	1.47	£73,909	1.31	0.83	£37,678	£56,111
Utility scenarios	**OAK (proximity to death) Base case**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**
	OAK (On/Off treatment)	2.22	1.50	£73,911	1.31	0.89	£37,702	£59,189
	Nafees et al., 2008	2.22	1.16	£73,911	1.31	0.70	£37,702	£79,407
	Chouaid et al., 2013	2.22	1.38	£73,911	1.31	0.85	£37,702	£67,953
NMA scenarios	**Frac. Poly**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**

	Base case							
	OAK Doc arm	2.22	1.47	£73,911	1.31	0.83	£37,702	£56,076
Time horizon (years)	**25 Base case**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**
	10	1.97	1.30	£72,082	1.30	0.82	£37,614	£71,788
	15	2.11	1.39	£73,093	1.31	0.82	£37,685	£62,186
	20	2.18	1.44	£73,624	1.31	0.83	£37,699	£58,064
	30	2.25	1.49	£74,061	1.31	0.83	£37,703	£55,108
TTD KM proportion at risk (%)	**15 Base case**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**
	10	2.22	1.47	£74,884	1.31	0.83	£37,702	£57,483
	20	2.22	1.47	£72,720	1.31	0.83	£37,702	£54,349
PFS KM proportion at risk (%)	**15 Base case**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**
	10	2.22	1.47	£73,911	1.31	0.83	£38,319	£55,214
	20	2.22	1.47	£73,911	1.31	0.83	£37,378	£56,527
Cure fraction (%)	**2 Base case**	**2.22**	**1.47**	**£73,911**	**1.31**	**0.83**	**£37,702**	**£56,076**
	0	2.07	1.36	£72,885	1.31	0.83	£37,702	£65,453
	1	2.14	1.42	£73,395	1.31	0.83	£37,702	£60,361
	3	2.30	1.53	£74,433	1.31	0.83	£37,702	£52,420
	4	2.39	1.58	£74,961	1.31	0.83	£37,702	£49,263
	5	2.47	1.64	£75,495	1.31	0.83	£37,702	£46,510
OS HR cap	24 months (trial follow up)	2.22	1.47	£73,911	1.32	0.83	£37,706	£56,108
	36 months	2.22	1.47	£73,911	1.31	0.83	£37,703	£56,081
	48 months	2.22	1.47	£73,911	1.31	0.83	£37,702	£56,077
Roche RWD study	Rates and costs of AEs	2.22	1.47	£73,890	1.31	0.83	£37,773	£55,934
Post-discontinuation therapy cost	0% radiotherapy, 100%	2.22	1.47	£74,917	1.31	0.83	£38,768	£55,983

	pharmacological therapy							
Alternative nintedanib administration costs	£183.50: Deliver Exclusively Oral Chemotherapy (SB11Z)	2.22	1.47	£73,911	1.31	0.83	£39,495	£53,300

* Model structured on “on treatment” and “off treatment” for atezolizumab, therefore PFS only a driver for nintedanib (plus docetaxel) costs and effects.

5.8.4 Summary of sensitivity analysis

As seen in the probabilistic sensitivity analysis scatterplots, atezolizumab is associated with a clear clinical benefit over comparators. This is further validated in the one-way sensistivity analyses and scenario analyses whereby a change in the assumed treatment effect (by way of NMA methodology or capping of HRs over timepoints of atezolizumab) has either a minimum, or improved effect on the ICER.

The main drivers of the economic analysis include the price of atezolizumab, and the assumed cure fraction for the overall survival extrapolation. Caution must be exercised when analysing the results surrounding the different distributions available for extrapolating OS, PFS and TTD, as very few can be considered relevant due to lack of fit to the data.

The results included above have been conducted on the list price of atezolizumab. However, a PAS has been submitted to PASLU, hence the above results do not accurately reflect the true cost-benefit of atezolizumab. For the with-PAS results, please see the confidential PAS appendix.

5.9 Subgroup analysis

No subgroup analyses were performed. Clinical benefit was observed in all subgroups of patients in the OAK study. As such no analyses were conducted on restricted populations as compared to the anticipated indication.

5.10 Validation

The outcomes of the atezolizumab and docetaxel arms of the OAK and POPLAR trials have been compared to the outcomes from the model to assess the accuracy of the modelled survival.

Results for PFS and OS from the model are compared to trial data in Table 85. Generally, the model is accurate in both PFS and OS estimation, supporting the approach taken in the extrapolations. The extrapolated 5 and 10 year OS results for atezolizumab were also validated by clinical experts as being clinically plausible (Table 87) (see Executive Summary). In addition, the docetaxel extrapolation was cross-checked against the NLCA registry dataset (available up to 5 years), and also deemed reflective of clinical practice (Table 88).

Table 97: Summary of model results compared with observed clinical data: atezolizumab

	Model	OAK	POPLAR
Median PFS (months)	2.76	2.8	2.7
Median OS (months)	13.34	13.8	12.6
12-month OS	54%	55%	51.6%
18-month OS	39.7%	40%	38.1%

Table 98: Summary of model results compared with observed clinical data: docetaxel

	Model	OAK	POPLAR
Median PFS (months)	3.96	4.0	3.0
Median OS (months)	9.84	9.6	9.7
12-month OS	42%	41%	41.9%
18-month OS	25.9%	27%	24.5%

Table 99: Comparison of modelled and expert opinion results for OS: atezolizumab

	5 year OS	10 year OS	20 year OS	25 year OS
Expert clinical advice*	10%	7.5%	2%	NR
Model: atezolizumab	12%	5.6%	2.2%	1.4%

* Clinicians emphasiced that predicting survival for atezolizumab patients would be difficult without more data, but provided an estimated approximation of the OS rates that might be seen

Table 100: Comparison of modelled and NLCA registry data for OS: docetaxel

	2 year OS	3 year OS	5 year OS
NLCA (OS Stage IIIB/IV; PS0-1 with chemotherapy)	20%	13%	7%
NLCA (OS stage IV)	7%	4%	2%
Model: Docetaxel	17%	8%	2%

The economic model was constructed specifically from the UK-NHS perspective. The structure is broadly consistent with other oncology models and previous NSCLC submissions to NICE and all costs are sourced from UK published literature.

In addition, the model approach and inputs were validated by a number of external health economists, and UK clinical experts on two separate occasions to ensure the model was reflective of clinical practice (see Executive Summary). This includes, but is not limited to: resource use; health state methodologies; OS 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

conducted, often using extreme values. The results of the model using these values were then compared to expected outputs to assess functionally accuracy.

5.11 Interpretation and conclusions of economic evidence

This is the first economic evaluation focused on assessing the cost-effectiveness of atezolizumab for the treatment of patients with metastatic NSCLC who have progressed following chemotherapy.

The economic evaluation utilises the data available from an ITC and the OAK trial: A phase III open label RCT conducted in 194 centres in 31 countries, including the UK. The baseline characteristics of patients within the OAK trial have been validated by clinical experts and can be considered largely representative of the UK population. Therefore the population included in the economic evaluation can be considered relevant to clinical practice in England and Wales. In addition, the UK-NHS perspective has been taken throughout, with all costs from published UK sources.

Atezolizumab provided 2.22 life-years, an increase of 1.04 compared to docetaxel, and 0.91 compared to nintedanib (plus docetaxel). These results demonstrate the significant survival benefit that atezolizumab is expected to provide over current treatment options.

Atezolizumab provides an incremental gain of 0.75 QALYs over docetaxel, and 0.65 over nintedanib (plus docetaxel). The utility differential is derived from both the “on treatment” and “off treatment” health states, with the largest proportion generated from extending patient life.

The base-case ICERs comparing atezolizumab at list price to docetaxel is £72,356 and to nintedanib (plus docetaxel) is £56,076 (Table 83). The equivalent ICERs incorporating the proposed PAS for atezolizumab are [redacted] vs. docetaxel, and [redacted] vs. nintedanib (plus docetaxel).

Extensive sensitivity analyses were conducted to test how robust the model results were to change in parameter values, and to consider alternative approaches or sources related to the estimation of QALYs, costs, and clinical inputs.

The main drivers of the cost effectiveness results include the price of atezolizumab, and the assumed cure fraction for the overall survival extrapolation. However, the outcome of 75% of the scenario analyses are within a 10% range of the base case ICER versus docetaxel. Of those with a larger impact, the predominant uncertainty is generated from the overall survival extrapolation technique. However, caution must be exercised when analysing the results

surrounding the different distributions available for extrapolating OS, PFS and TTD, as very few can be considered relevant due to lack of fit to the data.

The key strengths associated with the cost-effectiveness analysis surround its use of the best available evidence to inform the model:

- Head-to-head data from the OAK trial comparing atezolizumab to docetaxel monotherapy (the UK standard of care in 2L management of patients with locally advanced or metastatic NSCLC) was used in the economic evaluation for overall survival, progression free survival and time to treatment discontinuation
- Utility values were obtained from EQ-5D OAK data, and applied through a time-to-death and health-state methodology to provide the most robust estimates
- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from previous NICE appraisals, accounting for the feedback provided by ERGs in the most recent submissions
- Extensive sensitivity and scenario analyses were conducted to inform the uncertainty around the above limitations, which helped understand what key variables could potentially have a major impact on the cost-effectiveness results.

Nevertheless, as with all economic evaluations conducted early in the product life-cycle, long term data are limited. The OAK trial is ongoing, so the follow-up period to-date in OAK is shorter than the time horizon of the economic model (25 years to represent a lifetime horizon), therefore extrapolation of OS, PFS and TTD from OAK was required for the AUC partitioned survival approach taken for the economic model.

All extrapolations are subject to limitations as the aim is to predict future benefits for treatments. Nevertheless, by utilising the fractional polynomial NMA methodology, and 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.

Further, as described in the NMA methods (section 4.10), in order to conduct a like-with-like comparison of atezolizumab and nintedanib (plus docetaxel), the “total population” from the nintedanib (plus docetaxel) trial was compared to the atezolizumab ITT population. Nintedanib (pus docetaxel) is only licensed (and recommended by NICE) for the adenocarcinoma population. Consistent with the favorable prognosis seen in patients with non-squamous vs. squamous forms of NSCLC[12] in other trial programmes (Kawase et al.,

[12] Adenocarcinoma makes up at least 85% of all non-squamous histologies (see section 3.1 & 4.8)

2012), the OAK and POPLAR studies demonstrated improved outcomes in the subgroup of patients with non-squamous NSCLC (Figure 14, Figure 16). Therefore, the impact of this approach is not anticipated to significantly affect overall results.

Finally, the economic model does not adjust for treatment switching, despite 17% of docetaxel treated patients receiving a subsequent immunotherapy. Subsequent immunotherapy treatment costs were removed following expert clinical opinion that it would not be clinical practice to treat with another immunotherapy post atezolizumab discontinuation (subsequent therapy costs pooled across treatment arms). By not including the cost of subsequent immunotherapy treatment after docetaxel failure, the economic model is currently underestimating the total costs associated with docetaxel treatmet, whilst overestimating the efficacy associated with docetaxel. Hence, the current ICER is considered a conservative estimate. If addressed, it is anticipated the ICER would reduce.

5.12 Further analyses

The evidence base for this economic analysis was derived from the first data cut of OAK. The OAK trial is ongoing, and patients are still receiving treatment with atezolizumab. An additional data cut for OAK (including OS, PFS and TTD) is expected to be available in September 2017. In addition, an overall survival update will also become available from the phase II POPLAR study. This additional data is expected to confirm the data already presented here, and is expected to support the extrapolation approaches implemented.

6. Assessment of factors relevant to the NHS and other parties

6.1 Patients eligible for treatment in England and Wales

It is estimated that [redacted] patients will be eligible to receive atezolizumab in the previously treated setting (Table 101) in 2018. However, a market share assumption has also been assumed, decreasing this figure.

Table 101: Eligible population for atezolizumab: 2018

Population	Proportion of patients	Number of patients	Comment/Reference
Total NSCLC in UK	NA	28545	Roche assumption
Total NSCLC 2L in UK	81.15%	23128	Roche assumption: Patients progressing from 1L pharmacological treatment whom are not EGFR or ALK+
England and Wales proportion of UK	89.18%		Office for National Statistics population estimate
Total NSCLC 2L in England and Wales	89.18%	20625	Roche assumption
Prior chemotherapy treatment rate	[redacted]	[redacted]	Roche assumption: Removes 17% of patients whom it is anticipated will receive immunotherapy in 1L (assuming Pembrolizumab 1L access rate)
Treatment rate	[redacted]	[redacted]	Roche assumption: removing patients whom are not treated with an active therapy in 2L setting
Non clinical trial	[redacted]	[redacted]	Roche assumption: removing patients included in a clinical trial
Resulting Atezolizumab-eligible		[redacted]	Roche assumption

6.2 Market share assumptions

The estimated number of patients that will be treated with atezolizumab for the five years commencing 2018 (guidance assumed to be issued October 2017) is given in Table 103. Market shares are based on Roche forecasting. We assume that once introduced into the

market, a proportion of patients will receive atezolizumab, with these patients being those who would otherwise have been treated with one of the comparator treatments (docetaxel and nintedanib (plus docetaxel)), as well as a share of the PD-1/PD-L1 class.

In addition, the Roche forecast anticipates adaptations in the clinical pathway, such as a change in the 1L treatment, and its respective impact on 2L therapy, hence the reduction of eligible patients towards the end of the 5 years.

Table 102: Estimated market share: England and Wales

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
	2018	2019	2020	2021	2022	2023
Estimated atezolizumab share of market	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assumed number of atezolizumab treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3 Resource impact

Technology costs and other significant costs associated with treatment with atezolizumab are identical to those assumed in the cost-effectiveness model and are described in section 5.5.

Introduction of atezolizumab in the NSCLC treatment pathway is not anticipated to significantly impact NHS resource use or capacity. Compared to current standard of care in England and Wales, no additional tests or monitoring are required for treatment with atezolizumab. Atezolizumab has shown benefit in patients expressing all levels of PDL1 biomarker. As such, no additional diagnostic tests are required.

As mentioned in section 5 some patients may experience long-term survival. Mean overall survival is currently based on extrapolation method, and the true mean overall survival observed in the population is not yet known. Although the assumptions used in the model are conservative there may be a significant number of patients treated with atezolizumab who will be experiencing long term survival benefit and therefore long-term treatment with atezolizumab.

Atezolizumab is administered every 3 weeks, which is less frequently than some of the available chemotherapies, and the administration time required per cycle is shorter than for some other chemotherapies (i.e. 60 minutes for the initial dose, 30 minutes for subsequent infusions if well tolerated, instead of 60 minutes or longer for all doses). In addition, all other

available treatments are weight based doses, thus requiring per-patient reconstitution and at least some drug wastage, even if vial sharing is adopted. Administration of atezolizumab is at a fixed dose, limiting pharmacy impact, and resulting in no vial wastage.

6.4 Estimated budget impact

The introduction of atezolizumab in the market in England and Wales is expected to displace the use of docetaxel (either as monotherapy or in combination with nintedanib) to subsequent treatment lines. As a result, azezolizumab would potentially share the 2L space with the Anti-PD-1 antibodies (pembrolizumab and potentially nivolumab). Unit costs for the budget impact were derived from the total year 1 costs generated in the economic analysis. This accounts for drug acquisition costs, administration costs, supportive care costs and AE management.

The estimated budget impact on the NHS in England for the first 5 years is presented in Table 103. This is presented at list prices. For with-PAS budget impact, please see the confidential appendix.

Table 103: Estimated budget impact of atezolizumab over 5 years

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
	2018	2019	2020	2021	2022	2023
Total eligible patients (England and Wales)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (Docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (atezolizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The budget impact analyses utilise year one costs only, and applies this costs for each subsequent year. This does not account for the reducing proportional cost of treating patients after year one, and assumes 100% of patients are new each year in the analysis. In addition, a number of assumptions were made in terms of proportion of patients eligible for treatment, which introduced uncertainty into the estimates here presented.

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Appendices

The following appendices are provided in a separate file to accompany this submission.

Appendix 1: Draft summary of product characteristics for atezolizumab

Appendix 2: Search criteria for clinical SLR

Appendix 3: Studies identified in Clinical Systematic Literature Review

Appendix 4: Methods, results, outcomes and quality assessment of relevant RCTs for NMA

Appendix 5: Economic systematic literature search strategy

Appendix 6: Studies excluded from the economic systematic literature review

Appendix 7: Quality assessment of cost-effectiveness studies

Appendix 8: Parametric survival curve fitting

Appendix 9: Summary of health-related quality of life SLR

Appendix 10: Summary of utilities – relevant to the UK

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

April 2017

Atezolizumab for the treatment of locally advanced or metastatic non-small-cell lung cancer after chemotherapy [ID970]

1 Introduction

The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2104) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If companies and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a technology appraisal, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Company evidence submission template' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal. The 'User guide for company evidence submission template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal'

If you are submitting the Patient Access Scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the technology and the disease area to which the Patient Access Scheme applies.

Atezolizumab (brand name: Tecentriq) for the treatment of locally advanced or metastatic non-small-cell lung cancer after chemotherapy

3.2 Please outline the rationale for developing the Patient Access Scheme.

Roche is committed to ensuring all patients can have access to atezolizumab. As such, a simple patient access scheme (PAS) has been submitted to the Patient Access Schemes Liaison Until (PASLU) to reduce the uncertainty surrounding the most appropriate incremental cost effectiveness ratio (ICER).

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price.

A confidential simple PAS of [redacted] discount from the proposed list price (not yet confirmed with the Department of Health). Proposed list price is £3807.69 per 1200mg vial, with resulting net price following PAS application of [redacted] per 1200mg vial

3.4 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

As the proposed PAS is a simple PAS, the discount applies to all populations within the anticipated marketing authorisation

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The simple PAS will be a condition of positive NICE guidance; as such will apply from the point of NICE guidance

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All patient populations as per the anticipated marketing authorisation

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

A simple discount, which will be applied at the point of sale to the NHS and appear on the original invoice.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

A simple discount, which will be applied at the point of sale to the NHS and appear on the original invoice.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable – simple discount applied at the point of sale to the NHS and appearing on the original invoice.

3.10 Please provide details of the duration of the scheme.

The commercial access agreement will operate in the form of a simple PAS, and will be a condition of any positive NICE guidance.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No identified equity or equality issues.

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Company evidence submission template'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

Not applicable – the populations are consistent with the company submission

4.2 If you are submitting the Patient Access Scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable – NICE Appraisal Committee Meeting not yet occurred.

4.3 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

A reduction in the net price of atezolizumab for the first, and all subsequent administrations by [redacted] to [redacted] per 1200mg vial.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

Clinical effectiveness data for atezolizumab is taken from OAK, a Phase III, open-label, multicentre, randomised study to investigate the efficacy and

safety of atezolizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC who had progressed during or following a platinum-containing regimen. Details of the clinical effectiveness and evidence synthesis are available in section 4 of the company submission, and are unchanged with application of this simple PAS.

4.5 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 3.5 of the 'User guide for company evidence submission template'.

Simple PAS at invoice applied to all populations of atezolizumab. As such, no additional PAS administration -related costs incurred.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Simple PAS at invoice applied to all populations of atezolizumab. As such, no additional treatment-related costs incurred. Please see section 5.5 of company submission for details.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

A suggested format is shown below (table 3).

Table 1: Base-case cost-effectiveness results (without PAS)

	Atezolizumab	**Docetaxel**	**Nintedanib + Docetaxel**
Intervention cost (£)	£44783.85	£124.10	£14911.80
Other costs (£)	£29127.31	£19816.82	£22790.51
Total costs (£)	£73911.15	£19940.92	£37702.31
Difference in total costs (£)		£53970.24	£36208.84
LYG	2.22	1.19	1.31
LYG difference		1.04	0.91
QALYs	1.47	0.73	0.83
QALY difference		0.75	0.65
ICER (£)		£72,356*	£56,076*

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

*difference in cost/QALY stated compared to calculated, due to rounding

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 2: Base-case cost-effectiveness results (with PAS)

	Atezolizumab	Docetaxel	Nintedanib + Docetaxel
Intervention cost (£)	[redacted]	[redacted]	[redacted]
Other costs (£)	£29127.31	£19816.82	£22790.51
Total costs (£)	[redacted]	[redacted]	[redacted]
Difference in total costs (£)		[redacted]	[redacted]
LYG	2.22	1.19	1.31
LYG difference		1.04	0.91
QALYs	1.47	0.73	0.83
QALY difference		0.75	0.65
ICER (£)		[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

*difference in cost/QALY stated compared to calculated, due to rounding

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 3: Base-case incremental results (without PAS)

				Versus Docetaxel				Versus N+D			
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	£19,941	1.19	0.73	-	-	-	-	-	-	-	-
Nintedanib + Docetaxel[3]	£37,702	1.31	0.83	£17,761	0.13	0.10	Ext. dominated[4]	-	-	-	-
Atezolizumab	£73,911	2.22	1.47	£53,970	1.04	0.75	£72,356	£36,209	0.91	0.65	£56,076
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years											

[3] Nintedanib PAS not included

[4] The ICER associated with the nintedanib (plus docetaxel) versus docetaxel comparison should be interpreted with caution. This is an artefeact of the data used for nintedanib (plus docetaxel) (total population as opposed to adenocarcinoma population). However, as this is an assessment of atezolizumab, and based on the rationale and assumptions set out in section 5.2, this is not anticipated to have a major bearing on the results

Table 4: Base-case incremental results (with PAS)

				Versus Docetaxel				Versus N+D			
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Docetaxel	[redacted]	1.19	0.73	-	-	-	-	-	-	-	-
Nintedanib + Docetaxel[5]	[redacted]	1.31	0.83	£17,761	0.13	0.10	Ext. dominated[6]	-	-	-	-
Atezolizumab	[redacted]	2.22	1.47	[redacted]	1.04	0.75	[redacted]	[redacted]	0.91	0.65	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years											

[5] Nintedanib PAS not included

[6] The ICER associated with the nintedanib (plus docetaxel) versus docetaxel comparison should be interpreted with caution. This is an artefact of the data used for nintedanib (plus docetaxel) (total population as opposed to adenocarcinoma population). However, as this is an assessment of atezolizumab, and based on the rationale and assumptions set out in section 5.2, this is not anticipated to have a major bearing on the results

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main company/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Figure 1: Comparison to docetaxel univariate sensitivity analysis (with-PAS)

Figure 2: Comparison to nintedanib+docetaxel univariate sensitivity analysis (with-PAS)

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

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 section 5.6 of the company submission.

Table 5: PSA results compared to base-case (without PAS)

	Costs		QALYs		ICERs (vs. docetaxel)		ICERs (vs. N+D)	
	Base case	PSA	Base case	PSA	Base case	PSA	Base case	PSA
Docetaxel	£19,941	£20,880	0.73	0.74	-	-	-	-
Nintedanib + docetaxel	£37,702	£38,676	0.83	0.84	Ext. dominated	Ext. dominated	-	-
Atezolizumab	£73,911	£73,033	1.47	1.47	£72,356	£73,934	£56,076	£57,777

Table 6: PSA results compared to base-case (with PAS)

	Costs		QALYs		ICERs (vs. docetaxel)		ICERs (vs. N+D)	
	Base case	PSA	Base case	PSA	Base case	PSA	Base case	PSA
Docetaxel	£19,941	£20,748	0.73	0.74	-	-	-	-
Nintedanib + docetaxel	£37,702	£38,731	0.83	0.84	Ext. dominated[7]	Ext. dominated	-	-
Atezolizumab	[redacted]	[redacted]	1.47	1.48	[redacted]	[redacted]	[redacted]	[redacted]

[7] The ICER associated with the nintedanib (plus docetaxel) versus docetaxel comparison should be interpreted with caution. This is an artefact of the data used for nintedanib (plus docetaxel) (total population as opposed to adenocarcinoma population). However, as this is an assessment of atezolizumab, and based on the rationale and assumptions set out in section 5.2, this is not anticipated to have a major bearing on the results

Figure 3: Scatterplot of PSA results for cost effectiveness plane (with PAS)

Figure 4: Cost-effectiveness acceptability curve (with PAS)

4.11 Please present scenario analysis results as described for the main company/sponsor submission of evidence for the technology appraisal.

Table 7: Results from scenario analyses: atezo vs. docetaxel (with PAS)

		Atezolizumab			Docetaxel			Atezo vs. doce
	Description	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	ICER
OS distribution	Cure log logistic Base case	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Exponential	1.56	1.02	[redacted]	1.09	0.66	[redacted]	[redacted]
	Weibull	1.48	0.96	[redacted]	1.07	0.64	[redacted]	[redacted]
	Log-normal	1.95	1.28	[redacted]	1.14	0.69	[redacted]	[redacted]
	Gen Gamma	1.60	1.04	[redacted]	1.08	0.65	[redacted]	[redacted]
	Log-logistic	1.98	1.31	[redacted]	1.14	0.69	[redacted]	[redacted]
	Gompertz	1.48	0.96	[redacted]	1.07	0.64	[redacted]	[redacted]
	KM with Gamma tail	1.61	1.05	[redacted]	1.09	0.66	[redacted]	[redacted]

	KM with log-logistic tail			[redacted]			[redacted]	[redacted]
	Piecewise exponential	1.54	1.00	[redacted]	1.07	0.65	[redacted]	[redacted]
PFS distribution	KM with Gamma tail Base case	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Exponential	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Weibull	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Log-normal	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Gen Gamma	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Log-logistic	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Gompertz	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	KM with Log-normal tail	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Piecewise exponential	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
TTD distribution	KM with Gamma tail	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]

	Base case							
	Exponential	2.22	1.47	[redacted]	1.19	0.72	[redacted]	[redacted]
	Weibull	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Log-normal	2.22	1.50	[redacted]	1.19	0.75	[redacted]	[redacted]
	Gen Gamma	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Log-logistic	2.22	1.50	[redacted]	1.19	0.76	[redacted]	[redacted]
	Gompertz	2.22	1.47	[redacted]	1.19	0.72	[redacted]	[redacted]
	KM with Weibulll tail	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Piecewise exponential	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
Treatment duration	Actual treatment duration Base case	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Until progression	2.22	1.47	[redacted]	1.19	0.74	[redacted]	[redacted]
Dosing scenarios	Planned dose w. vial sharing Base case	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]

	Planned dose wo. vial sharing	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Actual dose wo. vial sharing	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Actual dose w. vial sharing	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Planned ind. dose wo. vial sharing	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	Planned ind. dose w. vial sharing	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
Utility scenarios	OAK (proximity to death) Base case	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	OAK (On/Off treatment)	2.22	1.50	[redacted]	1.19	0.78	[redacted]	[redacted]
	Nafees et al., 2008	2.22	1.16	[redacted]	1.19	0.64	[redacted]	[redacted]
	Chouaid et al., 2013	2.22	1.38	[redacted]	1.19	0.76	[redacted]	[redacted]

				[redacted]			[redacted]	[redacted]
NMA scenarios	Frac. Poly Base case	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	OAK Doc arm	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
Time horizon (years)	25 Base case	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	10	1.97	1.30	[redacted]	1.18	0.72	[redacted]	[redacted]
	15	2.11	1.39	[redacted]	1.19	0.72	[redacted]	[redacted]
	20	2.18	1.44	[redacted]	1.19	0.73	[redacted]	[redacted]
	30	2.25	1.49	[redacted]	1.19	0.73	[redacted]	[redacted]
TTD KM proportion at risk (%)	15 Base case	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	10	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	20	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
PFS KM proportion at risk	15 Base case	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]

(%)	10	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	20	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
Cure fraction (%)	2 Base case	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	0	2.07	1.36	[redacted]	1.19	0.73	[redacted]	[redacted]
	1	2.14	1.42	[redacted]	1.19	0.73	[redacted]	[redacted]
	3	2.30	1.53	[redacted]	1.19	0.73	[redacted]	[redacted]
	4	2.39	1.58	[redacted]	1.19	0.73	[redacted]	[redacted]
	5	2.47	1.64	[redacted]	1.19	0.73	[redacted]	[redacted]
OS HR cap	24 months (trial follow up)	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	36 months	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
	48 months	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
Roche RWD study	Rates and costs of AEs	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]
Post-discontinuation therapy cost	0% radiotherapy, 100% pharmacological therapy	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]

Alternative nintedanib plus docetaxel administration costs	£183.50: Deliver Exclusively Oral Chemotherapy (SB11Z)	2.22	1.47	[redacted]	1.19	0.73	[redacted]	[redacted]

Table 8: Results from scenario analyses: atezo vs. nintedanib+docetaxel (with PAS)

		Atezolizumab			Nintedanib+Docetaxel			Atezo vs. N+D
	Description	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	ICER
OS distribution	Cure log logistic Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Exponential	1.56	1.02	[redacted]	1.18	0.73	[redacted]	[redacted]
	Weibull	1.48	0.96	[redacted]	1.15	0.71	[redacted]	[redacted]
	Log-normal	1.95	1.28	[redacted]	1.26	0.79	[redacted]	[redacted]
	Gen Gamma	1.60	1.04	[redacted]	1.17	0.73	[redacted]	[redacted]
	Log-logistic	1.98	1.31	[redacted]	1.26	0.79	[redacted]	[redacted]
	Gompertz	1.48	0.96	[redacted]	1.15	0.71	[redacted]	[redacted]

	KM with Gamma tail	1.61	1.05	[redacted]	1.18	0.73	[redacted]	[redacted]
	KM with Log-logistic tail	2.01	1.32	[redacted]	1.28	0.80	[redacted]	[redacted]
	Piecewise exponential	1.54	1.00	[redacted]	1.16	0.72	[redacted]	[redacted]
PFS distribution	KM with Gamma tail Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Exponential	2.22	1.47	[redacted]	1.31	0.82	[redacted]	[redacted]
	Weibull	2.22	1.47	[redacted]	1.31	0.82	[redacted]	[redacted]
	Log-normal	2.22	1.47	[redacted]	1.31	0.82	[redacted]	[redacted]
	Gen Gamma	2.22	1.47	[redacted]	1.31	0.82	[redacted]	[redacted]
	Log-logistic	2.22	1.47	[redacted]	1.31	0.82	[redacted]	[redacted]
	Gompertz	2.22	1.47	[redacted]	1.31	0.82	[redacted]	[redacted]
	KM with Log-normal tail	2.22	1.47	[redacted]	1.31	0.82	[redacted]	[redacted]
	Piecewise exponential	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]

TTD distribution	KM with Gamma tail Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Exponential	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Weibull	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Log-normal	2.22	1.50	[redacted]	1.31	0.83	[redacted]	[redacted]
	Gen Gamma	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Log-logistic	2.22	1.50	[redacted]	1.31	0.83	[redacted]	[redacted]
	Gompertz	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	KM with Weibulll tail	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Piecewise exponential	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
Treatment duration	Actual treatment duration Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Until progression	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]

Dosing scenarios	Planned dose w. vial sharing Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Planned dose wo. vial sharing	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Actual dose wo. vial sharing	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Actual dose w. vial sharing	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Planned ind. dose wo. vial sharing	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	Planned ind. dose w. vial sharing	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
Utility scenarios	OAK (proximity to death) Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	OAK (On/Off treatment)	2.22	1.50	[redacted]	1.31	0.89	[redacted]	[redacted]

	Nafees et al., 2008	2.22	1.16	[redacted]	1.31	0.70	[redacted]	[redacted]
	Chouaid et al., 2013	2.22	1.38	[redacted]	1.31	0.85	[redacted]	[redacted]
NMA scenarios	Frac. Poly Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	OAK Doc arm	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
Time horizon (years)	25 Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	10	1.97	1.30	[redacted]	1.30	0.82	[redacted]	[redacted]
	15	2.11	1.39	[redacted]	1.31	0.82	[redacted]	[redacted]
	20	2.18	1.44	[redacted]	1.31	0.83	[redacted]	[redacted]
	30	2.25	1.49	[redacted]	1.31	0.83	[redacted]	[redacted]
TTD KM proportion at risk (%)	15 Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	10	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	20	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]

PFS KM proportion at risk (%)	15 Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	10	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	20	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
Cure fraction (%)	2 Base case	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	0	2.07	1.36	[redacted]	1.31	0.83	[redacted]	[redacted]
	1	2.14	1.42	[redacted]	1.31	0.83	[redacted]	[redacted]
	3	2.30	1.53	[redacted]	1.31	0.83	[redacted]	[redacted]
	4	2.39	1.58	[redacted]	1.31	0.83	[redacted]	[redacted]
	5	2.47	1.64	[redacted]	1.31	0.83	[redacted]	[redacted]
OS HR cap	24 months (trial follow up)	2.22	1.47	[redacted]	1.32	0.83	[redacted]	[redacted]
	36 months	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
	48 months	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
Roche RWD study	Rates and costs of AEs	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]

Post-discontinuation therapy cost	0% radiotherapy, 100% pharmacological therapy	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]
Alternative nintedanib plus docetaxel administration costs	£183.50: Deliver Exclusively Oral Chemotherapy (SB11Z)	2.22	1.47	[redacted]	1.31	0.83	[redacted]	[redacted]

4.12 If any of the criteria on which the Patient Access Scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable – simple PAS on invoice.

Impact of Patient Access Scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the Patient Access Scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the Patient Access Scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Please see Table 7 and Table 8 above for scenario analyses versus docetaxel and nintedanib + docetaxel respectively. These are reflections of Tables 95 and 96 of the company submission, with the PAS price applied to all scenarios.

5 Appendix A: Details for outcome-based schemes only

Not applicable

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Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [ID970]

Dear [redacted]

The Evidence Review Group, Liverpool Reviews and Implementation Group, and the technical team at NICE have looked at the submission received on 16 February 2017 from Roche Products Limited. 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 **28 March 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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 Jessica Maloney, Technical Lead (Jessica.Maloney@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. Priority Question. It is stated within the company submission (page 31) that atezolizumab binds to and inactivates PD-L1. In view of this mechanism of action, please explain the finding (company submission page 49) that 'A significant improvement in overall survival with atezolizumab was observed regardless of PD-L1 status, with a similar effect observed in PD-L1 negative patients (TC0/IC0) to that seen in the ITT population'.

A2. Priority Question. It is stated in the company submission that it is not possible to compare pembrolizumab with atezolizumab as different measures were used to identify PD-L1 expression in the two key trials. Please explain what these measures are and why their outcomes are not comparable.

A3. Priority Question. The company submission (page 49) states that analyses of data from the OAK trial showed a statistically significant and clinically meaningful improvement in overall survival when treatment with atezolizumab was compared with docetaxel in patients with ≥1% PD-L1 expression (hazard ratio 0.74, 95% CI: 0.58 to 0.93, p=0.012). Which TC/IC (tumour cell/tumour-infiltrating immune cell) measure was used to identify patients with ≥1% PD-L1 from the OAK trial?

A4. As part of either the OAK or POPLAR trials, was progression-free survival determined by any independent assessment (for example, blinded independent central review [BICR])? If so, please provide results of the independent assessment.

A5. All-cause adverse events (AE) of any grade experienced by ≥20% of patients in the OAK trial are presented in Table 45 of the company submission. In the clinical study report (CSR) for the OAK trial, the company states that details of all-cause AEs (any grade) reported in ≥10% of patients are available in an appendix to the CSR. Please provide the CSR appendix regarding all-cause AEs experienced by ≥10% of patients in the OAK trial.

Statistical clarification questions

A6. Priority question. Please provide the statistical analysis plans for the OAK and POPLAR trials, including details of amendments to the original plans, where applicable.

A7. Priority question. Indirect treatment comparison.

The ERG makes four comments regarding the approach of the company to the indirect treatment comparison within the company submission, noting that all four comments

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should be considered in the clarification response. Requests for additional analyses or additional results are marked with a star (*).

a) Study selection

The company states (page 96) that the indirect treatment comparison was 'conducted to support pricing and reimbursement submission across all countries, and also included comparators not listed in the final scope (afatinib, dacomitinib, erlotinib; gefitinib; paclitaxel; pemetrexed)' and that the final efficacy comparison results presented are those relevant to the present appraisal only (docetaxel, nintedanib+docetaxel).

The ERG notes that the methods used by the company leads to the final efficacy comparison results being adjusted for the entire network of treatments (presented in company submission, Figures 23 and 24), and includes many comparators which are not relevant to this appraisal.

i) **Priority request:** Please provide indirect treatment comparison results including the relevant comparators only (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib+docetaxel 75mg/m^2) using only the OAK, POPLAR and LUME-Lung 1 trials for the outcomes of overall survival and progression-free survival*

b) Histology

As stated within Section 4.10 of the company submission, nintedanib+docetaxel is only recommended by NICE for patients with adenocarcinoma histology, but the company presents results consistent with the anticipated licence of atezolizumab (for patients with both non-squamous and squamous NSCLC). For completeness:

i) **Priority request:** Please provide indirect treatment comparison results for a reduced network of relevant comparators (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib+docetaxel 75mg/m^2) using data from the adenocarcinoma subgroups of the OAK, POPLAR and LUME-Lung 1 trials only for the outcomes of overall surivival and progression-free survival*

ii) If adenocarcinoma subgroup results are not available from the OAK and POPLAR trials, please provide indirect treatment comparison results for a reduced network of relevant comparators (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib+docetaxel 75mg/m^2) using data from the non-squamous subgroups of the OAK and POPLAR trials and the adenocarcinoma subgroup of the LUME-Lung 1 trial for the outcomes of overall survival and progression-free survival*

c) Scope of the appraisal

The final scope for the present appraisal includes pembrolizumab as a comparator to atezolizumab. Although pembrolizumab is included within the overall survival and progression-free survival networks as a relevant comparator, it is excluded from the indirect treatment comparison results as the company does not consider it to be a relevant comparator for this appraisal. For completeness:

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i) **Priority request:** Please provide indirect treatment comparison results for a reduced network of comparators (atezolizumab 1200mg, docetaxel 75mg/m^2, pembrolizumab 2mg); in other words, results from an indirect treatment comparison of the OAK, POPLAR and KEYNOTE-010 trials only for the outcomes of overall survival and progression-free survival.*

d) Model selection

The company describes five fractional polynomial models (two first order and three second order) within 'Network Meta-Analysis Methodology' of Section 4.10 of the company submission and describes criteria for 'Model Selection' in the subsequent section. The company then presents indirect treatment comparison results for the model judged to be best fitting according to the Deviance Information Criteria (DIC) and by viewing fitted curves.

The company states that upon viewing fitted curves for the second order models, an apparent survival 'plateau' was observed which would lead to 'very large HRs at later time points for some treatment comparisons.'

The company bases their choice between fixed and random effects models on the DIC, interpreting little difference in DIC to indicate no evidence of substantial heterogeneity. The ERG considers that the DIC is a measure of model fit rather than heterogeneity and that choices between fixed and random effects models within network meta-analysis should be made taking into account consistency of trial populations and evidence sources (Dias 2013, referenced within the company submission), rather than based on model fit alone.

i) The company states that the use of DIC to assess heterogeneity is based on the recommendations of the NICE Decision Support Unit (Dias 2013). The ERG cannot find this recommendation within the Dias 2013 reference, please clarify where the recommendation is made.

ii) **Priority Request**: Please provide indirect treatment comparison results for a reduced network of relevant comparators (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib+docetaxel 75mg/m^2) for all five fractional polynomials models to allow the ERG to also make an assessment of the visual appearance of fitted curves for the outcomes of overall survival and progression-free survival.*

If additional analyses of the reduced network of relevant comparators cannot be performed, please provide the entire network results for all five fractional polynomial models fitted in a similar format to the results presented in Tables 37 and 38 for the outcomes of overall survival and progression-free survival.*

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iii) Please provide indirect treatment comparison results for a network of relevant comparators (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib+docetaxel 75mg/m^2) for all fitted random effects models to allow the ERG to make an assessment of the impact of any heterogeneity on results for the outcomes of overall survival and progression-free survival.*

If additional analyses of the reduced network of relevant comparators cannot be performed, please provide results for all random effects models in a similar format to the results presented in Tables 37 and 38 for the outcomes of overall survival and progression-free survival.*

iv) The methods employed by the company allow for estimation of a heterogeneity parameter for all random effects models (Jansen 2011). The ERG prefers this parameter as a measure of heterogeneity in the network (rather than the DIC). Please provide estimates of this parameter for each random effects model fitted (see point iii) for the outcomes of overall survival and progression-free survival.*

v) The ERG assumes that the hazard ratios presented in Figure 26 (overall survival) are calculated from the information in Table 37 and 38 of the CS, and that the hazard ratios in Figure 28 (progression-free survival) are calculated from the information in Table 40 and 41 of the submission. In other words, from the beta parameter estimates in Table 37, a comparison of atezolizumab 1200mg and docetaxel 75mg/m^2 for a first order Weibull fractional polynomial model would be:

$$\ln(HR(t) = \big(-2.987 + (-2.951)\big) + (0.012 - 0.180)(\log(t)) \quad (1)$$

$$= \ln(HR(t) = (-0.036) + (-0.168)(\log(t)) \quad (2)$$

$$= HR(t) = \exp((-0.036) + (-0.168)(\log(t))) \quad (3)$$

Is the ERG correct to assume that the hazard ratio presented in Figure 26 for atezolizumab 1200mg compared to docetaxel 75mg/m^2 corresponds to equation (3) above?

A8. Sample size calculations and analysis populations (OAK and POPLAR)

a. Within the Lancet publication of the OAK trial (Rittmeyer et al 2017) it is stated that 'the OAK statistical design was amended on Jan 28 2016, according to a pre-specified modification plan'. Please provide further details of this modification plan or indicate where details can be found within the protocol or statistical analysis plan.

b. It is stated within the company submission (Section 4.14) that results for the secondary population of OAK and further analyses from POPLAR will be presented in 2017. Are any additional results from either of these follow-up analyses available at this time?

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c. Section 4.4 of the company submission outlines 'Assumptions for POPLAR' and 'Assumptions for OAK.' It is stated that 'Study design assumptions in OAK were based on results from POPLAR.' Please clarify the basis of the 'Assumptions for POPLAR.'

A9. Proportional versus non-proportional hazards

It is demonstrated within Section 4.10 and Section 5.3 of the company submission that the proportional hazards assumption is unlikely to hold for the OAK trial for overall survival, progression-free survival and time-to-treatment discontinuation. However, clinical effectiveness results within Section 4.7 of the company submission are presented in terms of hazard ratios from Cox regression models and p values from log-rank tests; methods which require the assumption of proprtional hazards.

a. For the OAK trial, did the company consider or employ any alternative methods of analysis for the clinical effectiveness results, given that it has been established that the proportional hazards assumption is unlikely to hold for the main efficacy outcomes of OAK? If so, please describe the method(s) used and provide results
b. Was the proportional hazards assumption checked for the main efficacy outcomes (overall survival and progression-free survival) of POPLAR? If so, please describe the method(s) used and present results.

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City Tower
Manchester
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+44 (0)300 323 0140

Section B: Clarification on cost effectiveness data

B1. Priority request: Kaplan-Meier data. Please provide the Kaplan-Meier analyses listed in a to c below to the following specifications:

Trial data set: OAK trial
Censoring: Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, i.e. not when last known to be alive
Format: Please present analysis outputs using the format of the sample table shown below this question
Population: ITT population including all patients lost to follow-up or withdrawing from the trial

a. Time to death from any cause (overall survival) Kaplan-Meier analysis for patients in the atezolizumab arm of the trial

b. Time to death from any cause (overall survival) Kaplan-Meier analysis for patients in the docetaxel arm of the trial

c. Time to study treatment discontinuation Kaplan-Meier analysis.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54

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SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

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B2. Priority request: Utility data: Please complete the table below using data collected during the OAK trial for European patients only and valued using the UK TTO value set.

Time	Atezolizumab		Docetaxel		Average	
	n	Mean (sd)	n	Mean (sd)	n	Mean (sd)
Baseline						
>360 days to death						
>180-360 days to death						
30-180 days to death						
<30 days to death						

B3. Priority request. Utility data: Please complete the example table below using all EQ-5D data collected during the OAK trial (if time to death has not occurred then please use time between utility value being taken and data cut-off point for that patient).

Patient ID	Patient alive at data-cut off?	Time to death in days	Time to data-cut off in days	EQ-5D utility value using UK TTO data set
A	No	370	NA	0.712
A	No	160	NA	0.635
A	No	100	NA	0.481
B	Yes	NA	380	0.693
B	Yes	NA	200	0.658

Section C: Textual clarifications and additional points

C1. The number of participants withdrawn from treatment is presented in Figure 6 and Table 23 of the company submission, however, even when accounting for the actual numbers of patients receiving each treatment, the numbers do not correspond. Should the number withdrawn from atezolizumab treatment in Table 23 be 364? If so, please clarify the number of patients who withdrew for each reason listed in Table 23 of the company submission.

C2. It is stated in the company submission (p162) that:

> 'Based on their experience and knowledge of immunotherapies, unanimous opinion suggested that an overall survival rate of approximately 10% of patients treated with

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atezolizumab at 5 years would not be implausible. This is supported by the recent appraisal for pembrolizumab (National Institute for Health and Care Excellence, 2017), where under the Committee's preferred assumptions, the resulting 5-year overall survival estimate was 10.4% (and was specifically acknowledged in the FAD).'

The ERG can find no reference in the final appraisal determination (FAD) to either 10.4% or a statement that sets out the Committee's preferred assumptions. Please specify the exact location within the FAD of these details.

C3. Please provide a clear definition of 'traditional parameterisation' as described for the scenario analyses (company submission, p210).

C4. Please provide a justification for the sensitivity analysis range used for 'cure fraction' (table 94 p207), as this parameter had the largest impact on the ICER.

Single technology appraisal

Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [ID970]

Section B: Clarification on cost effectiveness data v2

B1. Priority request: Kaplan-Meier data. Please provide the Kaplan-Meier analyses listed in a to c below to the following specifications:

Trial data set: OAK trial
Format: Please present analysis outputs using the format of the sample table shown below this question
Population: ITT population including all patients lost to follow-up or withdrawing from the trial

a. Time to death from any cause (OS) Kaplan-Meier analysis for patients in the atezolizumab arm of the trial

b. Time to death from any cause (OS) Kaplan-Meier analysis for patients in the docetaxel arm of the trial

c. Time to study treatment discontinuation Kaplan-Meier analysis.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

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8.000		.	.	.	6	56
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Single technology appraisal

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Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. Priority Question. It is stated within the company submission (page 31) that atezolizumab binds to and inactivates PD-L1. In view of this mechanism of action, please explain the finding (company submission page 49) that 'A significant improvement in overall survival with atezolizumab was observed regardless of PD-L1 status, with a similar effect observed in PD-L1 negative patients (TC0/IC0) to that seen in the ITT population'.

We are pleased that the ERG acknowledges the effectiveness of atezolizumab across all patients with non-small cell lung cancer. The objective evidence of efficacy seen in PD-L1 expressers and non-expressers forms the basis of our expected European licence in all patients. For this reasoning, the population included in our submission is also for all patients irrespective of PD-L1 expression.

The mechanism of action of atezolizumab allows for several possible reasons for this result:

The first is the biological hypothesis that atezolizumab increases anticancer immunity through enhanced priming of new anticancer immune responses (Rittmeyer et al., 2016). PD-L1 is expressed on T cells and antigen presenting cells (APCs) present in the lymph nodes. Here it binds to B7.1, which is also expressed on T cells and APCs; as with PD-1 to PD-L1 interactions, this interaction can downregulate T cell activity and subsequent immune responses. Inhibition of this interaction in the lymph node environment may therefore prevent this downregulation and stimulate an immune response in tumours that are PD-L1 negative (Butte et al., 2007, Yang et al., 2011).

The second reason is that a PD-L1 negative tumour is defined as PD-L1 expression on less than 1% expression of tumour cells (TCs) and tumour-infiltrating immune cells (ICs), i.e. TC0 and IC0. Consequently, there could still be low levels of PD-L1 expression within the tumour environment that are sufficient to induce anti-tumoural immune responses following treatment with atezolizumab.

Finally, PD-L1 expression in tumours may be heterogeneous and variable over time in a subset of tumours. This means that a biopsies taken from different areas of a tumour may show different levels of PD-L1 expression, or that the PD-L1 expression level may have changed since the biopsy was taken and may not reflect the current PD-L1 status (Chaft J et al., 2015, Cree et al., 2016, Kerr and Hirsch, 2016, Kowanetz M et al., 2015).

A2. Priority Question. It is stated in the company submission that it is not possible to compare pembrolizumab with atezolizumab as different measures were used to identify PD-L1 expression in the two key trials. Please explain what these measures are and why their outcomes are not comparable.

PD-L1 expression in OAK and POPLAR was assessed in a central laboratory using the Ventana PD-L1 (SP142) immunohistochemistry (IHC) assay. The SP142 assay stratified PD-L1 expression on both tumour cells (TCs) and tumour-infiltrating immune cells (ICs). TC1/2/3 or IC1/2/3 was defined as PD-L1 expression on 1% or more of TCs or ICs, TC2/3 or IC2/3 was defined as PD-L1 expression on 5% of these cells; TC3 was defined as PD-L1

expression on 50% or more of TCs and IC3 was defined as 10% or more of ICs; and TC0 as PD-L1 expression on less than 1% of TCs and IC0 on less than 1% of ICs.

PD-L1 expression in the pembrolizumab KEYNOTE-010 clinical trial was assessed in a central laboratory using the Dako 22C3 IHC assay (Herbst et al., 2016). The 22C3 assay stratified PD-L1 expression on TCs only using a tumour proportion score (TPS). Tumours staining for PD-L1 with ≥1% were considered expressers (TPS ≥1%), with a further analysis of those expressing 50% or greater (TPS ≥50%). Tumours with <1% cells for PD-L1 staining were considered non-expressers (TPS <1%). Only people whose tumours expressed PD-L1 (based on a TPS of ≥1%) were eligible for randomisation to the study.

Given these differences, it is not appropriate to compare atezolizumab PD-L1 expressers to pembrolizumab PD-L1 expressers, as the patient populations identified with these two different assays are not equivalent.

Table 1: PD-L1 tests used in atezolizumab and pembrolizumab clinical studies

	Atezolizumab	Pembrolizumab
Detection antibody	SP142	22C3
IHC platform	Ventana	Dako
Cell types scored for NSCLC	IC and TC	TC
Cut-offs in NSCLC	TC3 or IC3: ≥50% of TCs or ≥10% of ICs TC2/3 or IC2/3: ≥5% of TCs or ICs TC1/2/3 or IC1/2/3: ≥1% of TCs or ICs TC0 and IC0: <1% of TCs and ICs *(proportion of cells stained at any intensity)*	PDL1-selected as ≥50% (treatment-naïve) or ≥1% (previously treated) of viable TCs showing partial or complete membrane PD-L1 expression

A3. Priority Question. The company submission (page 49) states that analyses of data from the OAK trial showed a statistically significant and clinically meaningful improvement in overall survival when treatment with atezolizumab was compared with docetaxel in patients with ≥1% PD-L1 expression (hazard ratio 0.74, 95% CI: 0.58 to 0.93, p=0.012). Which TC/IC (tumour cell/tumour-infiltrating immune cell) measure was used to identify patients with ≥1% PD-L1 from the OAK trial?

See response to A2. PD-L1 expression was assessed using the Ventana SP142 IHC assay. TC1/2/3 or IC1/2/3 was defined as PD-L1 expression on 1% or more of TCs or ICs.

A4. As part of either the OAK or POPLAR trials, was progression-free survival determined by any independent assessment (for example, blinded independent central review [BICR])? If so, please provide results of the independent assessment.

There was no blinded independent central review of any endpoints explored in either OAK or POPLAR.

A5. All-cause adverse events (AE) of any grade experienced by ≥20% of patients in the OAK trial are presented in Table 45 of the company submission. In the clinical study

report (CSR) for the OAK trial, the company states that details of all-cause AEs (any grade) reported in ≥10% of patients are available in an appendix to the CSR. Please provide the CSR appendix regarding all-cause AEs experienced by ≥10% of patients in the OAK trial.

The submission mistakenly referred to these details only appearing in an appendix to the CSR: all cause AEs experienced by ≥10% of patients in the OAK trial is reported in the main body of the CSR, and also presented below.

Table 1: Adverse events related to study treatment, incidence of at least 10% in any arm (safety evaluable population)

n (%)	Atezolizumab n=609	Docetaxel n=578
Total number of patients with at least one AE	231 (37.9)	454 (78.5)
General disorders and administration site conditions	133 (21.8)	261 (45.2)
Total number of patients with at least one AE	87 (14.3)	177 (30.6)
Fatigue	51 (8.4)	96 (16.6)
Asthenia		
Gastrointestinal disorders		
Total number of patients with at least one AE	96 (15.8)	210 (36.3)
Nausea	53 (8.7)	112 (19.4)
Diarrhoea	47 (7.7)	109 (18.9)
Stomatitis	13 (2.1)	59 (10.2)
Blood and lymphatic system disorders		
Total number of patients with at least one AE	31 (5.1)	214 (37.0)
Anaemia	24 (3.9)	114 (19.7)
Neutropenia	7 (1.1)	85 (14.7)
Febrile neutropenia	0	61 (10.6)
Skin and subcutaneous tissue disorders		
Total number of patients with at least one AE	3 (0.5)	198 (34.3)
Alopecia	3 (0.5)	198 (34.3)
Metabolism and nutrition disorders		
Total number of patients with at least one AE	52 (8.5)	116 (20.1)
Decreased appetite	52 (8.5)	116 (20.1)
Musculoskeletal and connective tissue disorders		
Total number of patients with at least one AE	21 (3.4)	81 (14.0)
Myalgia	21 (3.4)	81 (14.0)
Nervous system disorders		
Total number of patients with at least one AE	6 (1.0)	58 (10.0)
Neuropathy peripheral	6 (1.0)	58 (10.0)

Statistical clarification questions

A6. Priority question. Please provide the statistical analysis plans for the OAK and POPLAR trials, including details of amendments to the original plans, where applicable.

Statistical analysis plans for both OAK and POPLAR have been supplied as part of this response.

A7. Priority question. Indirect treatment comparison.

The ERG makes four comments regarding the approach of the company to the indirect treatment comparison within the company submission, noting that all four comments should be considered in the clarification response. Requests for additional analyses or additional results are marked with a star (*).

a) Study selection

The company states (page 96) that the indirect treatment comparison was 'conducted to support pricing and reimbursement submission across all countries, and also included comparators not listed in the final scope (afatinib, dacomitinib, erlotinib; gefitinib; paclitaxel; pemetrexed)' and that the final efficacy comparison results presented are those relevant to the present appraisal only (docetaxel, nintedanib+docetaxel).

The ERG notes that the methods used by the company leads to the final efficacy comparison results being adjusted for the entire network of treatments (presented in company submission, Figures 23 and 24), and includes many comparators which are not relevant to this appraisal.

i) **Priority request:** Please provide indirect treatment comparison results including the relevant comparators only (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib+docetaxel 75mg/m^2) using only the OAK, POPLAR and LUME-Lung 1 trials for the outcomes of overall survival and progression-free survival*

Graphical indirect treatment comparison results for the reduced network using only OAK, POPLAR and LUME-Lung 1 as compared to the original analyses are presented below. As demonstrated, the results of the two analyses are comparable, confirming the validity of the extended network for this decision problem. The impact on the ICER is marginal, with less than a £100 cost/QALY decrease for the comparison versus Docetaxel and less than a £100 cost/QALY increase for the comparison versus Nintedanib+Docetaxel.

Overall survival

Both the original analysis (all comparators) and new reduced network analysis use the Weibull fixed effects:

Figure 1: OS original network result (Weibull FE)

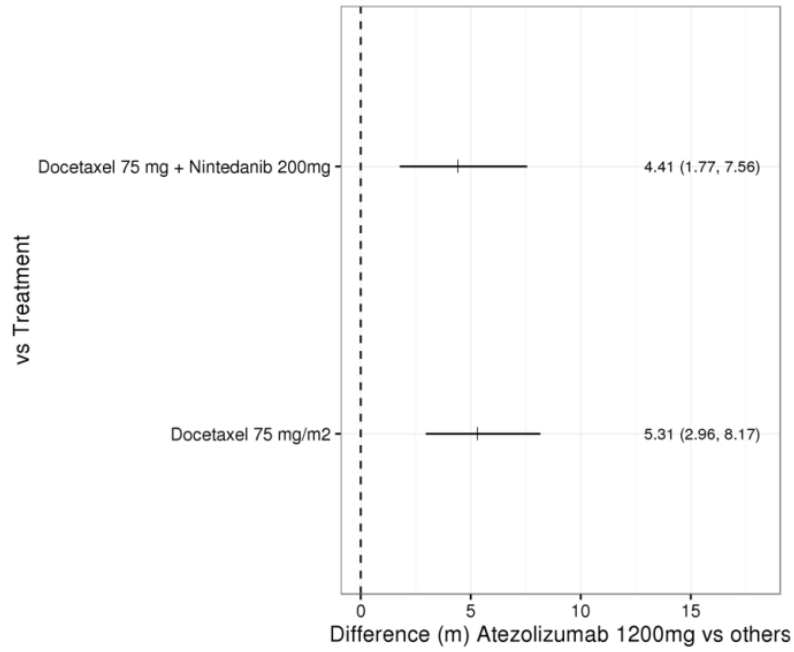


Figure 2: OS reduced network result (Weibull FE)

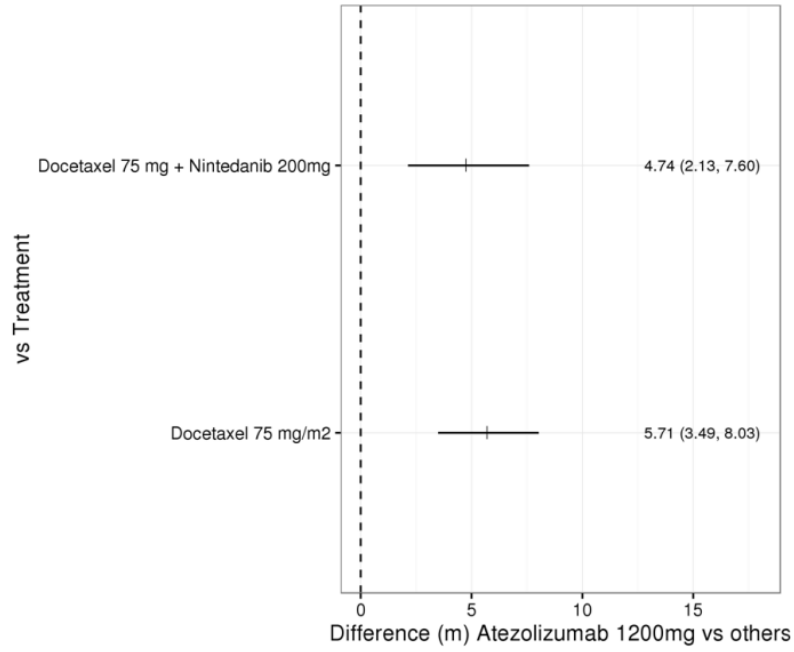


Figure 3:OS original network HR result (Weibull FE)

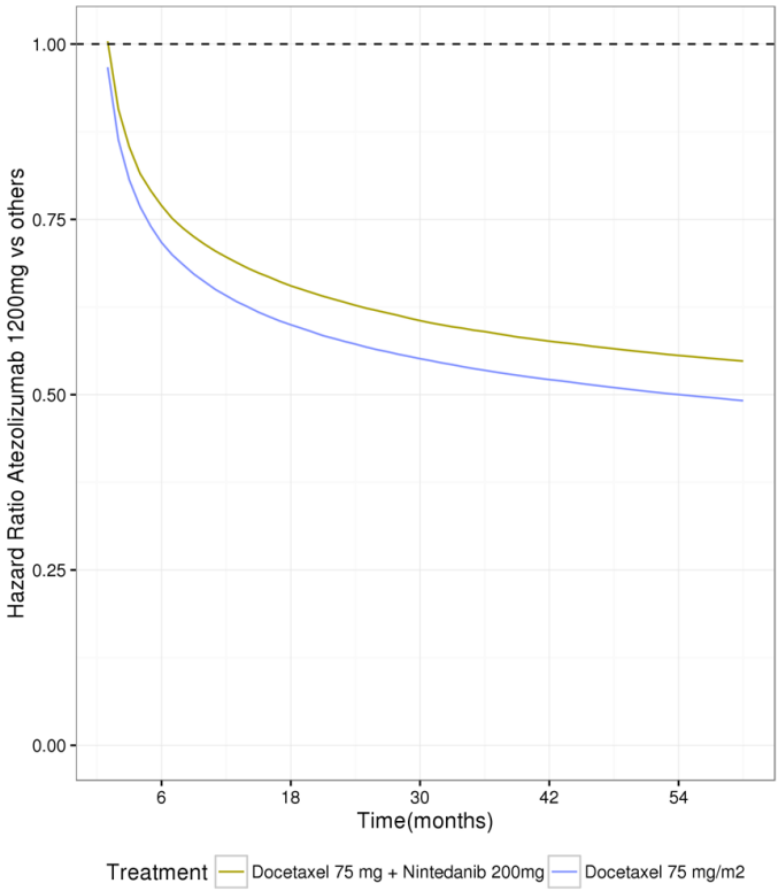
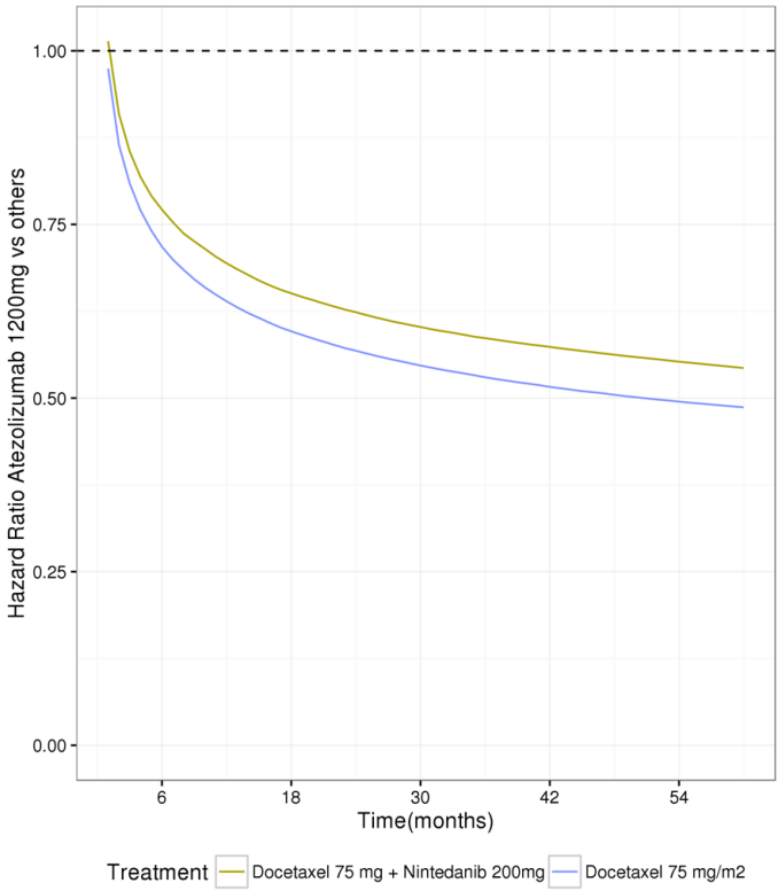


Figure 4:OS reduced network HR result (Weibull FE)



Progression free survival

The original analysis (all comparators) initially used a Gompertz fixed effects model. However, Weibull has a lower DIC in the reduced network analysis, and is therefore employed using fixed effects.

Figure 5: PFS original network result (Gompertz FE)

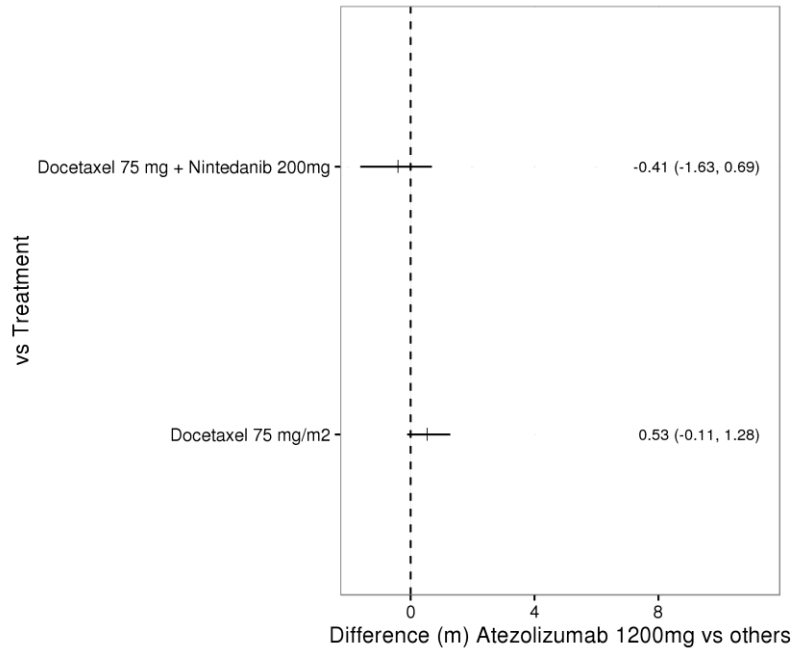


Figure 6: PFS reduced network result (Weibull FE)

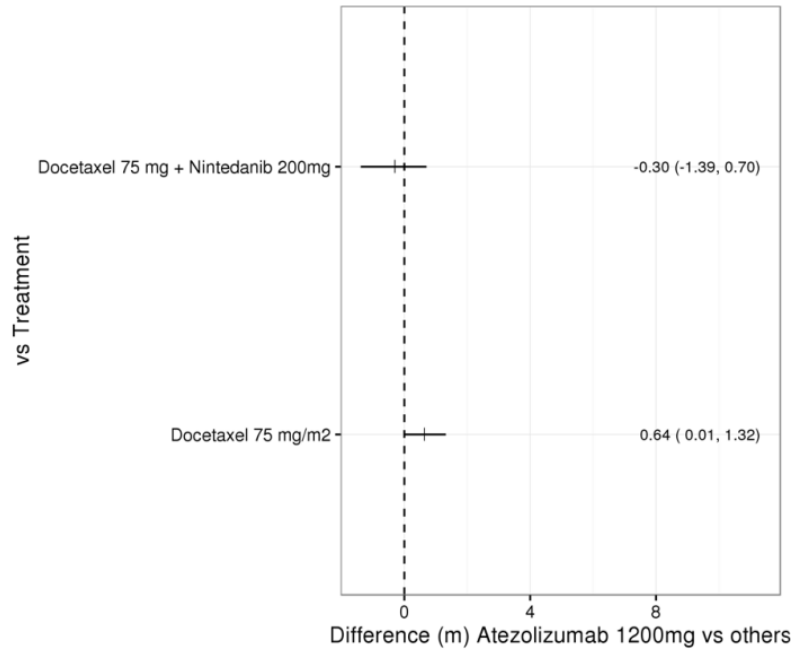


Figure 7: PFS original network HR result (Gompertz FE)

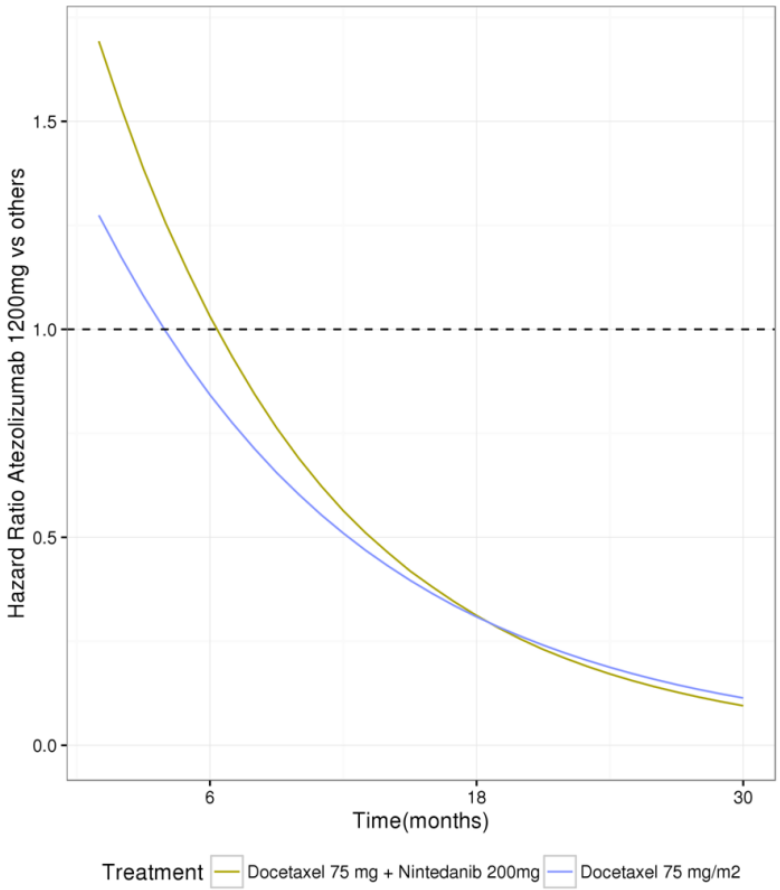
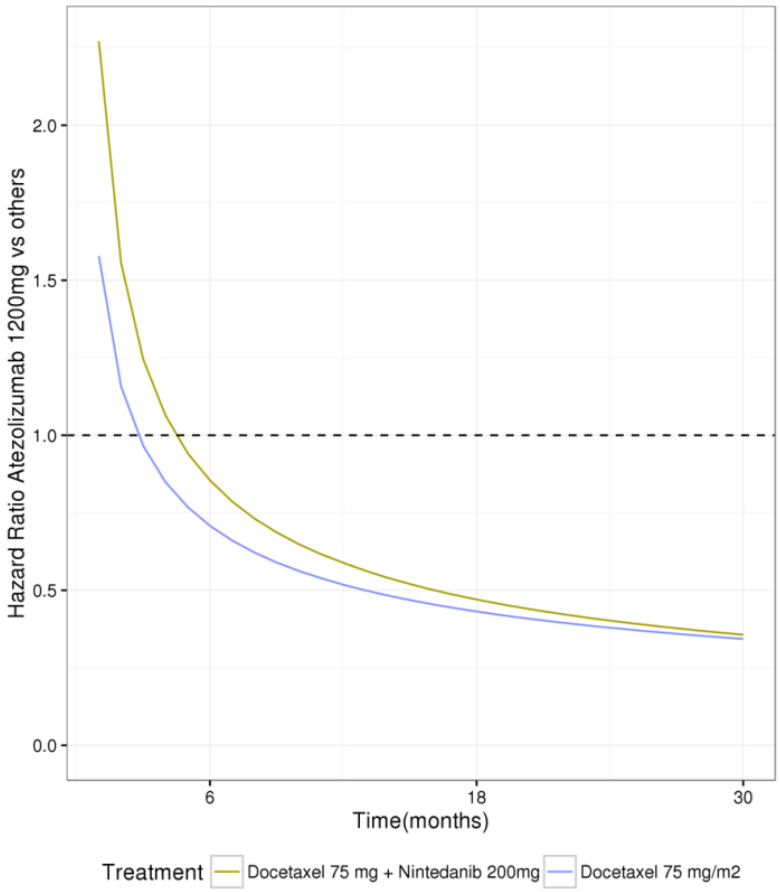


Figure 8: PFS reduced network HR result (Weibull FE)



b) Histology

As stated within Section 4.10 of the company submission, nintedanib+docetaxel is only recommended by NICE for patients with adenocarcinoma histology, but the company presents results consistent with the anticipated licence of atezolizumab (for patients with both non-squamous and squamous NSCLC). For completeness:

i) **Priority request:** Please provide indirect treatment comparison results for a reduced network of relevant comparators (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib+docetaxel 75mg/m^2) using data from the adenocarcinoma subgroups of the OAK, POPLAR and LUME-Lung 1 trials only for the outcomes of overall surivival and progression-free survival*

ii) If adenocarcinoma subgroup results are not available from the OAK and POPLAR trials, please provide indirect treatment comparison results for a reduced network of relevant comparators (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib+docetaxel 75mg/m^2) using data from the non-squamous subgroups of the OAK and POPLAR trials and the adenocarcinoma subgroup of the LUME-Lung 1 trial for the outcomes of overall survival and progression-free survival*

The statistical analysis plans for the OAK and POPLAR trials did not include subgroups for the presence of adenocarcinoma.

Consistent with our approach to the comparison of atezolizumab to relevant existing treatments (described further in A7c), results of the indirect treatment comparison provided

below compare atezolizumab in its licensed indication (all-comers), to nintedanib+docetaxel in its licensed indication (adenocarcinoma patients).

The impact on the ICER using this methodology is more substantial (cf. A7a), with the comparison versus Docetaxel decreasing by over £3000 per QALY (new ICER = £69,260), and the comparison versus Nintedanib+Docetaxel decreasing by almost £30,000 per QALY (£26,181).

Overall survival

Figure 9: OS original network result (Weibull FE): N+D all-comers

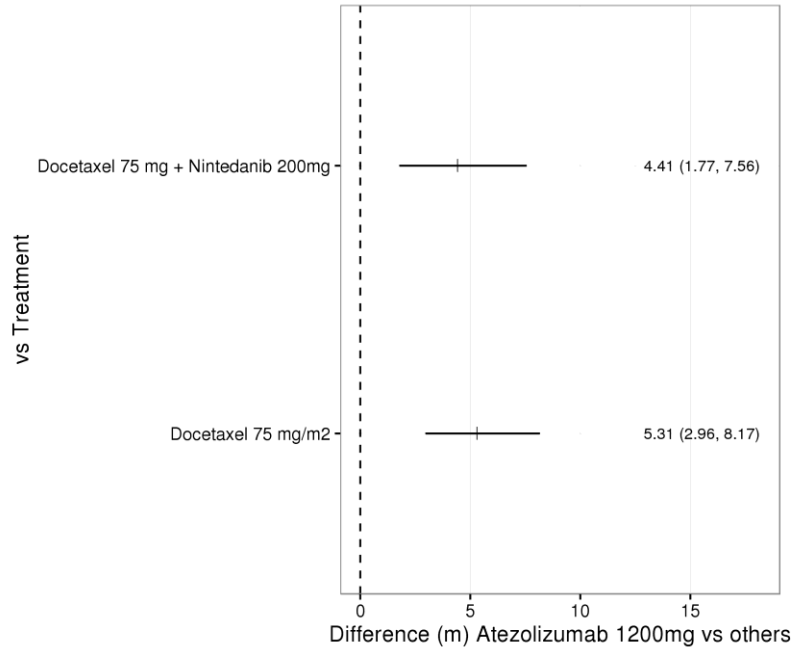


Figure 10: OS reduced network result (Weibull FE): N+D adenocarcinoma

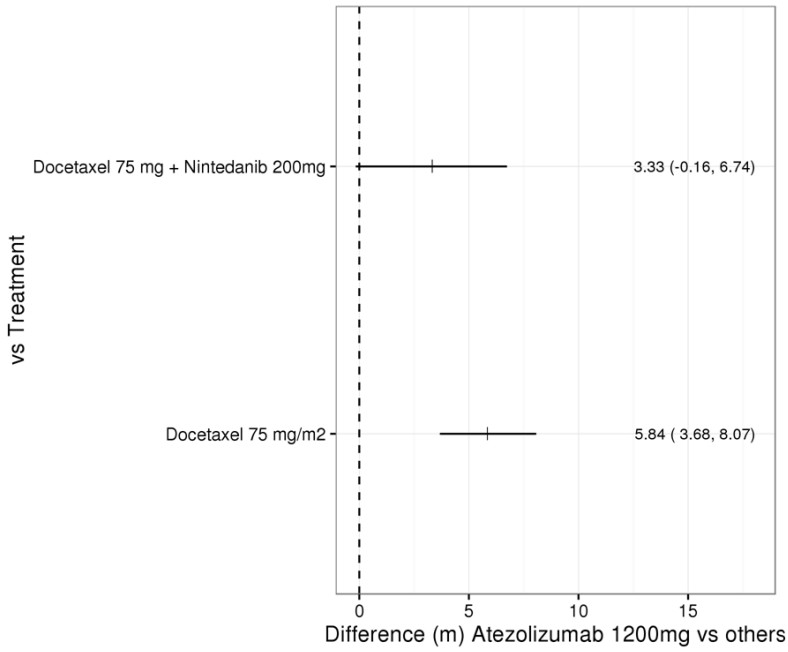


Figure 11: OS original network HR result (Weibull FE): N+D all-comers

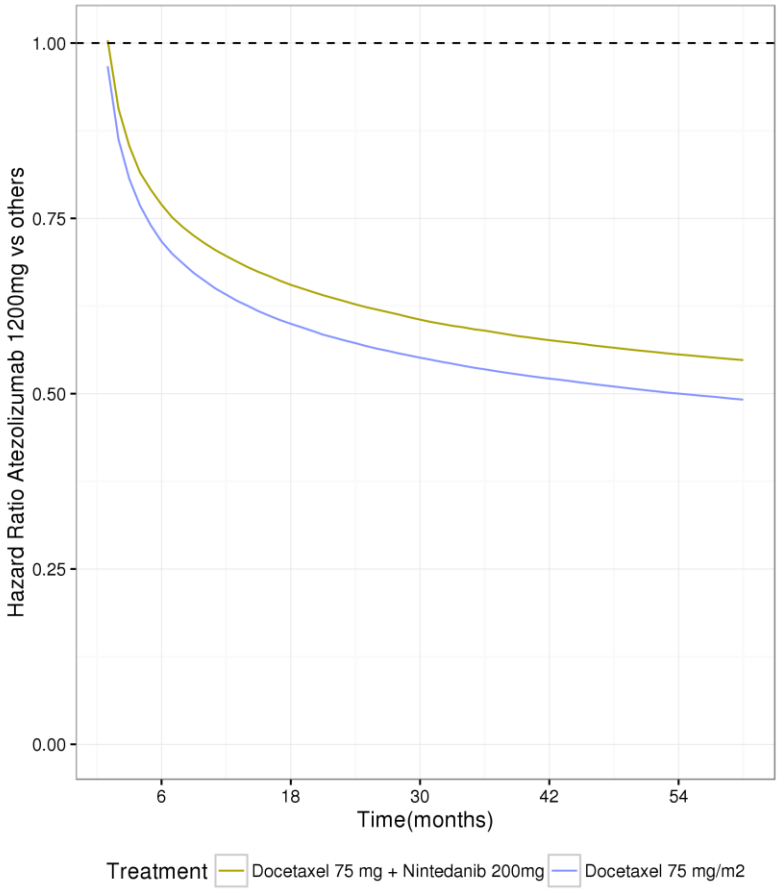
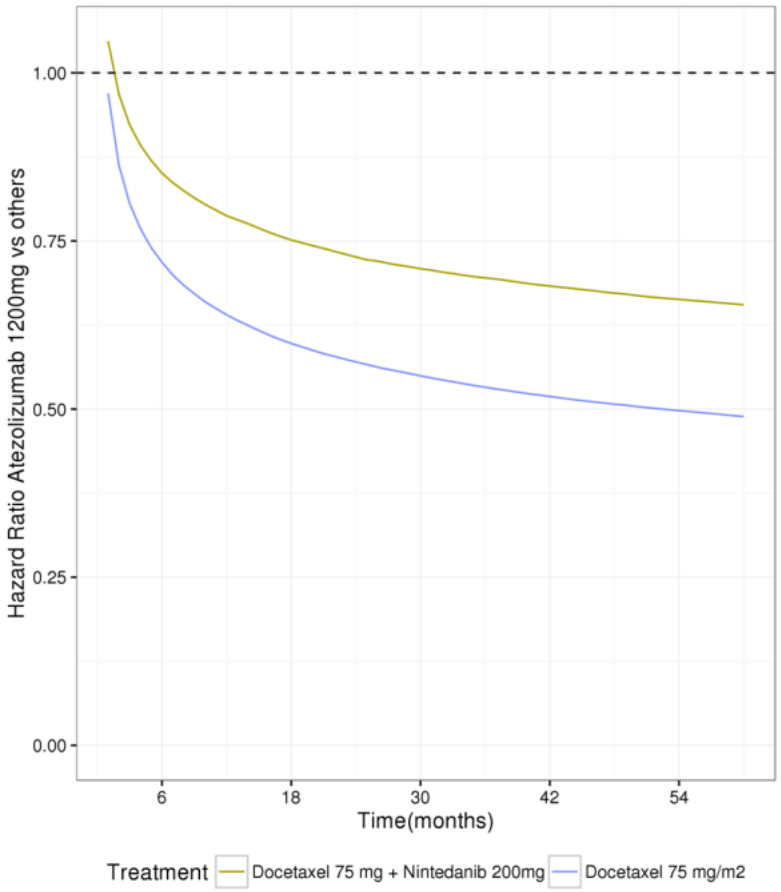


Figure 12: OS reduced network HR result (Weibull FE): N+D adenocarcinoma



Progression free survival

Figure 13: PFS original network result (Gompertz FE): N+D all-comers

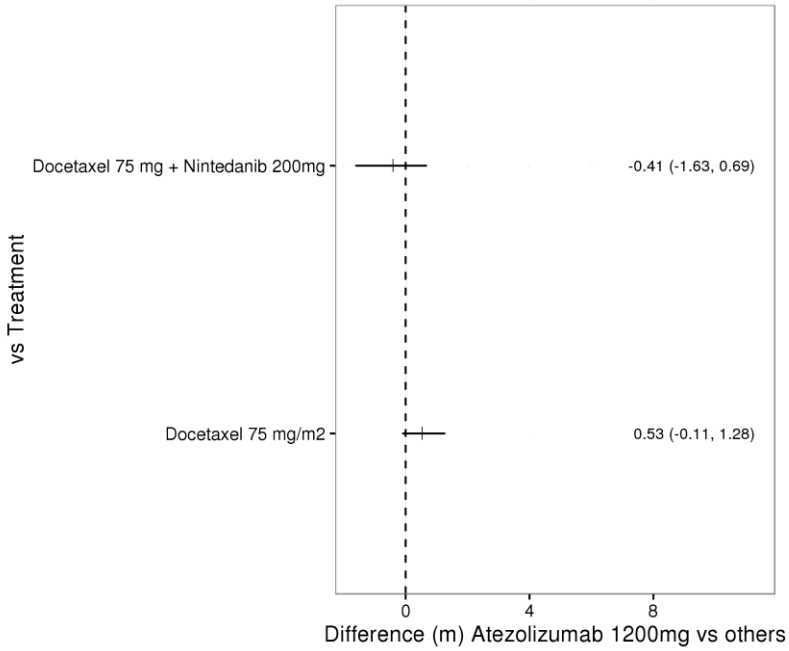


Figure 14: PFS reduced network result (Gompertz FE): N+D adenocarcinoma

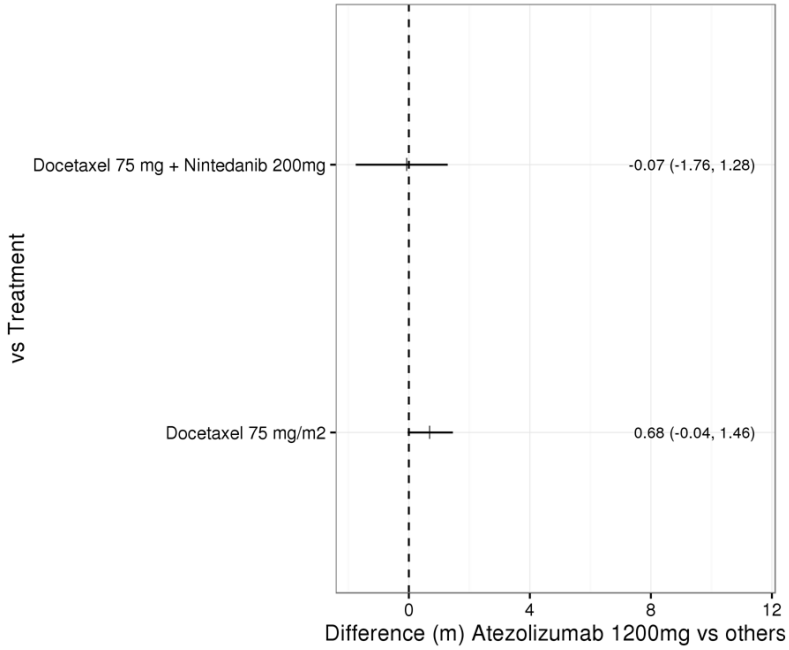


Figure 15: PFS original network HR result (Gompertz FE): N+D all-comers

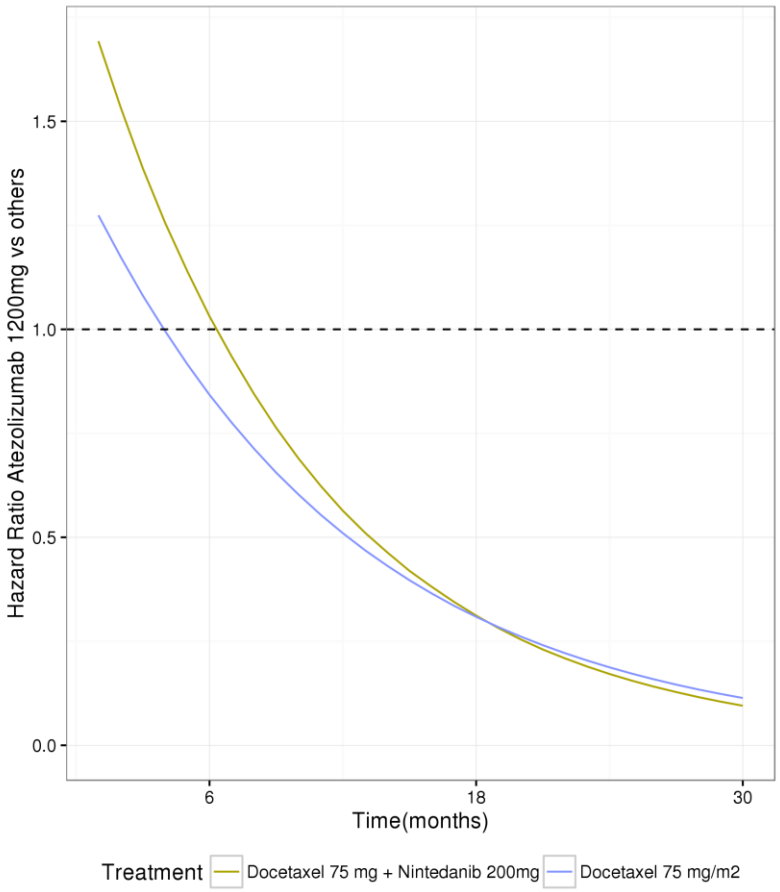
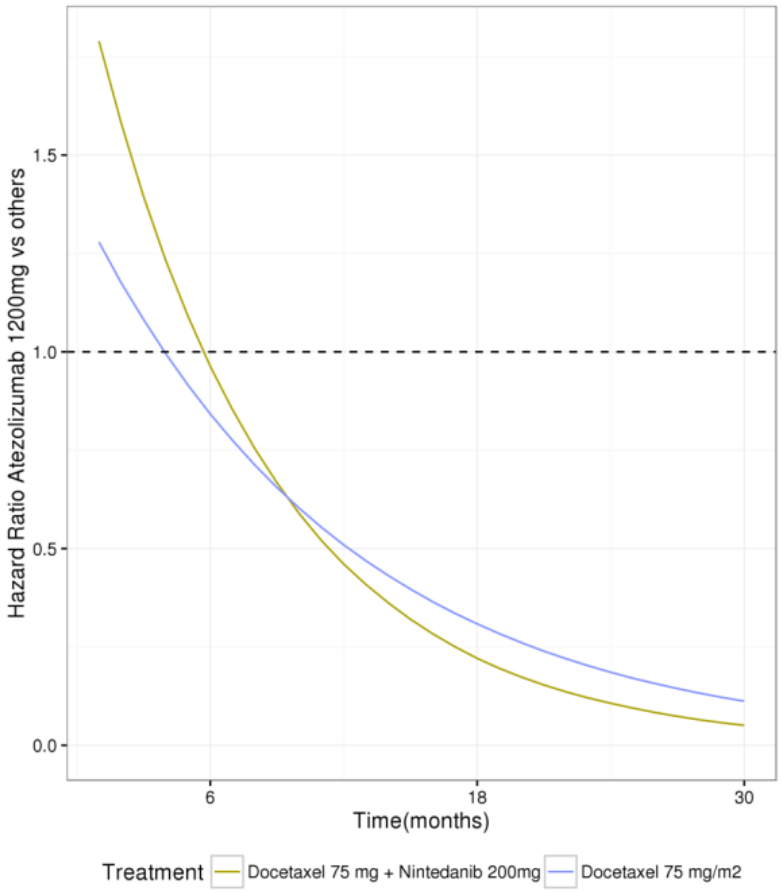


Figure 16: PFS reduced network HR result (Gompertz FE): N+D adenocarcinoma



c) <u>Scope of the appraisal</u>

The final scope for the present appraisal includes pembrolizumab as a comparator to atezolizumab. Although pembrolizumab is included within the overall survival and progression-free survival networks as a relevant comparator, it is excluded from the indirect treatment comparison results as the company does not consider it to be a relevant comparator for this appraisal. For completeness:

i) **Priority request:** Please provide indirect treatment comparison results for a reduced network of comparators (atezolizumab 1200mg, docetaxel 75mg/m^2, pembrolizumab 2mg); in other words, results from an indirect treatment comparison of the OAK, POPLAR and KEYNOTE-010 trials only for the outcomes of overall survival and progression-free survival.*

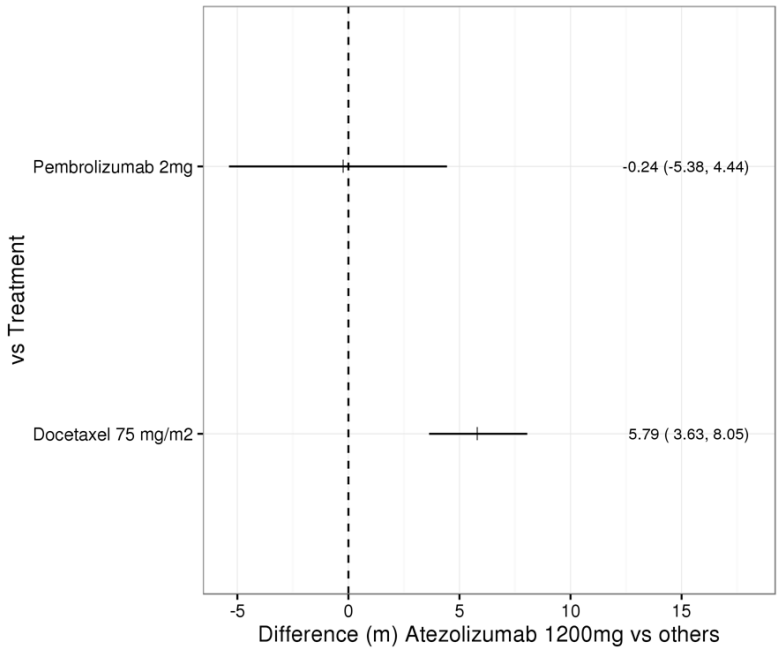
The results below are from the ITC of atezolizumab in its licensed indication (all-comers), versus pembrolizumab in its licensed indication (PD-L1 positive). However, as detailed within the submission (and response to A2), by comparing two non-equivalent populations, there is a risk the relative clinical benefits of pembrolizumab are overestimated. Therefore, this analysis should not be considered as a robust and true reflection of the comparative efficacy of pembrolizumab versus atezolizumab.

When estimating the impact of these results over the economic model's 25-year time horizon, the pembrolizumab treatment cap (TA428) must be incorporated. Given the uncertainty associated with the treatment benefit beyond discontinuation, and in order to provide the most conservative estimate for the cost-effectiveness of atezolizumab, the treatment benefit is assumed to continue whilst the costs associated with treatment stop.

Based on this approach, there is a predicted QALY difference of 0.04, and slightly lower costs for atezolizumab at list prices[1]. This places a point estimate for the comparison in the south-west quadrant of a cost-effectiveness plane. Based on the marginal difference in QALY yield, there is significant scope for any adjustment in the conservative approach taken to incorporate the 2 treatment cap to shift the point estimate to the south-east quadrant. Therefore, any comparisons should be interpreted with extreme caution.

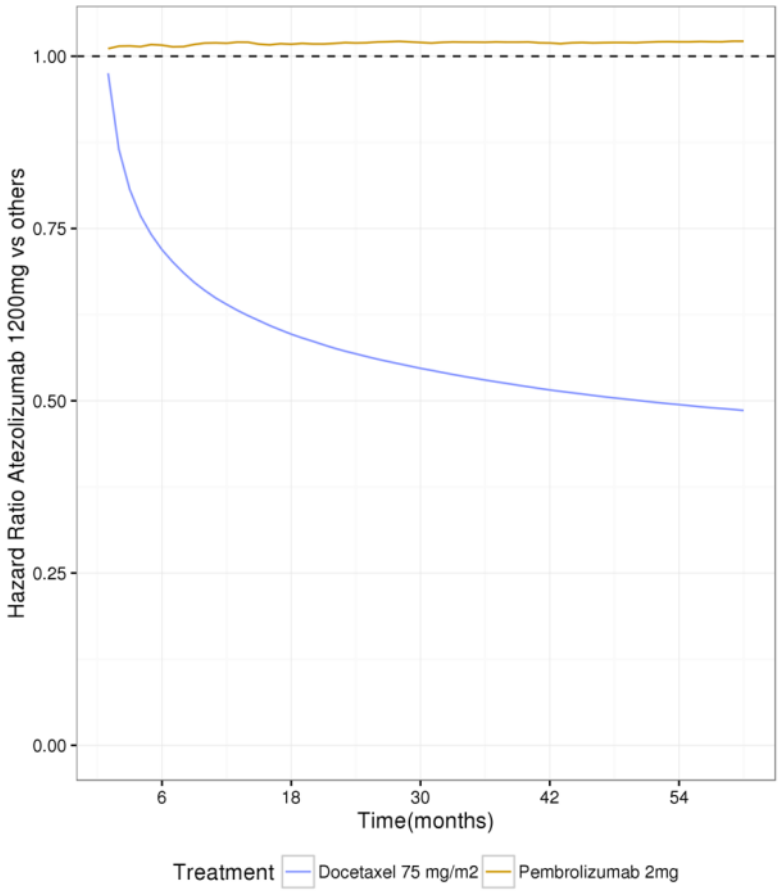
Overall survival

Figure 17: OS reduced network result (Weibull FE): pembrolizumab



[1] Whilst the pembrolizumab PAS is unknown, exploratory analyses estimate that at a common PAS level across both products, differences in total costs are marginal.

Figure 18: OS reduced network HR result (Weibull FE): pembrolizumab



Progression free survival

Figure 19: PFS reduced network result (Gompertz FE): pembrolizumab

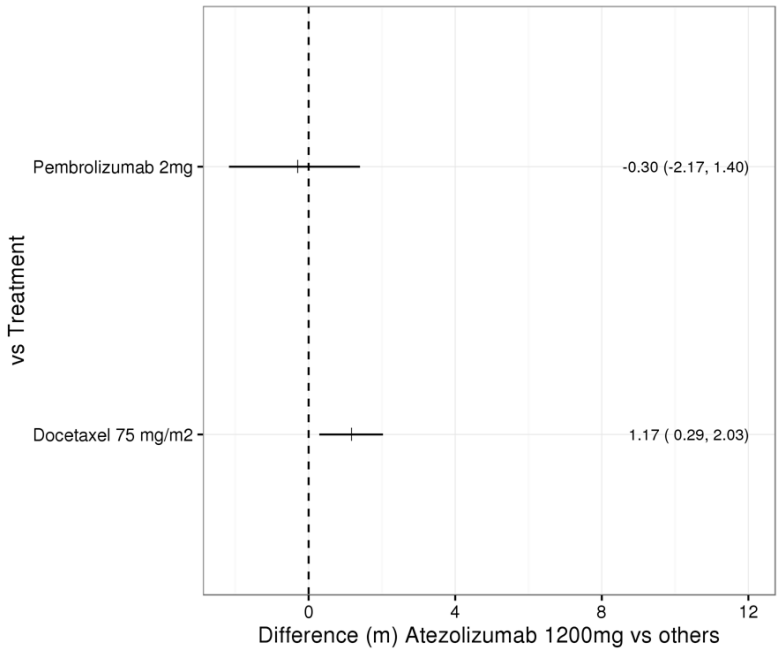
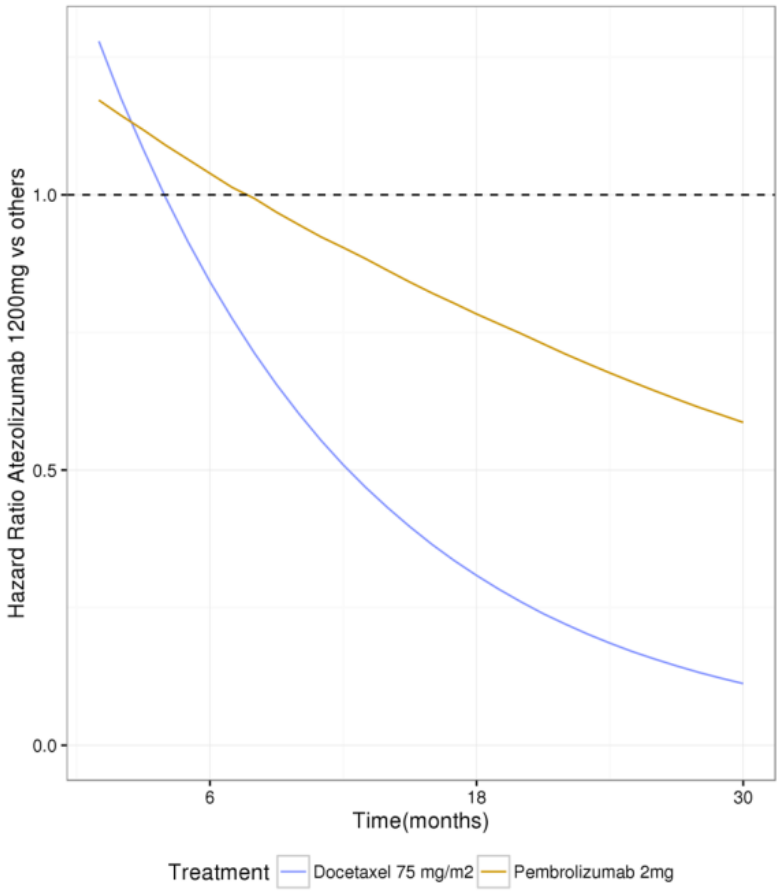


Figure 20: PFS reduced network HR result (Gompertz FE): pembrolizumab



d) Model selection

The company describes five fractional polynomial models (two first order and three second order) within 'Network Meta-Analysis Methodology' of Section 4.10 of the company submission and describes criteria for 'Model Selection' in the subsequent section. The company then presents indirect treatment comparison results for the model judged to be best fitting according to the Deviance Information Criteria (DIC) and by viewing fitted curves.

The company states that upon viewing fitted curves for the second order models, an apparent survival 'plateau' was observed which would lead to 'very large HRs at later time points for some treatment comparisons.'

The company bases their choice between fixed and random effects models on the DIC, interpreting little difference in DIC to indicate no evidence of substantial heterogeneity. The ERG considers that the DIC is a measure of model fit rather than heterogeneity and that choices between fixed and random effects models within network meta-analysis should be made taking into account consistency of trial populations and evidence sources (Dias 2013, referenced within the company submission), rather than based on model fit alone.

i) The company states that the use of DIC to assess heterogeneity is based on the recommendations of the NICE Decision Support Unit (Dias 2013). The ERG cannot find this recommendation within the Dias 2013 reference, please clarify where the recommendation is made.

This is referenced on page 16 of Dias 2013 (Dias, 2013), but also within Dias 2011 (Dias S et al., 2011):

Dias 2013 specifically references Dias 2011 on page 16: "*A number of standard methods for measuring between-trials heterogeneity have been proposed … The approach taken in TSD2, in keeping with the Bayesian framework, has been to compare the Fixed and Random Effects models' residual deviance and DIC statistics. An advantage of the Bayesian approach is that it provides a posterior distribution of the between-trials variance – or, perhaps easier to interpret – the between trial standard deviation, which gives investigators some insight into the range of values that are compatible with the data. It is also possible to obtain a measure of uncertainty for the between-trials variance using classical approaches*"

ii) **Priority Request**: Please provide indirect treatment comparison results for a reduced network of relevant comparators (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib+docetaxel 75mg/m^2) for all five fractional polynomials models to allow the ERG to also make an assessment of the visual appearance of fitted curves for the outcomes of overall survival and progression-free survival.*

Graphical indirect treatment comparison results for all five fractional polynomial models for the reduced network using only OAK, POPLAR and LUME-Lung 1 are presented below. Both the differences plots, and the resulting survivor plots are presented.

Overall survival

Figure 21: Overall survival – differences (p1=0 [Weibull; chosen])

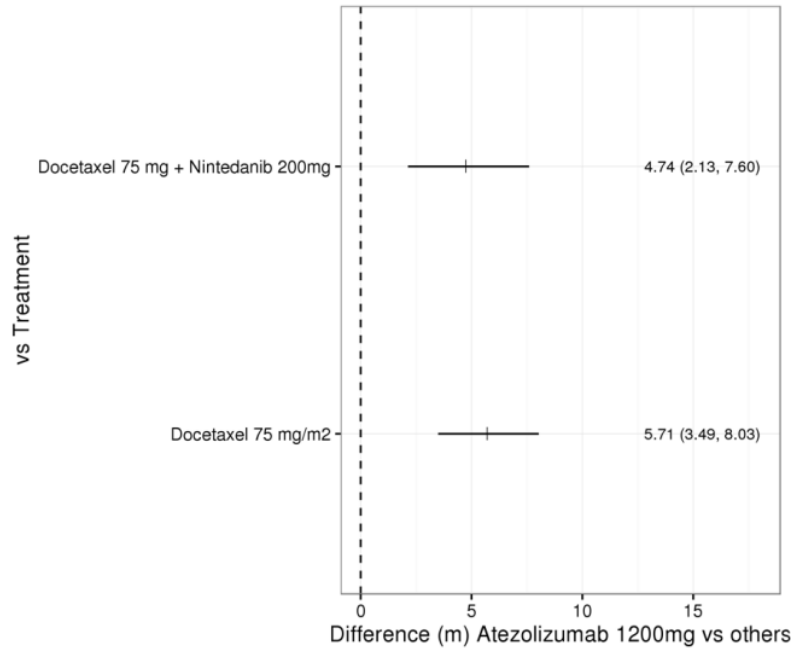


Figure 22: Overall survival - Survivor plots (p1=0 [Weibull; chosen])

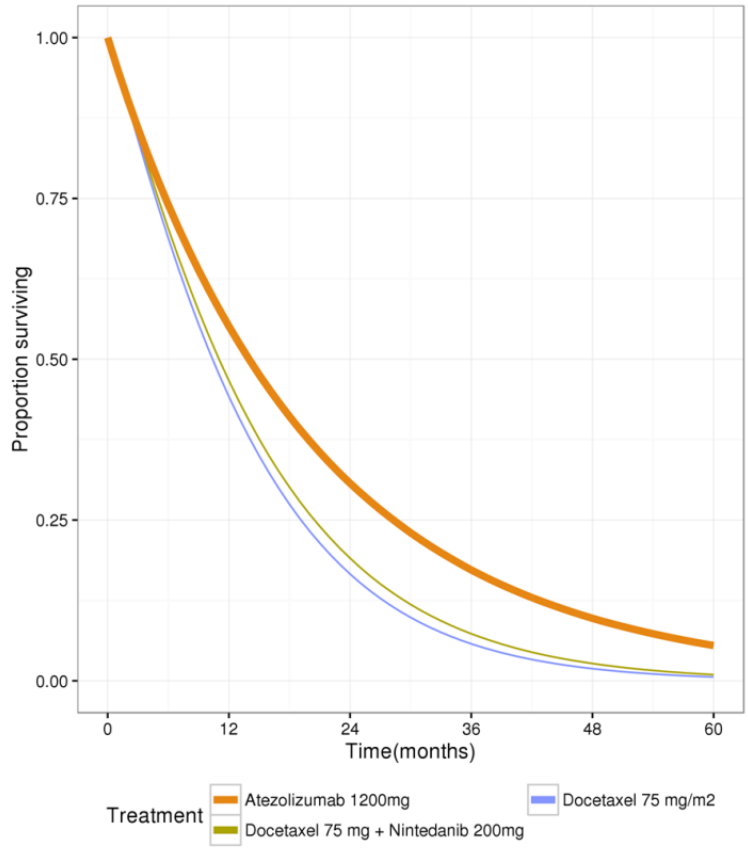


Figure 23: Overall survival – differences (p1=1)

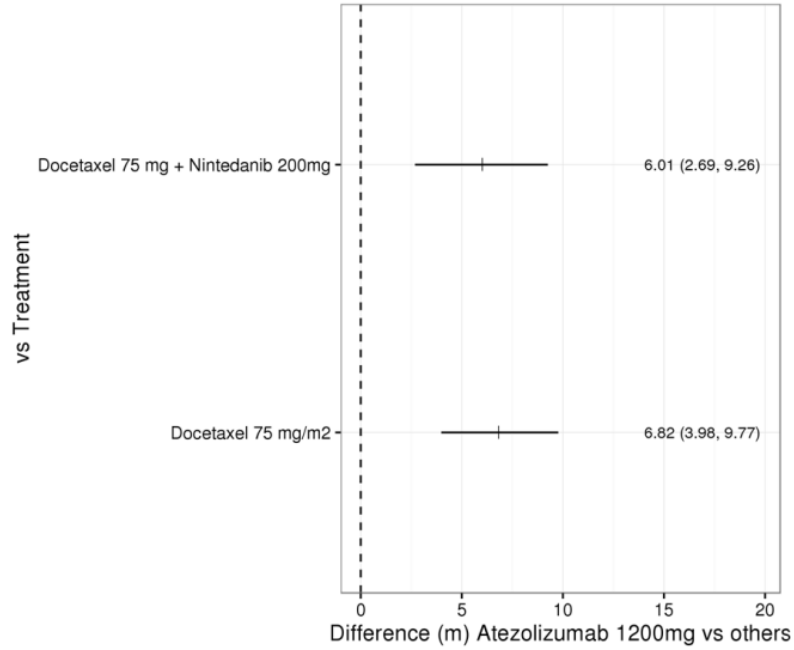


Figure 24: Overall survival - Survivor plots (p1=1)

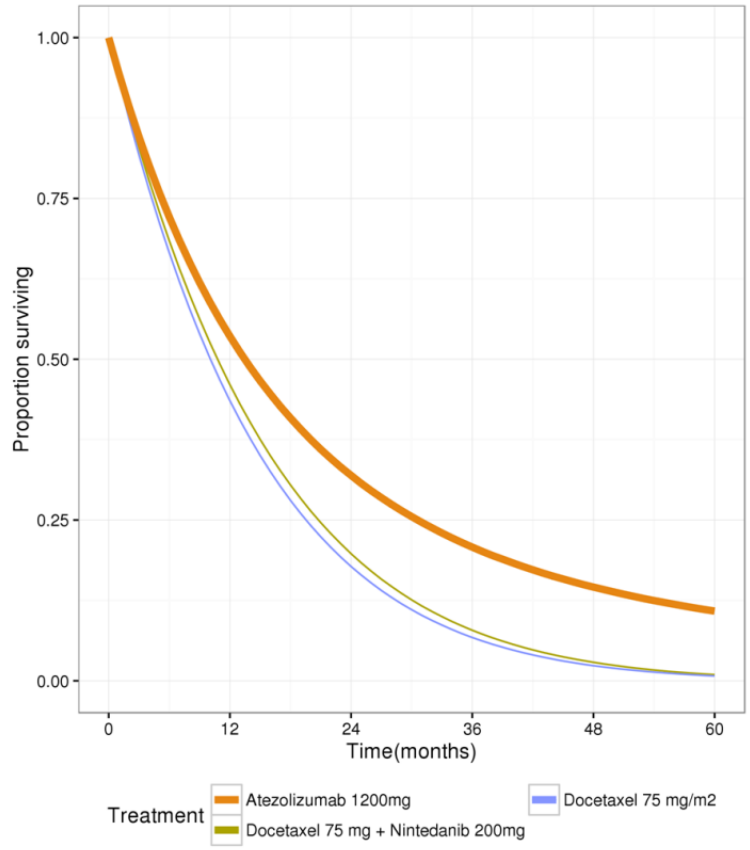


Figure 25: Overall survival – differences (p1=0, p2=0)

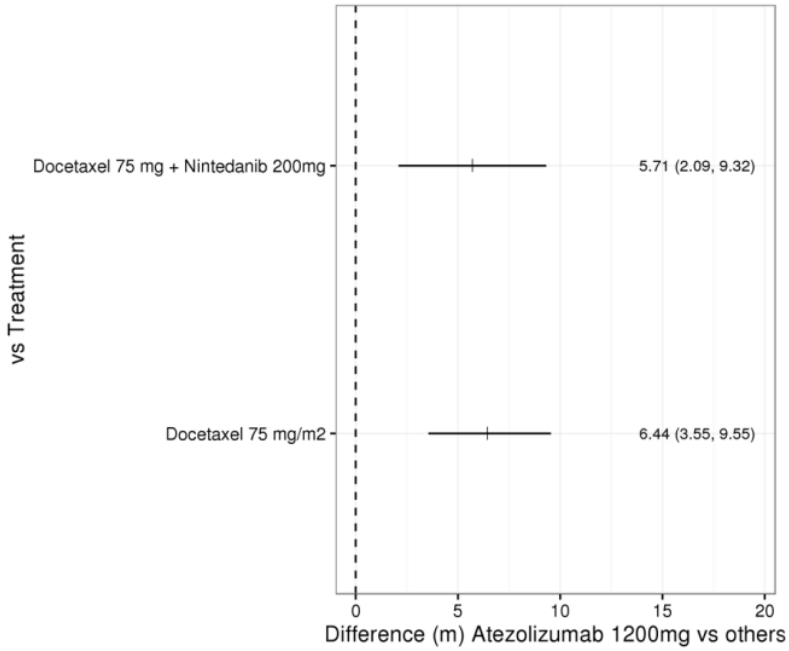


Figure 26: Overall survival - Survivor plots (p1=0, p2=0)

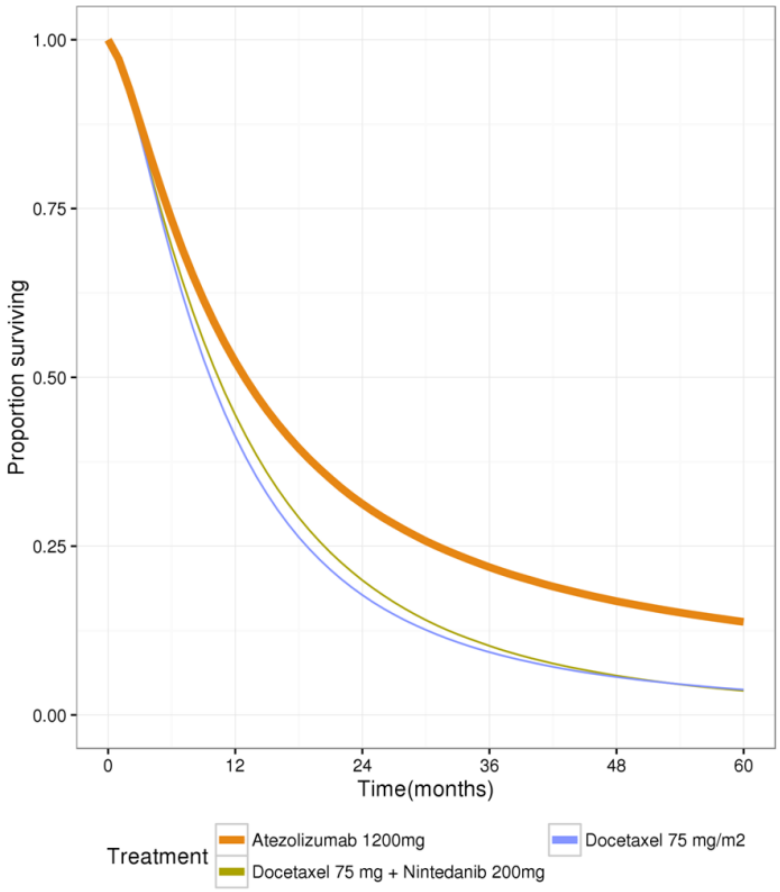


Figure 27: Overall survival – differences (p1=0,p2=1)

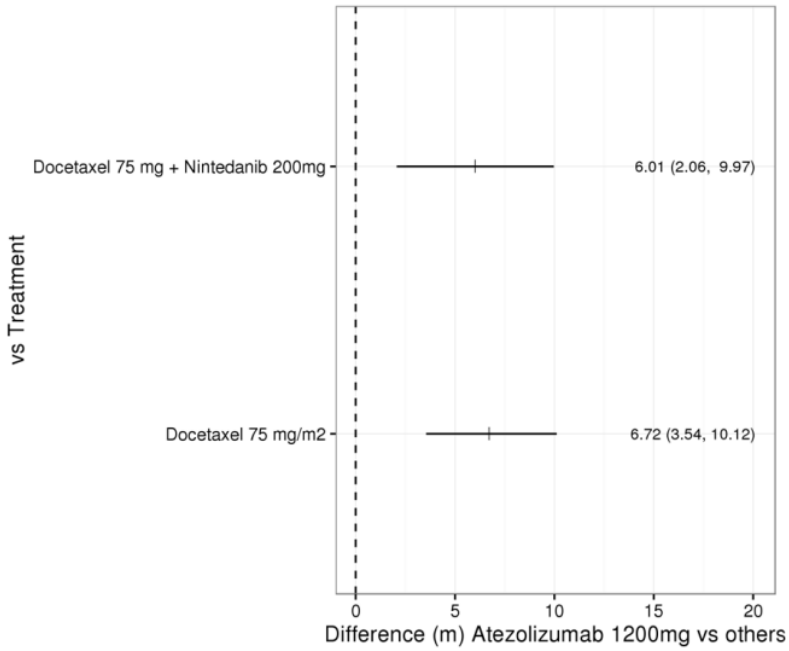


Figure 28: Overall survival - Survivor plots (p1=0, p2=1)

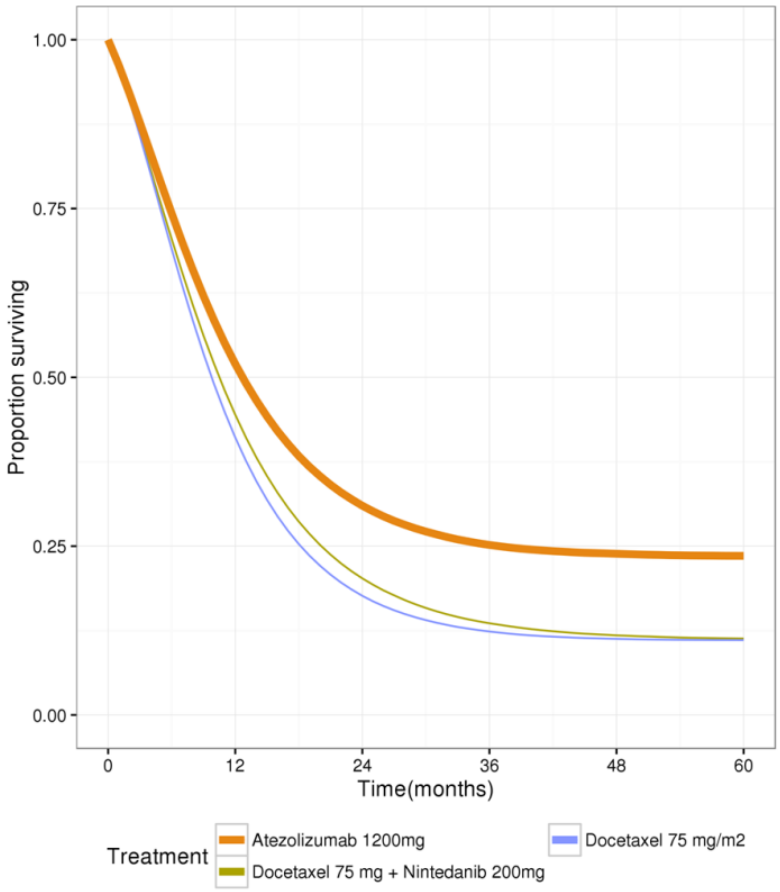


Figure 29: Overall survival – differences (p1=1, p2=1)

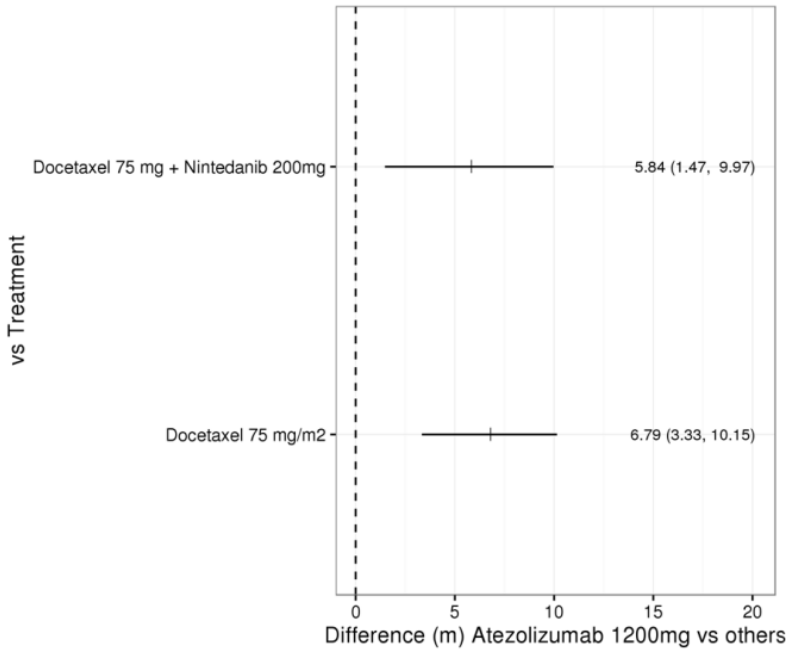
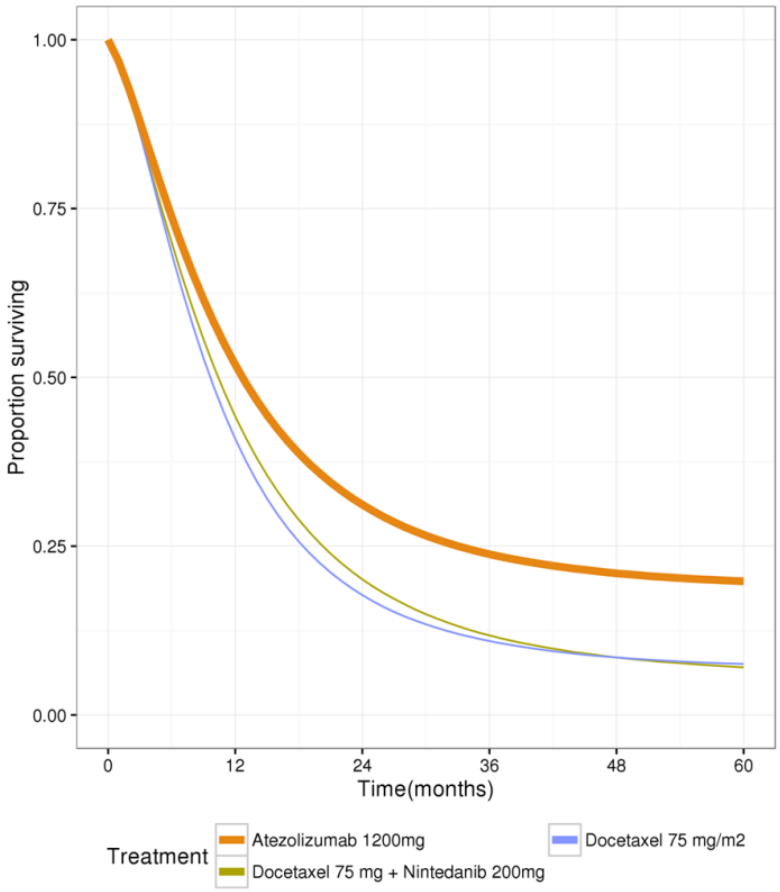


Figure 30: Overall survival - Survivor plots (p1=1, p2=1)



Progression free survival

Figure 31: Progression free survival – differences (p1=0 [Weibull; chosen])

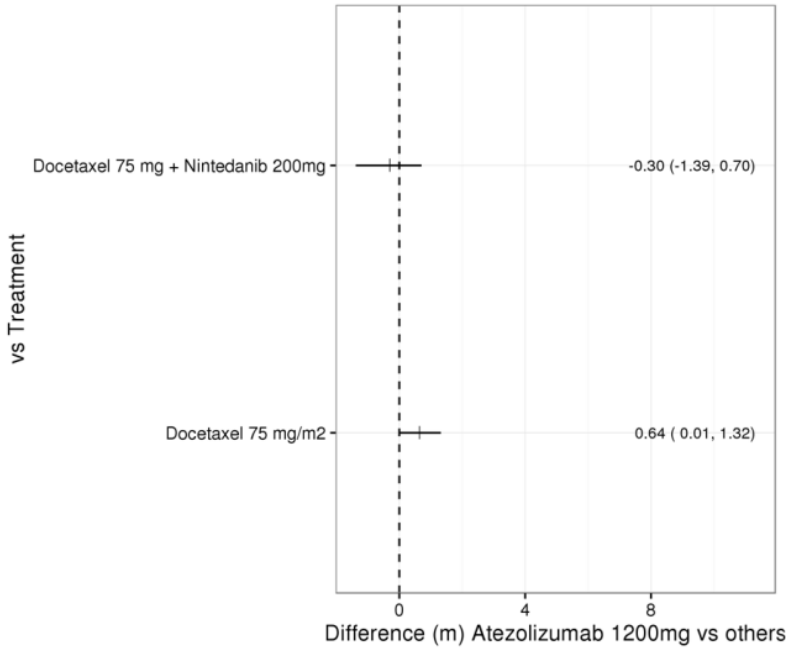


Figure 32: Progression free survival – Survivor plots (p1=0 [Weibull; chosen])

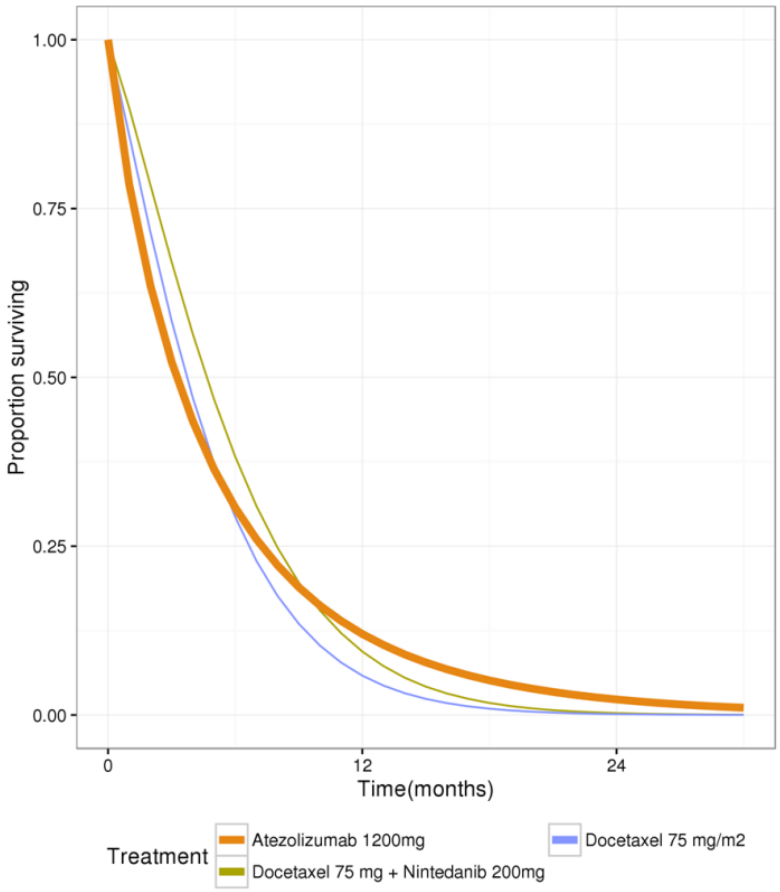


Figure 33: Progression free survival – differences (p1=1)

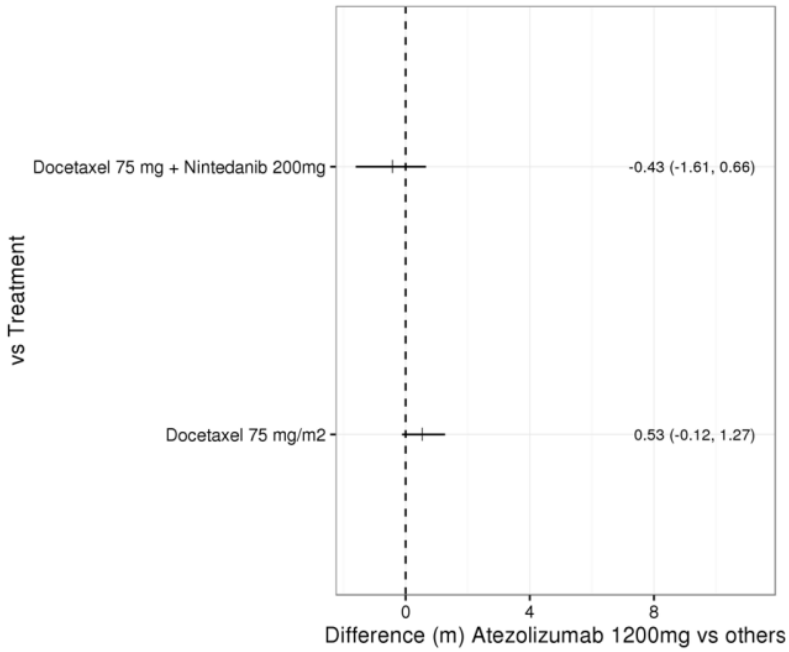


Figure 34: Progression free survival – Survivor plots (p1=1)

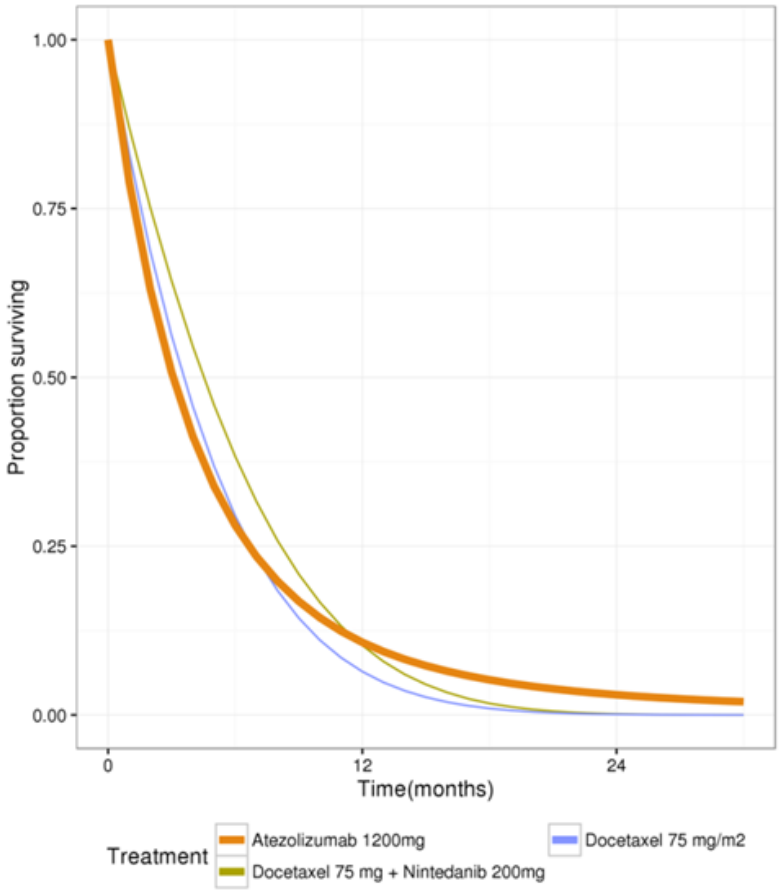


Figure 35: Progression free survival – differences (p1=0, p2=0)

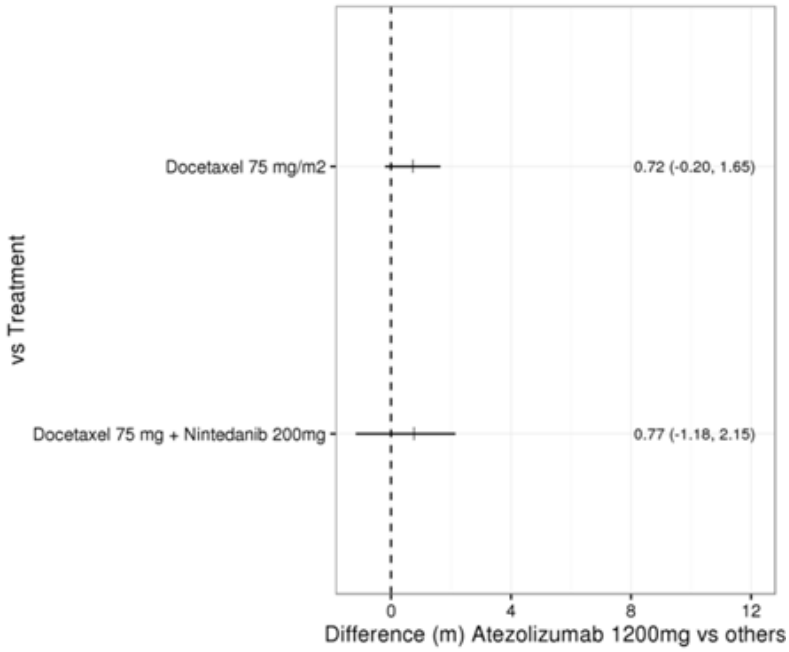


Figure 36: Progression free survival – Survivor plots (p1=0, p2=0)

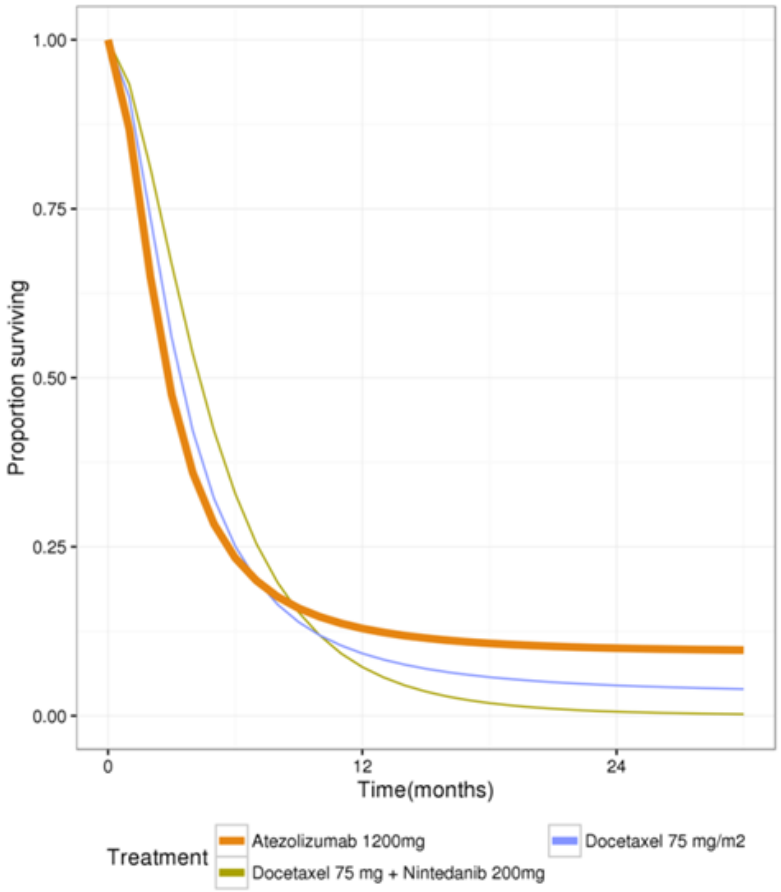


Figure 37: Progression free survival – differences (p1=0, p2=1)

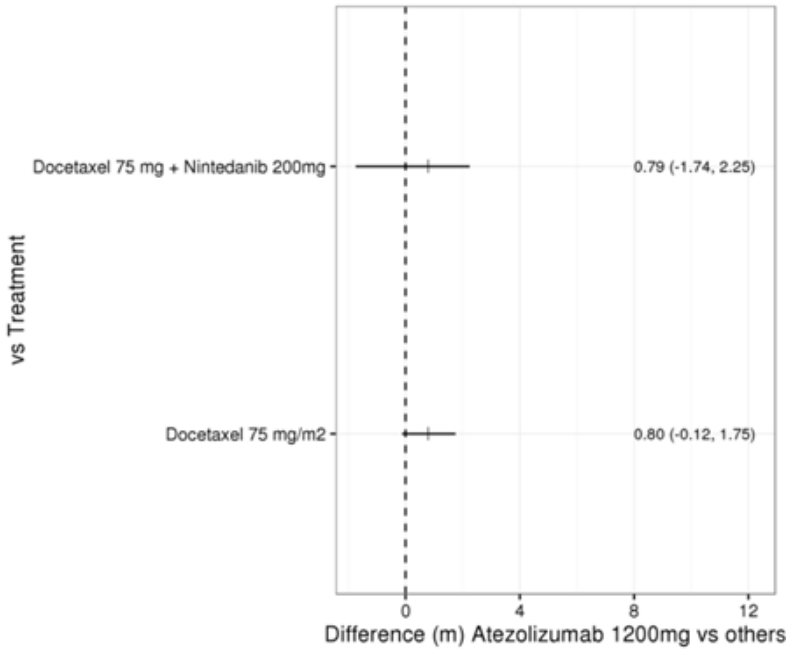


Figure 38: Progression free survival – Survivor plots (p1=0, p2=1)

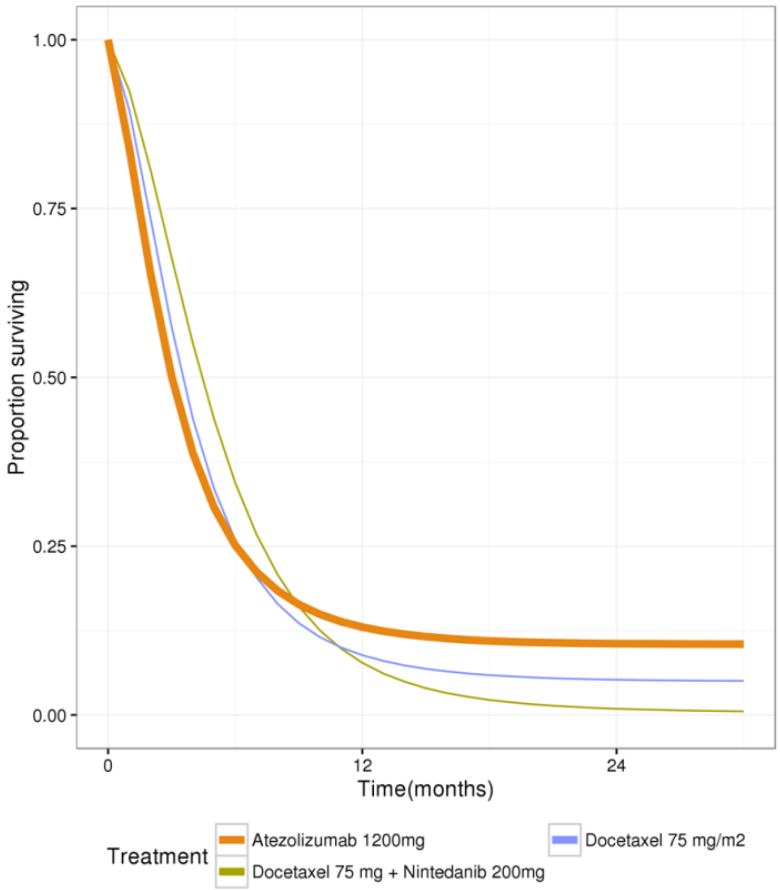

1.00
0.75
0.50
0.25
0.00
Proportion surviving
0
12
24
Time(months)
Treatment
Atezolizumab 1200mg
Docetaxel 75 mg/m2
Docetaxel 75 mg + Nintedanib 200mg

Figure 39: Progression free survival – differences (p1=1, p2=1)

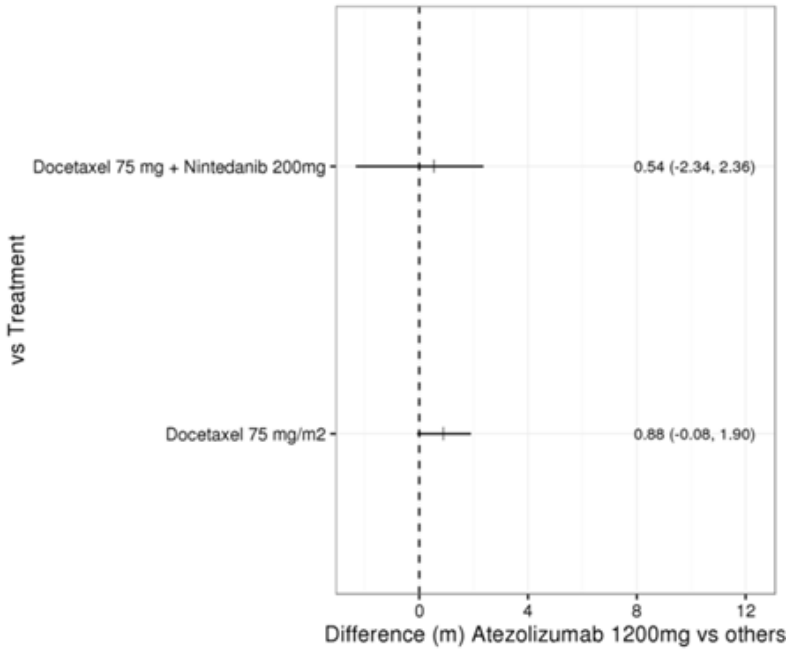
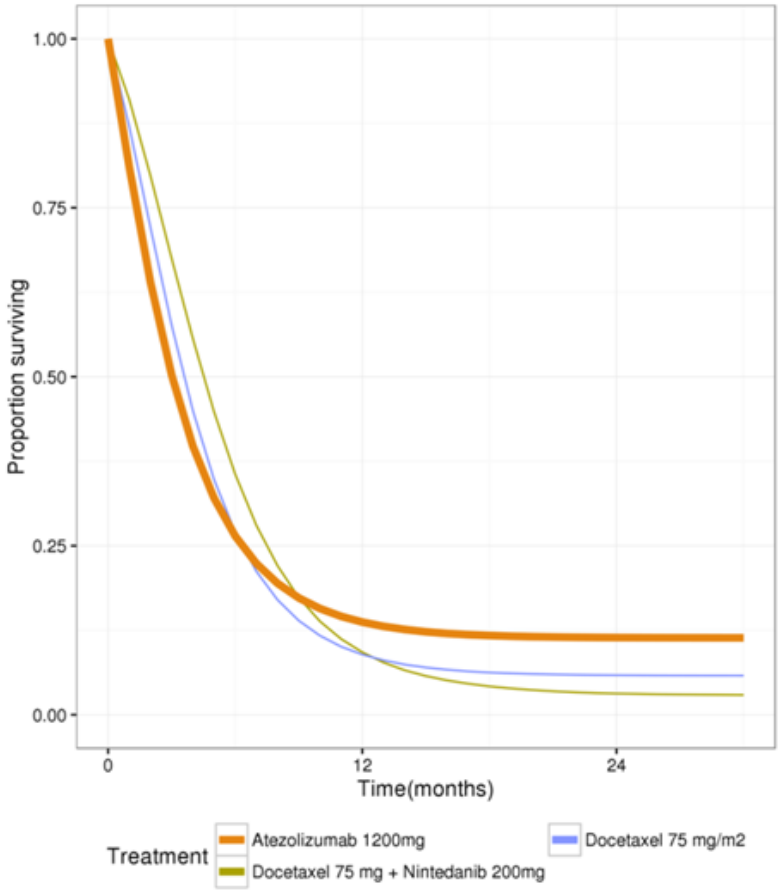


Figure 40: Progression free survival – Survivor plots (p1=1, p2=1)



iii) Please provide indirect treatment comparison results for a network of relevant comparators (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib+docetaxel 75mg/m^2) for all fitted random effects models to allow the ERG to make an assessment of the impact of any heterogeneity on results for the outcomes of overall survival and progression-free survival.*

Graphical indirect treatment comparison results for all fitted random effects models for the reduced network using only OAK, POPLAR and LUME-Lung 1 are presented below.

Overall survival

Figure 41: Overall survival – differences (p1=0)

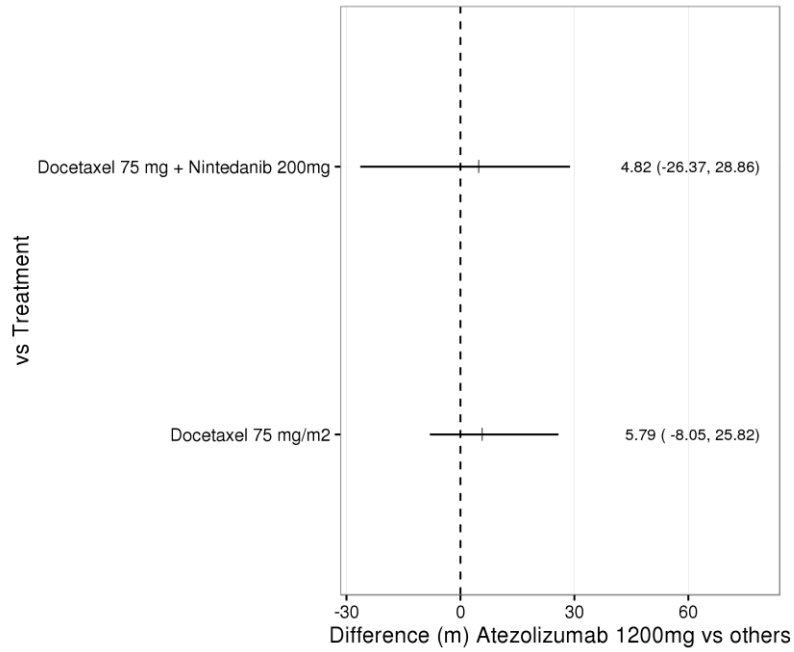


Figure 42: Overall survival – differences (p1=1)

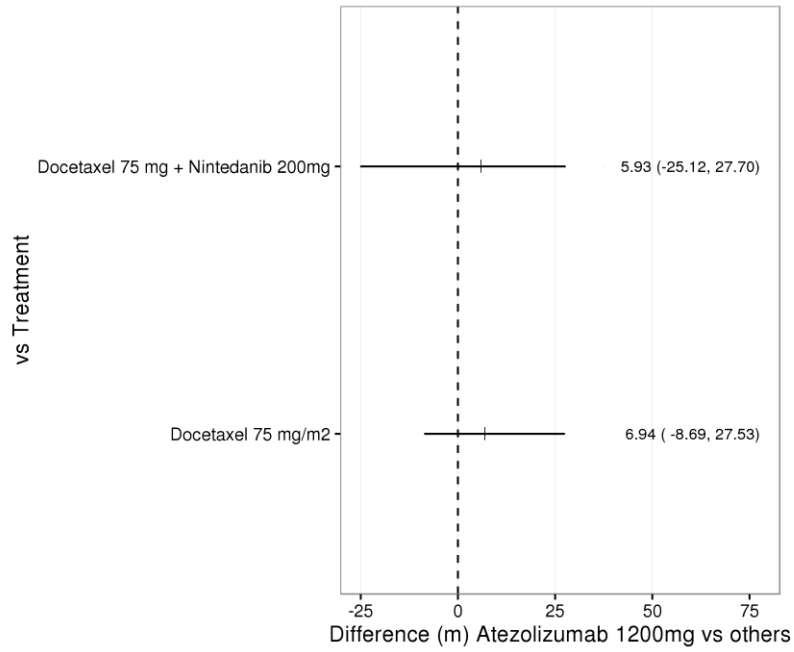


Figure 43: Overall survival – differences (p1=0, p2=1)

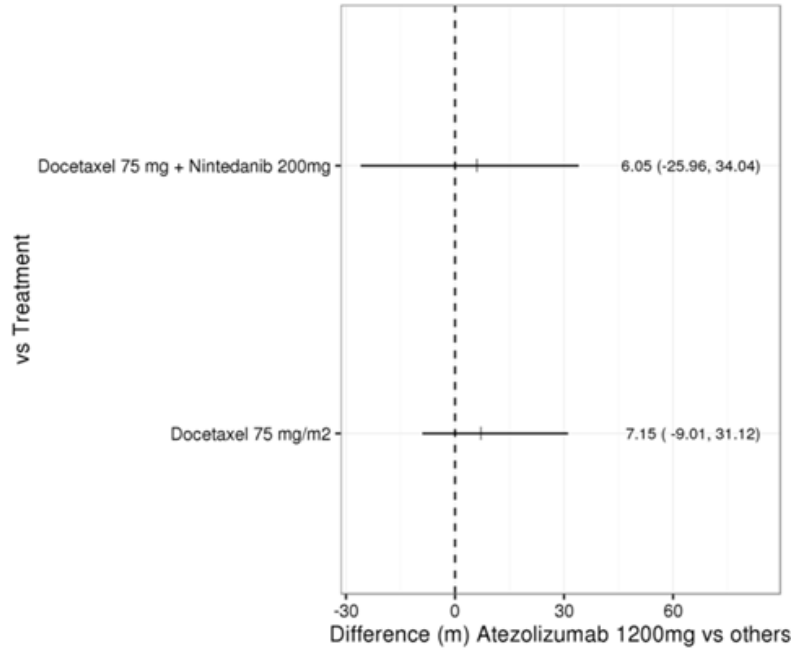


Figure 44: Overall survival – differences (p1=0, p2=0)

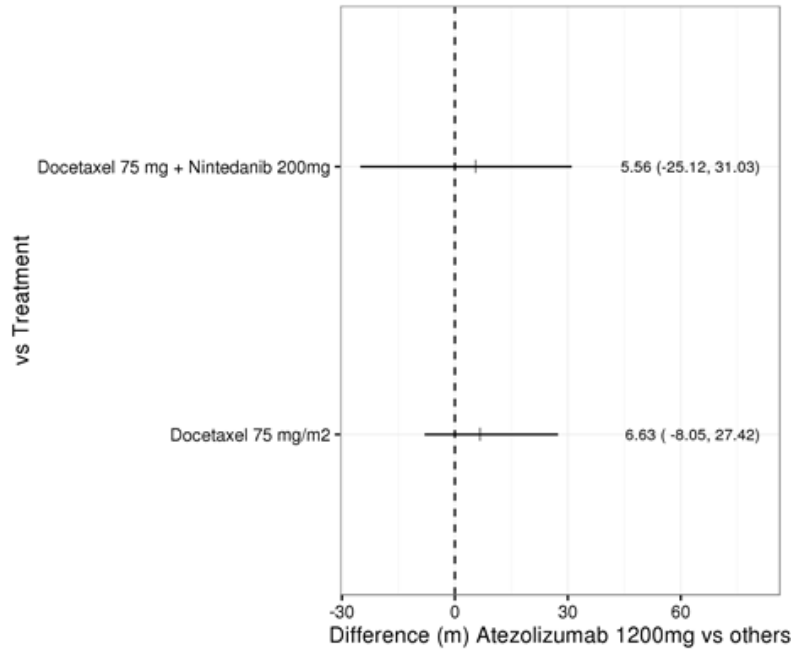
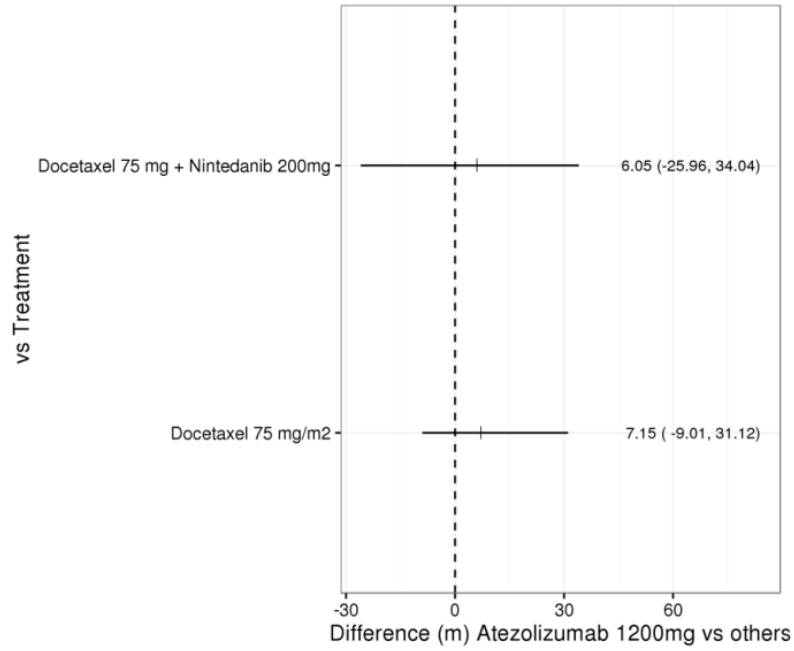


Figure 45: Overall survival – differences (p1=1, p2=1)



Progression free survival

Figure 46: Progression free survival – differences (p1=0)

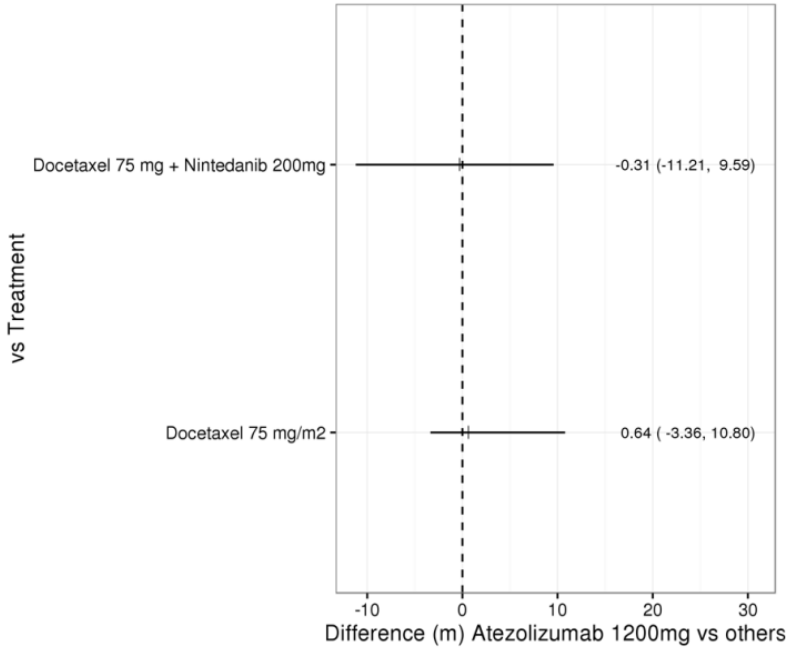


Figure 47: Progression free survival – differences (p1=1)

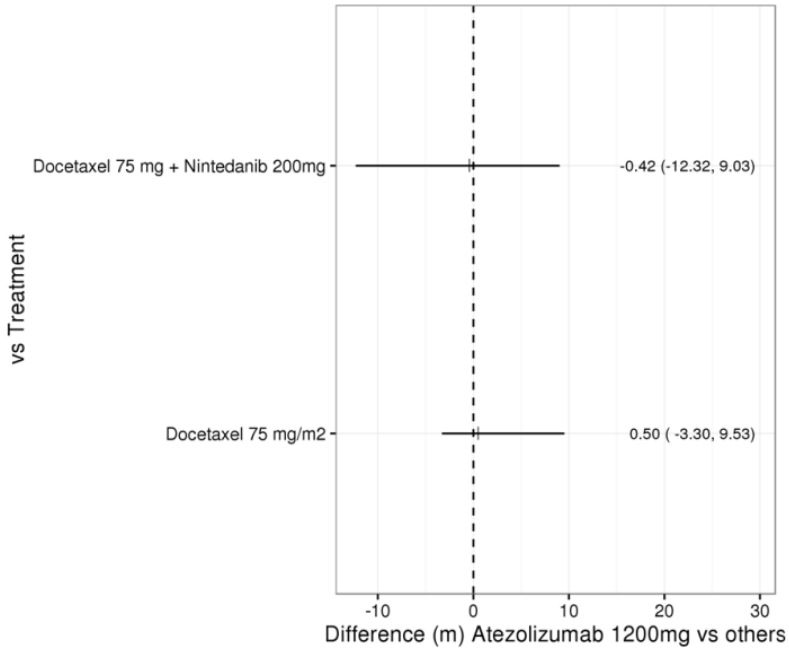


Figure 48: Progression free survival – differences (p1=0, p2=0)

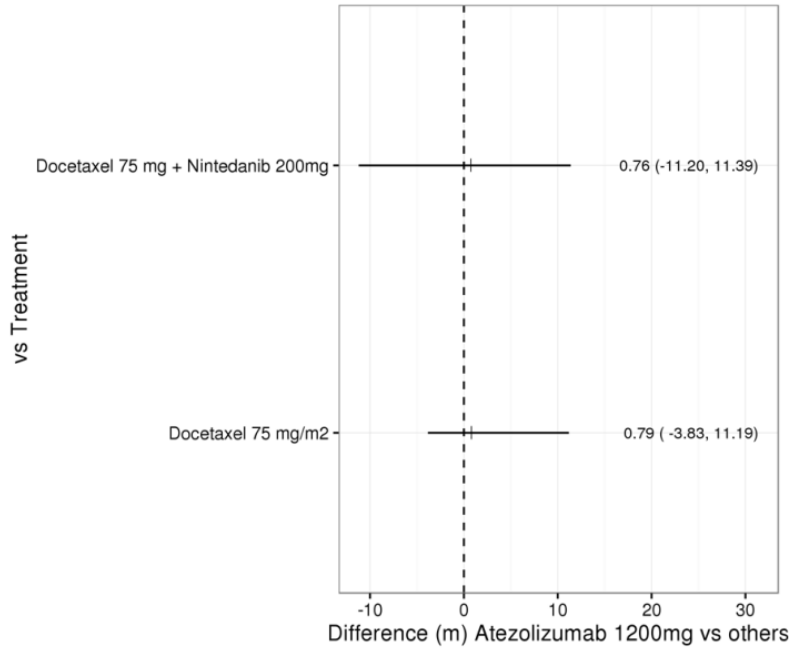


Figure 49: Progression free survival – differences (p1=0, p2=1)

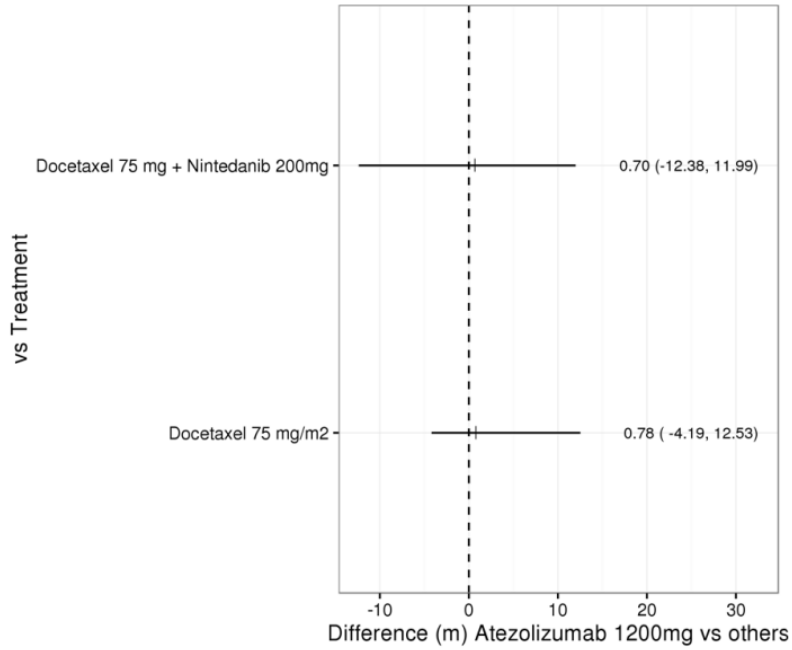
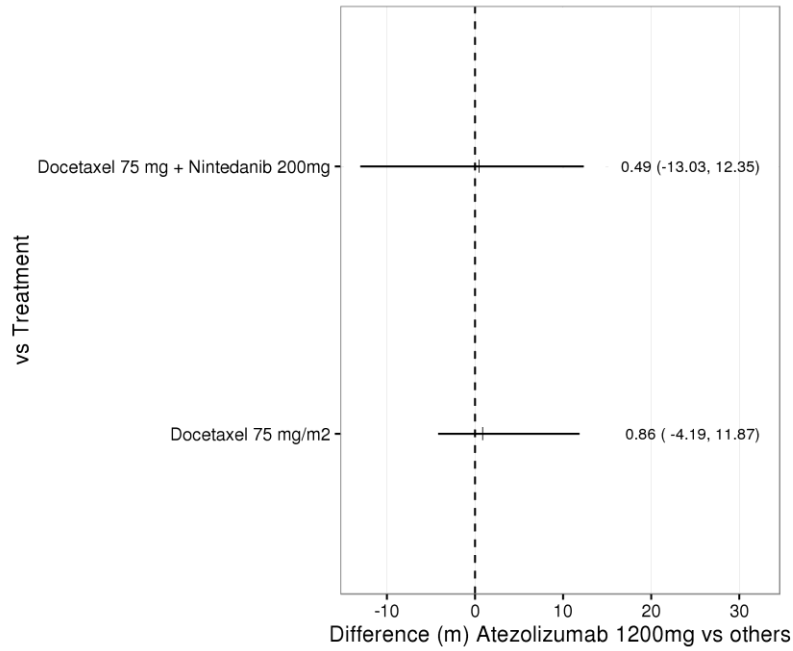


Figure 50: Progression free survival – differences (p1=1, p2=1)



iv) The methods employed by the company allow for estimation of a heterogeneity parameter for all random effects models (Jansen 2011). The ERG prefers this parameter as a measure of heterogeneity in the network (rather than the DIC). Please provide estimates of this parameter for each random effects model fitted (see point iii) for the outcomes of overall survival and progression-free survival.*

The posterior median and 95% credible interval for the between study heterogeneity parameter (sd; as proposed by Jansen 2011) is presented in Table 2 for OS, and Table 3 for PFS. With such a small reduced network, it is difficult to estimate the heterogeneity (as supported by the wide credible intervals).

As explained in the company submission, and supported by NICE DSU guidance (please refer to question A7 di), heterogeneity was assessed using DIC, whereby the model with the lowest DIC (fixed or random effects) depicts the best fit to the data.

Based on smallest DIC alone, the second order models appeared to be the best fit for all analyses. However, upon viewing the fitted curves from the second order models, there was a survival “plateau” for some treatments, where the curves flattened and a proportion of patients did not experience the event during the time horizon.

This is consistent between both the extended and reduced networks, and is demonstrated in the survivor plot graphs in question A7 dii. Therefore, the simpler first order models were considered more appropriate.

The lowest DIC comparing fixed and random effects is shown in bold. Fixed effects were consistently the best fit to the data.

Table 2: Overall survival assessment of heterogeneity

Model	p1	p2	Notes	Fixed effects DIC	Random effects DIC	sd (95% CrI)
1st order	0	NA	Weibull	**910.4255**	911.4979	0.368 (0.013, 1.872)
1st order	1	NA	Gompertz	**934.1241**	935.3138	0.373 (0.012, 1.838)
2nd order	0	0		**837.1486**	838.3337	0.384 (0.012, 1.824)
2nd order	0	1		**837.6918**	839.1147	0.379 (0.011, 1.851)
2nd order	1	1		**853.9698**	854.9049	0.365 (0.010, 1.858)

Table 3: Progression free survival assessment of heterogeneity

Model	p1	p2	Notes	Fixed effects DIC	Random effects DIC	sd (95% CrI)
1st order	0	NA	Weibull	**1123.1981**	1124.8598	0.328 (0.010, 1.832)
1st order	1	NA	Gompertz	**1157.5673**	1159.3184	0.313 (0.010, 1.837)
2nd order	0	0		**874.2588**	875.9772	0.320 (0.008, 1.838)
2nd order	0	1		**974.3060**	975.6571	0.340 (0.012, 1.849)
2nd order	1	1		**1056.2331**	1057.4362	0.308 (0.010, 1.868)

v) The ERG assumes that the hazard ratios presented in Figure 26 (overall survival) are calculated from the information in Table 37 and 38 of the CS, and that the hazard ratios in Figure 28 (progression-free survival) are calculated from the information in Table 40 and 41 of the submission. In other words, from the beta parameter estimates in Table 37, a comparison of atezolizumab 1200mg and docetaxel 75mg/m^2 for a first order Weibull fractional polynomial model would be:

$$\ln(HR(t) = \big(-2.987 + (-2.951)\big) + (0.012 - 0.180)(\log(t)) \quad (1)$$
$$= \ln(HR(t) = (-0.036) + (-0.168)(\log(t)) \quad (2)$$
$$= HR(t) = \exp((-0.036) + (-0.168)(\log(t))) \quad (3)$$

Is the ERG correct to assume that the hazard ratio presented in Figure 26 for atezolizumab 1200mg compared to docetaxel 75mg/m^2 corresponds to equation (3) above?

We do not believe this to be a correct assumption.

For a first order model with p1=0 (Weibull), the log hazard functions over time for atezolizumab (A) and docetaxel (D) are:

$$\log h_A(t) = \beta_{0A} + \beta_{1A}\log(t)$$

$$\log h_D(t) = \beta_{0D} + \beta_{1D}\log(t)$$

where $\beta_{0,}\beta_1$ are as defined for Tables 37 and 40 in the CS.

Therefore the hazard ratio over time comparing atezolizumab and docetaxel is :

$$HR_{AD}(t) = \exp\left(\log\frac{h_A(t)}{h_D(t)}\right)$$
$$= \exp((\beta_{0A} - \beta_{0D}) + (\beta_{1A} - \beta_{1D})\log(t))$$
$$= \exp((d_{0A} - d_{0D}) + (d_{1A} - d_{1D})\log(t))$$

where $d_{0,}d_1$ are as defined for Tables 38 and 41 in the CS.

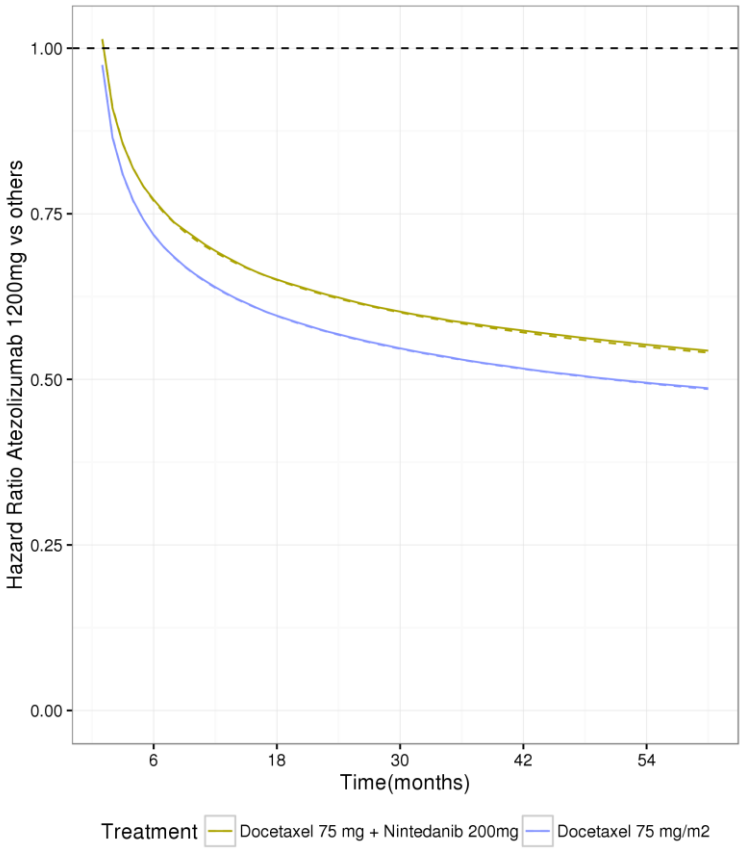
For plotting the HR over time, there are two possible approaches:

1. Obtain the posterior distribution of the HR based on the posterior distributions of the d (or equivalently β) parameters. For each posterior sample run, a set of d parameters will be generated, from which the HR at each time point is calculated using the equation above. Plot the median (or mean) of the resulting posterior distribution of the HR. This is consistent with the approach used in the code of Jansen 2011.
2. Use the median of the posterior distributions of the d (or equivalently β) parameters and calculate the HR over time using those median parameter values in the equation above.

Figures 26 and 28 were generated using approach 1. The method described in the question from NICE is approach 2. The two methods give very similar results, as shown in Figure 51, where the solid lines are generated using approach 1 and the dashed lines are generated using approach 2.

Please note that in the first line of the equation provided by the ERG, 2.987+(-2.951) should be 2.987-(-2.951).

Figure 51: Hazard ratios over time plot using approach 1 (solid lines) and approach 2 (dashed lines), Atezolizumab 1200mg vs others: Overall survival (OS) (FE fractional polynomials model, first order p1=0)



A8. Sample size calculations and analysis populations (OAK and POPLAR)

a. Within the Lancet publication of the OAK trial (Rittmeyer et al 2017) it is stated that 'the OAK statistical design was amended on Jan 28 2016, according to a pre-specified modification plan'. Please provide further details of this modification plan or indicate where details can be found within the protocol or statistical analysis plan.

The OAK modification plan can be found in as a separate document along with this response.

b. It is stated within the company submission (Section 4.14) that results for the secondary population of OAK and further analyses from POPLAR will be presented in 2017. Are any additional results from either of these follow-up analyses available at this time?

Not at this time. [redacted]

c. Section 4.4 of the company submission outlines 'Assumptions for POPLAR' and 'Assumptions for OAK.' It is stated that 'Study design assumptions in OAK were

based on results from POPLAR.' Please clarify the basis of the 'Assumptions for POPLAR.'

POPLAR was designed to enroll a minimum of approximately 54 PD-L1 IC2 or IC3 patients. In the case that the PD-L1 IC2 or IC3 prevalence was lower than 18%, up to a maximum of 300 total patients could be enrolled although the study was expected to enroll 285 total patients (with 55 PD-L1 IC2 or IC3 patients). The assumptions for POPLAR highlighted in the company submission were made to calculate the power and 95% CIs for OS and PFS in the ITT population (based on the expected sample size). These assumptions are not based on any specific data set.

Study design assumptions in the OAK study were based on POPLAR where interim data demonstrated clinical efficacy in all PD-L1 subgroups, suggesting that fewer than 1,225 patients (the planned final enrolment for OAK) would be required for a fully powered study for OS evaluation in an ITT population. The primary OS analyses in OAK were therefore conducted on the primary population of the first 850 randomised patients.

A9. Proportional versus non-proportional hazards

It is demonstrated within Section 4.10 and Section 5.3 of the company submission that the proportional hazards assumption is unlikely to hold for the OAK trial for overall survival, progression-free survival and time-to-treatment discontinuation. However, clinical effectiveness results within Section 4.7 of the company submission are presented in terms of hazard ratios from Cox regression models and p values from log-rank tests; methods which require the assumption of proprtional hazards.

a. For the OAK trial, did the company consider or employ any alternative methods of analysis for the clinical effectiveness results, given that it has been established that the proportional hazards assumption is unlikely to hold for the main efficacy outcomes of OAK? If so, please describe the method(s) used and provide results

No alternative methods of analysis were considered for the clinical effectiveness results. We consider this to be a typical situation for the analysis of clinical effectiveness results. As trials are powered using an expected treatment difference (a hazard ratio at a set period in time), proportional hazards are inherently assumed. All analyses from the SAP are therefore based on Cox PH to measure a single estimate of treatment effect. The importance and potential impact of the proportional hazards assumption increases when modelling survival beyond the observed data to estimate the mean, therefore requiring more rigorous testing.

b. Was the proportional hazards assumption checked for the main efficacy outcomes (overall survival and progression-free survival) of POPLAR? If so, please describe the method(s) used and present results.

Non-proportional analyses were conducted for OS and PFS using the hazard plots, log of negative log plots, and log of survival plot.

The three diagnostic plots for OS and PFS indicated the potential non-proportional hazards between the arms.

Hazard Function Plot

- For the OS hazard function plot, the two hazard curves crossed over at around 1 month and started to separate from each other around 8 months (Figure 52)
- For the PFS hazard function plot, the two curves were approximately parallel until around 13 months, corresponding to the minimum follow-up time (Figure 50)

Log of Negative Log Plots

- The two curves of the log of negative log plots for OS overlapped at various time points and were clearly not parallel (
-
- Figure 54)
- The atezolizumab and docetaxel curves for PFS were also overlapped (Figure 55)

Log of Survival Plot for OS and PFS

- For OS, a trend of two lines passing the origin was observed, with one on top of the other, the overlap from randomization to approximately 3 months revealed a potential non-proportionality between the hazards of the two arms (Figure 56)
- The PFS plot showed a cross-over pattern between the atezolizumab and docetaxel arms, where the crossing occurred approximately at 4-5 months (Figure 57)

Figure 52: OS hazard function plot

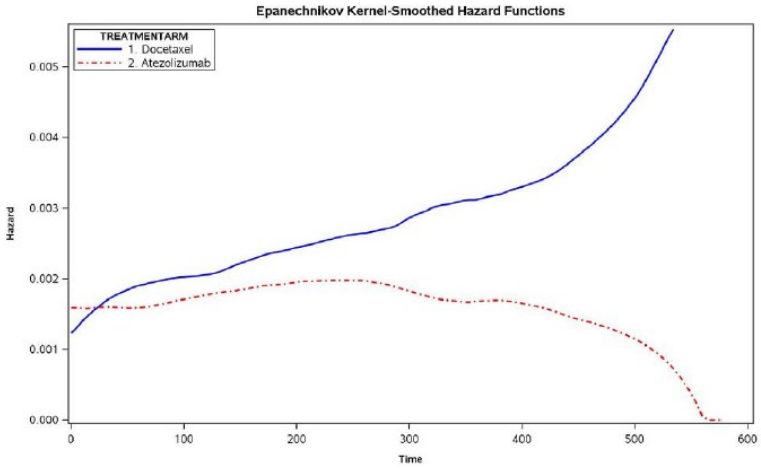


Figure 53: PFS hazard function plot

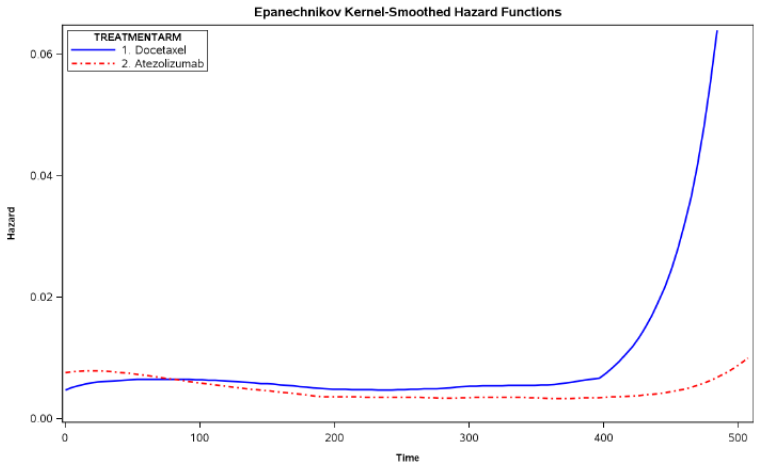


Figure 54: OS Log of Negative Log Plots

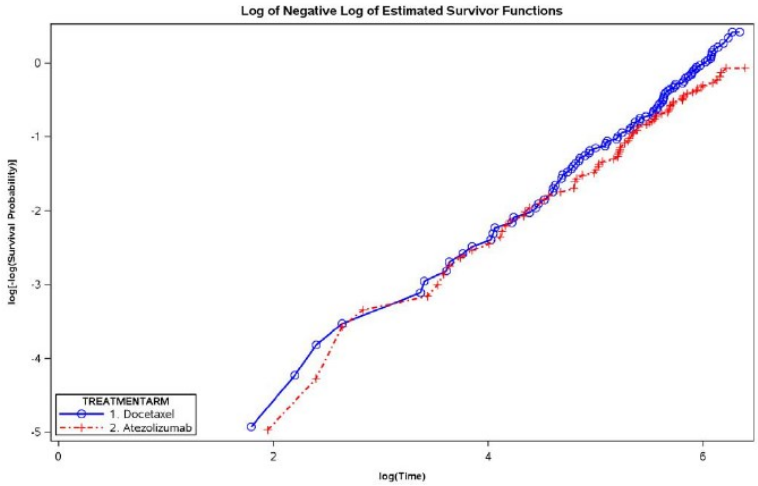


Figure 55: PFS Log of Negative Log Plots

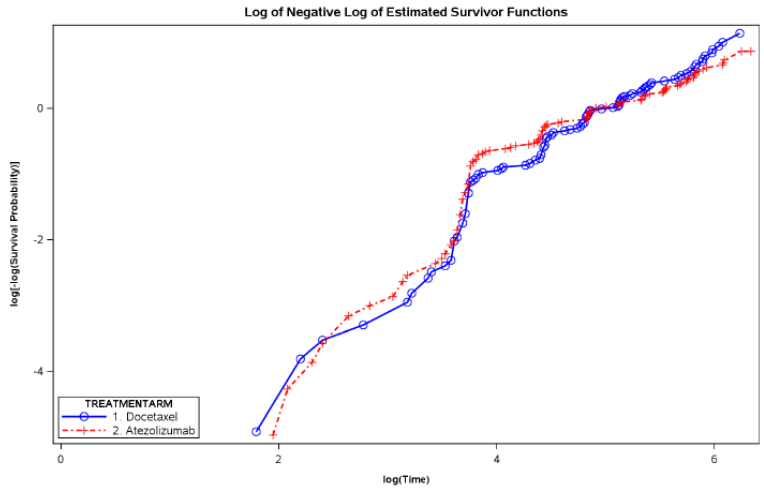


Figure 56: OS Log of Survival Plot

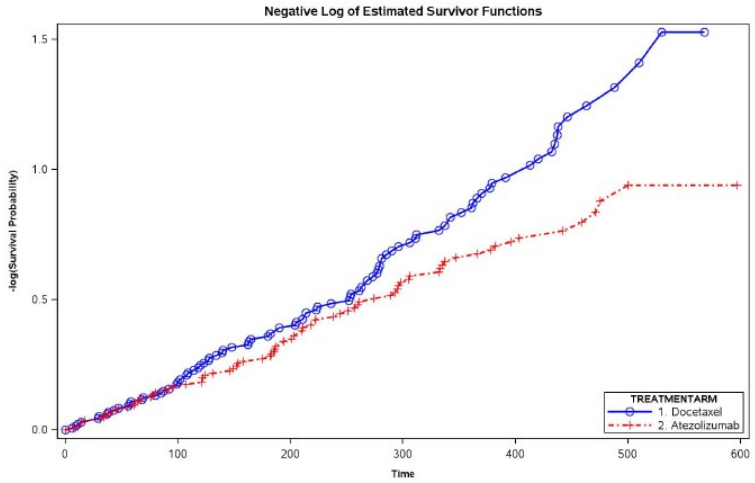
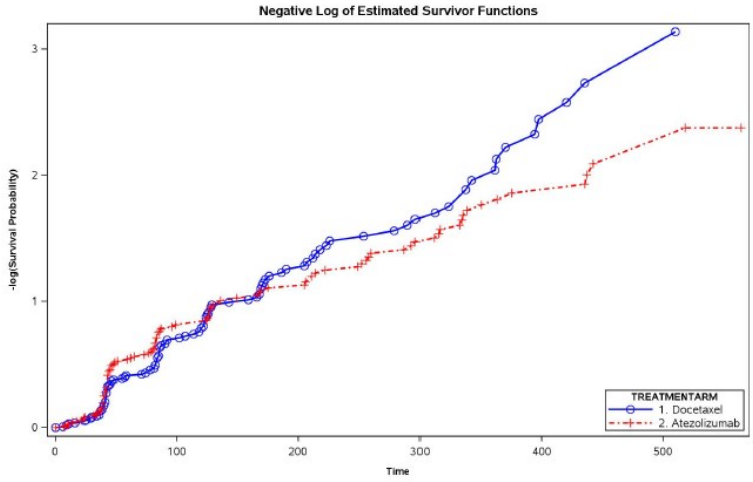


Figure 57: PFS Log of Survival Plot



Section B: Clarification on cost effectiveness data

B1. Priority request: Kaplan-Meier data. Please provide the Kaplan-Meier analyses listed in a to c below to the following specifications:

Trial data set: OAK trial
Censoring: Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, i.e. not when last known to be alive
Format: Please present analysis outputs using the format of the sample table shown below this question
Population: ITT population including all patients lost to follow-up or withdrawing from the trial

a. Time to death from any cause (overall survival) Kaplan-Meier analysis for patients in the atezolizumab arm of the trial

Censoring methodology for the OAK trial was pre-specified in the statistical analysis plan. The methodology is stated as follows: “Data for patients who are not reported as having died at the time of analysis will be censored at the date they were last known to be alive”. This approach is consistent with that taken to censoring in all atezolizumab publications to date, and the approach taken for the submissions to the regulatory authorities, providing the basis of the anticipated atezolizumab marketing authorisation.

We believe this request is beyond the intended scope of the clarification questions, and consider it inappropriate to re-run analyses such as this post-hoc.

Both censoring methodologies are statistically accepted, and widely used in clinical trials. However, the approach of censoring patients at the date of data-cut off (vs. last observation) implicitly considers patients who had been lost to follow up to have remained alive for the course of the study. We do not believe this to be reasonable based on our experience from engaging with members of the global statistical and regulatory community. In addition, such an approach would skew the indirect treatment comparison, given the data in the NMA would not be recensored.

Finally, we note that data from the KEYNOTE-010 trial, which formed the basis of the pembrolizumab appraisal, was censored in a similar manner: “Patients without documented death at the time of the final analysis were censored at the date of the last follow-up” (National Institute for Health and Care Excellence, 2016). This approach was considered acceptable for the pembrolizumab appraisal which received positive guidance in January 2017.

b. Time to death from any cause (overall survival) Kaplan-Meier analysis for patients in the docetaxel arm of the trial

Please refer to the response to B1a.

c. Time to study treatment discontinuation Kaplan-Meier analysis.

Please refer to the response to B1a.

B2. Priority request: Utility data: Please complete the table below using data collected during the OAK trial for European patients only and valued using the UK TTO value set.

Please see the completed table below:

Time	Atezolizumab			Docetaxel			Average		
	n	Mean	sd	n	Mean	sd	n	Mean	sd
Baseline	254	[redacted]	[redacted]	272	[redacted]	[redacted]	526	[redacted]	[redacted]
>360 days to death	438	[redacted]	[redacted]	257	[redacted]	[redacted]	695	[redacted]	[redacted]
>180-360 days to death	580	[redacted]	[redacted]	459	[redacted]	[redacted]	1039	[redacted]	[redacted]
30-180 days to death	507	[redacted]	[redacted]	466	[redacted]	[redacted]	973	[redacted]	[redacted]
<30 days to death	46	[redacted]	[redacted]	40	[redacted]	[redacted]	86	[redacted]	[redacted]

B3. Priority request. Utility data: Please complete the example table below using all EQ-5D data collected during the OAK trial (if time to death has not occurred then please use time between utility value being taken and data cut-off point for that patient).

Please see Appendix 1 for this completed table.

Section C: Textual clarifications and additional points

C1. The number of participants withdrawn from treatment is presented in Figure 6 and Table 23 of the company submission, however, even when accounting for the actual numbers of patients receiving each treatment, the numbers do not correspond. Should the number withdrawn from atezolizumab treatment in Table 23 be 364? If so, please clarify the number of patients who withdrew for each reason listed in Table 23 of the company submission.

Yes, the number of patients withdrawn from atezolizumab treatment in Table 23 should be 364. To confirm: of the 422 subjects that received atezolizumab, 364 subjects discontinued treatment with atezolizumab. Of these subjects, 316 discontinued treatment due to progressive disease, 36 due to an adverse event, 9 due to withdrawal by patient, 2 due to physician decision, and 1 due to "other". The 1 subject that discontinued due to "other" was randomised to receive to docetaxel, but received atezolizumab in error.

C2. It is stated in the company submission (p162) that:

> 'Based on their experience and knowledge of immunotherapies, unanimous opinion suggested that an overall survival rate of approximately 10% of patients treated with atezolizumab at 5 years would not be implausible. This is supported by the recent appraisal for pembrolizumab (National Institute for Health and Care Excellence, 2017), where under the Committee's preferred assumptions, the resulting 5-year overall survival estimate was 10.4% (and was specifically acknowledged in the FAD).'

The ERG can find no reference in the final appraisal determination (FAD) to either 10.4% or a statement that sets out the Committee's preferred assumptions. Please specify the exact location within the FAD of these details.

This is a typographical error. Page 12 of the pembrolizumab FAD refers to a 5 year OS projection of 9.6% based on the March 2016 data submitted during consultation. Hence, this figure should be 9.6%.

C3. Please provide a clear definition of 'traditional parameterisation' as described for the scenario analyses (company submission, p210).

"Traditional parameterisations" refers to the more standard parametric curves, such as Weibull, Exponential, Log-normal etc.

C4. Please provide a justification for the sensitivity analysis range used for 'cure fraction' (table 94 p207), as this parameter had the largest impact on the ICER.

There is considerable uncertainty in the long-term benefit and continued treatment effect of new immunotherapies, as referred to in the pembrolizumab ACD for untreated PD-L1-positive metastatic non-small-cell lung cancer (National Institute of Health and Care Excellence, 2017)).

Whilst we believe a 2% cure fraction is appropriate for this patient population, validated through OAK and POPLAR data, as well as NLCA registry data, it is acknowledged that data availability is limited to 5 years. Beyond this period, there is less clarity on the performance of NSCLC patients, and atezolizumab.

Hence, to address this uncertainty the sensitivity analysis was conducted. Both the lower, and upper limits were selected to aid decision making: providing a sufficient range around our selected base case.

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Single technology appraisal

Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [ID970]

Section B: Clarification on cost effectiveness data v2

B1. Priority request: Kaplan-Meier data. Please provide the Kaplan-Meier analyses listed in a to c below to the following specifications:

Trial data set: *OAK trial*
Format: *Please present analysis outputs using the format of the sample table shown below this question*
Population: *ITT population including all patients lost to follow-up or withdrawing from the trial*

This updated clarification question has removed the request for data to be re-censored, therefore we are happy to provide a response.

a. Time to death from any cause (OS) Kaplan-Meier analysis for patients in the atezolizumab arm of the trial

This information was already available as part of the economic model submitted to the ERG. However, it has been provided again in Appendix 2.

b. Time to death from any cause (OS) Kaplan-Meier analysis for patients in the docetaxel arm of the trial

This information was already available as part of the economic model submitted to the ERG. However, it has been provided again in Appendix 3.

c. Time to study treatment discontinuation Kaplan-Meier analysis.

This information was already available as part of the economic model submitted to the ERG. However, it has been provided again in Appendix 4. It was unclear from the question which treatment arm the ERG was interested in reviewing. Therefore, both arms have been provided.

Submission from **Roy Castle Lung Cancer Foundation,** for consideration by NICE, in their review of **Atezolizumab** in the treatment of non small cell lung cancer, after platinum-based chemotherapy [**ID970**].

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 55 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 10%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of Non Small Cell Lung Cancer (NSCLC).

General Points

1. The current outlook for patients with NSCLC, who have relapsed after platinum based chemotherapy, is poor. In this scenario, improving quality of life and even small extensions in duration of life are of considerable significance to the individual and their family.

2. Active treatment options after previous chemotherapy treatment, until recently, were limited to further chemotherapy with Docetaxel or combination Docetaxel/Nintedanib. Significant toxicity is associated with these regimens. We are pleased to note the recent NICE approval of Pembrolizumab (PDL-1 positive patients) in second line. At time of writing, Nivolumab appraisals in this second line setting are ongoing. The addition of Immunotherapy in the treatment of NSCLC has been a major development.

3. 'End of life' considerations are very important to this patient group. When considering the cost of treatment, it is not appropriate, for example, to give the same weighting to the final six months of life as to all other six months of life. It is important for this to be part of any numeric equation, which is looking at cost and quality of life. This point is of crucial importance to patients and relatives in this situation

4. Improvement in symptoms. Patients with relapsed NSCLC are often debilitated with multiple and distressing symptoms. Symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief.

This Product

1. Immunotherapy
   At the time of this submission, Pembrolizumab has been approved by NICE, in second line, after platinum chemotherapy, for PDL-1 positive patients. It is the first immunotherapy agent to be approved for routine use in lung cancer patients in the NHS.
   A different immunotherapy agent, Nivolumab, is currently undergoing NICE appraisal for use in lung cancer – currently licenced for both squamous cell and non squamous cell NSCLC (note - NICE Appraisal Committee decisions have so far been negative).

   Atezolizumab is therefore, the third immunotherapy agent being developed in lung cancer treatment. These agents work by harnessing the ability of the immune system to find and fight cancer. They are described as PD-1 (Programmed Death-1) Immune Checkpoint Inhibitors.

   By blocking PD-1, Atezolizumab prevents its binding to PD-L1 on the surface of the tumour cells, hence restoring the capacity of T-cells to fight cancer cells.

2. Improvement in survival
   We do not have any information or trial data for this therapy, beyond that which is published and publicly available.

   However, we note the randomised Phase 3, OAK study, published in the Lancet in December 2016. This study compared Atezolizumab with Docetaxel in previously treated NSCLC patients. The median overall survival in the Atezolizumab arm was 13.8 months, compared with 9,6 months in the Docetaxel arm. The study found that Atezolizumab worked better for patients with higher levels of PDL-1 (greater than or equal to 1%). – (15.7months, compared to 10.3months). Survival was still higher compared to chemotherapy for those where tumour samples showed low or no levels of PDL-1 (12.6months, compared to 8.9months)

   Patients with relapsed advanced/metastatic NSCLC are a group with significant unmet medical need. Thus, existing chemotherapy has provided these patients with a modest improvement in survival. Immunotherapy provides an additional option which can significantly extend survival.

3. Side effects
   Atezolizumab is administered as a three weekly intravenous infusion.

   The most common side effects associated with Atezolizumab include fatigue, shortness of breath, decreased appetite, cough, nausea, musculoskeletal pain and constipation. More serious side effects, though uncommon, can occur if the immune system attacks healthy tissues in the body, such as the lungs, colon, liver, kidneys or hormone producing glands. In the anecdotal patient experience reported to us, these immunotherapeutic agents appear to be well tolerated – in particular, when compared with current standard second line cytotoxic therapy for NSCLC.

4. As noted above, even relatively small benefits can be disproportionately large for patients.

Our observations come from a combination of one-to-one discussion with lung cancer patients, published research and our patient information helpline.

In summary

Patients with advanced and metastatic lung cancer, which have relapsed after chemotherapy are in a particularly devastating situation. At the time of writing, Atezolizumab is the third PDL-1 inhibitor to be considered for treatment in NSCLC, in this second line patient group. Pembrolizumab has been approved by NICE in PDL-1 positive patients. Nivolumab is undergoing NICE appraisal in both squamous cell and non squamous cell histology.

Atezolizumab has been reported to show improvement in overall survival, versus Docetaxel chemotherapy, regardless of PDL-1 expression or histology.

[redacted]

February 2017.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Thoracic Society
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The British Thoracic Society welcomes the appraisal of atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy.

We note the proposed methodology and have no additional points to make. We look forward to seeing the appraisal report.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: NCRI/RCP/RCR/ACP/BTOG

Comments coordinated by [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

Background

Lung cancer is one of the most common cancers in the UK with over 46 thousand new cases being diagnosed each year. In 2014, there were 35,895 deaths from lung cancer, a statistic that demonstrates how very poor the prognosis is for these patients[1] (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/lung). Lung cancer is the most common cause of cancer mortality in the UK, accounting for more than a fifth of all cancer deaths (22%) and almost a quarter (23%) of all male deaths from cancer. About 16,300 women in the UK die from lung cancer each year, 5,000 more than the next most common cause, breast cancer.

The majority of patients with non-small cell lung cancer (NSCLC) present with advanced disease and although treatment rates vary across the UK, only of 64% of patients who have good performance status (PS 0-1) receive first line chemotherapy[2] (http://www.hscic.gov.uk/lung) with around 25% of all patients diagnosed undergoing any systemic treatment.

Only 25-30% of patients who have received 1st line chemotherapy go on to receive a second or subsequent line of therapy.

Clinical Practice

First line treatment

Clinical practice for patients with NSCLC is consistent across the NHS in England:

- the standard 1st line treatment for fit patients without an oncogenic driver is platinum doublet chemotherapy (cisplatin or carboplatin with pemetrexed, gemcitabine, vinorelbine or taxane)
- for patients who are not eligible to receive platinum doublet chemotherapy, single agent treatment with gemcitabine or vinorelbine is an option
- for patients with an EGFR activating mutation an EFGR TKI (Gefitinib TA192, Erlotinib TA 258 or Afatinib TA310) is used
- for patients with an ALK gene rearrangement crizotinib (TA406) is recommended.

Second line treatment

For patients with an EGFR mutation, who remain of good performance status, platinum doublet chemotherapy is a 2nd line treatment option and for those who develop a T790M resistance mutation to an EGFR TKI, osimertinib is available via the CDF as superior alternative to chemotherapy (ID874). For patients with an ALK gene rearrangement Ceritinib is recommended following crizotinib (TA395).

The vast majority of patients (approximately 90%) do not have an oncogenic driver and for those patients who reman PS0-1 the options are:

- Docetaxel
- Docetaxel with nintedanib for pateints with adenocarcinoma (TA347)
- Pembrolizumab for patients with expression of PDL-1 on 1% or more of tumour cells (TA428) – approved December 2016

Immunotherapy in NSCLC

The body of supporting evidence for immunotherapy in NSCLC has developed rapidly over the past 2-3 years resulting in EMA approval of two anti PD-1 therapies, Nivolumab[3,4]and Pembrolizumab[5] in previously treated patients.

The SMC in Scotland has approved Nivolumab for use in prevously treated patients without PD-L1 selection, and NICE appraisal process is ongoing (ID811 and ID900).
The recent NICE approval of pembrolizumab in patients with previously treated NSCLC whose tumours express PD-L1 in >/=1% was welcomed by health professionals and patients but is only just beginning to impact on clinical practice. The resulting change in treatment has resulted in modifications to pathology pathways in order to obtain PD-L1 testing and these pathways are still evolving. Furthermore, as the nature of adverse events and toxicity management it significantly different for immunotherapy compared to chemotherapy, the oncology community is working with acute medical teams to improve awareness of immune related toxicity and management algorithms.
The success of immunotherapy in post platinum treated NSCLC patients has led to investigation of PD-1/PD-L1 therapies in the 1st line setting. Pembrolizumab has recently demonstrated a 4.3 month improvement in PFS compared to chemotherapy (HR 0.60, CI 0.37-0.68, p<0.001) with response rates of 44.8% versus 27.8% compared to chemotherapy,[6] resulting in a change in the EMA authorisation in December 2016 to include first line treatment in patients with >/= 50% PD-L1 expression on tumour cells.

The Technology

The "OAK" phase 3 study[7] of atezolizumab (Tecentriq) versus docetaxel randomised 1,225 patients with locally advanced or metastatic NSCLC who had previously received 1-2 lines of chemotherapy (at least 1 was platinum containing). Data has been presented on the first 850 patients enrolled. The primary end points were overall survival (OS) in the intent to treat (ITT) population and OS in patients with 1% or more PD-L1 expression on tumour or immune cells. Secondary endpoints were overall respose rate (ORR), progression free survival (PFS), duration of response (DoR) and safety.
Atezolizumab was administered at 1200mg iv on a 3 weekly schedule until PD and docetaxel was given in standard doses of 75mg/m^2 3 weekly.
Thev median age of patients was 63 years and 64 years on the atezolizumab and docetaxel arms respectively, 74% of patients had non-squamous NSCLC and 75% had had one previous line of therapy. The arms were well balanced for other clinical characteristics.

Efficacy
At a median follow up of 19 months, the median overall survival in the ITT population was improved from 9.6 months (95% CI 8.6-11.2 months) with docetaxel to 13.8 months (CI 11.8-15.7 months) with atezolizumab (hazard ratio 0.73, 95% CI 0.62-0.87, p=0.0003). The 12 month survival was 41% versus 55%.
For patients who expressed >/=1% PD-L1 on tumour and/or immune cells (55% of the population), these numbers improved to median survival 10.3 months (CI 8.8, 12.0) versus 15.7 months (CI 12.6-18.0), hazard ratio 0.74 (CI 0.58-0.93, p=0.0102) for docetaxel versus atezolizumab respectively.
For patients with high levels of PD-L1 expression (16% of population who had >/=50% PD-L1 expression on tumour cells or >/=10% expression on immune cells), the improvement demonstrated with atezolizumab was even more marked: median survival 8.9 months (CI 5.6-11.6) with docetaxel to 20.5 months (CI 17.5 – NR) with atezolizumab, hazard ratio 0.41 (CI 0.27-0.64, p<0.0001).
There was no difference in survival outcomes by histology (HR 0.73 for both non-squamous and squamous). Consistent with other anti PD-1/PD-L1 immunotherapy studies in NSCLC, the subgroup of patients with EGFR mutations appeared to be the only cohort that did not demonstrate improved survival with atezolizumab.

The proportion of patients receiving post trial treatment was similar in both groups, with 49% of patients in the atezolizumab arm receiving subsequent therapy and 45% of patients in the docetaxel arm. A modest number of patients in the docetaxel arm (17%) were subsequently treated with an immunotherapy, reflecting the limited access to immunotherapy around the trial period.
ORR was similar in the ITT population: 13% versus 14%, which improved to 11% versus 31% in the high (>/=50%) PD-L1 expressing group for docetaxel and atezolizumab respectively.
For those patients achieving a response to therapy, the duration of response was 6.2 months for docetaxel versus 16.3 months for atezolizumab, in the ITT population. Interestingly the DoR was not significantly different in various PD-L1 cohorts, demonstrating that PD-L1 is not an ideal biomarker. Some PD-L1 negative patients respond to therapy and if a patient achieves response, the degree of benefit does not appear to be correlated with PD-L1 expression.

Safety
The treatment was well tolerated with no treatment related deaths in the atezolizumab arm and 8% adverse events (AE's) leading to treatment withdrawal, compared to 0.2% deaths with docetaxel and 19% AE's leading to treatment withdrawal.
The rates of immune related events were low and consistent with other studies and there no new safety concerns.

- Pneumonitis 1.0% (0.2% grade 3 or worse)
- Hepatitis 0.3% (0.3% grade 3 or worse)
- Colitis 0.3 (0% grade 3 or worse)

The toxicity profile is significantly more tolerable than chemotherapy.

Where is the technology used?

The technology is used in secondary care and administered on the oncology chemotherapy suite. There is precedent from other forms of antibody treatment to consider delivery of treatment closer to home.

Guidelines

At present the NCCN guidelines version 4.2017[8] recommend atezolizumab (and the other checkpoint inhibitors nivolumab and pembrolizumab) for PS0-2 patients after progression on 1st line systemic therapy.
ESMO guidelines recommend nivolumab and pembrolizumab for PS0-2 patients with tumours expressing PD-L1>1%[9].
ASCO guidelines have not yet been updated to incorporate the emerging immunotherapy data.

The advantages and disadvantages of the technology

The main advantages of the technology under appraisal are:

1. Atezolizumab provides a well tolerated effective treatment for PS 0-1 NSCLC as an alternative to chemotherapy
2. The median overall survival is improved from 9.6 months (95% CI 8.6-11.2 months) with docetaxel to 13.8 months (CI 11.8-15.7 months) with atezolizumab (hazard ratio 0.73, 95% CI 0.62-0.87, p=0.0003) and the 12 month survival was 41% versus 55% 61% (95% CI 52% to 70%) in the ITT population, unselected by PD-L1 expression

3. PD-L1 expression appears to help identify a subgroup of patients who derive greater benefit from treatment. For patients with high levels of PD-L1 expression (16% of population had >/=50% PD-L1 expression on tumour cells or >/=10% expression on immune cells), the improvement in OS demonstrated with atezolizumab is even more marked with a median survival of 8.9 months (CI 5.6-11.6) for docetaxel increasing to 20.5 months (CI 17.5 – NR) with atezolizumab, hazard ratio 0.41 (CI 0.27-0.64, p<0.0001).
4. The treatment is well tolerated with no treatment related deaths documented and only 8% of patients experiencing AE's leading to treatment withdrawal.

The main disadvantages of the technology under appraisal are:

1. The particular method of PD-L1 testing employed for atezolizumab is more complex than other PD-L1 assays and not necessarily interchangeable.
2. The advantages of atezolizumab compared to chemotherapy are clear, but there is no data to distinguish between different immunotherpies following 1st line chemotherapy
3. The optimal duration of therapy remains to be identified. It is possible that future studies may demonstrate efficacy with a shorter duration of therapy, but at present there is no data to support modifying the treatment regimen.
4. Further studies are required to assess therapeutic benefit in less fit patients (PS2)

Any additional sources of information

More data, particularly with regard to the longer term survival benefit of immunotherapy will emerge as the trial data matures.
Clinical trials examining the potential benefit of immunotherapy in PS2 patients are underway, but are unlikely to report within the next 18 months.

Implementation issues

Until 2017, the majority of NSCLC patients who received 2nd line treatment in the UK recieved 4 cycles of docetaxel based chemotherapy. The improvement in outcomes which post platinum immunotherapy provides for our patients is welcomed, however 3 weekly intravenous treatment until progression is generating capacity issues due to:

- Increased number of oncology outpatient clinic appointments
- Increased chemotherapy suite appointments
- Increased radiological assessments (CT scans 2-3 monthly)
- Increased blood tests (3 weekly)
- Increased referrals for management of immune related toxicity (eg to endocrinology)

Balancing the increased resource utilisation due to longer longer treatment duration, there will be a reduced burden of toxicity from immunotherapy compared to standard chemotherapy (doctaxel). The change in practice will result in less prescription of supportive medication such as:

- Antibiotics
- Antiemetics
- Blood products

- Growth factors

Audit on standard UK practice of NSCLC treatment has demonstrated a 59% admission rate for patients receiving docetaxel.[10] Perhaps most importantly, there will be a reduced incidence of hospital admissions to treat chemotherapy associated toxicity, with consequent improvement in quality of life for patients.

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Equality

There are no equality issues identified.

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NHS England submission on atezolizumab as 2nd/3rd line systemic therapy for the treatment of locally advanced/metastatic squamous and non squamous non small cell lung cancer (NSCLC)

1. Different trials of PD-1 or PD-L1 checkpoint inhibitors have used different assays of PD-1 or PD-L1. The other drugs assessed by NICE in this place in the treatment pathway (pembrolizumab, nivolumab) have used assays based on expression on tumour cells. The atezolizumab trial used an assay on tumour cells (TC) or tumour infiltrating immune cells (IC). NHS England awaits the results of a large study funded by a consortium of the FDA, ASCO, AACR, drug and diagnostic manufacturers and research organisations which is assessing the performances of the 4 major PD-L1 companion assays. Given that it is quite possible that two or three different checkpoint inhibitors may be recommended by NICE in different places in the treatment pathway, it is important to know how transferable the results will be from one assay to the next.
2. The primary end point (EP) in the atezolizumab phase III trial (the OAK trial) is overall survival in all the ITT population but a primary EP has also been designed in this trial for overall survival according to the PD-L1 subgroup of TC 1/2/3 or IC 1/2/3 (ie ≥1% TC or IC, overall ≥1% PD-L1 subgroup). Published evidence is also available for the TC 0 or IC 0 subgroup (<1% TC or <1% IC, overall PD-L1 negative), the TC 2/3 or IC 2/3 subgroup (≥5% TC or ≥5% IC, overall ≥5% PD-L1) and TC 3 or IC 3 subgroup (≥50% TC or ≥10% IC). Evidence for overall survival in the latter two subgroups was not in the Roche submission but has been published.
3. The primary efficacy group presented for the OAK trial is on the first 850 patients of the 1225 patient trial ie more data is to come in terms of increasing the power of the study and maturity of further follow up
4. The OAK trial designed treatment with docetaxel to continue until disease progression/unacceptable toxicity. In NHS England, maximum treatment duration with docetaxel is 4-6 cycles although more often 4 rather than 6 cycles.
5. The OAK trial designed treatment with atezolizumab to continue until there was loss of clinical benefit or unacceptable toxicity, whichever was the sooner. Continuing clinical benefit was defined as an absence of symptoms or signs which indicated unequivocal progressive disease, an absence of a deterioration in performance status, an absence of progressive disease at critical anatomical sites (such as leptomeningeal disease) and continued clinical benefit as assessed by the investigator. Patients could thus have progressive disease as defined by RECIST criteria as long as there was continued evidence of clinical benefit.
6. The mean time on treatment with atezolizumab was 7.8 months whereas the median duration of progressive-free survival was 4.0 months.

7. Roche has not considered pembrolizumab as a relevant comparator although did later submit an indirect comparison with pembrolizumab but not within the indirect treatment comparison network. NHS England disagrees with this failure to primarily consider pembrolizumab as a comparator as pembrolizumab is recommended by NICE in the same place in the treatment pathway as in this TA, albeit for those patients expressing PD-LI with a tumour proportion score of 1-100%.
8. Roche has also not considered nivolumab as a relevant comparator. Although nivolumab has a current negative provisional NICE recommendation in the same place in the NSCLC treatment pathway, its evidence base is in a population that is unselected for PD-L1 (as is the case for atezolizumab). NHS England is disappointed that Roche did not do this analysis in view of the potential for NICE to recommend nivolumab as $2^{nd}/3^{rd}$ line treatment.
9. Maturity of follow up in the OAK trial is very important in view of the modelling required and there are few patients at risk after 24 months in the OAK trial.
10. The proportion of patients alive at 18 months is 40% with atezolizumab and 27% with docetaxel. Subsequent immunotherapy occurred in 4.5% vs 17% respectively. The use of immunotherapy in 17% of patients might have contributed to a small degree as to the high 27% survival at 18 months in the docetaxel arm.
11. The hazard ratios (HRs) for overall survival progressively diminish as TC/IC score increases. The ITT population has a HR of 0.73. The TC/IC 0 subgroup has a HR of 0.75. The TC/IC 1/2/3 subgroup has a HR of 0.74. The TC/IC 2/3 subgroup has a HR of 0.67. The TC/IC 3 subgroup has a HR of 0.41.
12. NHS England notes that a stopping rule at 2 years is part of the NICE recommendation for pembrolizumab in the same part of the clinical pathway as atezolizumab in this appraisal. Such an arrangement could also be implemented by NHS England if this is necessary to a conclusion as to cost effectiveness.
13. The OAK trial included patients with activated EGFR mutations who had progressive disease on erlotinib/gefitinib/afatinib, this group constituting 10% of the trial accrual. The HR for the EGFR mutant population was 1.24 whereas for the EGFR wildtype patients the HR was 0.69.
14. Although there were fewer treatment-related serious adverse events with atezolizumab vs chemotherapy, there are still very important toxicities with checkpoint inhibitors such as atezolizumab. This is a very important issue given the fact that the NHS has to cope with treating a wide range of uncommon, unusual and potentially severe toxicities from checkpoint inhibitors and that toxicities of treatment with checkpoint inhibitors increase with increasing comorbidities. No disutility for these toxicities has been incorporated into the cost effective analysis.
15. The OAK trial demonstrated similar HRs for overall survival between atezolizumab vs chemotherapy in squamous and non squamous histologies.

16. If NICE recommends atezolizumab for use, the NHS England treatment criteria (all of which have to be satisfied) are potentially likely to be (subject to any considerations by the NICE TA committee):
    - Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
    - The prescribing clinician is fully aware of the management of and the treatment modifications that may be required for the immune-related adverse reactions due to anti-PD-L1 treatments including pneumonitis, colitis, nephritis, endocrinopathies and hepatitis
    - Histologically or cytologically documented non small cell lung cancer being either of the squamous and non squamous varieties
    - Disease is either locally advanced stage (IIIB) or metastatic disease (stage IV)
    - The PD-L1 expression result has been done by an approved and validated test and for this patient, the result is …%.
    - There has been disease progression during or following previous platinum-based combination chemotherapy for inoperable locally advanced or metastatic disease
    - Patients treated with adjuvant or neoadjuvant intent AND who have relapsed within 6 months since completing platinum-based chemotherapy are eligible but must satisfy all other criteria
    - ECOG performance status score of 0 or 1
    - Patients must not have untreated or active metastases in the central nervous system
    - The patient has not received prior treatment with an anti-PD1, anti-PDL1, anti-PDL-2, anti-CD137 or anti-CTLA-4 antibody treatment
    - To be treated until loss of clinical benefit or excessive toxicity, whichever is the sooner
    - No treatment breaks of more than 4 weeks beyond the expected cycle length are allowed (unless solely to allow immune toxicities to settle)
    - Atezolizumab to be otherwise used as set out in its Summary of Product Characteristics

[redacted]

[redacted]

June 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: Jackie Fenemore

Name of your organisation: NLCFN

Your position in the organisation: Vice Chair on the committee

Brief description of the organisation: Organisation to support lung cancer nurses who are the lung cancer patient's key worker. We have over 300 lung CNS members and it is funding by the members who pay a subscription to be a member. An annual conference is sponsored by pharma and solicitors to run the event.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: none

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Lung cancer can be a very difficult prognosis and some patients struggle to cope

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Extra progression free survival or life expectancy

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Chemotherapy is first line treatment for a lot of our lung patients with stage 4 disease

4. *What do patients or carers consider to be the advantages of the treatment being appraised?*

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms improving
- pain lessening due to response
- level of disability
- mental health
- quality of life (such as lifestyle and work)

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

All of the above

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

If patients respond better overall survival and quality of life

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

none

5. *What do patients and/or carers consider to be the disadvantages of the treatment being appraised?*

Disadvantages of a treatment might include:

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)

Please list any concerns patients or carers have about current NHS treatments in England.

none

Please list any concerns patients or carers have about the treatment being appraised.

none

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

none

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

I need more information before I can comment on this treatment

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

As above

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes ☑ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Yes

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

yes

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

not to my knowledge

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☑ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

N/a

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

N/a

9. *Other issues*

Do you consider the treatment to be innovative?

☑ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Immunotherapy is a new way to treat and manage cancer and is proving effective for lung cancer

Are there any other issues that you would like the Appraisal Committee to consider?

10. *Key messages*

In no more than 5 bullet points, please summarise the key messages of your submission.

- Immunotherapy is a new way to treat lung cancer
- Patient selection is important
- Side effect can be delayed + severe if not recognised
- Quality of life + time to progression can be improved
- More treatments available for lung cancer patients is important.

ID970 STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Atezolizumab for treating locally advanced or metastatic non-small cell lung cancer after chemotherapy [ID970]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 16/56/11

Completed 27 April 2017

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Sophie Beale, Research Associate (Decision Analyst), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Sarah Nevitt, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Marty Richardson, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Eleanor Kotas, Information Specialist, LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Pharmacy Practice Unit, Liverpool

John Green, Consultant in Medical Oncology, The Clatterbridge Centre NHS Foundation Trust, Liverpool

Correspondence to: Sophie Beale, Research Associate, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

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Contributions of authors:

Sophie Beale	Critical appraisal of the company submission
James Mahon	Critical appraisal of the submitted economic evidence
Sarah Nevitt	Critical appraisal of the submitted statistical evidence
Angela Boland	Critical appraisal of the company submission
Janette Greenhalgh	Critical appraisal of the submitted clinical evidence
Marty Richardson	Critical appraisal of the submitted statistical evidence
Eleanor Kotas	Cross checking of the submission search strategies
Joanne McEntee	Critical appraisal of the company submission
John Green	Clinical advice and critical appraisal of the clinical sections of the company submission

All authors read and commented on draft versions of this report.

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LIST OF ABBREVIATIONS

1º P	OAK trial primary population
2º P	OAK trial secondary population
AE	adverse event
ALK	anaplastic lymphoma kinase
BSA	body surface area
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CR	complete response
CrI	credible interval
CS	company submission
CSR	clinical study report
DIC	Deviance Information Criteria
DOR	duration of response
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	electronic market information tool
EORTC	European Organisation for the Treatment of Cancer
EQ-5D-3L	European quality of life - 5 dimensions, 3 levels questionnaire
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FE	fixed effect
FP	fractional polynomial
FAD	final appraisal determination
HR	hazard ratio
HRG	healthcare resource group
HRQoL	health-related quality of life
HTA	health technology assessment
IC	tumour-infiltrating immune cell
ICER	incremental cost effectiveness ratio
IHC	immunohistochemistry
ITC	indirect treatment comparison
ITT	Intention-to-treat
IV	intravenous
K-M	Kaplan-Meier
KRAS	Kirsten rat sarcoma
NA	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NLCA	National Lung Cancer Audit
NR	not reported
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PH	proportional hazards
PPS	post-progression survival
PR	partial response
PRO	patient reported outcome
PS	performance score
PSA	probabilistic sensitivity analysis
PSS	personal social services
PSSRU	Personal Social Services Research Unit
QALY	quality adjusted life year
RCT	randomised controlled trial
RE	random effect
RECIST	response evaluation criteria in solid tumours
sd	standard deviation
SD	Jansen method for assessing heterogeniety
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
TC	tumour cell
ToT	time on treatment
TRAE	treatment-related adverse event
TTD	time to treatment discontinuation

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Roche Products Limited in support of the use of atezolizumab (Tecentriq®) for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after chemotherapy.

1.2 Critique of the decision problem in the company submission

Population

The population described in the final scope issued by NICE is people with locally advanced or metastatic NSCLC whose disease has progressed after chemotherapy. This population can be considered to be the same as the population addressed in the company submission (CS).

Intervention

Atezolizumab does not currently have a UK marketing authorisation. The company made an application on 20th April 2016 and anticipates receiving the Committee for Medicinal Products for Human Use (CHMP) opinion in [redacted], with regulatory approval expected in [redacted] The application is for the treatment of adult patients with locally advanced or metastatic NSCLC) after prior chemotherapy.

Atezolizumab is a monoclonal antibody that binds to and inactivates a protein called programmed death-ligand 1 (PD-L1) on the surface of tumour cells (TCs) and tumour-infiltrating immune cells (ICs), inhibiting the binding to PD-1 and B7.1.

The treatment regimen for atezolizumab is a flat dose of 1200mg administered intravenously in a hospital setting, over a 30-minute period, every 3 weeks. It is stated within the draft Summary of Product Characteristics (SmPC) that patients should be treated with atezolizumab until loss of clinical benefit or unmanageable toxicity.

Comparators

The comparators specified in the final scope issued by NICE are docetaxel, nintedanib+docetaxel, pembrolizumab, nivolumab and best supportive care (BSC).

- Included comparators:
    - direct evidence is available for the comparison of the effectiveness of atezolizumab versus **docetaxel** (administered at a dose of 75mg/m^2 every three weeks) from the OAK and POPLAR trials
    - treatment with **nintedanib+docetaxel** is recommended by NICE as an option for treating locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy. In the absence of direct evidence to allow a comparison of the effectiveness of treatment with atezolizumab versus nintedanib+docetaxel, the company undertook an indirect treatment comparison (ITC).
- Excluded comparators:
    - **nivolumab** was not recommended by NICE for the treatment of locally advanced or metastatic NSCLC and hence cannot be considered a standard of care
    - the company provides three reasons for excluding **pembrolizumab**. First, marketing authorisation for pembrolizumab is only for patients with PD-L1 positive NSCLC and therefore does not match the anticipated marketing authorisation for atezolizumab. Second, accurate comparisons between treatments is not possible due to the differences between tests used in clinical studies to select patients. Third, pembrolizumab has only been recently recommended by NICE to treat patients with NSCLC and is unlikely to represent a standard of care at this time
    - **BSC** was excluded due to a clinically validated assumption that patients eligible for treatment with atezolizumab would be considered fit enough to receive other treatments.

Outcomes

Clinical evidence is presented in the CS for all five outcomes specified in the final scope issued by NICE: progression-free survival (PFS), overall survival (OS), objective response rate (ORR), adverse events (AEs) and health-related quality of life (HRQoL).

Subgroups

It is specified within the final scope issued by NICE that, if evidence allows, consideration will be given to subgroups based on biological markers. Within the CS, results have been provided from the OAK trial by baseline characteristics and for histology subgroups (squamous and non-squamous disease). Results have also been presented for patients with no measurable PD-L1 expression (TC0/IC0) and for patients with ≥1% PD-L1 expression.

Other considerations

- Agreed patient access schemes (PAS) are in place for atezolizumab and nintedanib
- The company has not identified any equality issues
- The company has presented a case for atezolizumab to be assessed against the NICE End of Life criteria.

1.3 Summary of clinical effectiveness evidence submitted by the company

The direct clinical evidence for the treatment of atezolizumab versus docetaxel was derived from the OAK and POPLAR trials.

Results from the OAK and POPLAR trials

Results from both the OAK and POPLAR trials show that treatment with atezolizumab is associated with a statistically significant and clinically meaningful improvement in median OS (4.2 months in the OAK trial and 2.9 months in the POPLAR trial) compared to docetaxel in patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 and 1. In the OAK trial, this statistically significant gain in OS is observed regardless of histology and PD-L1 status. However, in the POPLAR trial, statistically significant improvement is observed only in the non-squamous histology subgroup and for individuals with any type of NSCLC of ≥1% PD-L1 expression. Improvement in OS with atezolizumab compared with docetaxel is also generally consistent across patient baseline characteristics in both trials. No statistically significant difference in investigator-assessed PFS was observed between atezolizumab and docetaxel arms in either trial.

Results from the company's indirect treatment comparison (ITC) suggest that the best estimate of the expected difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (compared to a median OS gain of 4.2 months and 2.9 months in the OAK and POPLAR trials respectively). Results from the company's ITC suggest that the best estimate of the expected difference in OS is around 5 to 6 months for the comparison of atezolizumab versus nintedanib+docetaxel. Also, results from the company's ITC analyses suggest that there is no statistically significant difference in PFS survival for the comparison of atezolizumab versus docetaxel and for atezolizumab versus nintedanib+docetaxel.

The company has collected HRQoL outcome data using the European Organisation for Research and Treatment Cancer (EORTC) Quality of Life questionnaire, the EORTC Quality of Life in Lung Cancer questionnaire and the EQ-5D-3L questionnaire. Analyses of HRQoL data collected during the OAK trial show that there was no clinically meaningful worsening of commonly reported cancer treatment-related symptoms for patients treated with

atezolizumab, while there was a clinically meaningful worsening in alopecia and peripheral neuropathy throughout treatment for patients treated with docetaxel. In addition, patients treated with atezolizumab demonstrated prolonged time to deterioration of patient-reported chest pain compared with patients treated with docetaxel (hazard ratio [HR] 0.72, 95% confidence interval [CI]: 0.55 to 0.93).

1.4 Summary of the ERG's critique of submitted clinical effectiveness evidence

The ERG considers that the OAK and POPLAR trials were of good quality and well conducted; patient characteristics were balanced across the arms and the statistical methods were generally appropriate. However, the open-label design of these trials provides the opportunity for investigator-assessed outcomes to be biased. Also, the ERG notes that OS and PFS HRs must be interpreted with caution due to hazards not being proportional, as demonstrated by the company.

The ERG does not agree with the ITC approach taken by the company as the main network includes comparators that are not listed in the final scope issued by NICE. In addition, the ERG does not consider that the company was justified in excluding pembrolizumab from the ITC network of comparators relevant to this appraisal. During the clarification process, the ERG asked the company to undertake two further ITC analyses. However, the company undertook these using non-equivalent populations and results should be viewed with extreme caution:

- based on a (reduced) network using data from the intention-to-treat (ITT) populations of the OAK and POPLAR trials and the adenocarcinoma population from the LUME-Lung 1 trial, results suggest that the best estimate of expected difference in OS for atezolizumab versus nintedanib+docetaxel is 3.33 months (compared to 4.74 months when the analysis was carried out using LUME-Lung 1 trial total population) and is not statistically significant. However, this analysis was undertaken using non-equivalent populations and results should be viewed with caution.
- based on a (reduced) network using data from the ITT populations of the OAK, POPLAR and KEYNOTE-010 trials (the latter assessing the efficacy of pembrolizumab as a first-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% tumour proportion score) suggest that there is no statistically significant difference in OS or PFS for patients receiving atezolizumab when compared with pembrolizumab.

The ERG considers that the company's use of a fractional polynomial (FP) approach to conduct the ITC is appropriate. However, FP ITC results are influenced by a range of factors (e.g., comparators and population selected, type of FP model chosen and the use of FE or RE) which means that it is difficult to identify the most appropriate combination of factors to

use to generate ITC results. The ERG also considers that the expected values generated by the ITC are difficult to interpret. In addition, the ERG considers that the company's criteria for assessing the presence of heterogeneity in the analyses is inappropriate.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with atezolizumab versus docetaxel or nintedanib+docetaxel for previously treated patients with advanced NSCLC. The model comprises three mutually exclusive health states: 'on treatment', 'off treatment' and death. All patients start in the 'on treatment' state until they discontinue treatment or die. The model time horizon is set at 25 years with a 1-week cycle length. The model perspective is that of the UK NHS. Outcomes were measured in quality adjusted life years (QALYs), and both costs and QALYs were discounted at an annual rate of 3.5%, as recommended by NICE.

The OS of patients treated with atezolizumab was estimated using a mixed cure-rate model: survival for 98% of the population was a log-logistic distribution fitted to OAK trial data, while the remaining 2% were considered to have the same chance of survival as the general age-matched population. The OS models for patients receiving docetaxel and nintedanib+docetaxel were constructed by adjusting the trajectory for patients receiving atezolizumab using results from the company's FP ITC analyses. The company's base case analysis prediction is a mean of 2.22 life years gained (LYG) for patients receiving atezolizumab, 1.19 LYG for patients receiving docetaxel and 1.31 LYG for patients receiving nintedanib+docetaxel.

HRQoL data collected as part of the OAK trial using the EQ-5D-3L questionnaire were used in the company model. These data were differentiated by the time to a patient's death and by whether patients were 'on treatment' or 'off treatment' treatment. The mean EQ-5D utility scores by time to death used in the company base case for the 'on treatment' and 'off treatment' states are >30 weeks before death: 0.77 and 0.68; >15 weeks and ≤30 weeks before death: 0.71 and 0.58; >5 and ≤15 weeks before death: 0.61 and 0.43; and ≤5 weeks before death: 0.39 and 0.35.

Resource use and costs were estimated based on information from the OAK trial, published sources and clinical experts. For atezolizumab, the company provided the list price and the Department of Health PAS discount. Full list prices were used to represent the cost of the comparator drugs. The company is unaware of the PAS price for nintedanib.

Using list prices only, the company base case incremental cost effectiveness ratio (ICER) for the comparison of treatment with atezolizumab versus docetaxel is £72,356 per QALY gained; treatment with atezolizumab generates 0.748 additional QALYs at an additional cost of £53,970. For the comparison of treatment with atezolizumab versus nintedanib+docetaxel, the ICER is £56,076 per QALY gained; treatment with atezolizumab generates 0.646 additional QALYs at an additional cost of £36,209.

The company carried out a wide range of deterministic sensitivity analyses. The most influential parameters for both atezolizumab versus docetaxel and atezolizumab versus nintedanib+docetaxel are related to the cure fraction rate applied to atezolizumab, the monthly cost of atezolizumab and the discount rate used for effects.

The company's probabilistic sensitivity analysis (PSA) results show that when the cost effectiveness of treatment with atezolizumab is compared with docetaxel and nintedanib+docetaxel, there is a 1% probability of treatment with atezolizumab being cost effective at a threshold of £50,000 per QALY gained. The company carried out 12 scenario analyses and results from these demonstrate that the cost effectiveness of treatment with atezolizumab is only sensitive to the distribution chosen to extrapolate time to treatment discontinuation (TTD) with atezolizumab and then only if a log-logistic distribution is chosen.

1.6 Summary of the ERG's critique of submitted cost effectiveness evidence

The ERG considers that there are three errors in the company model that need to be corrected if the model is to produce accurate cost effectiveness results that reflect the underlying assumptions of the company base case. These errors are:

- incorrect application of discounting
- absence of age-dependent utility decrements
- incorrect use of a half-cycle correction to TTD data.

The ERG estimates that the accurate ICER, under the company base case assumptions for the comparison of the cost effectiveness of atezolizumab versus docetaxel is £77,569 per QALY gained and for the comparison of treatment with atezolizumab versus nintedanib+docetaxel it is £60,366 per QALY gained.

The ERG considers that the company's approach to modelling OS generates overly optimistic survival gains when treatment with atezolizumab is compared with docetaxel and when atezolizumab is compared with nintedanib+docetaxel. The ERG has identified three issues

with the mixed cure-rate approach taken by the company to model OS for patients receiving atezolizumab:

- use of the log-logistic function produces an implausibly long survival tail
- there is insufficient evidence for application of a cure-rate
- the value for the cure-rate used by the company was not justified by the company.

A further issue with the company's atezolizumab OS model relates to the company's assumption that treatment with atezolizumab has a lifetime protective effect. This assumption has been criticised by a previous NICE Appraisal Committee when considering the use of an immunotherapy for treating patients with previously treated advanced or metastatic NSCLC. In addition, the ERG highlights that the company's approach to modelling OS for patients receiving atezolizumab results in mortality rates that are, at some points, lower than the mortality rates of the UK general population of the same age.

The company approach to modelling of OS for docetaxel and for nintedanib+docetaxel involved adjusting the company's OS atezolizumab model using the relevant hazard rates generated by the company's FP ITC. Due to concerns relating to the company's FP ITC, including the fact that the FP ITC used to generate hazard rates involved inputs that are not relevant to this appraisal, the ERG has little confidence in the results produced by this approach. The ERG highlights that the expected docetaxel survival results produced by the company's FP ITC are optimistic when compared with median OS from the OAK trial. The ERG also highlights that the FP ITC used by the company to model OS for patients receiving nintedanib+docetaxel was not restricted to the nintedanib+docetaxel licensed population (patients with adenocarcinoma), meaning that the company's ITC results for this treatment are not relevant to this appriasal.

1.7 Summary of company's case for End of Life criteria being met

To meet the NICE End of Life criteria the company must demonstrate that:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months
- 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.

The company has put forward a case that atezolizumab meets NICE's End of Life criteria based on the following points:

- the company quotes data that show median survival for patients with Stage IIIb and Stage IV NSCLC is 7.5 months and 3.4 months, respectively
- base case results generated by the company's economic model suggest that the mean difference in OS between patients treated with atezolizumab versus docetaxel or nintedanib+docetaxel is more than 3 months.

1.8 ERG commentary on End of Life criteria

The ERG agrees with the company that patients with advanced NSCLC have a life expectancy of less than 24 months.

An examination of the ERG's remodelled OS suggests that treatment with atezolizumab generates a mean survival gain of 4.7 months compared to docetaxel. However, compared to treatment with nintedanib+docetaxel, the size of the survival gain is uncertain. The company has provided evidence that suggests there is no statistically significant difference in OS for atezolizumab (total population) compared to nintedanib+docetaxel (adenocarcinoma patients only). If this result is reliable, then, for the adenocarcinoma population, atezolizumab does not meet the NICE End of Life criteria for life extension.

1.9 ERG commentary on the robustness of evidence submitted by the company

1.9.1 Strengths

Clinical evidence

- OAK and POPLAR trials were of good quality and well conducted
- EQ-5D data were collected during the OAK trial
- the ERG recognises the considerable effort made by the company to generate ITC results employing a methodology which accounts for hazards not being proportional.

Cost effectiveness evidence

- the economic model was well constructed
- the company used TTD to cost study treatments
- the company used EQ-5D utility scores by time to death
- the company carried out a comprehensive range of deterministic sensitivity and scenario analyses.

1.9.2 Weaknesses and areas of uncertainty

Clinical evidence

- the company should have included pembrolizumab as a comparator
- only investigator-assessed PFS results are available from the OAK and POPLAR trials
- the ERG considers that the company should have included full subgroup analyses of effectiveness and cost effectiveness by levels of PD-L1 expression
- the PFS and OS HRs from OAK and POPLAR trial data were calculated using a pre-specified method that relies on an assumption that hazards are proportional. However, as demonstrated by the company, this assumption does not hold and therefore OS and PF HRs must be interpreted with caution
- the company approach to the ITC is influenced by a range of factors (e.g., comparators and population selected, type of FP model chosen and the use of FE or RE) which means that it is difficult to identify the most appropriate combination of factors to use to generate ITC results
- the FP ITC results are difficult to interpret
- the company's criteria for assessing the presence of heterogeneity in the ITC analyses is inappropriate
- clinical advice to the ERG is that AEs arising from treatment with atezolizumab and other immunotherapies in patients with NSCLC require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs.

Cost effectiveness evidence

- the ERG identified three model construction errors: incorrect application of discounting, absence of age-dependent utility decrements and incorrect use of a half-cycle correction to TTD data
- the company's approach to modelling of OS for patients treated with atezolizumab used a mixed cure-rate model; however, there is insufficient evidence for the application of a cure-rate and the value used for the cure-rate was not justified by the company the company's approach to modelling OS for patients treated with atezolizumab is implausible as it resulted in survival rates that, at some points, were higher than that of the UK general population
- the company assumed a lifetime duration of treatment effect for atezolizumab, an approach that has been criticised by a previous NICE Appraisal Committee when assessing an immunotherapy for the treatment of patients with advanced or metastatic NSCLC
- confidence in modelling OS for patients receiving docetaxel by adjusting the OS atezolizumab model by hazard rates generated by the company's ITC is limited by the ERGs concerns relating to the company's FP ITC, including the fact that the FP ITC used to generate hazard rates involved inputs that are not relevant to this appraisal

- confidence in modelling OS for patients receiving nintedanib+docetaxel by adjusting the OS atezolizumab model by the hazard rates generated by the company's ITC is limited by concerns relating to identifying the most relevant FP ITC, including the fact

that the FP ITC used to generate hazard rates involved inputs that are not relevant to this appraisal and that the FP ITC was not limited to patients with adenocarcinoma histology.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG's preferred method was to model OS for both atezolizumab and docetaxel by using Kaplan-Meier (K-M) data from the OAK trial for as long as possible, and then to append exponential curves to project OS for the remainder of the model time horizon. The ERG also limited the duration of treatment effect of atezolizumab to approximately 3 years.

The FP ITC results generated by the company showed that when treatment with atezolizumab (whole population) was compared with nintedanib+docetaxel (adenocarcinoma population) using the reduced network (i.e., comparators of relevance to this appraisal) there was no statistically significant difference in expected OS between the two therapies. The ERG, therefore, undertook an analysis in which the OS of patients receiving nintedanib+docetaxel was the same as that of patients receiving atezolizumab, and the treatment effect of both interventions was limited to 3 years. Hence, the only modelled differences were therapy costs and HRQoL (utility values were adjusted for each treatment to take into account the incidence of AEs).

1.11 Cost effectiveness conclusions

Application of the ERG model amendments results in an ICER for the comparison of treatment with atezolizumab versus docetaxel of £170,497 per QALY gained.

Application of the ERG model amendments results in an ICER for the comparison of treatment with atezolizumab versus nintedanib+docetaxel of £1,170,793 per QALY gained.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Section 3.1 of the company submission (CS[1]) includes an overview of non-small cell lung cancer (NSCLC). Section 3.2 of the CS includes a description of the effects of the disease on patients, carers and society. Key points from these sections of the CS are included as bulleted items in Box 1 and Box 2. The Evidence Review Group (ERG) considers that these points appropriately summarise the underlying health problems.

Box 1 Company overview of NSCLC

- Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (n=46,403) in 2014. It is responsible for 22% of all cancer deaths in the UK, making it the most common cause of cancer death. Around 35,900 people died of lung cancer in the UK in 2014. One in 13 men and 1 in 17 women will be diagnosed with lung cancer during their lifetime.
- Lung cancer is classified based upon its histology and can be broadly divided between small cell lung cancer and NSCLC. NSCLC represents approximately 85% of all lung cancer cases and includes several subtypes.
- Two subtypes are squamous and non-squamous histologies, with adenocarcinoma accounting for 96% of non-squamous cases.
- It has been observed the population with squamous disease suffers significantly poorer overall survival than the population with non-squamous disease.
- Early diagnosis of NSCLC is difficult as, at this stage, the disease is often asymptomatic, and symptoms of late-stage or advanced disease are non-specific. As a result, the majority of patients with lung cancer are initially diagnosed with disease that is already locally advanced or metastatic.
- NSCLC is staged according to the TNM classification, based on the primary tumour size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastases (M). This information is combined to assign an overall stage of 0, I, II, III, or IV. This submission focuses on locally advanced and metastatic NSCLC, i.e. unresectable Stage IIIA, Stages IIIB and IV.
- The discovery of the EGFR mutations and rearrangements of the ALK gene have led to a paradigm shift with the advancement of targeted therapies for the 10 to 20% of patients with metastatic NSCLC whose tumours harbour these oncogenic alterations.
- Disease progression is still inevitable in the majority of patients treated with targeted therapies. Furthermore, patients without a mutation conferring sensitivity to a targeted agent are typically treated with chemotherapy, especially platinum-based chemotherapy, which is associated with modest treatment benefits and significant toxicities.
- There, therefore, remains an unmet need for new treatments which do not cause significant toxicity or a deterioration in quality of life and that improve survival for those patients who progress following targeted therapy and for patients ineligible for targeted therapy that relapse after first-line chemotherapy for whom docetaxel-based treatments are currently the most widely used.

ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; TNM= Tumour-Node-Metastasis
Source: CS, Section 3.1

Box 2 Company overview of the effects of NSCLC on patients, carers and society

- The symptoms of lung cancer include persistent coughing (sometimes with blood present), chest pain, shortness of breath, recurrent chest infections, weight loss and tiredness. The high symptom burden in patients with advanced NSCLC has a highly negative impact on HRQoL, well-being and on family functioning.
- Due to its severe toxicity profile, chemotherapy is often associated with various complications and diminished HRQoL in patients with lung cancer. In addition, disease progression can also have a marked impact on patients' HRQoL.
- Advanced lung cancer can have a significant impact on the emotional and social wellbeing of the patient's family. The lives of patients and their families may become centred around clinic appointments, while increasing physical limitations can lead to changes in interpersonal roles and relationships, adversely affecting family relationships.
- Lung cancer is associated with a significant burden on caregivers, which can include social isolation, psychological impairment and poorer quality of life.
- Caregivers shoulder an economic burden with higher annual indirect costs with presenteeism-related impairment (impairment while working) and overall work impairment. A modelling study estimated the mean cost of providing informal care to lung cancer patients at the end of life in England and Wales was £73m, approximately one third of the total cost of care for this patient group.
- The direct costs associated with the treatment of lung cancer place a considerable burden on healthcare budgets, especially since the diagnosis, treatment and follow-up of lung cancer predominantly occurs within secondary care.
- A recent retrospective, descriptive cohort study conducted to evaluate the direct costs of hospital care in the diagnosis and management of 3,274 lung cancer patients, using routine NHS data (costs adjusted to 2013/14 prices) estimated mean cumulative costs to be £5,852 at 90 days and £10,009 at one year. The majority of costs (58.5%) were accrued within the first 90 days, with acute inpatient costs the largest contributor at one year (42.1%).

HRQoL=health-related quality of life; NSCLC=non-small cell lung cancer
Source: CS, Section 3.2

2.2 Company's overview of current service provision

The company presents an overview of the clinical care pathway in Section 3.3 of the CS. Details include a treatment algorithm outlining the existing treatment pathway for patients with advanced or metastatic NSCLC (reproduced in Figure 1). The algorithm is based on published NICE guidelines[2] and guidance[3-15] as listed in Section 3.5 of the CS. The guidelines and guidance that were identified by the company, along with additional guidance identified by the ERG, are summarised in Section 2.4.

The anticipated positioning of atezolizumab in the pathway is for patients who have progressed on a prior chemotherapy regimen. The ERG notes that two targeted therapies (erlotinib and crizotinib) are presented as comparators in the company's algorithm. However, expert advice to the company is that targeted therapy treatment options are likely to be preferred over immunotherapy in patients with confirmed epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations.

The ERG considers that the algorithm presented by the company reflects current clinical practice and would capture the treatment pathway in the event that atezolizumab were recommended by NICE for use in the NHS.

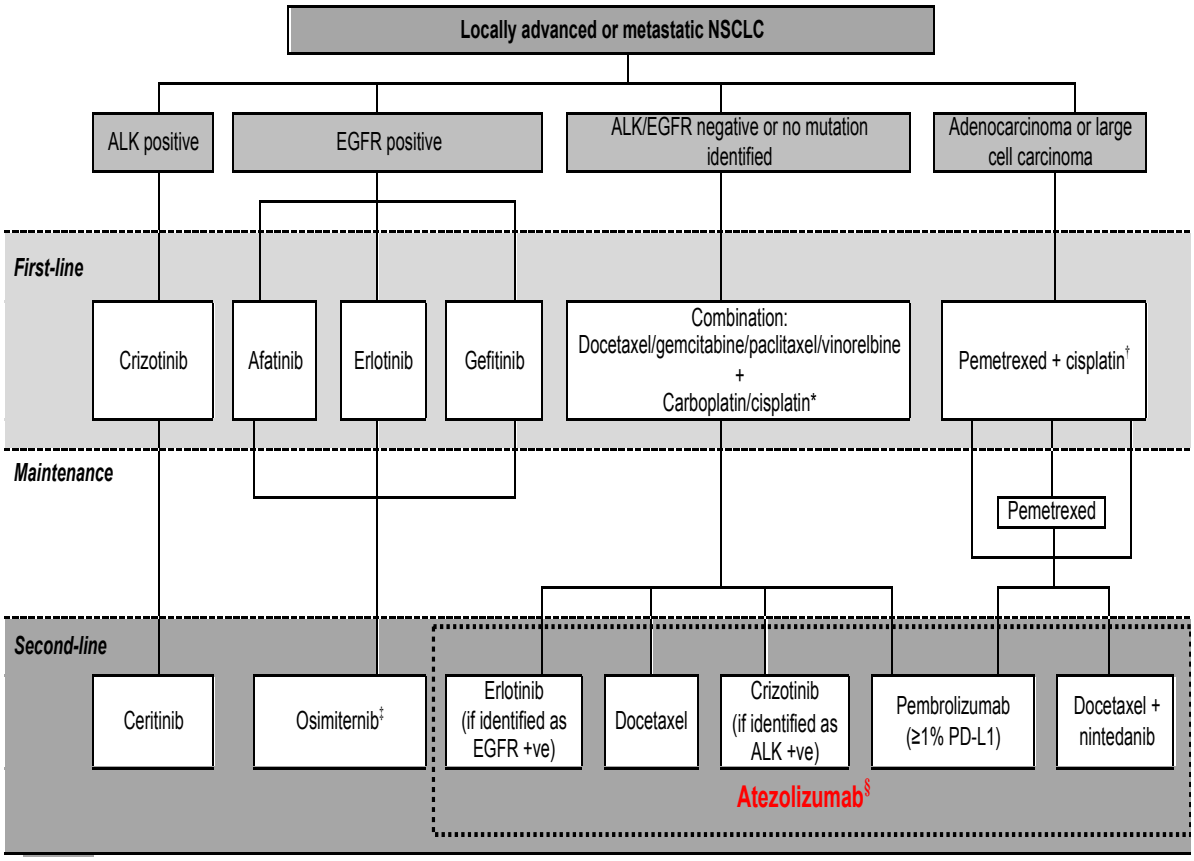

Figure 1 Treatment pathway based on NICE lung cancer clinical guideline (CG121)
§Dotted box indicates proposed position of atezolizumab based on anticipated indication
Source: CS, Figure 3

2.3 Life expectancy of people with NSCLC

The company presents information published by Cancer Research UK[16] that shows that lung cancer was the most common cause of cancer death in the UK in 2014 (approximately 35,900 deaths) and that it accounted for 22% of all cancer deaths in the UK that year. The company also provides data from a publication by Beckett et al[17] that suggest that the median survival for patients with Stage IIIb and Stage IV disease is 7.5 months and 3.4 months respectively (additional information can be found in CS, Table 9). In addition, the proportions of patients with Stage IIIb and Stage IV disease who are alive at 5 years are 7% and 3% respectively.

Table 1 Survival figures for patients with Stage IIIb/IV NSCLC and PS 0 or 1

	Chemotherapy	No chemotherapy
1-year survival	47%	25%
Median survival	11.2 months	5.3 months

PS=performance score; NSCLC=non-small cell lung cancer
Source: CS, Table 9

2.4 Summary of relevant clinical guidance and guidelines

The company provides details of relevant published guidance[3-15] and treatment guidelines[2] in Section 3.5 of the CS. NICE guidance and guidelines identified by the company and additional guidance identified by the ERG, are summarised in Table 2.

Table 2 Relevant NICE guidelines and guidance

NICE guideline or guidance	Summary of NICE recommendations
Guideline	
Lung cancer: diagnosis and management CG121[2] (2011)	• For patients with tumours of negative or unknown EGFR status and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) chemotherapy should be offered; where the chemotherapy should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) • Patients who are unable to tolerate combination therapy may be offered single-agent chemotherapy with a third-generation drug
First-line treatment	
TA181[5] (2009)	• **Pemetrexed in combination with cisplatin**: if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma
TA192[6] (2010)	• **Gefinitib**: patients whose tumours test positive for EGFR tyrosine kinase mutation
TA258[8] (2012)	• **Erlotinib**: patients whose tumours test positive for EGFR tyrosine kinase mutation
TA310[3] (2014)	• **Afatinib**: patients whose tumours test positive for EGFR tyrosine kinase mutation
TA406[12] (2016)	• **Crizotinib**: patients whose tumours test positive for ALK mutation
Maintenance treatment	
TA190[7] (2010)	• **Pemetrexed**: patients with other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel
TA402[13] (2016)	• **Pemetrexed**: patients with non-squamous disease whose disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and who have an ECOG PS 0 or 1 at the start of maintenance treatment
Second-line treatment	
TA374[9] (2015)	**Erlotinib** is an option for patients who have: • had non-targeted chemotherapy because of delayed confirmation that their tumour is EGFR-TK mutation-positive. • progressed after non-targeted chemotherapy and who have tumours of unknown EGFR-TK mutation status, but only if the result of an EGFR-TK mutation diagnostic test is unobtainable because of an inadequate tissue sample or poor-quality DNA; the treating clinician considers that the tumour is very likely to be EGFR-TK mutation-positive; and there is an observed response within the first 2 cycles of treatment.
TA395[11] (2016)	• **Ceritinib**: adults with advanced ALK positive disease who have previously received crizotinib
TA347[4] (2015)	• **Nintedanib+docetaxel**: for patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy,
TA416[14] (2016)	• **Osimertinib**: patients with EGFR T790M mutation-positive disease whose disease has progressed after first-line treatment with an EGFR-TK inhibitor (only available via the CDF)
TA422[10] (2016)	• **Crizotinib:** previously treated adults with ALK positive NSCLC (after a rapid re-review by the CDF)
TA428[15] (2017)	• **Pembrolizumab:** patients with PD-L1 positive NSCLC in adults who have had at least one prior chemotherapy (and EGFR/ALK targeted treatment, if relevant) if treatment is stopped at 2 years of uninterrupted treatment and no documented disease progression

ALK=anaplastic lymphoma kinase; CDF=Cancer Drugs Fund; ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1; TK=tyrosine kinase; WHO=World Health Organization

Other guidelines

Other relevant guidelines identified by the company (CS, Section 3.6) are:

- Lung cancer in adults: quality standards (QS17)[18]
- European Society for Medical Oncology (ESMO) Clinical Practice Guidelines, 2016[19]
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines.[20]

2.5 Innovation

The company states (CS, pp37-38) that atezolizumab:

- differs from other (anti-PD-1) antibodies approved for the treatment of NSCLC as it results in the dual blockade of PD-1 and B7.1 while leaving the PD-1/PD-L2 interaction intact, thereby potentially preserving peripheral immune homeostasis
- is anticipated to be approved for all locally advanced or metastatic NSCLC patients with prior chemotherapy, regardless of PD-L1 expression status.

The company considers that treatment with atezolizumab addresses a significant unmet need and represents a clinically significant innovative therapeutic option, which will provide significant positive impact on patients' lives.

The company highlights that a number of anti-PD-1 antibodies (e.g., pembrolizumab and nivolumab) are currently under development, along with anti-PD-L1 antibodies (e.g., atezolizumab) in a range of adult cancers. At the present time, the comparative efficacy of the two classes is unknown although the adverse events profiles are broadly similar and include immune-related effects on endocrine, neurological and pulmonary function. The role of the biomarker PD-L1 assessed by immunohistochemistry remains under development.

The ERG notes that atezolizumab is the first PD-L1 antibody to be assessed by NICE for the treatment of NSCLC (pembrolizumab and nivolumab are both PD-1 antibodies).

2.6 Number of patients eligible for treatment with atezolizumab

The company estimates that in England and Wales, approximately [redacted] patients will be eligible for treatment with atezolizumab in 2018. The company's method for calculating this number is described in the CS (Table 101, p228) and relies heavily on assumptions.

In 2014, the manufacturer of nintedanib estimated that 703 patients with locally advanced or metastatic adenocarcinoma would be eligible for second-line treatment with nintedanib+docetaxel and that there would be no population growth between 2014 and 2018.[21] The ERG, therefore, considers that the company estimate of [redacted] patients may be too high, even for the whole population.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE and that addressed within the CS is presented in Table 3. Each parameter in Table 3 is discussed in more detail in the text following the table (Section 3.1 to Section 3.7).

Table 3 Comparison between NICE scope and company decision problem

Final scope issued by NICE Parameter and specification	**Summary of a comparison between the decision problem stated in the NICE scope and addressed in the CS**
Population People with locally advanced or metastatic NSCLC whose disease has progressed after chemotherapy	Adult patients with locally advanced or metastatic NSCLC after prior (platinum containing) chemotherapy The company recognises that targeted therapies are likely to be the preferred second-line option in patients with confirmed or suspected mutations and these are excluded from the company's economic analysis (CS, Figure 3, footnote)
Intervention Atezolizumab	Atezolizumab
Comparators • Docetaxel • Nintedanib with docetaxel (for people with adenocarcinoma histology) • Nivolumab (subject to ongoing NICE appraisal) • Pembrolizumab (PD-L1-expressing tumours) • Best supportive care	**Direct evidence** • Docetaxel The OAK[22,23] and POPLAR[24,25] trials were designed to compare the clinical effectiveness of atezolizumab versus docetaxel **Indirect evidence** • Nintedanib+docetaxel The company used an indirect comparison to compare the effectiveness of treatment with atezolizumab versus nintedanib+docetaxel in the ITT populations of the OAK and POPLAR trials versus the whole population participating in the LUME-Lung 1[26] trial (nintedanib+docetaxel vs docetaxel). However, nintedanib+docetaxel is only recommended by NICE for the treatment of patients with adenocarcinoma histology **No evidence** • Nivolumab At the time of submission, nivolumab had not been recommended by NICE for the treatment of any patients with NSCLC and, therefore, could not be considered a standard of care • Pembrolizumab The company considered that: ○ the marketing authorisation for pembrolizumab is only for people with PD-L1 positive NSCLC, i.e. a sub-set of the population described in the anticipated marketing authorisation for atezolizumab ○ accurate comparison between the two treatments is not possible as different, non-comparable, PD-L1 expression tests have been used in the pembrolizumab and atezolizumab studies ○ at the time of the submission, pembrolizumab had only recently been recommended by NICE and, therefore, it was unlikely that, at this time, it would represent a standard of care • Best supportive care Clinical advice to the company is that patients eligible for treatment with atezolizumab would be considered fit enough for other treatment The ERG agrees with the company's arguments for not including nivolumab and best supportive care as comparators but considers that pembrolizumab is a relevant comparator

Final scope issued by NICE Parameter and specification	**Summary of a comparison between the decision problem stated in the NICE scope and addressed in the CS**
Outcomes OS PFS ORR AEs HRQoL	The company has presented results for all outcomes detailed in the final scope issued by NICE
Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY	Cost effectiveness has been assessed using ICERs per QALY gained
If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices	Not applicable – the anticipated marketing authorisation for atezolizumab is the whole population of patients with NSCLC
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	The model time horizon is 25 years
Costs will be considered from an NHS and Personal Social Services perspective	Costs have been considered from an NHS perspective
The availability of any patient access schemes (PAS) for the intervention or comparator technologies will be taken into account	Details relating to the PAS for atezolizumab have been provided in a confidential appendix that formed part of the CS. The PAS for nintedanib is confidential and, therefore, not known to the company. However, the ERG has re-run the company's base case analysis using the PAS price for nintedanib (see confidential appendix of this ERG report for results)
Subgroups to be considered If the evidence allows, consideration will be given to subgroups based on biological markers	The company states that clinical benefit is observed in all subgroups of patients with NSCLC who are treated with atezolizumab and that, as such, no analyses have been conducted on restricted populations
Special considerations None identified	None identified

AE=adverse event; CS=company submission; ERG=evidence review group; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; ITT=intention to treat; NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PAS=patient access scheme; PD-L1=programmed death ligand 1; PFS=progression-free survival; PSS=Personal Social Services; QALY=quality adjusted life year
Source: CS, Table 1 and ERG assessment

3.1 Population

The population described in the final scope issued by NICE is people with locally advanced or metastatic NSCLC whose disease has progressed after chemotherapy. The population discussed in the CS is the population recruited to the OAK[22,23] trial and POPLAR[24,25] trial. The ERG notes that these two populations are identical, except that the recruitment criteria for the trials specify that the population should be adults who had received a maximum of two previous chemotherapies and that prior chemotherapy should have been platinum containing.

Clinical advice to the ERG is that the clinical evidence submitted by the company is relevant to NHS patients with NSCLC whose disease has progressed following chemotherapy, except that the OAK and POPLAR trial populations are younger and fitter than those likely to be treated in the NHS.

3.2 Intervention

The intervention specified in the final scope issued by NICE, and discussed in the CS, is atezolizumab. Atezolizumab does not currently have a UK marketing authorisation. The company made an application on 20th April 2016 and anticipates receiving the Committee for Medicinal Products for Human Use (CHMP) opinion [redacted] The application is for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy.

Atezolizumab is a monoclonal antibody that binds to and inactivates a protein called PD-L1 on the surface of tumour cells (TCs) and tumour-infiltrating immune cells (ICs), inhibiting the binding to PD-1 and B7.1.[27] The company explains that atezolizumab differs from anti-PD-1 antibodies already approved for the treatment of NSCLC as it results in the dual blockade of PD-1 and B7.1 while leaving the PD-1/programmed death-ligand 2 (PD-L2) interaction intact, thereby potentially preserving peripheral immune homeostasis.[28]

The company has presented evidence for the effectiveness of atezolizumab from two trials (the OAK trial and the POPLAR trial). The randomisation protocol for both trials included PD-L1 status as a stratification factor. However, the company states that phase I data did not demonstrate a clear relationship between PD-L1 expression and response to atezolizumab (CS, p16). In view of the pathway that is blocked by treatment with atezolizumab, as part of the clarification process, the ERG asked the company to explain why atezolizumab might be effective in treating tumours that do not express PD-L1. The company provided three possible reasons (Box 3).

Box 3 Possible reasons why atezolizumab might be effective in treating tumours that are PD-L1 negative

The first is the biological hypothesis that atezolizumab increases anticancer immunity through enhanced priming of new anticancer immune responses.[23] PD-L1 is expressed on T cells and antigen presenting cells (APCs) present in the lymph nodes. Here it binds to B7.1, which is also expressed on T cells and APCs; as with PD-1 to PD-L1 interactions, this interaction can downregulate T cell activity and subsequent immune responses. Inhibition of this interaction in the lymph node environment may therefore prevent this downregulation and stimulate an immune response in tumours that are PD-L1 negative.[29,30]

The second reason is that a PD-L1 negative tumour is defined as PD-L1 expression on less than 1% expression of tumour cells (TCs) and tumour-infiltrating immune cells (ICs), i.e. TC0 and IC0. Consequently, there could still be low levels of PD-L1 expression within the tumour environment that are sufficient to induce anti-tumoural immune responses following treatment with atezolizumab.

Finally, PD-L1 expression in tumours may be heterogeneous and variable over time in a subset of tumours. This means that a biopsies taken from different areas of a tumour may show different levels of PD-L1 expression, or that the PD-L1 expression level may have changed since the biopsy was taken and may not reflect the current PD-L1 status.[31-34]

APC=antigen presenting cells; IC=immune cells PD-1=programmed death-1; PD-L1=programmed death-ligand 1; T=tumour; TC=tumour cells
Source: Company clarification letter response

The ERG highlights that the company has provided OAK trial results comparing OS for patients treated with atezolizumab versus docetaxel (CS, Section 4.7) for patients with ≥1% (TC1/2/3 or IC1/2/3) PD-L1 expression (HR 0.74, 95% CI: 0.58 to 0.93; p=0.0102). Furthermore, OAK trial OS results by level of PD-L1 expression are in the public domain.[23] The ERG, therefore, considers that the company should have presented clinical and cost effectiveness results within the CS, or justified their absence.

Atezolizumab is currently being assessed by NICE for the treatment of locally advanced or metastatic urothelial carcinoma[35] (company submission: 18 January 2017) and is already available in the UK for patients with this condition under the Early Access to Medicines Scheme (EAMS). In October 2016 the US Food and Drug Administration (FDA)[36] approved atezolizumab for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. Regulatory approval for this indication has also been received in Kuwait and South Korea.

The treatment regimen for atezolizumab is a flat dose of 1200mg intravenous infusion administered in a hospital setting every 3 weeks (Q3W). The initial dose must be administered over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be administered over 30 minutes. It is stated within the draft Summary of Product Characteristics[1] (SmPC) that patients should be treated with atezolizumab until loss of clinical benefit or unmanageable toxicity.

3.3 Comparators

The comparators specified in the final scope issued by NICE are docetaxel, nintedanib+docetaxel, pembrolizumab, nivolumab and best supportive care (BSC).

3.3.1 Included comparators

Docetaxel

Direct evidence is available for the comparison of the effectiveness of atezolizumab versus docetaxel from the OAK and POPLAR trials. The company states that docetaxel monotherapy is regarded as the standard of care in the NHS for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy. The ERG, however, notes that nintedanib+docetaxel is a standard of care for the subgroup of patients with NSCLC of adenocarcinoma histology.

Docetaxel is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy.[37] Within the OAK and POPLAR trials, docetaxel 75mg/m^2 is administered intravenously on day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity. Clinical advice to the ERG is that, within the NHS, patients typically only receive between four and six cycles of treatment.

Nintedanib+docetaxel

Treatment with nintedanib+docetaxel is recommended by NICE as an option for treating locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy.[38]

In the absence of direct evidence to allow a comparison of the effectiveness of treatment with atezolizumab versus nintedanib+docetaxel, the company undertook an indirect treatment comparison (ITC). The company states that, to allow for a like-with-like comparison versus atezolizumab according to its anticipated licence, the ITC used data from the intention to treat (ITT) populations of the OAK, POPLAR and LUME-Lung-1[26] trials. However, the ERG notes that treatment with nintedanib+docetaxel is only licensed[39] (and recommended by NICE[40]) for the treatment of patients with adenocarcinoma and that results from the LUME-Lung 1 trial show that treatment with nintedanib+docetaxel results in better PFS and OS outcomes for the population with adenocarcinoma histology than for the whole LUME-Lung 1 trial population. The ERG, therefore, considers that the relevance of the indirect comparison undertaken by the company is limited as the comparison undertaken by the company underestimates the efficacy of nintedanib+docetaxel in the NHS patient population for which it is recommended. A full critique of the company's ITC can be found in Section 4.6 of this report.

3.3.2 Excluded comparators

Nivolumab

The ERG agrees with the company that nivolumab is not a relevant comparator. This is because, at the time the CS was sent to NICE, nivolumab had not been recommended by NICE as a treatment for the population under consideration in this appraisal. However, the ERG notes that at the time of submitting the ERG report to NICE (April 2017), two STAs considering the use of nivolumab for the treatment of locally advanced or metastatic NSCLC were on-going, one for patients with squamous disease (ID811)[41] and the other for patients with non-squamous disease (ID900).[42]

Pembrolizumab

The ERG notes that, in the CS (Figure 2) the company has placed pembrolizumab in the same position in the treatment pathway as atezolizumab. In addition, the company highlights that the European marketing authorisation for pembrolizumab is similar to the anticipated European marketing authorisation for atezolizumab in that both are targeted at adults with locally advanced or metastatic NSCLC who have received at least one prior chemotherapy treatment. However, pembrolizumab is only recommended by NICE[15] for the treatment of people with PD-L1 positive NSCLC. The company considers that this discrepancy means that a comparison of the effectiveness of treatment with atezolizumab versus pembrolizumab would not be meaningful as the relative clinical benefits of treatment with pembrolizumab would be overestimated. The ERG considers that, as results from the OAK trial (CS, p81) show that treatment with atezolizumab versus docetaxel was associated with a similar improvement in OS in the ITT population (hazard ratio [HR] 0.73, 95% CI: 062 to 0.87; p=0.0003) and in patients with ≥1% (TC1/2/3 or IC1/2/3) PD-L1 expression (HR 0.74, 95% CI: 0.58 to 0.93; p=0.0102), the company's argument is not compelling.

The company also highlights that, in studies of the effectiveness of atezolizumab and pembrolizumab, the tools used to assess PD-L1 expression differ significantly, both in how expression is measured (atezolizumab: TC and IC, pembrolizumab: TC only) and also in terms of which patients are considered positive expressors. The company considers that this means that even a subgroup analysis of PD-L1 positive patients would not be appropriate. As part of the clarification process the ERG requested an explanation from the company as to how the two tests differ. The response provided by the company focused on the differences in terms of detection antibody, immunohistochemistry (IHC) platform, cell types scored (TC and IC versus TC) and cut-off points. However, the company states (CS, p49) that analyses of data from the OAK trial showed a statistically significant and clinically meaningful improvement in OS when treatment with atezolizumab was compared with docetaxel in patients with ≥1% PD-

L1 expression (HR 0.74, 95% CI: 0.58 to 0.93, p=0.012) and, in the clarification response, the company explained that TC1/2/3 or IC1/2/3 was defined as PD-L1 expression of 1% or more of TCs or ICs. It, therefore, appears that the company considers that it is possible to compare the output measures from the two tests used to determine level of PD-L1 expression

In addition, the company highlights that pembrolizumab has only recently been recommended by NICE[15] for use in patients with NSCLC (guidance issued 11th January 2017) and, therefore, considers it unlikely to represent a standard of care at this time (February 2017). The ERG considers that while there may not have been wide use of pembrolizumab within the NHS at the time of the CS, it is likely to have become an established option by the time the final appraisal determination (FAD) for this appraisal of atezolizumab is published. The ERG, therefore, does not find this line of argument compelling.

The ERG considers that it is difficult accept the company's argument that a difference in marketing authorisations/study populations is a barrier to undertaking a comparison between atezolizumab and pembrolizumab. In addition, the ERG highlights that the company has included nintedanib+docetaxel as a comparator even though this treatment is only recommended by NICE for the population with adenocarcinoma histology.

The ERG considers that pembrolizumab is an appropriate comparator, but only for the population for which it is currently recommended by NICE, i.e., patients whose tumours express PD-L1 (≥1%) and who have had at least one prior chemotherapy regimen (and targeted treatment if they have an EGFR- or ALK-positive tumour).

Best supportive care

Clinical advice to the company is supported by clinical advice to the ERG, namely that patients who are eligible for treatment with atezolizumab would be fit enough for other treatments and, therefore, BSC is not an appropriate comparator.

Erlotinib and crizotinib

Erlotinib and crizotinib were not included in the final scope issued by NICE but they are included in the company's treatment pathway algorithm (CS, p46). However, clinical advice to the company is that targeted therapy treatment options are likely to be preferred over immunotherapy in patients with confirmed EGFR or ALK mutations. The ERG considers that as the prevalence of EGFR and ALK oncogenic alterations are low (EGFR: 10% to 28%[43] of patients with NSCLC; ALK: approximately 3.4%[12] of the non-squamous population), and as EGFR and ALK testing is now routinely carried out in the NHS, very few patients are likely to receive erlotinib or crizotinib after prior chemotherapy. In addition, there is no evidence to allow

a direct comparison of the effectiveness of atezolizumab with either erlotinib or crizotinib. The ERG, therefore, agrees with the company that it was appropriate not to include either erlotinib or crizotinib as comparators.

3.4 Outcomes

Clinical evidence from the OAK and POPLAR trials is reported for all five outcomes specified in the final scope issued by NICE: (investigator assessed) progression-free survival (PFS), overall survival (OS), objective response rate (ORR), i.e. proportion of patients achieving best overall response of partial response (PR) or complete response (CR), adverse events (AEs) of treatment and health-related quality of life (HRQoL).

The ERG notes that duration of response (DOR; interval between first documented objective response [CR or PR] and first documented progressive disease) was also a secondary endpoint of both the OAK and POPLAR trials.

3.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 25-year time-period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

3.6 Subgroups

It is specified within the final scope issued by NICE that, if evidence allows, consideration will be given to subgroups based on biological markers. Within the CS, the company has provided OS results from the OAK trial by demographic (sex and age) and baseline prognostic characteristics:

- Eastern Cooperative Oncology Group (ECOG) PS
- prior lines of chemotherapy
- smoking history
- prior metastases (OAK trial: central nervous system metastases, POPLAR trial: liver metastases and bone metastases)
- mutational status (Kirsten rat sarcoma [KRAS] and EGFR)
- histology (squamous and non-squamous).

Efficacy was also evaluated by level of PD-L1 expression but results are only presented in the CS from the OAK trial for the comparison of the effectiveness of treatment with atezolizumab versus docetaxel for patients with no measurable PD-L1 expression (TC0/IC0) and for patients with ≥1% PD-L1 expression (CS, p16). However, results have been presented for four PD-L1

subgroups (TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3 and TC0 and IC0) in a published paper.[23]

3.7 Other considerations

The company did not identify any equity or equality issues. Details relating to the patient access scheme (PAS) for atezolizumab have been provided by the company in a confidential appendix that formed part of the CS. A PAS is also in place for nintedanib. Both PAS prices are confidential and, therefore, the PAS price for nintedanib is not known to the company. However, the ERG has re-run the company's base case analysis using the PAS price for nintedanib (see confidential appendix to this ERG report for results).

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

The company carried out a systematic search of the literature in June 2016 to identify phase II-IV randomised controlled trials (RCTs) investigating the efficacy and safety of pharmacological interventions for second- and further-line treatment for locally advanced or metastatic NSCLC. The purpose of the review was to identify studies to include in the company's ITC, which was conducted to support pricing and reimbursement submissions across all markets, and included comparators not listed in the final scope issued by NICE.

The data sources searched and the time spans for the searches are provided in Table 4, while a summary of, and ERG comments on, the review methods used by the company are presented in (Table 5).

Table 4 Data sources for the clinical systematic review

Search strategy component	Source	Search date range	
		Start	End
Electronic database searches	EMBASE	1988	Not provided
	MEDLINE	1946	
	MEDLINE In-Process	1946	
	Cochrane Central Library of Controlled Trials (CENTRAL)	January 2012	June 2016
	Cochrane Database of Systematic Reviews (CDSR)		
Congress proceedings	American Society of Clinical Oncology (ASCO) European Society for Medical Oncology (ESMO) International Association for the Study of Lung Cancer (IASLC)/World Conference on Lung Cancer (WCLC) International Lung Cancer Congress (ILCC) European Lung Cancer Conference (ELCC) British Thoracic Oncology Group (BTOG)	1 January 2013	17 June 2016
Clinical trial registries	ClinicalTrials.gov	1 January 2012	21 July 2016
	WHO's meta-registry 'International Clinical Trials Registry Platform Search Portal' (ICTRP)		
	EU Clinical Trial Registry	1 January 2012	30 August 2016

Source: CS, pp50-51

Table 5 Summary of, and ERG comment on, company systematic review methods

Review method	Results	ERG comment
Searching		
Sources searched: • Electronic databases • Congress proceedings • Clinical trial registries	22,502 studies	• The searches were completed in summer 2016, meaning that there is a risk that some relevant studies will not have been included in the search results • The search terms were relevant but could have been expanded regarding the search terms relating to cancer • The searches only included population terms and not indication terms
Formal eligibility criteria		
Two analysts independently assessed study eligibility based on the criteria presented in Table 10 of the CS (pp52-54)	303 studies	• Use of two independent assessors improves the quality of reviews • The high number of results from the initial search tests the concentration of reviewers
Additional eligibility criteria		
1. Although no language restrictions were included in the search strategies, the company excluded Asian language publications at the data extraction stage due to the extra complexity associated with translating these articles and the limited relevant additional data these would provide 2. Based on input from clinical experts, studies that compared investigational interventions and interventions that have not yet been labelled/approved for treating NSCLC in Europe or the USA were excluded 3. Based on further expert input, erlotinib combination arms were also excluded	38 Asian articles were excluded, leaving 265 publications from 184 different studies 49 RCTs 19 RCTs reporting 16 active treatments	• The need to employ two further sets of eligibility criteria highlights the very un-focused nature of the original searches undertaken by the company
Quality assessment		
The company conducted a quality assessment exercise using the minimum criteria recommended by NICE in the company submission template. The company applied guidance from the Cochrane Handbook of Systematic Reviews to assess each of the criteria. The results of the company assessment of the OAK and the POPLAR trials are presented in the CS. The results of the assessment of the RCTs included in the company's ITC are presented in Appendix 4 of the CS.		

CS=company submission; ERG=Evidence Review Group; NSCLC=non-small cell lung cancer; RCT=randomised controlled trial
Source: CS, pp55-56 and pp96-97

4.1.1 Evidence synthesis

The company presents direct evidence to support the clinical efficacy of atezolizumab from two RCTs (the OAK trial and the POPLAR trial). The CS includes a narrative description of both of these trials. No evidence synthesis was undertaken.

4.2 ERG critique of direct clinical effectiveness evidence

4.2.1 Identified trials

Key trials: the OAK and POPLAR trials

The company presents evidence for the clinical effectiveness of atezolizumab from the OAK (phase III) and POPLAR (phase II) trials. Both are open-label multicentre RCTs that were designed to investigate the efficacy and safety of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC whose disease had progressed during or following a platinum-containing regimen. Patients were randomised to receive either: atezolizumab 1200mg Q3W or docetaxel 75mg/m^2 Q3W. Details relevant to the OAK and POPLAR trials are reported in the CS, in the trial clinical study reports (CSRs[22,24]) and in published papers.[23,25] Details of these trials have also been presented at a number of conferences.[44-48]

Other trials

The clinical development programme of atezolizumab in NSCLC included two single-arm phase II studies, BIRCH[49] (study GO28754) and FIR[50] (study GO28625). The company states that these trials have not been discussed in the CS as the patient populations in both trials had PD-L1 positive disease and, therefore, are not relevant to this appraisal.

The ERG is not aware of any trials that directly compare the clinical effectiveness of atezolizumab with any of the comparators, other than docetaxel, as per the final scope issued by NICE.

4.2.2 Key characteristics of the OAK and POPLAR trials

The key characteristics of the OAK and POPLAR trials are provided in the CS (pp58-77) and are summarised in Table 6.

Eligibility criteria for entry into the OAK and POPLAR trials were provided by the company (CS, pp61-63). Clinical advice to the ERG is that the eligibility criteria are reasonable. The OAK and POPLAR trials were conducted internationally (in 31 and 13 countries respectively). The OAK trial included eight UK sites (31 patients) and the POPLAR trial included four UK sites (11 patients). Patients were randomly assigned (1:1) to receive either atezolizumab or docetaxel using an interactive voice or web response system. Randomisation was stratified by previous lines of chemotherapy (one versus two) and histology (non-squamous versus squamous). In addition, randomisation was stratified by PD-L1 IC status (four categories: IC0, IC1, IC2, and IC3). The ERG notes that an exploratory objective of the OAK and POPLAR trials was the evaluation of the relationship between PD-L1 expression and measures of efficacy.

Table 6 Key characteristics of the OAK and POPLAR trials

	OAK trial	POPLAR trial
Location	International (31 countries, 194 centres, including 8 in the UK [31 patients])	International (13 countries, 61 centres, including 4 in the UK [11 patients])
Design	Randomised (1:1), phase III, open-label	Randomised (1:1), phase II, open-label
Population	Primary population: a total of 825 patients were randomised, 425 to the atezolizumab arm and 425 to the docetaxel arm Secondary population: following the interim analysis of data from the POPLAR trial, the population size was increased to ensure at least 220 patients with PD-L1 TC3 or IC3 (assuming a 20% prevalence) were enrolled. In total, 1225 patients were randomised (614 to the atezolizumab arm and 611 to the docetaxel arm)	A total of 287 patients were randomised, 143 patients to the docetaxel arm and 144 patients to the atezolizumab arm
Intervention	Atezolizumab (1200mg Q3W) was administered as long as patients experienced a clinical benefit as assessed by an investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression	Atezolizumab (1200mg Q3W) was administered as long as patients experienced a clinical benefit as assessed by an investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression
Comparator	Docetaxel (75mg/m^2 Q3W) was administered until disease progression or unacceptable toxicity	Docetaxel (75mg/m^2 Q3W) was administered until disease progression or unacceptable toxicity
Primary outcome	Co-primary: • OS in the ITT population • OS in patients with ≥1% PD-L1 expression (TC1/2/3, IC1/2/3)	OS
Secondary outcomes	PFS, ORR and DOR	PFS, ORR and DOR
Safety endpoints	Safety and tolerability of treatment with atezolizumab compared with docetaxel	Safety and tolerability of treatment with atezolizumab compared with docetaxel
Patient reported outcomes	Data collected using: • EQ-5D-3L tool • EORTC-QLC-C30 and its lung cancer module (LC13)	Data collected using EORTC-QLC-C30 and its lung cancer module (LC13)
Duration of study	• First patient randomised: 11 March 2014 • Last patient randomised in the primary population: 28 November 2014 • Last patient randomised in the secondary population: 29 April 2015	• First patient randomised: 5 August 2013 • Last patient randomised: 31 March 2014
Data analyses	Primary analysis: clinical cut-off 7 July 2016	Interim analysis: clinical cut-off 30 January 2015 Primary analysis: clinical cut-off 8 May 2015 Updated efficacy analysis (OS and DOR): clinical cut-off 1 December 2015
Median duration of follow-up (primary analysis)	Atezolizumab: 21.4 months Docetaxel: 21.3 months	Atezolizumab: 14.8 months Docetaxel: 15.7 months

DOR=duration of response; EORTC-QLC-C30=European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30; EQ-5D-3L=EuroQol-5 Dimensions-3 Levels; IC=immune cell; ITT=intention to treat; OS=overall survival; ORR=objective response rate; PD-L1=programmed death-ligand 1; PFS=progression-free survival; PR=partial response; Q3W=every 3 weeks; TC=tumour cell
Source: CS, Section 4.3

4.2.3 Characteristics of patients enrolled in the OAK and POPLAR trials

The key baseline characteristics of patients included in the OAK and POPLAR trials are listed in Table 7. The company reports (CS, p75) that the patients enrolled in the OAK trial were predominately white (70%), male (61%) with a median age of 64 years (range 33.0-85.0 years) and an ECOG PS of 1 (63%). In addition, the majority of patients had a history of tobacco use: 67% were previous smokers and 15.0% were current smokers. Similarly, the company reports (CS, p79) that the patients enrolled in the POPLAR trial were predominantly white (78.7%), male (58.9%) with a median age of 62 years (range 36-84 years) and an ECOG PS of 1 (68.0%). The majority of patients in this trial also had a history of tobacco use: 64.5% were previous smokers and 16.0% were current smokers.

The ERG considers that patients' baseline characteristics are generally well balanced across the treatment arms. In addition, clinical advice to the ERG is that the patients recruited to the two trials can be considered to be broadly representative of patients with advanced NSCLC, treated in the NHS, albeit slightly younger and fitter.

Table 7 Demographic and baseline characteristics (ITT populations)

	OAK trial		POPLAR trial	
	Atezolizumab	**Docetaxel**	**Atezolizumab**	**Docetaxel**
N	425	425	144	143
Male n (%)	261 (61)	259 (61)	93 (64.6)	76 (53.1)
Mean months from initial diagnosis to randomisation (sd)	21.04 (21.45)	20.06 (23.0)	16.96 (15.52)	20.27 (19.66)
Age				
Age, years, median (range)	63.0 (33.0 to 82.0)	64.0 (34.0 to 85.0)	62.0	62.0
<65 years n (%)	235 (55)	218 (51)	87 (60.4)	87 (60.8)
≥65 years n (%)	190 (45)	207 (49)	57 (39.6)	56 (39.2)
ECOG PS n (%)			n=142	n=142
0	155 (36)	160 (38)	46 (32.4)	45 (31.7)
1	270 (64)	265 (62)	96 (67.6)	97 (68.3)
Histology				
Non-squamous	313 (74)	315 (74)	95 (66.0)	95 (66.4)
Squamous	112 (26)	110 (26)	49 (34.0)	48 (33.6)
Current disease status (%)				
Locally advanced	29 (7)	19 (5)	8 (5.6)	5 (3.5)
Metastatic	396 (93)	406 (95)	136 (94.4)	138 (96.5)
Number of prior therapies n (%)				
1	320 (75)	320 (75)	93 (64.6)	96 (67.1)
2	105 (25)	105 (25)	51 (35.4)	47 (32.9)
Smoking status n (%)				
Never	84 (20)	72 (17)	27 (18.8)	29 (20.3)
Current	59 (14)	67 (16)	25 (17.4)	21 (14.7)
Previous	282 (66)	286 (67)	92 (63.9)	93 (65.0)
Metastases				
Number of metastatic sites at enrolment, mean (sd)	2.89 (1.43)	2.97 (1.32)	2.97 (1.38)	3.1 (1.39)
Confirmed metastases at enrolment n (%)				
Liver	83 (20)	94 (22)	33 (22.9)	33 (23.1)
Bone	135 (32)	133 (31)	35 (24.3)	46 (32.2)
Brain	38 (9)	47 (11)	8 (5.6)	15 (10.5)
Lung	386 (91)	391 (92)	132 (91.7)	125 (87.4)
Pleural effusion	84 (20)	96 (23)	41 (28.5)	27 (18.9)
Lymph nodes	277 (65)	291 (66)		
PD-L1 expression				
TC3 or IC3, n (%)	72 (16.9)	65 (15.3)	24 (16.7)	23 (16.1)
TC2/3 or IC2/3, n (%)	129 (30.4)	136 (32.0)	50 (34.7)	55 (38.5)
TC1/2/3 or IC1/2/3, n (%)	241 (56.7)	222 (52.2)	93 (64.6)	102 (71.3)

ECOG PS=Eastern Cooperative Oncology Group performance score; IC=immune cell; PD-L1=programmed death-ligand 1; sd=standard deviation; TC=tumour cell
Source: CS, Table 24 and Table 26

4.2.4 Statistical approach adopted in the OAK and POPLAR trials

In this section, the ERG provides a description and critique of the statistical approaches used to analyse data collected during the OAK and POPLAR trials that relate to the outcomes stipulated in the final scope issued by NICE. Information relevant to the statistical approach taken by the company has been extracted from the CSRs, the trial protocols,[51,52] the trial statistical analysis plans (TSAPs),[53,54] which included a modification plan for OAK and the CS.

Determination of sample size and trial design

The original sample size of the OAK trial was calculated as 850 patients in an ITT population so that approximately 255 PD-L1 IC2/3 patients and 425 PD-L1 IC1/2/3 patients would be enrolled. Following interim analysis of the POPLAR trial (clinical cut-off date 30th January 2015) and additional data from PCD4989g[55] (phase I trial) and FIR[50] (single-arm, phase II trial), the TSAP was modified according to a pre-specified modification plan (OAK TSAP, p24 and Appendix 4). The sample size of the OAK trial was increased to approximately 1100 patients (up to a maximum of 1300) to ensure at least 220 patients with PD-L1 TC3 or IC3 status, assuming a 20% prevalence of the TC3 or IC3 subgroup, were recruited. The final enrolment in the OAK trial was 1225 patients.

Subsequently, the results from the primary analysis of the POPLAR trial (POPLAR CSR, Table 21, data cut-off 8th May 2015) showed that clinical efficacy was observed in all PD-L1 subgroups including patients with PD-L1 negative NSCLC. Therefore, assuming that the OAK trial would also show clinical efficacy in all defined subgroups based on PD-L1 expression (herein referred to as PD-L1 subgroups), the OAK trial would be fully statistically powered for OS evaluation in an ITT population with fewer than 1225 patients.

Therefore, prior to unblinding the data, the OAK trial TSAP was modified again on 28th January 2016 (OAK TSAP, p24 and Appendix 4) to conduct the analysis of OS in the OAK trial on the primary population (1°P) of the first 850 randomised patients. The data cut-off of the 1°P would occur when approximately 595 deaths had occurred, which would correspond to an estimated 384 deaths in the TC 1/2/3 or IC 1/2/3 subgroup (TSAP, p14).

If the null hypothesis for OS in the 1°P was rejected, an analysis of the secondary population (2°P) of 1225 randomised ITT patients would be performed at the secondary analysis time (OAK TSAP, Appendix 4; Section 1.1). To control the type I error rate in the evaluation of OS in the 1°P and 2°P, alpha was split between the ITT population and the TC1/2/3 or IC1/2/3 subgroup (OAK TSAP, Appendix 4; Table 2).

Treatment crossover from the docetaxel arm to the atezolizumab arm was not originally permitted in the OAK trial; however, it was subsequently allowed following the primary analysis time (CS, Section 4.7). No efficacy results for the 2°P are available at the time of writing this ERG report and the company informed the ERG that [redacted] The ERG notes that any crossover between treatment arms will potentially confound the results of the planned analysis of the 2°P.

The ERG is satisfied that the modification plan for the sample size calculation was pre-specified (final date: 21st November 2013). The ERG is also satisfied that the modifications were made before the date of primary analysis of the OAK trial (data cut-off: 7th July 2016) and were, therefore, unlikely to have been driven by the results of the trial.

The POPLAR trial was designed to enrol a minimum of 54 patients with PD-L1 IHC 2/3 NSCLC, with a maximum of 300 patients enrolled in the case that the prevalence of PD-L1 IHC 2/3 NSCLC was lower than 18%. The trial was expected to enrol 285 patients, including 55 patients with PD-L1 IHC 2/3 NSCLC. The ERG is satisfied that this sample size calculation was pre-specified (POPLAR TSAP, p7-8).

Design assumptions of the OAK and POPLAR trials are summarised in Table 8.

Table 8 OAK and POPLAR trial design assumptions

OAK trial	POPLAR trial
Event times are exponentially distributed A 7.5% 24-month dropout rate assumed for both treatment arms Over 95% power for the primary analysis of OS in the ITT population Median survival of 10 months in the docetaxel arm 65% prevalence rate for TC1/2/3 or IC1/2/3	Event times are exponentially distributed Median PFS in the control arm is 3 months Median OS in the control arm is 8 months Patients are enrolled over 8 months

IC=tumour-infiltrating immune cell; ITT=intention-to-treat; OS=overall survival, PFS=progression-free survival; TC=tumour cell
Source: CS, adapted from Section 4.4

Outcomes and analysis approach in the OAK and POPLAR trials

The primary therapeutic aims of the OAK and POPLAR trials were to reduce tumour burden, delay disease progression and ultimately prolong life. Therefore, the primary endpoint of the two trials was OS, selected to explore the impact of treatment with atezolizumab in reaching these aims. In the OAK trial, OS was measured as a co-primary endpoint in both the ITT population and in patients with ≥1% PD-L1 expression.

The company argues that PFS is a less suitable endpoint to assess the activity of immunotherapies, but includes PFS as a secondary outcome in both trials.

Definitions and methods of statistical analysis for OS and PFS are provided in Table 9. The ERG is satisfied that the analysis method for each of these efficacy outcomes was pre-specified in the TSAPs, and that all results are reported fully in the CSRs.

The ERG notes that the log-rank and Cox regression methodology employed for the analysis of OS and PFS in both the OAK and POPLAR trials require the assumption of proportional hazards (PH) for the interpretation of estimated log-rank p-values and HRs. The company demonstrates that the PH assumption does not hold for OS and PFS in either the OAK trial (CS, Figure 20 and Figure 21) or the POPLAR trial (company response to ERG clarification letter, reproduced in Section 10.1]). This violation of the PH assumption is taken into account in the statistical approach used in the ITC and also in the approach to cost effectiveness analysis (CS, Section 5.3).

The ERG notes that methodology for the analysis of OS and PFS was pre-defined in both TSAPs before the data cut-off dates in the OAK and POPLAR trials, and that violation of the PH assumption could not have been known when the TSAPs were written. However, use of HRs to summarise treatment effect of OS and PFS is not appropriate in the absence of PH; therefore, the HRs reported in the Section 4 of the CS must be interpreted with caution.

Table 9 Definition and analysis method for key efficacy outcomes (OAK and POPLAR trials)

Outcome	Outcome definition	Censoring definition	Statistical analysis[a]
Primary efficacy outcome			
OS	Time from the date of randomisation to the date of death due to any cause OAK trial: further defined in patients with a ≥1% PD-L1 expression (TC1/2/3 or IC1/2/3)	Date patient last known to be alive or at date of randomisation (plus 1 day for those without baseline information)	OAK trial: K-M methodology, log-rank test, and Cox regression, stratified in the 1°P and TC1/2/3 or IC1/2/3 subgroup POPLAR trial: K-M methodology and stratified log-rank test for ITT, unstratified log-rank test for biomarker subsets, Cox regression, stratified for ITT and unstratified for biomarker subsets
Secondary efficacy outcome			
PFS	Interval between date of randomisation and date of first documented PD per RECIST v1.1 or death	Last tumour assessment for those without PD and alive or at date of randomisation (plus 1 day for those without post-baseline assessments)	OAK trial: K-M methodology, Cox regression, stratified in the 1°P ITT population and TC1/2/3 or IC1/2/3 subgroup, unstratified for all other subgroups POPLAR trial: K-M methodology, Cox regression, stratified for ITT and unstratified for biomarker subsets

[a] The stratification factors used in analysis in both trials were those used in randomisation i.e., tumour PD-L1 status (four categories of PD-L1 IC expression), the number of prior lines of therapy (1 vs 2), and histology (non-squamous vs squamous)
1°P=primary population; IC=tumour-infiltrating immune cell; ITT=intention-to-treat; K-M=Kaplan-Meier; OS=overall survival, PD=progressive disease; PD-L1=programmed death-ligand 1; PFS=progression-free survival; RECIST=response evaluation criteria in solid tumours; TC=tumour cell
Source: CS, adapted from Table 19, Table 21 and Table 22

Objective response rate (ORR) and DOR were also secondary efficacy outcomes in both trials. For completeness, the definitions and methods of analysis of ORR and DOR are described in Section 10.1). Patient-reported outcomes (PROs) and safety endpoints were also measured in both trials. Further details of these outcomes are described in Section 4.4 and Section 4.5 respectively.

All primary and secondary outcomes measured in both trials were investigator-assessed. In their response to the clarification letter, the company confirmed that no blinded independent central review of any endpoints had been explored in either the OAK or POPLAR trials.

Analysis populations

The populations used for analyses of different outcomes of the OAK and POPLAR trials are summarised in Table 10. The ERG is satisfied that these populations were pre-defined in the TSAPs, except for the analysis populations of the PROs which are specified in the CS but not explicitly mentioned in the TSAPs. The ERG also notes a differently defined analysis population for ORR in the OAK trial in the TSAP (the analysis population of ORR will be all randomised patients with measurable disease at baseline) compared to the CS (see Table 10). The ERG is satisfied that all results are reported within the CSRs for the relevant population of each outcome.

Table 10 OAK and POPLAR trial analysis populations

Analysis	Population
Efficacy	Efficacy outcomes (OS, PFS, ORR and DOR) were analysed in the randomised (ITT) populations OAK trial: Two ITT populations were defined as follows: The primary population (1°P) was defined as the first 850 ITT patients, regardless of whether they received any trial drug The secondary population (2°P) was defined as all 1225 randomised ITT patients POPLAR trial: The ITT population was defined as all randomised patients, regardless of PD-L1 expression and whether they received any trial drug
PROs	OAK trial: The PRO evaluable population was defined as patients in the ITT population who had a non-missing baseline PRO assessment and at least one on-trial non-missing post-baseline PRO assessment POPLAR trial: The PRO evaluable population was defined as patients with a baseline PRO assessment and at least one post-treatment PRO assessment
Safety	OAK trial: Primary safety analyses were based on all 1225 randomised patients who received any dose of a trial drug during the treatment period POPLAR trial: Primary safety analyses were based on all randomised patients who received any dose of a trial drug during the treatment period

DOR=duration of response; ITT=intention-to-treat; ORR=objective response rate OS=overall survival, PD-L1=programmed death-ligand 1; PFS=progression-free survival; PRO=patient-reported outcome.
Source: CS, Section 4.4, OAK protocol and POPLAR protocol

Additional ERG assessments of the statistical approach of the OAK and POPLAR trials

A summary of the additional checks made by the ERG in relation to the statistical approach used by the company to analyse data from the OAK and POPLAR trials is provided in Table 11. Having carried out these checks, the ERG is satisfied with the statistical approach employed by the company.

Table 11 ERG assessment of statistical approach used to analyse trial data

Component	Statistical approach with ERG comments	
	OAK trial	**POPLAR trial**
Protocol amendments	Protocol amendments are provided within the CSR (p86-87) The largest amendments to the protocol were related to the sample size and statistical testing procedure of the trial (as outlined in 'Determination of sample size and analysis populations' above). This amendment was made on 28th January 2016, before the date of the primary analysis (data cut-off 7th July 2016) All other protocol amendments and rationale for amendments are outlined in detail. All amendments were made before the date of primary analysis, and so were unlikely to have been driven by the results of the trial	Protocol amendments are provided within the CSR (p91-93) All protocol amendments and rationale for amendments are outlined in detail. All amendments were made before the date of primary analysis, and so were unlikely to have been driven by the results of the trial
Subgroup analyses for OS	Subgroup analyses of OS performed in the primary population based on (CS, Section 4.4 and CSR p81): • Demographic characteristics (e.g. age, sex, ethnicity) • Baseline prognostic characteristics (e.g. PD-L1 expression subgroups, ECOG performance status, prior lines of chemotherapy, histology, smoking history) Summaries of OS, including the unstratified HR estimated from a Cox proportional hazards model and K-M estimates of median survival time, were produced separately for each level of the categorical variables The ERG is satisfied that subgroups were pre-defined in the TSAP (p20)	Subgroup analyses of OS performed based on (CS, Section 4.4 and CSR p83): • Demographic characteristics (e.g. age, sex, ethnicity) • Baseline prognostic characteristics (e.g. PD-L1 expression subgroups, ECOG performance status, prior lines of chemotherapy, histology, smoking history) Summaries of OS, including the unstratified HR estimated from a Cox proportional hazards model and Kaplan-Meier estimates of median survival time, were produced separately for each level of the categorical variables The ERG is satisfied that subgroups were pre-defined in the TSAP (p19)
Sensitivity analyses for OS	Two sensitivity analyses of OS were presented in the CSR for non-protocol anti-cancer therapy (p152-155) The ERG is satisfied that these sensitivity analyses were pre-defined in the TSAP (p20)	No sensitivity analyses were pre-specified in TSAP or presented in the CS or CSR for any analyses

Component	Statistical approach with ERG comments	
	OAK trial	**POPLAR trial**
Analysis of AEs	Many different summaries of AEs are provided in the CSR. Protocol defined adverse events of special interest (AESIs) (CS, Table 20) were summarised separately. AEs, SAEs, AESIs, and imAEs are summarised by treatment arm and grade (per NCI CTCAE v4.0). AEs, SAEs, severe AEs (Grade ≥ 3), AESIs, imAEs, and AEs leading to trial drug discontinuation or interruption are summarised separately. Additionally, AE summaries are provided by PD-L1 expression subgroups (TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3, TC0 and IC0) for each treatment arm A complete list of the different summary tables is provided on p180-241 of the CSR. Further details of AEs are presented in Section 4.7 of this report The ERG is satisfied that the methodology used to analyse the AEs is appropriate and was pre-specified in the TSAP (p21-22)	Many different summaries of AEs are provided in the CSR; AEs were summarised by treatment arms and overall in incidence tables by NCI CTCAE grade, seriousness, relationship to trial drug, AEs leading to death, trial drug discontinuation, and dose modification/interruption Protocol defined AESIs (CS, Table 20) were summarised separately. A complete list of the different summary tables is provided on p195 to 226 of the CSR. The ERG is satisfied that the methodology used to analyse the AEs is appropriate and was pre-specified in the TSAP (p20)
Analysis of PROs	Analysis of PROs is presented in the CSR (p85-86) Global health status/ HRQoL, functioning, treatment-related symptoms and lung cancer symptoms were assessed by the EORTC QLQ-C30 and LC13. All the scales and single-item measures were linearly transformed so that each score ranged from 0 to 100. Summary statistics (mean, sd, median, range and mean change from baseline (and 95% CI) of linearly transformed scores) are reported for all the items and subscales of the EORTC QLQ-C30 and the EORTC QLQ-LC13 questionnaires Time to confirmed symptomatic deterioration was also measured, defined as the time from baseline to the first time the patient's score showed a ≥ 10-point increase above baseline in any of the lung cancer symptom scores and analysed by K-M and Cox regression methodology The ERG is satisfied that the methodology used to analyse PROs is appropriate and was pre-specified in the TSAP (p23)	Analysis of PROs is presented in the CSR (p77, p90) HRQoL and lung cancer symptoms were assessed using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. All the scales and single-item measures were linearly transformed so that each score ranged from 0 to 100. Summary statistics (mean, sd, median, range and mean change from baseline (and 95% CI) of linearly transformed scores) are reported for all the items and subscales of the EORTC QLQ-C30 and the EORTC QLQ-LC13 questionnaires The ERG is satisfied that the methodology used to analyse PROs is appropriate and was pre-specified in the TSAP (p21-22)

AE=adverse event; AESI=adverse events of special interest; CI=confidence interval CS=company submission; CSR=clinical trial report; EORTC=European Organisation for the Research and Treatment of Cancer; ERG=Evidence Review Group; HRQoL=health-related quality of life; IC=tumour-infiltrating immune cell; K-M=Kaplan-Meier; NCI CTCAE=National Cancer Institute common terminology criteria for adverse events; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression-free survival; PRO=patient-reported outcome; QLQ-C30=quality of life questionnaire in cancer (30 items); QLQ-LC13=quality of life questionnaire in lung cancer (13 items); SAE=serious adverse events; sd=standard deviation; TC= tumour cell; TSAP=trial statistical analysis plan; imAEs=immune-mediated adverse events
Source: adapted from the CS, OAK CSR, POPLAR CSR, OAK TSAP, POPLAR TSAP, the company's response to the ERG clarification letter, and ERG comment

4.2.5 Risk of bias assessment for the OAK and POPLAR trials

The ERG considers that the risk of bias for the OAK and POPLAR trials is low for the of the criteria in

Table 12. However, the open-label design provides the opportunity for investigator-assessed outcomes to be biased.

An additional possible source of bias is the fact that, in both the OAK and POPLAR trials, the treatment stopping rules for patients receiving atezolizumab and docetaxel differed. Treatment with atezolizumab was administered as long as patients experienced a clinical benefit (as assessed by an investigator) in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression. Treatment with docetaxel was continued until disease progression or unacceptable toxicity.

Effectiveness evidence is immature. However, although a further analysis of OAK trial data is planned, the ERG notes that results from this analysis may be difficult to interpret as, although crossover from the docetaxel arm to the atezolizumab arm was not originally permitted in the OAK trial, it was allowed following the primary analysis of the primary population (n=850).

Table 12 Risk of bias assessment of the OAK and POPLAR trials

Study question	Company assessment		ERG comment
	OAK trial	POPLAR trial	
Was randomisation carried out appropriately?	Yes	Yes	Agree
Was the concealment of treatment allocation adequate?	N/A (open-label study)	N/A (open-label study)	Disagree that this question is N/A Patients were randomised via IVRS and therefore treatment allocation was concealed
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A (open-label study)	N/A (open-label study)	Disagree that this question is N/A The open-label nature of the trials provides an opportunity for subjective results to be biased
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	N/A (full data available)	N/A (full data available)	Only limited details by PD-L1 status are presented in the CS
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Agree

ERG=Evidence Review Group; IVRS=interactive voice response system; N/A=not applicable; CS=company submission; PD-L1=programmed death ligand 1
Source: CS, Table 27

4.3 Results from the OAK and POPLAR trials

All of the data from the OAK trial presented in this section correspond to the data cut-off date of 7th July 2016 which was the primary analysis time in the 1°P (see Section 4.2.4 for definitions of populations).

The data presented in the CS from the POPLAR trial correspond to the data cut-off date of 1st December 2015, which was the date of an updated efficacy analysis. The POPLAR trial data presented in the CSR correspond to a data cut-off date of 8th May 2015, which was the date of the primary analysis. Unless otherwise stated, POPLAR trial results presented in this section are those from the updated analysis presented in the CS.

As outlined in Section 4.2.4 of this report, the assumption of PH for the outcomes of OS and PFS were demonstrated not to be valid for either the OAK or POPLAR trials. Therefore, the ERG notes that HRs reported in this section must be interpreted with caution.

4.3.1 Participant flow in OAK and POPLAR

OAK

Within the 1°P of the OAK trial, a total of 850 participants were randomised; 425 to each treatment arm. The participant flow in the 1°P of the OAK trial is presented in Figure 6 of the CS and reasons for treatment discontinuation are provided in Table 23 of the CS. The ERG noted an error in Table 23 of the CS and, in their response to the clarification letter, the company clarified that the number of participants withdrawn from treatment with atezolizumab was 364; 316 discontinued treatment due to progressive disease, 36 due to an AE, 9 due to withdrawal by patient, 2 due to physician decision, and 1 due to "other" (the participant was randomised to receive docetaxel, but received atezolizumab in error).

The median duration of survival follow-up was 21.4 months (range 0.1 to 27.1 months) in the atezolizumab arm and 21.3 months (range 0 to 26.9 months) in the docetaxel arm at the time of primary analysis. The minimum length of follow-up in both treatment arms was 19 months (duration from last patient randomised date to clinical cut-off date).

POPLAR

A total of 287 participants were randomised; 144 participants to the atezolizumab arm and 143 participants to the docetaxel arm. The participant flow in the POPLAR trial is presented in Figure 7 of the CS and reasons for treatment discontinuation are provided in Table 25 of the CS.

The median duration of survival follow-up was 14.8 months (range 0.2 to 19.6 months) in the atezolizumab arm and 15.7 months (range 0 to 18.7 months) in the docetaxel arm at the time of primary analysis. The updated analysis provided an additional 7 months of follow-up and, at this time, the minimum length of follow-up was 20 months (duration from last patient randomised date to clinical cut-off date for updated analysis).

4.3.2 Primary efficacy outcome: overall survival

The primary outcome of both trials was OS. At the time of the primary analysis, in the OAK trial, 569 out of 850 randomised participants in the 1°P had died and, at the time of updated analysis in the POPLAR trial, 200 out of 287 randomised participants had died. OS results from the OAK and POPLAR trials are presented in

Table 13.

Table 13 OS results from the OAK and POPLAR trials

Outcome	Atezolizumab	Docetaxel
OAK trial		
Number of participants analysed	425	425
Median OS, months (95% CI)	13.8 (11.8 to 15.7)	9.6 (8.6 to 11.2)
HR (95% CI) - stratified in the 1°P and TC1/2/3 or IC1/2/3 subgroup	0.73 (0.62 to 0.87, log-rank p-value=0.0003)	
POPLAR trial		
Number of participants analysed	144	143
Median OS, months (95% CI)	12.6 (9.7 to 16.0)	9.7 (8.6 to 12.0)
HR (95% CI) – stratified for ITT population	0.69 (0.52 to 0.92, log-rank p-value=0.011)	

1°P=primary population; CI=confidence interval; IC=tumour-infiltrating immune cell; HR=hazard ratio; ITT=intention-to-treat; OS=overall survival; PD-L1=programmed death-ligand 1; TC=tumour cell
Source: CS, adapted from Section 4.7, Figure 8 and Figure 11

Results of earlier interim and primary analyses of data from the POPLAR trial are presented for completeness in (Section 10.2)

In the OAK trial, compared to docetaxel, treatment with atezolizumab was associated with a statistically significant and clinically meaningful improvement in OS in the 1°P (stratified HR 0.73, 95% CI: 0.62 to 0.87; log-rank p-value=0.0003). From Kaplan-Meier (K-M) data (CS, Figure 8), the company considers that the curves separate at around 3 months, and the benefit for atezolizumab over docetaxel is maintained thereafter.

In the POPLAR trial, compared to docetaxel, treatment with atezolizumab was also associated with a statistically significant and clinically meaningful improvement in OS in the ITT population (stratified HR 0.69, 95% CI: 0.52 to 0.92; log-rank p-value=0.011). From K-M data (CS, Figure 11), the company considers that the curves separate at around 3 months, and the benefit for atezolizumab over docetaxel is maintained thereafter, with further separation of the K-M curves at around 9 months and increased benefit shown with atezolizumab compared to docetaxel with extended follow-up (CS, Figure 12).

Overall survival according to histology and to PD-L1 status in the OAK and POPLAR trials

In the OAK trial, a statistically significant improvement in OS with treatment with atezolizumab compared to docetaxel was observed regardless of histology; however, a longer median OS was observed in atezolizumab treated patients with non-squamous NSCLC (15.6 months) compared to patients with squamous NSCLC (8.9 months). This pattern was also observed in the docetaxel arm (non-squamous: 11.2 months, squamous: 7.7 months). In line with clinical advice to the ERG, the company states that this result reflects the inherently worse prognosis of patients with squamous cancers.

Results of the OAK trial also showed statistically significant improvements in OS with treatment with atezolizumab compared to docetaxel for people regardless of PD-L1 status; for individuals with NSCLC of ≥1% PD-L1 expression (TC 1/2/3 or IC 1/2/3; stratified HR 0.74, 95% CI: 0.58 to 0.93; p=0.0102) and for individuals with NSCLC of no measurable PD-L1 expression (TC0/IC0; HR 0.75, 95% CI: 0.59 to 0.96; p=0.0205). Results for OS according to histology and according to PD-L1 status subgroups are presented in Table 14. Additionally, results for OS according to individual TC or IC expression levels are presented in Figure 18 of the CSR for the OAK trial.

Primary and updated analysis results for OS in the POPLAR trial, according to histology and according to PD-L1 status are presented in Section 10.3. Results of the POPLAR trial showed a statistically significant improvement in OS with atezolizumab compared to docetaxel in patients with non-squamous NSCLC but no statistically significant difference between treatment arms for patients with squamous NSCLC, despite separation of survival curves over time. Results from the POPLAR trial also show a statistically significant improvement for individuals with NSCLC of ≥1% PD-L1 expression but not for individuals with NSCLC of no measurable PD-L1 expression.

Table 14 OS results in the OAK trial according to histology and to PD-L1 status

Outcome	Atezolizumab	Docetaxel
ITT population		
Number of participants analysed	425	425
Median OS, months (95% CI)	13.8 (11.8 to 15.7)	9.6 (8.6 to 11.2)
HR (95% CI) - stratified in the 1°P and TC1/2/3 or IC1/2/3 subgroup	0.73 (0.62 to 0.87, log-rank p-value=0.0003)	
Histology: non-squamous NSCLC		
Number of participants analysed	313	315
Median OS, months (95% CI)	15.6 (13.3 to 17.6)	11.2 (9.3 to 12.6)
HR (95% CI) – unstratified	0.73 (0.60 to 0.89, log-rank p-value=0.0015)[a]	
Histology: squamous NSCLC		
Number of participants analysed	112	110
Median OS, months (95% CI)	8.9 (7.4 to 12.8)	7.7 (6.3 to 8.9)
HR (95% CI) – unstratified	0.73 (0.54 to 0.98, log-rank p-value=0.0383)[a]	
PD-L1 subgroup: TC3 or IC3		
Number of participants analysed	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI) – unstratified	[redacted]	
PD-L1 subgroup: TC2/3 or IC2/3		
Number of participants analysed	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI) – unstratified	[redacted]	
PD-L1 subgroup: TC2/3 or IC2/3 excluding TC3 or IC3		
Number of participants analysed	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI) – unstratified	[redacted]	
PD-L1 subgroup: TC1/2/3 or IC1/2/3		
Number of participants analysed	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI) – stratified for PD-L1 status	[redacted]	
PD-L1 subgroup: TC1/2/3 or IC1/2/3 excluding TC2/3 or IC2/3		
Number of participants analysed	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI) – unstratified	[redacted]	
PD-L1 subgroup: TC0/IC0		
Number of participants analysed	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI) – unstratified	[redacted]	

[a] The company state that p-values for histology subgroups are presented for descriptive purposes only
1°P=primary population; CI=confidence interval; HR=hazard ratio; IC=tumour-infiltrating immune cell; ITT=intention-to-treat; NE=not evaluable; NR=not reported; NSCLC=non-small cell lung cancer; OS=overall survival; PD-L1=programmed death-ligand 1; TC=tumour cell
Source: CS, adapted from Section 4.7, Section 4.8, Figure 8 and Figure 14; OAK trial CSR, adapted from Table 23, Table 33, Table 34 and Figure 14

Overall survival according to baseline characteristics in the OAK and POPLAR trials

Subgroup analyses were also performed in both the OAK and POPLAR trials based on demographic characteristics (e.g. age, sex, ethnicity) and baseline prognostic characteristics (e.g. PD-L1 expression subgroups, ECOG PS, prior lines of chemotherapy, histology, smoking history).

Figure 15 and Figure 18 of the CS show results of OS according to these demographic and baseline characteristics in the OAK and POPLAR trials respectively. The company states that improvement in OS with atezolizumab compared with docetaxel is consistent across baseline characteristics and highlights the result for participants with central nervous system (CNS) metastases in the OAK trial (HR 0.54, 95% CI 0.31 to 0.94; OAK CSR, Figure 20). The ERG generally agrees with the company's interpretation of these subgroup analyses but notes that improvement with atezolizumab does not seem to be consistent in the subgroup of patients with positive NSCLC EGFR mutation in the OAK trial (HR 1.24, 95% CI 0.71 to 2.18; OAK CSR, Figure 20). The ERG also notes that the findings of these subgroup analyses should be treated with caution, due to small numbers of patients included in some of the subgroups, such as CNS metastases, EGFR and KRAS mutation subgroups, leading to wide CIs around subgroup-specific HRs.

4.3.3 Secondary efficacy outcome: progression-free survival

A secondary efficacy outcome of both the OAK and POPLAR trials was investigator-assessed PFS per response evaluation criteria in solid tumours (RECIST) v.1.1. OAK and POPLAR trial PFS results are presented in Table 15.

Table 15 Investigator-assessed PFS results in the OAK and POPLAR trials

Outcome	Atezolizumab	Docetaxel
OAK trial		
Number of participants analysed	425	425
Median PFS, months (95% CI)	2.8 (2.6 to 3.0)	4.0 (3.3 to 4.2)
HR (95% CI) - stratified in the 1°P and TC1/2/3 or IC1/2/3 subgroup	0.95 (0.82 to 1.10, log-rank p-value=0.4928)	
POPLAR trial		
Number of participants analysed	144	143
Median PFS, months (95% CI)	2.7 (2.0 to 4.1)	3.4 (2.8 to 4.1)
HR (95% CI) – stratified for ITT population	0.92 (0.71 to 1.20, log-rank p-value=0.556)	

1°P=primary population; CI=confidence interval; HR=hazard ratio; IC=tumour-infiltrating immune cell; ITT=intention-to-treat; PD-L1=programmed death-ligand 1; PFS=progression-free survival; TC=tumour cell
Source: CS adapted from Section 4.7, Figure 9 and Figure 13

Results from earlier interim and primary analyses of the POPLAR trial are presented for completeness in Section 10.4.

There was no statistically significant difference in investigator-assessed PFS between atezolizumab and docetaxel in the OAK trial (Table 15) or in any of the analyses of the POPLAR trial (Section 10.3). The company states that this is consistent with the known profiles and mechanism of action of immunotherapies.

The ERG notes numerical inconsistency in the investigator-assessed PFS results from the OAK trial. Specifically, the stratified HR and log-rank p-value indicate no statistically significant difference between treatments, but the 95% CIs of median PFS do not overlap, suggesting a potentially longer median PFS for patients treated with docetaxel (4.0 [95% CI: 3.3 to 4.2] months) compared to atezolizumab (2.8 [95% CI: 2.6 to 3.0] months). The ERG suggests that the apparent inconsistency between these results may be due to the use of a HR to summarise the relative treatment effect, when the PH assumption required for the interpretation of this effect measure is violated (CS, Figure 34).

The company also states that late separation of K-M curves in the updated analysis of the POPLAR trial reflects the prolonged responses seen in some atezolizumab recipients.[46]

4.3.4 Other secondary efficacy outcomes

The company reported ORR and DOR as additional secondary efficacy outcomes. These are described in Section 10.2 and Section 10.5 of this report.

4.3.5 Subsequent therapies in the OAK and POPLAR trials

OAK

The proportion of patients receiving a non-protocol anti-cancer therapy was similar in the two treatment arms (48.5% of patients randomised to atezolizumab and 45.2% of patients randomised to docetaxel; CS, Table 28). The proportion of patients receiving a subsequent cancer immunotherapy was 5% in the atezolizumab arm and 17% in the docetaxel arm. Further information about subsequent therapies is presented in Table 28 of the CS.

POPLAR

The proportion of patients receiving a non-protocol anti-cancer therapy was similar in the two treatment arms (40.3% of patients randomised to atezolizumab and 41.3% of patients randomised to docetaxel, POPLAR CSR; Table 24). No patients randomised to atezolizumab, and 5% of patients in the docetaxel arm received a subsequent cancer immunotherapy. Further information of subsequent therapies is presented in Table 24 of the POPLAR CSR.

4.4 Health-related quality of life

Three patient reported outcome questionnaires were used in the OAK and POPLAR trials to collect data on the impact of treatment with atezolizumab and docetaxel on patients' disease-related symptoms and HRQoL:

- The EQ-5D-3L[56] questionnaire
- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30[57])
- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13[58])

The company reports that completion rates in the OAK trial were consistently high over the course of treatment. Key findings from data collected using the EORTC QLC-C30/LC13 questionnaires are summarised in Section 4.4.1. The ERG describes how utility results generated from analyses of data collected using the EQ-5D-3L[56] questionnaire are used in the company model in Section 5.5.1 of this ERG report.

4.4.1 EORTC QLQ-30/LC13 results

A summary of the main EORTC-QLQC-C30/LC13[57,58] results presented by the company in the CS is provided in Table 16.

Table 16 EORTC-QLQ-C30/LC13 results

Measure	OAK trial		POPLAR trial
	Atezolizumab	Docetaxel	
Average global health status and functioning scores (i.e. physical, role, social, emotional and cognitive)	No clinically meaningful deterioration over time for both treatment arms		Patients in the atezolizumab arm did not demonstrate any clinically meaningful change (improvement or decline) on any of the subscales assessed, while patients in the docetaxel arm had a meaningful increase in alopecia
Commonly reported cancer treatment-related symptoms	Patients in the atezolizumab arm did not show clinically meaningful worsening of symptoms, while patients in the docetaxel arm demonstrated a clinically meaningful worsening in alopecia and peripheral neuropathy throughout treatment		
Chest pain: time to deterioration of patient-reported chest pain	Patients treated with atezolizumab demonstrated prolonged time to deterioration compared with patients treated with docetaxel (HR 0.72, 95% CI: 0.55 to 0.93)		There was no difference between the arms in the time to deterioration of lung cancer symptoms
Chest pain: baseline			
No chest pain	57.7%	60.6%	N/A
Other categories (not at all, a little, quite a bit, very much)	Similar proportions		N/A
Chest pain: at radiographic disease progression			
Asymptomatic	66.4%	54.2%	N/A
Clinically meaningful worsening in chest pain severity (≥10 point increase from baseline)	11.4%	25.4%	N/A

CI=confidence interval; HR=hazard ratio; N/A=not applicable
Source: CS, pp84-86 and p89

4.5 Adverse events reported in the OAK and POPLAR trials

Clinical advice to the ERG is that AEs arising from treatment with immunotherapy in patients with NSCLC require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs.

Details of the AEs experienced by patients participating in the OAK trial are presented in Section 4.12 of the CS (pp116-124). The ERG notes that the safety evaluable population of the OAK trial includes all patients randomised to the trial who received a dose of study drug (N=1187). The 1°P includes only the first 850 patients randomised to the OAK trial.

Details of AEs experienced by patients in the POPLAR trial are not presented in the CS, but are available in the CSR and the published report.[25] The company has focussed on the AE data from the OAK trial (as this trial is bigger than the POPLAR trial) and reports that the rates

of AEs experienced by patients participating in the POPLAR trial were similar to those experienced by patients in the OAK trial (Table 17). The ERG agrees with the company that the rates and types of AEs experienced by patients in both trials are similar.

The ERG notes that, with the exception of serious adverse events (SAEs), the incidence rates of all categories of AEs, in the OAK and POPLAR trials, are lower in the atezolizumab arms than in the docetaxel arms (Table 17).

Table 17 Overview of adverse events (OAK and POPLAR trials)

Category of event	OAK trial		POPLAR trial	
	Atezolizumab N=609 n (%)	Docetaxel N=578 n (%)	Atezolizumab N=142 n (%)	Docetaxel N=135 n (%)
Patients with at least one event	573 (94)	555 (96)	136 (96)	130 (96)
Treatment-related AEs	390 (64)	496 (86)	95 (67)	119 (88)
Grade 3 and 4 AEs	227 (37)	310 (54)	57 (40)	71 (53)
Treatment-related Grade 3 and 4 AEs	90 (15)	247 (43)	16 (11)	52 (39)
Grade 5 AEs	10 (2)	14 (2)	6 (4)	5 (4)
Treatment-related deaths	0 (0)	1 (0.2)	1 (1)	3 (2)
Serious AEs	194 (32)	181 (31)	50 (35)	46 (34)
AEs leading to withdrawal from treatment	46 (8)	108 (19)	11 (8)	30 (22)
AE leading to dose modification/interruption	152 (25)	210 (36)	34 (24)	44 (33)

AE=adverse event
Source: CS, Table 43

Study drug exposure in the OAK trial

The company reports (CS, p117) that the median duration of treatment for patients in the atezolizumab arm was longer than that for patients in the docetaxel arm (3.4 months and 2.1 months respectively). In addition, the median number of treatment cycles for patients in the atezolizumab arm was higher than that for patients in the docetaxel arm, six and four cycles respectively (Table 18).

Table 18 Study drug exposure in the OAK trial

	Atezolizumab (n=609)	Docetaxel (n=578)
Median treatment duration, months (range)	3.4 (0-26)	2.1 (0-23)
Treatment duration, n (%)		
0 to ≤3 months	294 (48)	351 (61)
>3 to ≤6 months	113 (19)	162 (28)
>6 to ≤12 months	77 (13)	51 (9)
>12 months	125 (21)	14 (2.4)
Median number of doses (range)	6.0 (1-38)	4.0 (1-30)

Source: CS, Table 44

Adverse events of any grade and any cause in the OAK trial

The majority of patients in the atezolizumab and docetaxel arms of the OAK trial experienced at least one AE of any grade (94% and 96%). In Table 19 of the CS, the company has provided details of the specific AEs (any grade) experienced by ≥20% of patients in the OAK trial. The ERG notes that the rates of anaemia and alopecia are substantially lower in the cohort of patients who were treated with atezolizumab than in the cohort of patients treated with docetaxel.

Table 19 Adverse events (any grade) reported by ≥20% of patients (OAK trial)

Adverse event	Atezolizumab (n=609) n (%)	Docetaxel (n=578) n (%)
Nausea	108 (18)	131 (23)
Diarrhoea	94 (15)	141 (24)
Fatigue	163 (27)	205 (36)
Decreased appetite	143 (24)	136 (24)
Cough	141 (23)	105 (18)
Anaemia	70 (12)	136 (24)
Alopecia	3 (0.5)	202 (35)

Source: adapted from the CS, Table 45

The ERG requested (via the clarification process) details of all-cause AEs of any grade that were reported in ≥10% of patients; however, the company's clarification response included only details of treatment-related AEs of any grade that were reported in ≥10% of patients. The ERG notes that data for AEs reported by ≥10% of patients in the OAK trial are available in Table S5 of the supplementary appendix of the published report[23] of the OAK trial. The ERG is satisfied that the AEs reported in the supplementary appendix do not signal any safety concerns.

The AEs (any grade, any cause) for which there was a ≥5% difference in incidence between either of the arms of the OAK trial are illustrated in Figure 29 of the CS (p118). Adverse events

reported by a higher proportion of patients in the atezolizumab arm compared to the docetaxel arm include musculoskeletal pain (10.5% versus 4.3%) and pruritus (8.2% versus 3.1%). The company reports (CS, p118) that the majority (94%) of the musculoskeletal and pruritus events were Grade 1 or Grade 2 events and that there were no AEs for which the incidence in the atezolizumab arm was ≥10% higher than the incidence in the docetaxel arm.

Treatment-related adverse events in the OAK trial

More patients in the docetaxel arm (86%) than in the atezolizumab arm (64%) of the OAK trial experienced at least one treatment-related AE (Table 17). The company has provided details of the treatment-related AEs reported in ≥10% of patients (Table 20). The ERG notes that the incidence rates for all treatment-related AEs listed in Table 20 are higher in the docetaxel arm than in the atezolizumab arm.

The company reports (CS, p119) that compared with patients in the docetaxel arm, a lower proportion of patients treated with atezolizumab experienced Grade 3 or 4 treatment-related AEs (42.7% versus 14.8%). The Grade 3 and Grade 4 events experienced by ≥10% of patients treated with docetaxel included: fatigue, asthenia, nausea, diarrhoea, stomatitis, alopecia, anaemia, neutropenia, febrile neutropenia, peripheral neuropathy, decreased appetite, and myalgia. The single Grade 3 and 4 event reported in the atezolizumab arm was fatigue.

Table 20 Treatment-related AEs (any grade) in ≥10% of patients (OAK trial)

Adverse event	Atezolizumab (n=609) n (%)	Docetaxel (n=578) n (%)
Alopecia	3 (0.5)	198 (34)
Fatigue	87 (14)	177 (31)
Decreased appetite	52 (9)	116 (20)
Anaemia	24 (4)	114 (20)
Nausea	53 (9)	112 (19)
Diarrhoea	47 (8)	109 (19)
Asthenia	51 (8)	96 (17)
Neutropenia	7 (1)	85 (15)
Myalgia	21 (3)	81 (14)
Febrile neutropenia	0	61 (11)
Stomatitis	13 (2)	59 (10)
Peripheral neuropathy	6 (1)	58 (10)

Source: CS, Table 46

Serious adverse events in the OAK trial

Similar rates of SAEs were reported between patients treated with atezolizumab and patients treated with docetaxel (31.9% and 31.3%). The SAEs considered by the trial investigators to be treatment-related are listed in Table 21. The ERG notes that fewer patients treated with atezolizumab experienced a treatment-related SAE (10.3% versus 17.6%).

The company also reports (CS, p123) the number of deaths due to AEs (rather than progressive disease) that occurred during the 30 days following the last study treatment. In the atezolizumab arm, 10 of 62 deaths (16.1%) were due to AEs rather than progressive disease. In the docetaxel arm, 14 of 42 deaths (33.3%) were due to AEs rather than progressive disease.

Table 21 Treatment-related SAEs reported by ≥2% of patients (OAK trial)

Adverse event	Atezolizumab (n=609) n (%)	Docetaxel (n=578) n (%)
Total number of patients with at least one event	63 (10.3)	102 (17.6)
Febrile neutropenia	0	36 (6.2)
Pneumonia	2 (0.3)	11 (1.9)
Diarrhoea	0	6 (1.0)
Pyrexia	3 (0.5)	5 (0.9)
Neutrophil count decreased	0	5 (0.9)
Anaemia	0	4 (0.7)
Pleural effusion	1 (0.2)	3 (0.5)
Vomiting	0	3 (0.5)
Dehydration	0	3 (0.5)
Neutropenia	0	3 (0.5)
Lung infection	0	3 (0.5)
Colitis	1 (0.2)	2 (0.3)
Acute kidney injury	1 (0.2)	2 (0.3)
Lower respiratory tract infection	0	2 (0.3)
Neutropenic sepsis	0	2 (0.3)
Urinary tract infection	0	2 (0.3)
Asthenia	0	2 (0.3)
Syncope	0	2 (0.3)
Pneumonitis	6 (1.0)	1 (0.2)
Hypersensitivity	3 (0.5)	0
Meningitis	3 (0.5)	0

Source: CS, Table 47

Adverse events of special interest in the OAK trial

The protocol-defined AEs of special interest (AESIs) in the OAK trial are summarised in (Table 22). The AESIs were events considered by the company to be potentially auto-immune mediated.

The company reports that the majority of AESIs in both trial arms were of Grade 1 or Grade 2 severity and that a higher rate of dermatological, hepatic and endocrine events was reported by patients treated with atezolizumab than by patients treated with docetaxel. A higher rate of neurological events was reported by patients treated with docetaxel than by patients treated with atezolizumab. The company considers the AESI profiles of atezolizumab and docetaxel are consistent with the mechanisms of action of the two drugs.

Clinical advice to the ERG is that [redacted] are difficult to treat and potentially dangerous.

Table 22 Summary of OAK trial adverse events of special interest

Adverse event	Atezolizumab (n=609) n (%)	Docetaxel (n=578) n (%)
Any AE	184 (30.2)	132 (22.8)
Grade 1	87 (14.3)	82 (14.2)
Grade 2	66 (10.8)	36 (6.2)
Grade 3	28 (4.6)	14 (2.4)
Grade 4	3 (0.5)	0
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ALT=alanine aminotransferase; AST=aspartate transaminase
Source: CS, Table 48

4.6 ERG summary and critique of the indirect evidence

The company states that the ITC was conducted to support pricing and reimbursement across a range of countries and, therefore, included several comparators (afatinib, dacomitinib, erlotinib, gefitinib, paclitaxel and pemetrexed) that are not relevant to the final scope of the present appraisal. Results presented in the CS are restricted to the relevant comparators within the UK.

The ERG has concerns about the company's approach to the ITC as the final efficacy results are adjusted for all comparators within the network, including comparators that are not included in the final scope issued by NICE (see Section 3.3 of this ERG report for further details). The ERG, therefore, as part of the clarification process, asked the company to repeat the ITC using a reduced network that included only the relevant drugs (atezolizumab 1200mg, docetaxel 75mg/m^2, nintedanib 200mg+docetaxel 75mg/m^2).

4.6.1 Trials identified for inclusion in the indirect treatment comparison

The company conducted a systematic search (see Section 4.1 of this report for further details) to identify phase II-IV RCTs investigating the efficacy and safety of pharmacological interventions for second- and further-line treatments for locally advanced/metastatic NSCLC.

Three trials (OAK, POPLAR and LUME-Lung 1 trials) that included comparators relevant to this appraisal were identified and included in the reduced network ITC. These three trials form a network (Figure 2), which enable an ITC of atezolizumab, docetaxel and nintedanib+docetaxel for the outcomes of OS and PFS to be carried out.

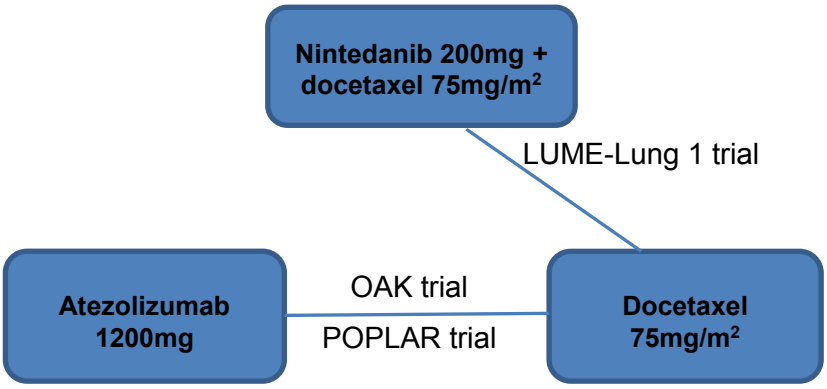

Figure 2 Network plots for ITCs of OS and PFS

For the OAK and POPLAR trials, characteristics are summarised in Table 6 of this report and an assessment of the risk of bias is provided in Section 4.2.5. Design characteristics and a risk of bias assessment for the LUME-Lung 1 trial are available in Section 10.6 and detailed

inclusion and exclusion criteria for recruitment to the LUME-Lung 1 trial can be found in Appendix 4 of the CS.

In summary, the ERG considers that design characteristics and eligibility criteria of the LUME-Lung 1 trial are similar to those of the OAK and POPLAR trials. The principal differences in design between the trials are that the LUME-Lung 1 trial is double-blinded, with nintedanib or matching placebo added to docetaxel, and the primary efficacy outcome of the LUME-Lung 1 trial is centrally assessed PFS; OAK and POPLAR are open-label trials, both with the primary efficacy outcome of OS. The company judged the LUME-Lung 1 trial to be at low risk for all domains of bias considered; the ERG agrees with this assessment.

Patient demographic and baseline characteristics of the three trials are summarised in Table 23. Further demographic and baseline characteristics of the OAK and POPLAR trials are summarised in Table 7. The ERG notes that the 'evaluable population' of the direct clinical effectiveness evidence for the OAK trial is the 1°P (the first 850 randomised participants) while the evaluable population of the OAK trial for the ITC is the 2°P (i.e. all 1225 randomised participants). Therefore, the baseline characteristics in Table 7 and in Table 23 for the OAK trial relate to different populations.

The comparability and representativeness of the OAK and POPLAR populations analysed for the direct clinical effectiveness evidence is discussed in Section 4.2 of this report. The evaluable populations of the OAK and POPLAR trials included within the ITC also have similar baseline characteristics, are balanced across treatment arms and generally are representative of patients with advanced NSCLC who are likely to be treated in the NHS, with the caveat that patients in the trials were slightly younger and fitter than NHS patients.

Table 23 Characteristics of evaluable patients

Parameter	OAK		POPLAR		LUME-Lung 1	
	Atezolizumab	Docetaxel	Atezolizumab	Docetaxel	Nintedanib+ docetaxel	Placebo+ docetaxel
Evaluable, n	613	612	144	143	655	659
Demographics						
Male, n (%)	378 (61.7)	379 (61.9)	93 (64.6)	76 (53.1)	476 (72.7)	479 (72.7)
Median age	63	64	62	62	60	60
Age <65 years, n (%)	335 (54.7)	326 (53.3)	87 (60.4)	87 (60.8)	200 (30.5)	214 (32.5)
Age ≥65 years, n (%)	278 (45.3)	286 (46.7)	57 (39.6)	56 (39.2)	455 (69.5)	445 (67.5)
Median (range) months since initial diagnosis	13.9 (2.4–285.6)	12.8 (2.3–215.0)	12.3 (2.3–114.3)	13.5 (3.4–115.7)	8.8 (5.4–13.6)[a]	8.6 (5.4–13.6)[a]
Ethnicity, n (%)						
White	438 (71.5)	432 (70.6)	110 (76.4)	116 (81.1)	533 (81.4)	530 (80.4)
Black	11 (1.8)	16 (2.6)	3 (2.1)	4 (2.8)	4 (0.6)	5 (0.8)
Asian	124 (20.2)	125 (20.4)	23 (16.0)	13 (9.1)	116 (17.7)	123 (18.7)
Other or unknown	11 (1.8)	12 (2.0)	8 (5.5)	10 (7.0)	2 (0.3)	1 (0.2)
Smoking history, n (%)						
Current or former smoker	501 (81.7)	516 (84.3)	117 (81.3)	114 (79.7)	490 (74.8)	498 (75.6)
Current smoker	83 (13.5)	107 (17.5)	25 (17.4)	21 (14.7)	-	-
Former smoker	418 (68.2)	409 (66.8)	92 (63.9)	93 (65.1)	-	-
Never smoked	112 (18.3)	96 (15.7)	27 (18.7)	29 (20.3)	165 (25.2)	161 (24.4)
Disease stage at initial diagnosis, n (%)						
< IIIB or unknown	183 (29.9)	151 (24.7)	31 (21.5)	39 (27.3)	108 (16.5)	105 (15.9)
IIIB	68 (11.1)	87 (14.2)	25 (17.4)	14 (9.8)	148 (22.6)	146 (22.2)
IV	362 (59.0)	374 (61.1)	88 (61.1)	90 (62.9)	399 (60.9)	408 (61.9)
Histology, n (%)						
Adenocarcinoma	-	-	-	-	322 (49.2)	336 (51.0)
Large cell	-	-	-	-	25 (3.8)	16 (2.4)
Squamous cell	161 (26.3)	160 (26.1)	49 (34.0)	48 (33.6)	276 (42.1)	279 (42.3)
Other[b]	452 (73.7)	425 (69.4)	95 (66.0)	95 (66.4)	28 (4.3)	23 (3.5)
ECOG PS, n (%)						
0	221 (36.1)	234 (38.2)	46 (32.4)	45 (31.7)	187 (28.5)	189 (28.7)
1	392 (63.9)	378 (61.8)	96 (67.6)	97 (68.3)	467 (71.3)	470 (71.3)

[a] Interquartile range rather than range reported for LUME-Lung 1
[b] 'Other' defined as non-squamous in the OAK and POPLAR trials.
ECOG PS=Eastern Cooperative Oncology Group performance status
Source: CS Appendix 4, adapted from Tables 9 to 11; POPLAR CSR, Table 11 and Table 19; OAK CSR, p1586-90; Reck et al[26]

The baseline characteristics of the patients in the LUME-Lung 1 trial are also well balanced across the treatment arms. When comparing the common docetaxel control arm of the three trials the ERG notes that:

- slightly more male patients are included in the LUME-Lung 1 trial compared to the OAK and POPLAR trials (72.7% compared to 61.9% and 53.1% respectively)
- substantially more patients over the age of 65 are included in LUME-Lung 1 compared to the OAK and POPLAR trials (67.5% compared to 46.7% and 39.21% respectively)
- slightly fewer white/Caucasian patients are included in the OAK trial than the POPLAR and LUME-Lung 1 trials (70.6% compared to 81.1% and 80.4% respectively)
- slightly more current or former smokers are included in the OAK trial than the POPLAR and LUME-Lung 1 trials (84.3% compared to 79.7% and 75.6% respectively)
- the median months since initial NSCLC diagnosis was shorter in the LUME-Lung 1 trial compared to the OAK and POPLAR trials (8.6 compared to 12.8 and 13.5 respectively)
- more patients with squamous cell histology are included in the LUME-Lung 1 trial compared to the OAK and POPLAR trials (42.3% compared to 26.1% and 33.6% respectively)
- slightly fewer patients with ECOG PS of 0 are included in the LUME-Lung 1 trial compared to the OAK and POPLAR trials (28.7% compared to 38.2% and 31.7% respectively)
- disease stage at initial diagnosis was similar across all three trials.

The ERG notes that these observed differences in design and characteristics of the three trials included in the ITC should be taken into account when interpreting numerical results. However, the ERG does not consider that the majority of the observed differences would violate the assumption of transitivity required for the inclusion of these three trials in the same network.

The ERG notes that, in Europe, nintedanib+docetaxel is licensed for the treatment of patients with NSCLC adenocarcinoma. The company states that this is not consistent with the anticipated marketing authorisation for atezolizumab. To conduct a 'like-with-like' comparison, the company conducted the ITC using data from the 'total population' of the LUME-Lung 1 trial (i.e. all participants regardless of histology) and the evaluable ITT populations of the OAK and POPLAR trials (i.e. including patients with non-squamous and squamous histology).

The ERG questioned whether it was appropriate to include data in the ITC from patients in the LUME-Lung-1 trial that were not specified in the licensed population for treatment with nintedanib+docetaxel. The ERG asked the company to repeat the ITC using only the three relevant trials (reduced network) and for adenocarcinoma subgroups or non-squamous subgroups only. These results are discussed in Section 4.9.4.

4.6.2 Methodological approach to the indirect comparison

The company performed ITCs on OS and PFS as time-to-event outcomes, and OS at 12 months, ORR and TRAEs as binary outcomes. ITCs of ORR and TRAE did not contribute to the company's cost effectiveness analyses; therefore, the methods and results presented in this ERG report relate only to the ITCs of OS and PFS as time-to-event outcomes. Methodology and results for ITCs of binary outcomes are available in Appendix 4 of the CS.

The company demonstrated that the PH assumption does not hold for OS and PFS in either the OAK trial (CS, Figure 20 and Figure 21) or the POPLAR trial (see Section 10.1). The company therefore used an ITC methodology that does not rely on the PH assumption, namely one using fractional polynomial (FP) models under a Bayesian framework in WinBUGS statistical software.[59] Specifically, the company employed the method of network meta-analysis of FPs, developed by Jansen.[60]

Under the assumption of PH, the HR is represented as a single parameter (i.e. a number) that is assumed to be constant over time. This alternative approach using FPs is designed to model the hazard function with multiple parameters as a function of time, allowing the HR to change over time in the presence of non-PH. FP models of any 'order' can be fitted to time-to-event data to capture the shape of the hazard functions; 1st order FP models model time as a function with one additional parameter, 2nd order FP models model time as a function with two additional parameters, and so on. However, as the order of the FP model increases, so too does the statistical complexity required to fit the model. Therefore, the company restricted their analysis to 1st and 2nd order FP models only; a range that the company considered broad enough to model the hazard function shapes of the given example.

Fixed effects (FE) FP models were fitted in the first instance, with random effects (RE) FP models fitted subsequently, if data allowed. Five FP models were considered; two 1st order FP models (equivalent to Weibull and Gompertz models) and three 2nd order FP models, herein referred to as models 2nd order (1), 2nd order (2) and 2nd order (3). Under the Bayesian framework, uninformative prior distributions, as outlined by Jansen,[60] were used in all analyses. Further methodological details including the statistical code of the FP models are available in Appendix 4 of the CS.

ITCs were conducted with individual participant data from the OAK and POPLAR trials and survival proportions across monthly time intervals were extracted from digitalised K-M curves. A 5-year time horizon for OS and a 2.5-year time horizon for PFS were used for presenting the time-dependent results of the ITC (expected difference in survival and functional HRs).

The ERG is satisfied that the company has applied the methods described by Jansen[60] appropriately (comparing the statistical code outlined in Appendix 4 of the CS to the template statistical code provided in the Appendix of the Jansen paper[60]) and that the restriction of analyses to 1st and 2nd order FP models was justified.

The ERG notes that due to the lack of a closed loop within the network (Figure 2), the HRs (modelled as FPs) generated by the ITCs are based on indirect evidence only. Subsequently, ITC methodological assumptions of consistency of direct and indirect evidence cannot be investigated statistically. The ERG considers that the unknown validity of this consistency assumption should be taken into account when interpreting numerical results, particularly for the indirect comparison between atezolizumab and nintedanib+docetaxel, where no direct evidence exists.

The ERG notes that the company fitted five FE FP models but, within the CS, only provided numerical results for the best fitting model for OS and PFS. The best fitting model was judged by the company according to the Deviance Information Criteria (DIC) statistic and visual inspection of fitted HR functions. Furthermore, the company repeated the ITC with RE but only for the best fitting FE FP model and interpreted the presence of heterogeneity as a difference in the DIC of the FE and RE models if greater than five points. The company cites two references to support this interpretation.[61,62] The ERG agrees that these references suggest that DIC (along with the residual deviance statistic) can be used to compare the fit of FE and RE models, but cannot find any mention within these references of using a difference in DIC of at least five points to indicate that heterogeneity is present in analyses.

The ERG considers that the DIC is a measure of model fit rather than of statistical heterogeneity and that choices between FE and RE models within an ITC should be made taking into account consistency of trial designs, populations and evidence sources,[61] rather than solely on model fit. The ERG also notes that the methods employed by the company allow for estimation of a heterogeneity parameter (referred to as SD by Jansen[60]) for all RE models, and considers that this SD is a more appropriate measure of statistical heterogeneity than the DIC statistic.

As part of the clarification process, the ERG asked the company to provide ITC results for all five FP models for the network outlined in Figure 2, fitted with both FE and RE and, for the RE FP models, estimates of SD. These results are reported in Section 4.6.3.

4.6.3 Results from the company's indirect treatment comparisons using a reduced network and total trial population data

As noted at the start of Section 4.6, the ERG, as part of the clarification process, asked the company to repeat the ITCs presented in the CS using a reduced network of relevant comparators (outlined in Figure 2). All results reported in this section relate to this reduced network, not to the results relating to the larger network, as reported within the CS.

Overall survival

Results from all FP models fitted to the reduced network (outlined in Figure 2) are shown in Table 24, Figure 3 and Figure 4. The company provided further survivor plot figures as a measure of the visual fit of the survival curves from the FE FP models; these plots are available in Section 10.7.1.

In the original ITC analysis presented in the CS, the company disregards the 2nd order models based on the fitted curves showing a survival 'plateau'; in other words, the curves flattened and a proportion of participants did not experience the event during the time horizon.

From visual inspection of the survivor plots of the reduced network (see Section 10.7.1) the ERG notes that the 2nd order (2) and 2nd order (3) models do begin to flatten at around 24 months, becoming completely flat at around 48 months but the 1st order models and 2nd order model (1) all appear to be of a visually similar shape, tending toward zero by the end of the 5-year time horizon (i.e. all participants will have experienced an event after 5 years).

In the clarification response letter, the company states that for the FE FP, the Weibull model is still the best fitting model in the reduced network, according to DIC and the fitted curves. The HR functions for the Weibull FE model were provided graphically by the company and are available in Section 10.7.1.

Table 24 OS results of FP models, model fit and heterogeneity

FP model	Expected survival difference in months (95% CrI)		DIC	SD (95% CrI)
	Atezolizumab vs docetaxel	Atezolizumab vs nintedanib+docetaxel		
Weibull, FE	5.71 (3.49 to 8.03)	4.74 (2.13 to 7.60)	910.4255	NA
Weibull, RE	5.79 (-8.05 to 25.82)	4.82 (-26.37 to 28.66)	911.4979	0.368 (0.013 to 1.872)
Gompertz, FE	6.82 (3.98 to 9.77)	6.01 (2.69 to 9.26)	934.1241	NA
Gompertz, RE	6.94 (-8.69 to 27.53)	5.93 (-25.12 to 27.70)	935.3138	0.373 (0.012 to 1.838)
2nd order (1)[a], FE	6.44 (3.55 to 9.55)	5.71 (2.09 to 9.32)	837.1486	NA
2nd order (1)[a], RE	6.63 (-8.06 to 27.42)	5.56 (-25.12 to 31.03)	838.3337	0.384 (0.012 to 1.824)
2nd order (2)[b], FE	6.72 (3.54 to 10.12)	6.01 (2.06 to 9.97)	837.6918	NA
2nd order (2)[b], RE	7.15 (-9.01 to 31.12)	6.05 (-25.96 to 34.04)	839.1147	0.379 (0.011 to 1.851)
2nd order (3)[c], FE	6.79 (3.33 to 10.15)	5.84 (1.47 to 9.97)	853.9698	NA
2nd order (3)[c], RE	7.15 (-9.01 to 31.12)	6.05 (-25.96 to 34.04)	854.9049	0.365 (0.010 to 1.858)

[a] 2nd order model (1) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(log t)^2; CS, page 108
[b] 2nd order model (2) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(t); CS, page 108
[c] 2nd order model (3) corresponds to a model of the form: log hazard=beta0+beta1(t)+beta2(t*log t), CS, page 108
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; DIC=deviance information criterion; NA=not applicable OS=overall survival; RE=random effects; SD=standard deviation of the heterogeneity parameter
Source: Company response to ERG clarification letter, adapted from Figure 18, Figure 20, Figure 22, Figure 24, Figure 26, Figure 38, Figure 39, Figure 40, Figure 41, Figure 42, Table 2

The ERG suggests that according to the model fit criteria defined by the company, 2nd order model (1) could also be deemed to be the best fitting model, but notes that any judgement of model fit is subjective and that numerical results of all FE FP models are similar (Table 24, Figure 3 and Figure 4).

Table 24, Figure 3 and Figure 4 show expected difference in survival (months) according to all FP models fitted in the FE and RE ITCs. The ERG notes that across all ten models fitted, the expected difference in survival is very similar, ranging between 5.7 and 7.2 months for atezolizumab compared to docetaxel and between 4.7 and 6.1 months for atezolizumab compared to nintedanib+docetaxel. The ERG also notes that heterogeneity seems to be present in all RE FP models according to SD as defined by Jansen (i.e., SD>0).[60] The SD range is estimated to be 0.36 to 0.39 across the five RE models (Table 24). Also, compared to the FE models, the resulting 95% CrI of the expected survival difference is substantially larger and crosses the line of no effect for all five RE models (Figure 3 and Figure 4).

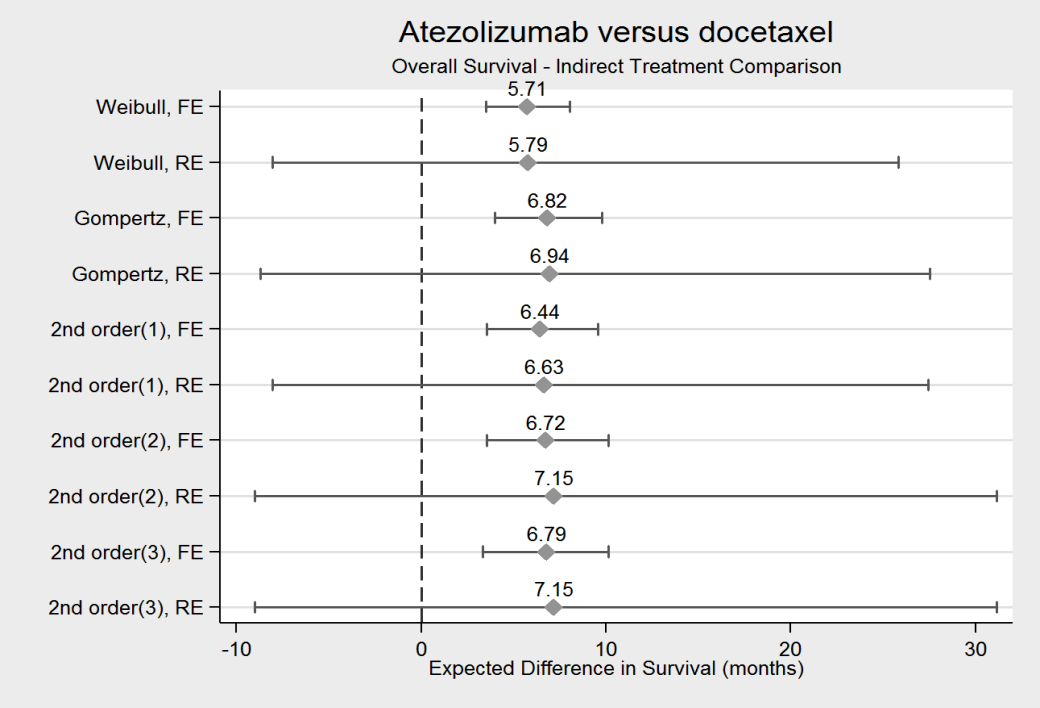

Figure 3 Results of FE and RE FP models, expected difference in OS (months) and 95% CrI for atezolizumab compared to docetaxel

See Table 10 for definitions of 2nd order models (1) (2) and (3)
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; OS=overall survival; RE=random effects
Source: Company response to ERG clarification letter, adapted from Figure 18, Figure 20, Figure 22, Figure 24, Figure 26, Figure 38, Figure 39, Figure 40, Figure 41, Figure 42

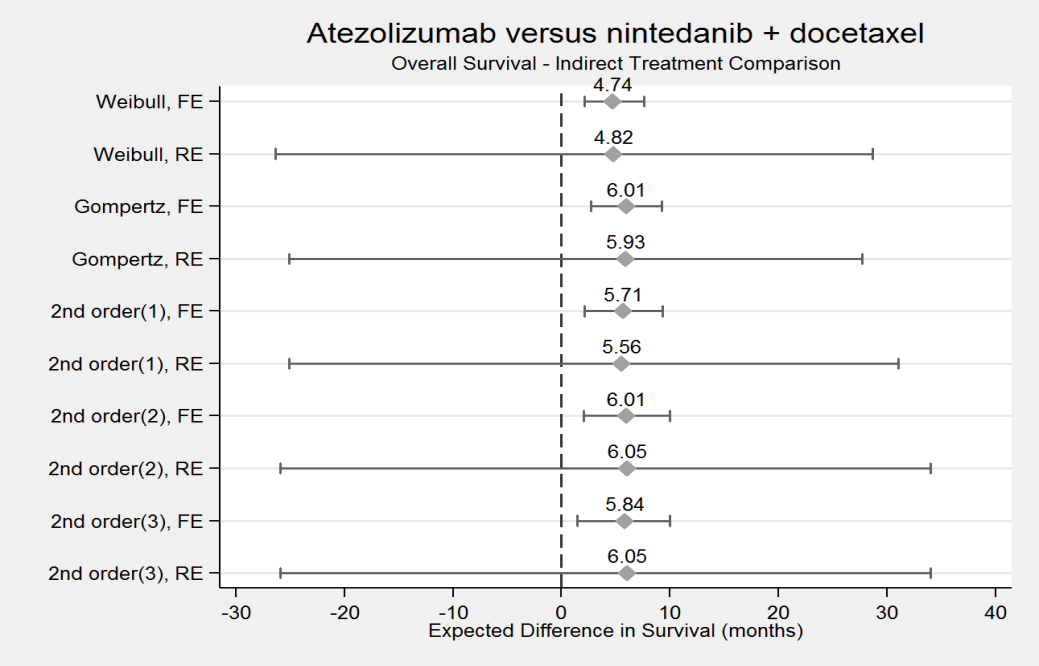

Figure 4 Results of FE and RE FP models, expected difference in OS (months) and 95% CrI for atezolizumab compared to nintedanib+docetaxel

See Table 24 for definitions of 2nd order models (1) (2) and (3)
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; OS=overall survival; RE=random effects
Source: company response to ERG clarification letter, adapted from Figure 18, Figure 20, Figure 22, Figure 24, Figure 26, Figure 38, Figure 39, Figure 40, Figure 41, Figure 42

The ERG was not provided with survivor plots for the RE FP models so was unable to visually inspect the fit of survival curves. Therefore, the ERG can only judge the fit RE models based on the DIC alone, which the ERG considers to be similar for each RE FP model fitted.

In the clarification response letter, the company states that an assessment of heterogeneity is difficult for a network as small as the reduced network and such a small network will result in RE models with wide 95% CrIs. The company considers that the model with the lowest DIC (FE or RE) depicts the best fit to the data and that the presence of heterogeneity is indicated by a difference between the model DIC scores of greater than five points. The ERG questions how, if there is no statistical heterogeneity present in the network as defined by the company (i.e. a difference in DIC of less than five points), the same model fitted with FE and RE can show a wide range of credible results. For example, when atezolizumab is compared with docetaxel, the Weibull FE model generates an expected difference in survival of 5.71 (95% CrI: 3.49 to 8.03) months while Weibull RE model generated an expected difference in survival of 5.79 (95% CrI: -8.05 to 25.82) months (Table 24).

The results suggest that the best estimate of the expected difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (compared to a median OS gain of 4.2 months and 2.9 months in the OAK and POPLAR trials from direct evidence) and around 5 to 6 months for atezolizumab versus nintedanib+docetaxel. The ERG notes that the precision and, therefore, the reliability of the ITC estimates are influenced by the choice of FP model and by potential statistical heterogeneity in the network which has not been acknowledged by the company, or accounted for in any ITC analyses.

Progression-free survival

Results from all FP models fitted to the reduced network (outlined in Figure 2) are shown in Table 25, Figure 5 and Figure 6. The company provided further survivor plot figures as a measure of the visual fit of the survival curves from the FE FP models; these plots are available in Section 10.7.2.

In the original ITC analysis described in the CS, the company disregards the 2nd order models based on visual inspection of the fitted curves. From visual inspection of the survivor plots of the reduced network (Section 10.7.2) the ERG notes that all models seem to 'plateau' at around 12 months, with the extent of the plateau being more prominent in the 2nd order models than the 1st order models.

In the clarification response letter, the company states that, within the reduced network for the FE FP, the Weibull model is the best fitting model; however, within the CS, the Gompertz

model was judged to be the best fitting model (CS, Table 34). The company provided HR functions for the Weibull FE model graphically and are available in Section 10.7.2).

Table 25 PFS results of ITC FP models, model fit and heterogeneity

FP model	Expected survival difference in months (95% CrI)		DIC	SD (95% CrI)
	Atezolizumab vs docetaxel	Atezolizumab vs nintedanib+docetaxel		
Weibull, FE	0.64 (0.01 to 1.32)	-0.30 (-1.39 to 0.70)	1123.198	NA
Weibull, RE	0.64 (-3.36 to 10.80)	-0.31 (-11.21 to 9.59)	1124.86	0.328 (0.010 to 1.832)
Gompertz, FE	0.53 (-0.12 to 1.27)	-0.43 (-1.61 to 0.66)	1157.567	NA
Gompertz, RE	0.50 (-3.30 to 9.53)	-0.42 (-12.32 to 9.03)	1159.318	0.313 (0.010 to 1.837)
2nd order (1)[a], FE	0.72 (-0.20 to 1.65)	0.77 (-1.18 to 2.15)	874.2588	NA
2nd order (1)[a], RE	0.79 (-3.83 to 11.19)	0.76 (-11.20 to 11.39)	875.9772	0.320 (0.008 to 1.838)
2nd order (2)[b], FE	0.80 (-0.12 to 1.75)	0.79 (-1.74 to 2.25)	974.306	NA
2nd order (2)[b], RE	0.78 (-4.19 to 12.53)	0.70 (-12.38 to 11.99)	975.6571	0.340 (0.012 to 1.849)
2nd order (3)[c], FE	0.88 (-0.08 to 1.90)	0.54 (-2.34 to 2.36)	1056.233	NA
2nd order (3)[c], RE	0.86 (-4.19 to 11.87)	0.49 (-13.03 to 12.35)	1057.436	0.308 (0.010 to 1.868)

[a] 2nd order model (1) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(log t)^2; CS, page 1118
[b] 2nd order model (2) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(t); CS, page 111
[c] 2nd order model (3) corresponds to a model of the form: log hazard=beta0+beta1(t)+beta2(t*log t), CS, page 111
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; DIC=deviance information criterion; NA=not applicable, PFS=progression-free survival; RE=random effects; SD=standard deviation of the heterogeneity parameter
Source: company response to ERG clarification letter, adapted from Figure 28, Figure 30, Figure 32, Figure 34, Figure 36, Figure 43, Figure 44, Figure 45, Figure 46, Figure 47, Table 3.

The ERG suggests that, according to the model fit criteria defined by the company, the 2nd order models with lower DIC values could be deemed to fit survival data better than the 1st order models, but notes that any judgement of model fit is subjective and that numerical results of all FE FP models are similar (Table 25, Figure 5 and Figure 6).

Table 25, Figure 5 and Figure 6 show expected difference in survival (months) according to all FP models using FE and RE. The ERG notes that, across all ten of the fitted models, the expected difference in PFS is similar, and not statistically significant for all except one result (Weibull FE model for atezolizumab compared to docetaxel, 0.64 [0.01 to 1.32] months).

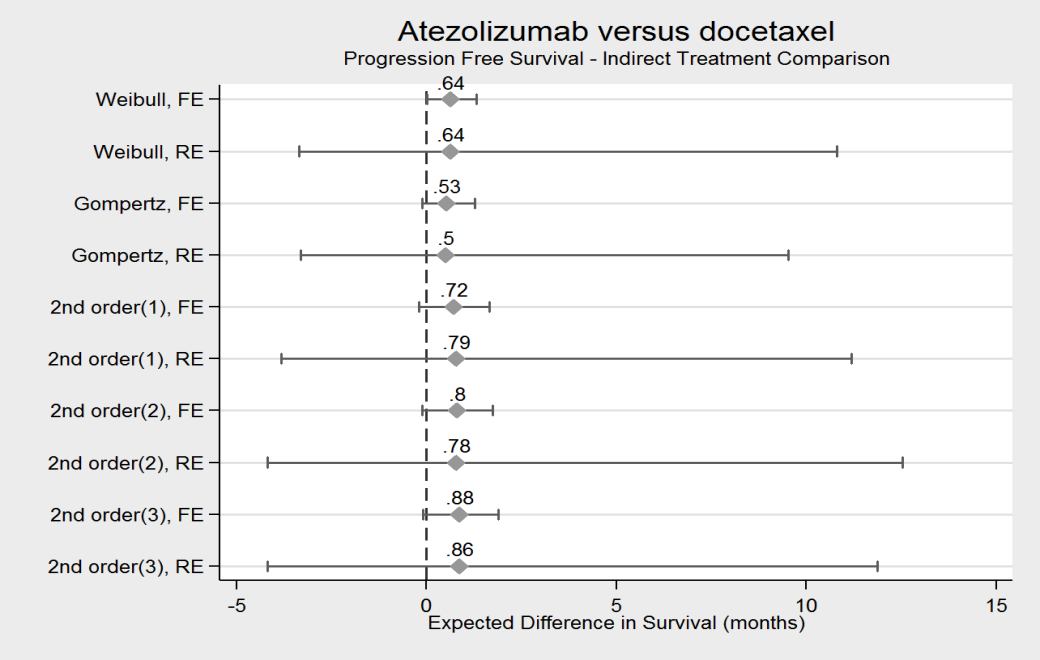

Figure 5 Results of FP models with FE and RE, expected difference in PFS (months) and 95% CrI for atezolizumab compared to docetaxel

See Table 11 for definitions of 2nd order models (1) (2) and (3)
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; PFS=progression-free survival; RE=random effects
Source: company response to ERG clarification letter, adapted from Figure 28, Figure 30, Figure 32, Figure 34, Figure 36, Figure 43, Figure 44, Figure 45, Figure 46, Figure 47

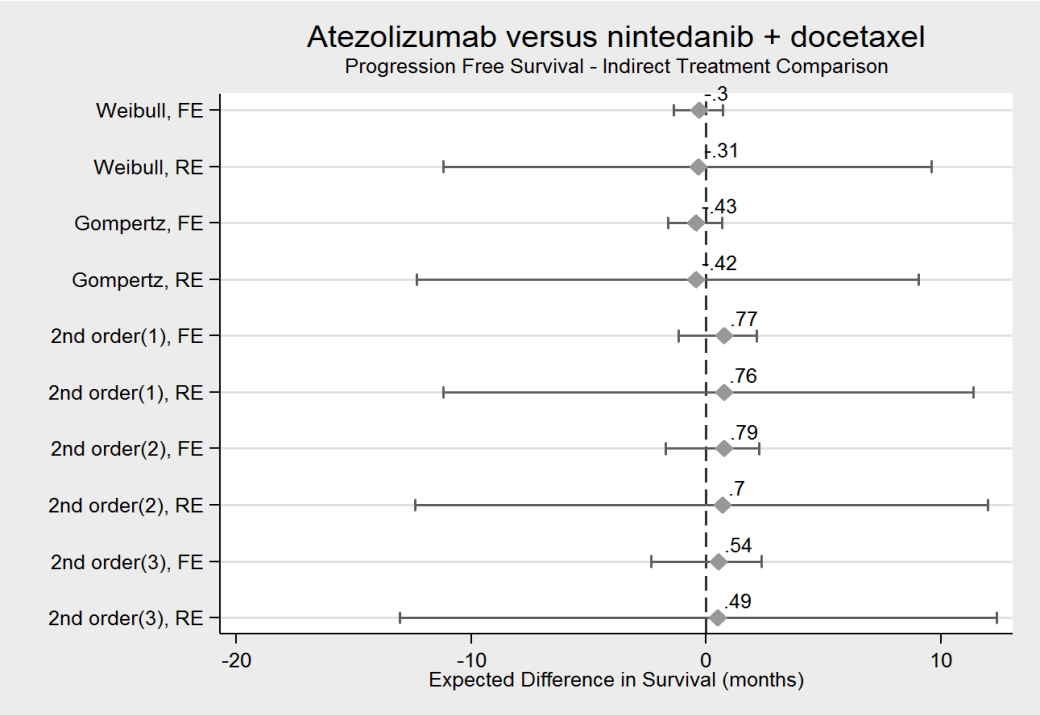

Figure 6 Results of FP models with FE and RE, expected difference in PFS (months) and 95% CrI for atezolizumab compared to nintedanib+docetaxel

See Table 11 for definitions of 2nd order models (1) (2) and (3)
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; PFS=progression-free survival; RE=random effects
Source: company response to ERG clarification letter, adapted from Figure 28, Figure 30, Figure 32, Figure 34, Figure 36, Figure 43, Figure 44, Figure 45, Figure 46, Figure 47

The ERG notes also that heterogeneity seems to be present in all RE FP models with SD (as defined by Jansen[60]) estimated to range from 0.31 to 0.34 across the five RE models (Table 25) and the resulting 95% CrI of the expected survival difference being substantially larger for all RE models compared to the FE models (Figure 5 and Figure 6).

The company did not provide survivor plots for the RE FP models and so the ERG was unable to visually inspect the fit of survival curves. Therefore, the ERG can only judge the fit of FE and RE models based on the DIC alone, which appears to be similar for each FP model fitted with FE and each fitted with RE (Table 25). As discussed for the ITC results for OS, the ERG questions how the same model fitted with FE and RE can show such a different range of credible results if there is no statistical heterogeneity present in the network as defined by the company (i.e. a difference in DIC of less than five points).

The ITC results consistently suggest that there are no statistically significant differences in expected PFS when comparing atezolizumab versus docetaxel (in line with the results of the OAK and POPLAR trials) and when comparing atezolizumab versus nintedanib+docetaxel. The ERG considers that the precision and reliability of the expected differences in PFS are influenced by the choice of FP model and by potential heterogeneity in the network, which has not been acknowledged by the company or accounted for in any of the ITC analyses.

4.6.4 Results from additional indirect comparisons requested by the ERG

As part of the clarification process, the ERG asked the company to perform additional ITCs. These are described in this section. The ERG assumes that the methodology the company applied to undertake these additional ITCs is the same as the methodology outlined in Section 4.6.2.

The ERG suggests that the results of these additional ITCs should be interpreted with caution, due to concerns regarding heterogeneity and the impact upon the reliability of FP results within the network as discussed in Section 4.6.3.

Adenocarcinoma histology

As outlined in Section 4.6.1 the ERG requested that the company repeat the ITC for the reduced network of relevant comparators (outlined in Figure 2) in the adenocarcinoma subgroups of the three trials as nintedanib+docetaxel is licensed only for participants with adenocarcinoma histology.

In the clarification response letter, the company states that the TSAPs for the OAK and POPLAR trials did not include subgroups according to the presence of adenocarcinoma and therefore did not provide results for the ITC requested by the ERG. The ERG anticipated that adenocarcinoma subgroups may not have been defined in the OAK and POPLAR trials and therefore, if this were the case, requested alternatively that the company repeat the ITCs using data from the non-squamous subgroups of the OAK and POPLAR trials and the adenocarcinoma subgroup of the LUME-Lung 1 trial. The company, however, provided results for a comparison between atezolizumab within its intended licensed population (total OAK and POPLAR trial populations) with nintedanib+docetaxel (in the subgroup of patients with adenocarcinoma histology). The ERG notes that these results are, therefore, derived from comparing non-equivalent populations and thus should also be treated with extreme caution.

The company applied the Weibull FE FP model; results for OS and PFS are provided in Table 26 and plots of HR functions provided by the company are provided in Section 10.7.3.

Table 26 Expected survival differences: atezolizumab (total population) and nintedanib+docetaxel (adenocarcinoma subgroup)

Expected survival difference in months (95% CrI)*		
Outcome	**Atezolizumab vs docetaxel**	**Atezolizumab vs nintedanib+docetaxel**
OS	5.84 (3.68 to 8.07)	3.33 (-0.16 to 6.74)
PFS	0.68 (-0.04 to 1.46)	-0.07 (-1.76 to 1.28)

*Results came from the 'best fitting' Weibull FE FP model
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; PFS=progression-free survival; OS=overall survival
Source: company response to ERG clarification letter, adapted from Figure 10, Figure 12

The ERG notes that when restricting the ITC to the adenocarcinoma subgroup for nintedanib+docetaxel, when comparing atezolizumab to nintedanib+docetaxel, the expected OS difference is reduced from around 4.74 months (see Table 24) to 3.33 months and the result is no longer statistically significant. The expected PFS difference when comparing atezolizumab to nintedanib+docetaxel is similar to the results showed in Table 25. The ERG also notes that OS and PFS results for the comparison of atezolizumab versus docetaxel are similar to those shown in Table 24 and Table 25.

The company states that using the 'total population' of the LUME-Lung 1 trial to conduct a 'like for like' comparison between atezolizumab and nintedanib+docetaxel is 'not anticipated to significantly affect overall results' (CS, Section 4.10). However, this statement is not supported by the additional results provided by the company (Table 26) which show that, when restricting the ITC to the adenocarcinoma subgroup of the LUME-Lung 1 trial, treatment with atezolizumab no longer shows a statistically significant difference in OS compared to nintedanib+docetaxel. The ERG considers that the results of an ITC conducted within the

adenocarcinoma subgroups of the OAK, POPLAR and LUME-Lung 1 trials are needed to fully appreciate the impact of the choice of trial population on comparative efficacy.

Inclusion of pembrolizumab in the network

The ITCs presented in the CS included comparators to atezolizumab that were not considered in the final scope issued by NICE. The ERG notes that pembrolizumab, which was specified in the final scope issued by NICE for this appraisal, was included within the ITCs for OS and PFS. However, the company did not present the ITC results for the comparison of atezolizumab versus pembrolizumab, as the company does not consider pembrolizumab to be a relevant comparator for this appraisal (see Section 3.3.2). As further outlined in Section 3.3.2, the ERG considers that pembrolizumab is an appropriate comparator but only for the population for which it is currently recommended by NICE (treatment of patients with PD-L1 ≥1% NSCLC after chemotherapy). Therefore, as part of the clarification process, the ERG asked the company to carry out an ITC for the network outlined in Figure 7, for OS and PFS. This network includes three trials, the OAK and POPLAR trials and the KEYNOTE-010 trial.[63] Further details of the design and participant characteristics of the KEYNOTE-010 trial can be found within the primary reference[63] and within Appendix 4 of the CS. Overall, the ERG considered the characteristics of the OAK, POPLAR and KEYNOTE-010 trials to be broadly similar and therefore suitable for inclusion in the same ITC.

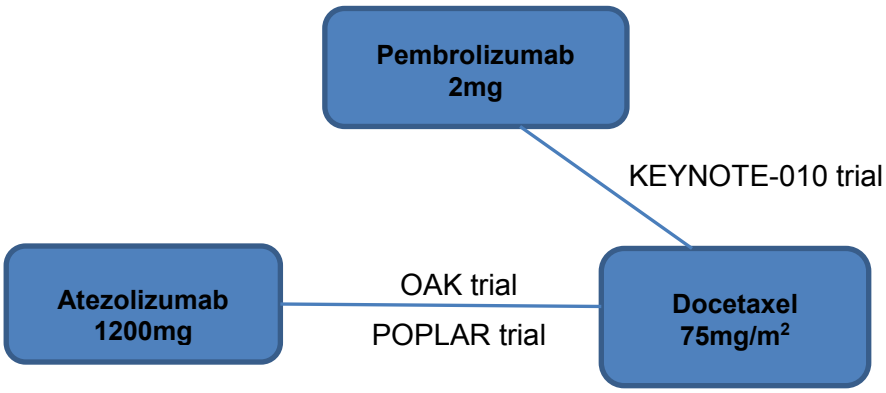

Figure 7 Network plots for ITCs of OS and PFS including pembrolizumab

The company provided results of the additional ITC as requested, applying the Weibull FE FP model (see Section 4.6.3 for further details of model fit); results for OS and PFS are provided in Table 26 and plots of HR functions provided by the company are provided in Section 10.4). Expected survival differences are shown in Table 27.

Table 27 Expected survival differences including pembrolizumab

Expected survival difference in months (95% CrI)*		
Outcome	**Atezolizumab vs docetaxel**	**Atezolizumab vs pembrolizumab**
OS	5.79 (3.63 to 8.05)	-0.24 (-5.38 to 4.44)
PFS	1.17 (0.29 to 2.03)	-0.30 (-2.17 to 1.40)

*Results came from the 'best fitting' Weibull FE FP model
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; PFS=progression-free survival; OS=overall survival
Source: company response to ERG clarification letter, adapted from Figure 14, Figure 16

Results for the comparison of atezolizumab versus docetaxel are similar to those shown in Table 24 for OS and the expected difference in PFS is slightly greater than the differences shown in Table 25. The ERG notes that there is no statistically significant difference between atezolizumab and pembrolizumab in terms of OS or PFS.

In the clarification response letter, the company states that the ITC of atezolizumab in its licensed indication versus pembrolizumab in its licensed indication (PD-L1 positive), compares two non-equivalent populations, and hence there is a risk the relative clinical benefits of pembrolizumab are overestimated. The company emphasises that this analysis should not be considered as a robust and true reflection of the comparative efficacy of pembrolizumab versus atezolizumab. The ERG agrees with this statement and advocates extreme caution when interpreting comparative results of atezolizumab versus pembrolizumab.

The ERG considers that robust analysis approaches are important but should not come at the expense of making inappropriate comparisons, such as including data for patients not specified in the licensed population for treatment with nintedanib+docetaxel.

The ERG considers that the approach to the ITC is influenced by a range of factors (e.g., comparators and population selected, type of FP model chosen and the use of FE or RE). This means that it is difficult to identify the most appropriate combination of factors to use to generate and interpret ITC results.

4.7 Additional work on clinical effectiveness undertaken by ERG

OS data from the OAK trial, for PD-L1 subgroups, were published in January 2017.[23] The ERG has reproduced these results for information (Table 28).

Table 28 OS in the ITT population and PD-L1 subgroups

Population	n (%)	Median OS (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
ITT	850 (100)	13.8	9.6	0.73 (0.62 to 0.87)
TC3 or IC3	137 (16)	20.5	8.9	0.41 (0.27 to 0.64)
TC2/3 or IC2/3	265 (31)	16.3	10.8	0.67 (0.49 to 0.90)
TC1/2/3 or IC1/2/3	463 (54)	15.7	10.3	0.74 (0.58 to 0.93)
TC0 and IC0	379 (45)	12.6	8.9	0.75 (0.59 to 0.96)

CI=confidence interval; HR=hazard ratio; IC=immune cell; ITT=intention to treat; OS=overall survival; TC=tumour cell
Source: Rittmeyer[23]

4.8 Conclusions of the clinical effectiveness section

Discrepancies between the decision and the final scope issued by NICE

The ERG considers that the submitted evidence largely reflects the decision problem defined in the final scope issued by NICE. However, there are a number of exceptions:

- Comparators:
  - the comparison of the efficacy of treatment with atezolizumab versus nintedanib+docetaxel should have been carried out using data from the population for which nintedanib+docetaxel is licensed, i.e. patients with adenocarcinoma rather than the whole trial population
  - the company should have compared the efficacy of treatment with atezolizumab versus pembrolizumab for the population for which pembrolizumab is licensed and recommended by NICE (people with PD-L1 positive NSCLC).
- Subgroups:
  - it is specified within the final scope issued by NICE that, if evidence allows, consideration will be given to subgroups based on biological markers. As analyses by level of PD-L1 expression are specified in the protocols for the OAK and POPLAR trials, full results from both trials (rather than just by no measurable PD-L1 expression and ≥1% PD-L1 expression from the OAK trial) should have been provided in the CS.

Direct clinical evidence

The direct clinical effectiveness evidence for the treatment of atezolizumab versus docetaxel was derived from the OAK and POPLAR trials. The ERG highlights the following points:

- both these trials were of good quality and were both well conducted; patient characteristics were balanced across the groups and statistical methods were generally appropriate. However, the open-label design provides the opportunity for investigator-assessed outcomes to be biased
- the studies included some UK sites and clinical advice to the ERG is that patients recruited to these trials are broadly similar to those treated within the NHS, with the caveat that patients in the trials were slightly younger and fitter than NHS patients
- within the OAK and POPLAR trials, docetaxel is administered intravenously until disease progression or unacceptable toxicity. However, clinical advice to the ERG is that, within the NHS, patients typically only receive between four and six cycles of treatment

- in both the OAK and POPLAR trials, the treatment stopping rules for patients receiving atezolizumab and docetaxel differed: treatment with atezolizumab was administered as long as patients experienced a clinical benefit (as assessed by an investigator) in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression and treatment with docetaxel was continued until disease progression or unacceptable toxicity
- the ERG agrees with the company that the AE data from the OAK trial are consistent with the known AE profile of atezolizumab and that no new safety concerns have been highlighted. In addition, treatment with atezolizumab is well-tolerated in comparison to treatment with docetaxel
- the ERG notes that OS and PFS HRs calculated from OAK and POPLAR trial data must be interpreted with caution due to non-PH (as demonstrated by the company). However, the ERG acknowledges that the methodology requiring the PH assumption was pre-specified and the company could not have known at the time this methodology was proposed that the PHs assumption would be violated
- results from both the OAK and POPLAR trials show that treatment with atezolizumab is associated with a statistically significant and clinically meaningful improvement in median OS (4.2 months in the OAK trial and 2.9 months in the POPLAR trial) compared to docetaxel in patients with ECOG PS 0 and 1
- in the OAK trial, this statistically significant gain in OS is observed regardless of histology and PD-L1 status. However, in the POPLAR trial, statistically significant improvement is observed only in the non-squamous histology subgroup and for individuals with NSCLC of ≥1% PD-L1 expression
- improvement in OS with atezolizumab compared with docetaxel is also generally consistent across baseline characteristics in both trials
- no statistically significant difference in investigator-assessed PFS was observed between atezolizumab and docetaxel groups in either trial.

Indirect clinical evidence

The ERG considers that the company applied the ITC methodology using FP models appropriately but does not agree with the company's criteria of using the DIC statistic (a measure of model fit) for assessing the presence of heterogeneity in the analyses. The ERG does not support the ITC approach taken by the company as:

- the main network includes comparators that are not listed in the final scope issued by NICE
- when considering the relative efficacy of atezolizumab versus nintedanib+docetaxel, the company compared effectiveness relating to the whole LUME-Lung 1 trial population, rather than considering the relevant population, i.e. the population for which nintedanib+docetaxel is licensed (patients with adenocarcinoma)
- the company was not justified in excluding pembrolizumab from the ITC network of comparators relevant to this appraisal.

The ERG asked the company to provide ITC results from a reduced network of comparators comprising those listed in the final scope issued by NICE. Based on this (reduced) network,

i.e., using data from the total populations of the OAK, POPLAR and LUME-Lung 1 trials, the company's FP ITC results suggest that:

- the company's best estimate of expected difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (compared to median OS gains of 4.2 months and 2.9 months from the OAK and POPLAR trials respectively)
- the company's best estimate of expected difference in OS is around 5 to 6 months for atezolizumab versus nintedanib+docetaxel
- there appears to be no significant difference in PFS when comparing atezolizumab to docetaxel and when comparing atezolizumab to nintedanib+docetaxel.

The ERG also asked the company to undertake two further subgroup analyses. However, the company undertook these using non-equivalent populations and results should be viewed with extreme caution:

- based on a (reduced) network using data the ITT populations from the OAK and POPLAR trials and the adenocarcinoma population from the LUME-Lung 1 trial, the company's FP ITC results suggest that the company's best estimate of expected difference in OS for atezolizumab versus nintedanib+docetaxel is 3.33 months (compared to 4.74 months when the analysis was carried out using LUME-Lung 1 trial total population) and is no longer statistically significant
- based on a (reduced) network using data the ITT populations from the OAK and POPLAR trials, and the KEYNOTE-010 trial (a trial assessing the efficacy of pembrolizumab as a first-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% tumour proportion score) the company found no statistically significant difference in OS or PFS when comparing atezolizumab (total population') versus pembrolizumab (PD-L1 positive NSCLC patients).

The ERG highlights that the precision and reliability of all additional results are influenced by the choice of FP model and greatly influenced by potential statistical heterogeneity in the network which has not been acknowledged by the company or accounted for in any ITC analyses. In summary, the ERG considers that the approach to the ITC is influenced by a range of factors (e.g., comparators and population selected, type of FP model chosen and the use of FE or RE). This means that it is difficult to identify the most appropriate combination of factors to use to generate ITC results. Furthermore, the ERG considers that the expected survival results generated by the FP ITC are difficult to interpret.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company in support of the use of atezolizumab for treating locally advanced or metastatic NSCLC after prior chemotherapy. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.2 Objective of the company's cost effectiveness review

The company's systematic review was carried out to identify cost effectiveness evidence for atezolizumab for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy. The stated aim of the review was to identify economic evidence from all lines of metastatic NSCLC to support the development of cost effectiveness models for atezolizumab. Electronic searches were carried out on 4th September 2016 and hand searches were performed on 21st November 2016. The databases searched and the initial date span for each search are summarised in Table 29.

Table 29 Details of searches for the company's economic systematic review

Database	Platform	Date span of search	Date searched
Embase	Embase.com	From database inception (1974) to 3-Sep-2016 (updated daily)	04-Sep-2016
Medline	Embase.com	From database inception (1966) to 3-Sep-2016 (updated daily)	04-Sep-2016
Medline InProcess & e-publications ahead of print	PubMed search interface	From database inception to 17-Nov-2016	04-Sep-2016 initially & weekly alerts received to cut-off date of 18-Nov-2016
NHS Economic Evaluation Database (NHS EED)	Cochrane library	From database inception to 31st March 2015 (database closed)	04-Sep-2016
Health Technology Assessment Database (HTA)	Cochrane library	From database inception to July 2016 (updated monthly)	04-Sep-2016

Source: CS, Table 51

5.2.1 Eligibility criteria used in study selection

The inclusion criteria that were used to select studies are shown in Table 30; more detailed exclusion criteria are presented in Table 52 of the CS. The ERG is satisfied that these criteria

are relevant to the aim of the company's systematic review but notes that they are not focussed on the specific decision problem set out in the final scope issued by NICE. As the inclusion/exclusion criteria are broad, the ERG is satisfied that use of these criteria is acceptable.

Table 30 Inclusion criteria

Characteristic	Inclusion criteria
Population	• Adult patients (16 years+) • Locally advanced or metastatic NSCLC, second/subsequent line
Interventions / comparators	• Licensed and unlicensed pharmacological interventions used in the second/subsequent line within the metastatic setting, compared to each other or to placebo or standard of care • Companion tests + pharmacological agent, if the objective is to assess the pharmacological agent primarily (tagged)
Outcomes	• Evaluation includes both costs and effectiveness/utility measures (need not necessarily report an incremental cost-effectiveness ratio) • Sub-outcomes of interest are: cost components, health states, interim/proxy efficacy measures, safety endpoints
Study design	• Economic evaluations (cost-effectiveness analysis, cost-utility analysis) • Economic evaluations alongside a clinical trial • Health technology assessments
Country	• EMEA countries, USA, Canada, Australia and New Zealand
Perspective	• Payer, societal
Time horizon	• Unlimited
Date limits	• Unlimited
Child citation	• Citation linked to another paper but with unique data
Language	• Any foreign language paper with an English abstract if sufficient information is present in the English abstract to ensure the eligibility criteria are met

Source: CS, Table 52

5.2.2 Included and excluded studies

The company did not identify any studies of atezolizumab in its systematic review. The company presented summary details of 11 studies and related risk of bias assessments (CS, Table 53 and Appendix 7 respectively) and three NICE appraisals (CS, Table 54) that were considered to be relevant to the decision problem; none of these publications included atezolizumab as an intervention or a comparator.

The ERG notes that the company conducted a systematic review from a global perspective (excluding Asia and South America) to support the health technology assessment process for countries including, and beyond, the UK. However, only data from 11 studies relevant to the decision problem, meeting the NICE Reference Case[64] and relevant to UK decision-making were extracted and reported in the CS.

5.2.3 Findings from cost effectiveness review

The company did not report any findings from the cost effectiveness review.

5.3 ERG critique of the company's literature review

The company reports full details of the searches used to identify cost effectiveness evidence in Section 5.1 and Appendix 5 of the CS. These searches included a cost effectiveness filter. The company used population terms but did not include any indication terms; the ERG considers this approach to be appropriate. The ERG notes that the search terms used to describe the population of interest in the economic literature searches were more comprehensive than the terms that were used in the main clinical searches.

The company also searched for HRQoL data and full details of these searches are reported in Appendix 9 of the CS. The searches included a HRQoL filter, broad population search terms and covered the same time period as the cost effectiveness searches. The ERG notes that the company could have used simpler search strings.

The ERG notes that the company went to great lengths to identify relevant economic studies of atezolizumab. However, despite a wide focus, broad inclusion/exclusion criteria and summary descriptions of potentially relevant studies, no studies of atezolizumab were identified for inclusion in the review. The ERG is satisfied that no relevant studies were missed during the review process.

5.4 NICE Reference Case checklist

Table 31 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	No, but the company provides justification as to why this is the case
Perspective costs	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective benefits	NHS and PSS	Partial - patient related direct health effects are considered. No PSS costs have been considered
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Based on systematic review	Yes
Outcome measure	Health effects should be expressed in QALYs.	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	No. However, UK valuations of data collected during the OAK trial were requested during the clarification process and these were similar to values used in the company model
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; HRQoL=health-related quality of life; PSS=personal social services

5.4.1 Drummond checklist

Table 32 Critical appraisal checklist completed by the ERG

Question*	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partially	The data come from a RCT but modelling of survival was required. This appears to have resulted in an over-estimate of the effectiveness of the intervention
Were all the important and relevant costs and consequences for each alternative identified?	Yes	Some of the assumptions in the model were unsupported by data
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Partially	There was an error in the calculation of treatment costs for all arms due to an error in applying a half-cycle correction. There was also an error in the discounting algorithm
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

*Questions from the Drummond 10-point checklist[65]

5.4.2 Model structure

Overview of the model

The company states that the model is designed to compare the cost effectiveness of atezolizumab versus docetaxel and atezolizumab versus nintedanib+docetaxel in patients with locally advanced or metastatic NSCLC who have progressed during or after prior chemotherapy. The model inputs (efficacy, safety and tolerability) were based on the results of the phase III OAK trial that compared the effectiveness of atezolizumab versus docetaxel. Clinical effectiveness data from the FP ITC were used to inform the comparison of atezolizumab versus docetaxel and atezolizumab versus nintedanib+docetaxel. Results are reported in terms of incremental cost per life year (LY) gained and incremental cost per quality adjusted life year (QALY) gained.

Model structure

The cost effectiveness model presented by the company is a partitioned survival model. The model structure (as shown in Figure 8) is slightly different to the type of model usually submitted to NICE as part of appraisals of interventions to treat metastatic cancer as it comprises three mutually exclusive health states: 'on treatment', 'off treatment' and death (rather than PFS, progressed disease [PD] and death). The company considers that this structure is better suited to the appraisal of atezolizumab than traditionally structured models, as patients receiving atezolizumab (an immunotherapy) are permitted to continue treatment with atezolizumab for some time after disease progression. However, the company explains that the comparators are not bound by this structure. For example, nintedanib+docetaxel, treatment duration, supportive care costs and utilities are all determined through the traditional PFS/PD/Death model; and so too are the supportive care costs associated with treatment with docetaxel. This is in comparison to atezolizumab where 'on treatment' drug costs and utility benefits are determined using a time to treatment discontinuation (TTD) approach.

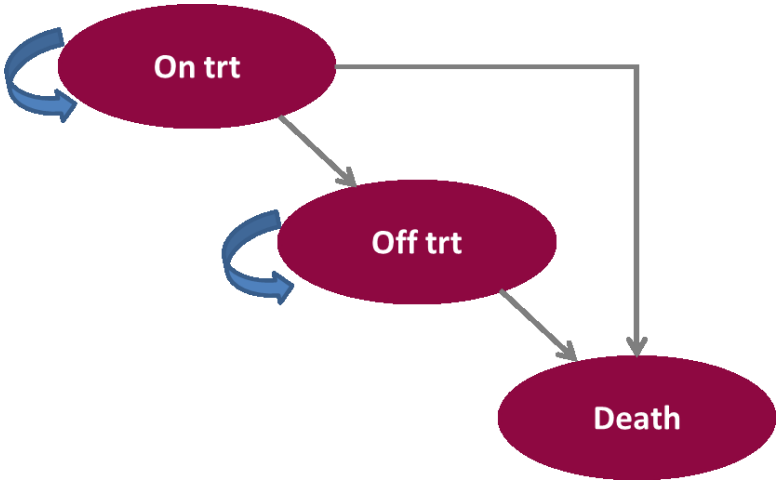

Figure 8 Area under the curve model structure

Trt=treatment
Source:CS, Figure 32

5.4.3 Population

The patient population in the company model is patients with locally advanced or metastatic NSCLC who have progressed during or after prior chemotherapy. The baseline characteristics of the modelled population reflect the characteristics of the patients in the OAK trial.

5.4.4 Interventions and comparators

In the base case, the intervention is atezolizumab, and the comparators are docetaxel and nintedanib+docetaxel. Atezolizumab is implemented in the model as per the anticipated licensed dosing regimen, i.e. fixed dose of 1200mg concentrate solution for IV infusion, administered over 60 minutes for the first infusion and, if well tolerated, as a 30 minute IV infusion every 3 weeks. Atezolizumab is administered beyond progression if the patient is considered to be continuing to receive benefit from treatment. The total drug cost per cycle is estimated to be £3,807.69 (CS, Table 65).

Docetaxel is administered at a dose of 75kg/m^2 every 3 weeks. The weighted average body surface area (BSA) for men and women from the OAK trial was used to estimate the average cost per dose of docetaxel per patient. In the model, full vial sharing is assumed for the administration of docetaxel and the maximum treatment duration is six cycles. The total drug cost per cycle is estimated to be £34.39 (CS, Table 65).

Nintedanib is administered orally (twice daily) as a 200mg soft capsule. In the model, the maximum treatment duration of docetaxel is six cycles. There is a PAS in place for nintedanib. The list price cost per cycle for nintedanib is estimated to be £1,434.07 (CS, Table 65).

Subsequent treatment

The economic model includes costs of subsequent treatment for patients who have progressed during or after initial treatment (see Table 33). At 25 months' follow-up, approximately 13% of patients were still receiving atezolizumab; this means there is no complete dataset of post-discontinuation treatments. The company states (CS, p182) that "…so as not to bias the analysis by giving a falsely low subsequent treatment cost to atezolizumab, an average has been taken by pooling the arms". As per the OAK trial, 45% of all patients were assumed to receive subsequent pharmacological treatment and 55% went on to receive radiotherapy. In line with clinical opinion, the company removes the costs of third-line immunotherapy from the base case analysis and considers the use of radiotherapy as a third-line treatment in a scenario analysis.

Table 33 Cost of subsequent treatment (drug and radiotherapy)

Cost and duration of subsequent drug and radiotherapy treatments	
Average time on subsequent drug treatment	13.59 weeks
Average cost	£1,987.06
Average number of subsequent radiotherapy doses per patient	20.58
Average cost	£1,353.08
Total cost of subsequent treatment	£3,340.14

Source: CS, Section 5.5.2.1

5.4.5 Perspective, time horizon and discounting

The company states that the economic evaluation was undertaken from the perspective of the NHS and Personal Social Services. The time horizon was set at 25 years and, in line with the NICE Guide to the Methods of Technology Appraisal,[64] both costs and outcomes were discounted at 3.5% per annum.

5.4.6 Treatment effectiveness and extrapolation

The primary data source for the company model was the OAK trial. The follow-up period over which trial data were available was shorter than the time horizon of the economic model. Therefore, modelling of OS, PFS and TTD data from OAK trial was required.

Overall survival

The company considered that the survival data available for immunotherapy agents suggest that it is plausible that some patients experience a sustained response. To model this sustained response the company constructed a mixed cure-rate model. The concept is that there is a subgroup of patients with stable disease for whom the risk of death attributable to cancer is equivalent to the risk of death from other causes. Thus, there are two populations,

those with a low risk of death and those with a high risk of death and OS is represented as an average of the two different risks for these two populations.

Following examination of data from the OAK trial, the POPLAR trial data and the NLCA, and consultation with clinicians, the company determined that 2% of patients are likely to be in the low risk of death group, i.e. have a risk of death equivalent to the age-adjusted general population mortality rate.

The company modelled the risk of death for the remaining 98% of the population based on data from the OAK trial. Standard parametric curves were fitted to OAK trial data and the company determined, based on visual assessment, the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), that the log-logistic distribution was the most appropriate fit.

To construct OS curves for the comparator agents, the curve constructed to represent OS for the population receiving atezolizumab was adjusted using the time-dependent FP log HRs over the span of the extrapolation.

Time to treatment discontinuation

Within the company model TTD K-M data for patients treated with atezolizumab are used directly until the point where 15% of patients are still at risk of an event. From this point, for the duration of the remaining time horizon, the company has used a parametric distribution to represent the proportion of patients still receiving their initial treatment. Based on visual inspection and AIC and BIC, the company utilised a Gamma distribution in the base case analysis.

When modelling TTD for patients receiving docetaxel, OAK trial TTD K-M data were used directly in the model with a maximum treatment duration of six cycles used for costing purposes which is stated in the CS as being consistent with NHS clinical practice in England.

TTD trial data for nintedanib+docetaxel were not available to the company. The company's approach to representing TTD for patients receiving nintedanib+docetaxel was to adjust their representation of PFS for patients receiving atezolizumab using the relevant ITC FP HR. The company modelled PFS for patients receiving atezolizumab using the same methodology as used to construct their TTD model. That is, using OAK trial PFS K-M data directly in the model until 15% of patients were still at risk, at which point the 'best fitting' parametric distribution, which, in this case was, again, considered to be a gamma distribution, was fitted. Again docetaxel was limited to six cycles for costing purposes but nintedanib was administered until progression.

5.4.7 Health-related quality of life

HRQoL data were collected as part of OAK trial using the EQ-5D 3L tool.[56] The values of the utility estimates used in the company model are based on: health states and time to death. Given that patients experience both health state disutility and end of life disutility, the company considers that the two options are complimentary. To capture HRQoL as appropriately as possible, the company divided utilities into four categories reflecting time to death. These values were applied in addition to the 'on treatment' and 'off treatment' health states. A summary of the utility values used in the model is shown in Table 34.

Table 34 Summary of health states utility values – NICE Reference Case

Time period	On treatment	Off treatment
≤ 5 weeks before death	0.39	0.35
> 5 and ≤ 15 weeks before death	0.61	0.43
> 15 and ≤ 30 weeks before death	0.71	0.58
> 30 weeks before death	0.77	0.68

Source: CS, Table 60

The ERG notes that, within the company model, utility scores for all patients were not adjusted over time using an annual utility decrement (i.e., no age-related utility estimates were used in the model), nor is it clear if the company calculated utility values using the UK valuation set.

Impact of adverse events on health-related quality of life

The company took into account the impact of AEs on HRQoL by including a HRQoL decrement for all Grade 3 to Grade 5 AEs that occurred in ≥2% of patients in either treatment arm of the OAK trial. The disutility value per episode for each of the AEs listed in the model (as shown in Table 35) was sourced from studies identified in a systematic review carried out by the company to identify HRQoL evidence describing patients with metastatic NSCLC (CS, Section 5.4.2). Disutilities are applied to each treatment arm whilst patients are still receiving treatment.

Table 35 Adverse event disutilities

Adverse event	Disutility	Source
Anaemia	-0.07346	Nafees 2008[66]
Fatigue	-0.07346	
Febrile neutropenia	-0.09002	

Neutropenia	-0.08973	
Leukopenia	-0.08973	Assumed equal to neutropenia Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [TA403][67] Lung cancer (non-small-cell, non-squamous, metastatic, after treatment) - nivolumab [ID900][42]
Neutropenic sepsis	-0.09002	Assumed equivalent to febrile neutropenia
Neutrophil count decreased	0	Assumption Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [TA403][67] Lung cancer (non-small-cell, non-squamous, metastatic, after treatment) - nivolumab [ID900][42]
Pneumonia	-0.008	Marti et al (2013)[68]
Respiratory tract infection	-0.096	Assumption adapted from Hunter 2015[69]
White blood cell count decreased	-0.05	Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non‑small‑cell lung cancer [TA347][4]

Source: CS, Table 62

5.4.8 Resources and costs

Drug costs

Atezolizumab is administered at a fixed dose of 1200mg over 60 minutes for the first IV infusion and, if well tolerated, as a 30-minute IV infusion every 3 weeks. The expected list price of a 20ml vial (dose per vial is 1200mg) is £3,807.69. The company base case incorporates a PAS discount of [redacted], which reduces the cost per administration to [redacted]. The PAS application is currently under review by the Department of Health.

Drug costs for docetaxel were taken from the electronic Medicines Information Tool (eMIT).[70] Drug costs for nintedanib+docetaxel were taken from the British National Formulary (BNF)[71] and eMIT[70] respectively. A PAS for nintedanib does exist; however, the company is unaware of the value of this PAS price.

The drug acquisition cost and drug cost per treatment cycle used in the company model are provided in Table 36.

Table 36 Drug acquisition cost and drug cost per treatment cycle

Drug	Vial/pack concentration	Vial/pack volume	Dose per vial/pack	Cost per vial/pack	Total drug cost per cycle

Atezolizumab *	1200mg/ml	20 ml	1200 mg	£3,807.69	£3,807.69
Docetaxel	20 mg/ml	7 ml	140 mg	£17.77	£34.39 (75mg/m^2*BSA =137.75mg)
	20 mg/ml	1 ml	20 mg	£4.92	
Nintedanib*	100 mg	120	12000	£2151.10	£1,434.07 (200mg twice daily on day 2-21 treatment cycle)
	150 mg	60	9000	£2151.10	

*List price
Source: CS, Table 64 and Table 65

Administration costs

The costs of administering the intervention and comparator drugs are shown in Table 37.

Table 37 Drug administration costs

Drug	Type of administration		NHS Reference Cost code	Cost per administration	Source
Atezolizumab	Deliver simple parenteral CTX at first attendance	Outpatient Setting	SB12Z (outpatient)	£198.94	NHS Reference Costs 2015-16, Department of Health[72]
Docetaxel	Deliver simple parenteral CTX at first attendance	Outpatient setting	SB12Z (outpatient)	£198.94	
Nintedanib (pre-docetaxel discontinuation) – base case	Deliver simple parenteral CTX at first attendance	Outpatient setting	SB12Z (outpatient)	£198.94	
	12 minutes pharmacist time every 30 days	Hospital pharmacist (band 6); radiographer cost/hour		£46 per hour= £9.20 per administration	PSSRU 2016[73]
Nintedanib (post-docetaxel discontinuation) – base case	12 minutes pharmacist time every 30 days	Hospital pharmacist (band 6); radiographer cost/hour		£46 per hour= £9.20 per administration	
Nintedanib (pre-docetaxel discontinuation) – scenario analysis	Deliver simple parenteral CTX at first attendance	Outpatient setting	SB12Z (outpatient)	£198.94	NHS Reference Costs 2015-16, Department of Health[72]
	Deliver exclusively oral CTX	Outpatient setting	SB11Z	£183.50	
Nintedanib (post-docetaxel discontinuation) – scenario	Deliver exclusively oral CTX	Outpatient setting	SB11Z	£183.50	

CTX=chemotherapy
Source: CS, Table 70

Monitoring and disease management costs

The costs of patient monitoring and disease management were applied to 'on treatment' and 'off treatment' health states. The company states (CS, Section 5.5.2.3) that the types of resource and frequency of use are derived from previous technology appraisals validated by UK clinicians. Full details of the monitoring costs, 'on treatment' health state resource use, 'off treatment health state resource use', unit costs for 'on treatment' and 'off treatment' health

states and terminal care/end of life resource use are reported in detail in the CS (Table 71 to 76).

In summary, the total cost per week for the 'on treatment' health state was £128.25, whilst the total cost per week for the 'off treatment' health state was £120.12. A one-off terminal care/end of life cost was applied to patients in the 'Death' state and this cost was assumed to be equal for all treatments. The total cost of end of life care used in the model was £3,679.37.

Cost of adverse events

The company model includes all Grade ≥3 AEs experienced by ≥2% of patients in either arm of the OAK trial, based on data from the first 850 randomised patients who received any dose of the study drug at the time of the primary analysis (n=823). In addition, the company included a Grade 5 AE, despite the low incidence of the event. Also, the company included neutropenic sepsis as clinical advice suggested that this was an appropriate approach to take given that febrile neutropenia and neutropenic sepsis are terms that are often used interchangeably.

Based on the list of AEs compiled from the OAK trial, the corresponding rates for nintedanib+docetaxel were sourced directly from the LUME-Lung 1 trial.

The weekly rate of occurrence for each AE is implemented in the model through the overall probability of any patient experiencing the event in any given cycle. This is calculated by using 'number of AE occurrence' divided by the total time (weeks) at risk, which is the sum of time on treatment for each patient in the trial. The probability of any patient experiencing the event is then multiplied by the average management costs of the AE to obtain an AE cost per patient per week. The AE costs were applied to each treatment arm whilst patients were still receiving treatment.

The costs of treating AEs are per episode. Where possible, NHS Reference Costs (2015/16)[72] were used to cost AEs. Where there were gaps in the data, costs were sourced from prior NICE submissions in NSCLC and inflated to the appropriate costing year (Table 38). Full details of this costing exercise are presented in the CS (Table 79). UK clinicians validated the assumptions around the costs of treating each AE.

Table 38 Adverse event costs

Adverse event	Unit cost used in the company model	Source	Range of AE costs used in previous appraisals

Anaemia	£1,313.09	HRG 2015/16 (SA04H)[74]	£978 to £1,313.09
Fatigue	£3,802.59	Lung cancer (non-small-cell, squamous, metastatic)-nivolumab (after chemotherapy) [ID811][41]	£2,317.20 to £3,015.13
Febrile neutropenia	£5,612.78		£2,339 to £7,331.78
Neutropenic sepsis	£5,612.78		£2,339 to £7,331.78
Leukopenia	£362.66		£354.72 to £362.66
Neutropenia	£362.66		£179.83 to ££560.08
Neutrophil count decreased	0	Lung cancer (non-small-cell, non-squamous, metastatic, after treatment)-nivolumab [ID900][42]	£0 to £179.83
Pneumonia	£2,783.99	HRG 2015/16 (DZ11T)[74]	£1,822.85 to £2,783.99
Respiratory tract infection	£3,515.13	HRG 2015/16 (DZ27P)[74]	£3,734.17 to £3,515.13
White blood cell count decreased	£432.47	Nivolumab (ID900,[42] ID811[41])	£423 to £560.08

AE=adverse event; HRG=healthcare resource group
Source: CS, Table 79

5.4.9 Cost effectiveness results (based on list price of atezolizumab)

Total costs, LYs gained, QALYs gained and the incremental cost effectiveness ratio (ICER) per QALY gained for the cost effectiveness comparison of treatment with atezolizumab versus docetaxel and versus nintedanib+docetaxel are shown in Table 39 and Table 40 respectively.

Treatment with atezolizumab generates 0.75 additional QALYs versus docetaxel at an additional cost of £53,970. The company base case ICER for the comparison of treatment with atezolizumab versus docetaxel is £72,356.07 per QALY gained.

Table 39 Base case results (atezolizumab versus docetaxel, list price)

Technologies	**Total**			**Incremental**			**ICER per QALY gained**
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	
Atezolizumab	£73,911	2.20	1.47				
Docetaxel	£19,941	1.19	0.73	£53,970	0.10	0.75	£72,356.07

LYs=life years; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
Source: CS, Table 83

Treatment with atezolizumab generates 0.65 additional QALYs versus nintedanib+docetaxel at an additional cost of £36,209. The company base case ICER for the comparison of treatment with atezolizumab versus nintedanib+docetaxel is £56,076.16 per QALY gained.

Table 40 Base case results (atezolizumab versus nintedanib+docetaxel, list price)

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Atezolizumab	£73,911	2.20	1.47				
Nintedanib+docetaxel	£37,702	1.31	0.83	£36,209	0.91	0.65	£56,076.16

LYs=life years; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
Source: CS, Table 83

5.4.10 Deterministic univariate sensitivity analyses

The company carried out a wide range of univariate sensitivity analyses for the base case comparison of treatment with atezolizumab versus docetaxel and versus nintedanib+docetaxel. For each of the comparisons, the same three most influential parameters were apparent: the cure fraction rate, monthly cost of atezolizumab and the discount rate. Results from the analyses involving the ten parameters which, when varied, had the most influence on the company's base case results are displayed in the CS in Tornado diagrams for atezolizumab versus docetaxel and atezolizumab versus nintedanib+docetaxel and reproduced as Figure 9 (CS, Figure 61) and Figure 10 (CS Figure 62), respectively.

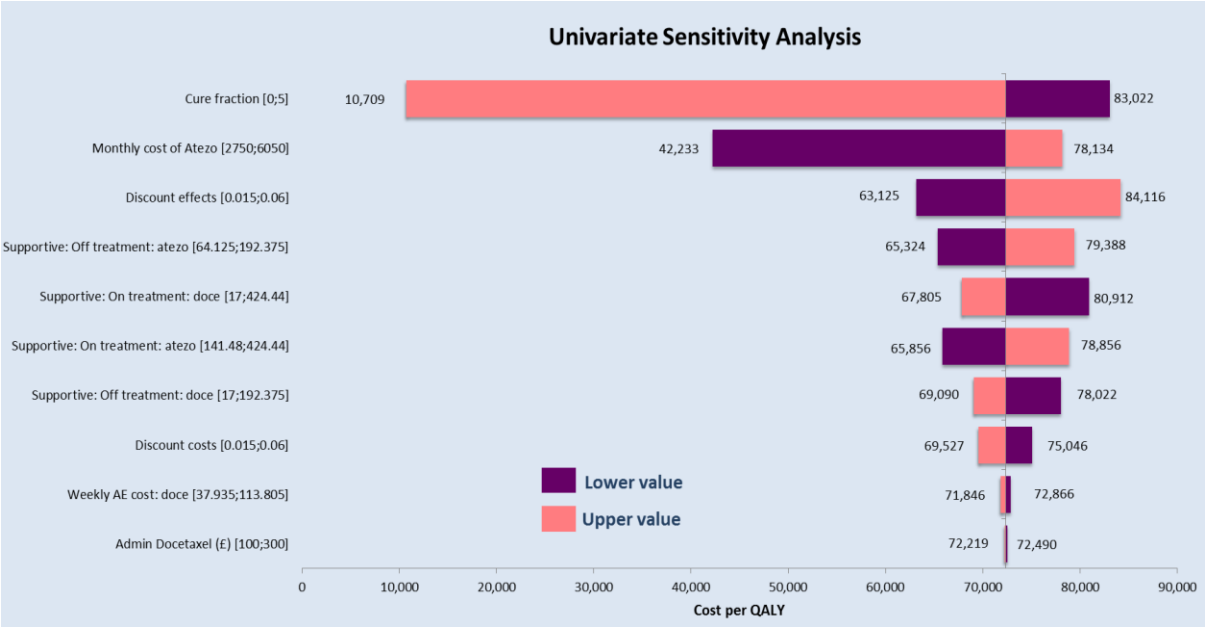

Figure 9 Univariate sensitivity analysis (atezolizumab versus docetaxel, list price)

Source: CS, Figure 61

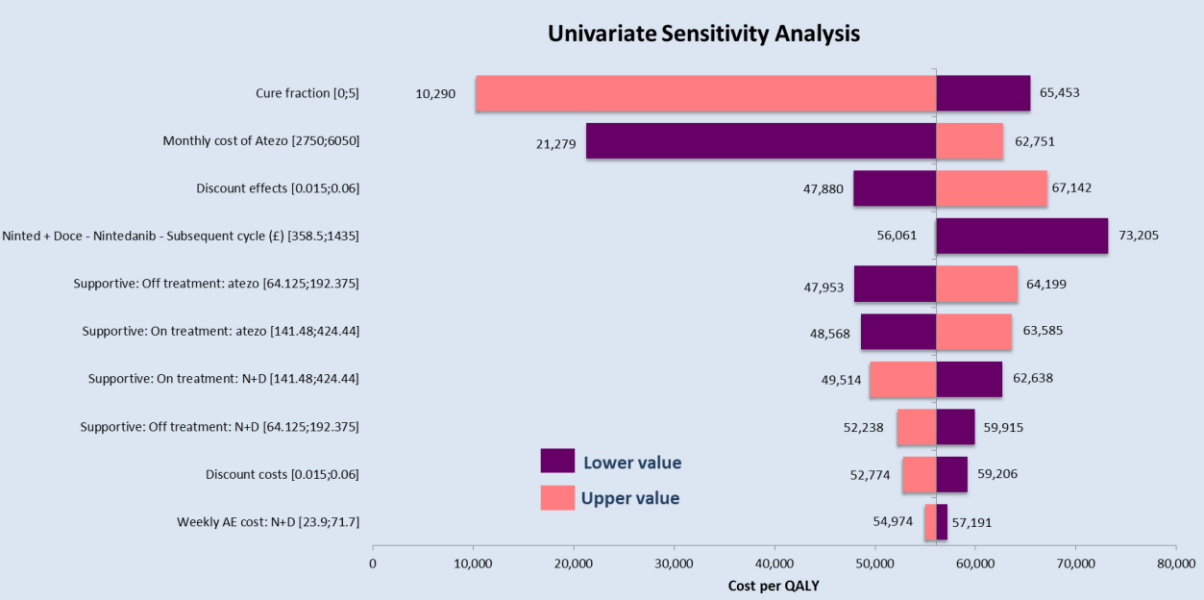

Figure 10 Univariate sensitivity analysis (atezolizumab versus nintedanib+docetaxel, list price)

Source: CS, Figure 62

Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to assess the uncertainty surrounding the parameter values used in the model. Results from this analysis are displayed in Table 41 and show ICERs per QALY gained that are slightly higher than the ICERs in the deterministic analysis. The PSA involved running the company model 1000 times. The scatterplot of PSA results and the cost effectiveness acceptability curve (CEAC) are presented in Figure 11 and Figure 12 respectively). Examination of the CEAC shows that the chance of atezolizumab being cost effective versus docetaxel (and versus nintedanib+docetaxel) at a threshold of £50,000 per QALY gained is approximately 45% (and 1%).

Table 41 PSA results compared to base-case analysis (list price)

Treatment	Costs		QALYs		ICERs (vs docetaxel)		ICERs (vs nintedanib+docetaxel)	
	Base case	PSA	Base case	PSA	Base case	PSA	Base case	PSA
Docetaxel	£19,941	£20,880	0.73	0.74	-	-	-	-
Nintedanib+ docetaxel	£37,702	£38,676	0.83	0.84	Extendedly dominated	Extendedly dominated	-	-
Atezolizumab	£73,911	£73,033	1.47	1.47	£72,356	£73,934	£56,076	£57,777

QALYs=quality adjusted life years; ICERs=incremental cost effectiveness ratios; PSA=probabilistic sensitivity analysis
Source: CS, Table 93

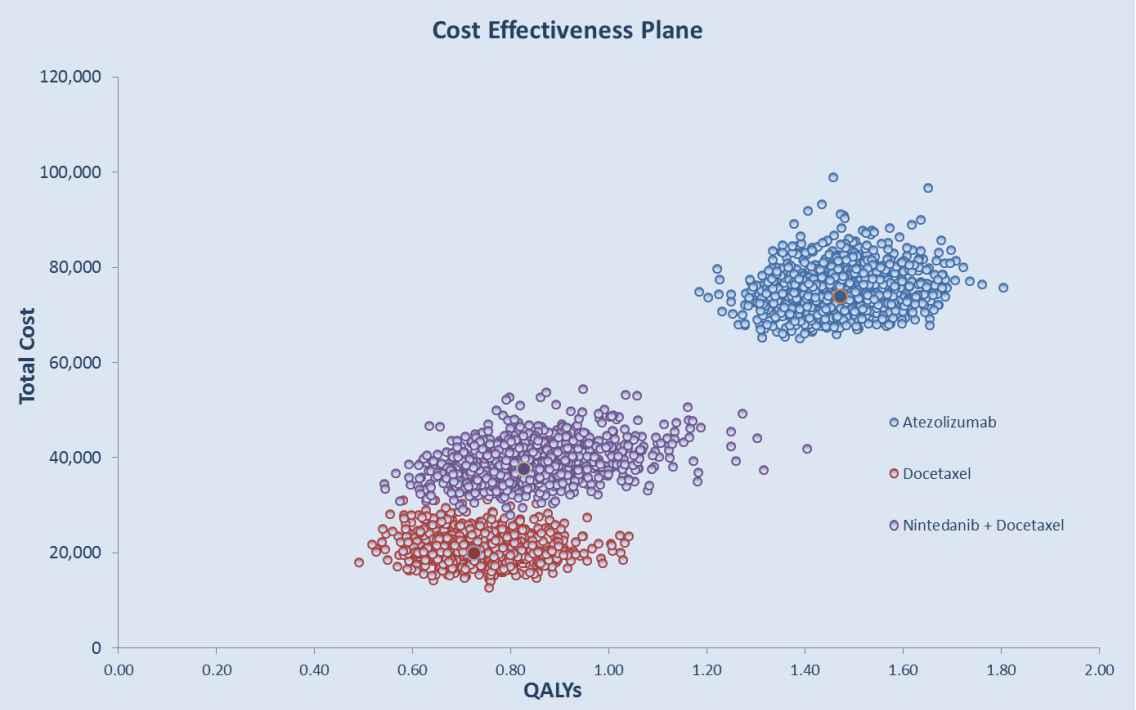

Figure 11 Scatterplot of PSA results for cost effectiveness plane

Source: CS, Figure 59

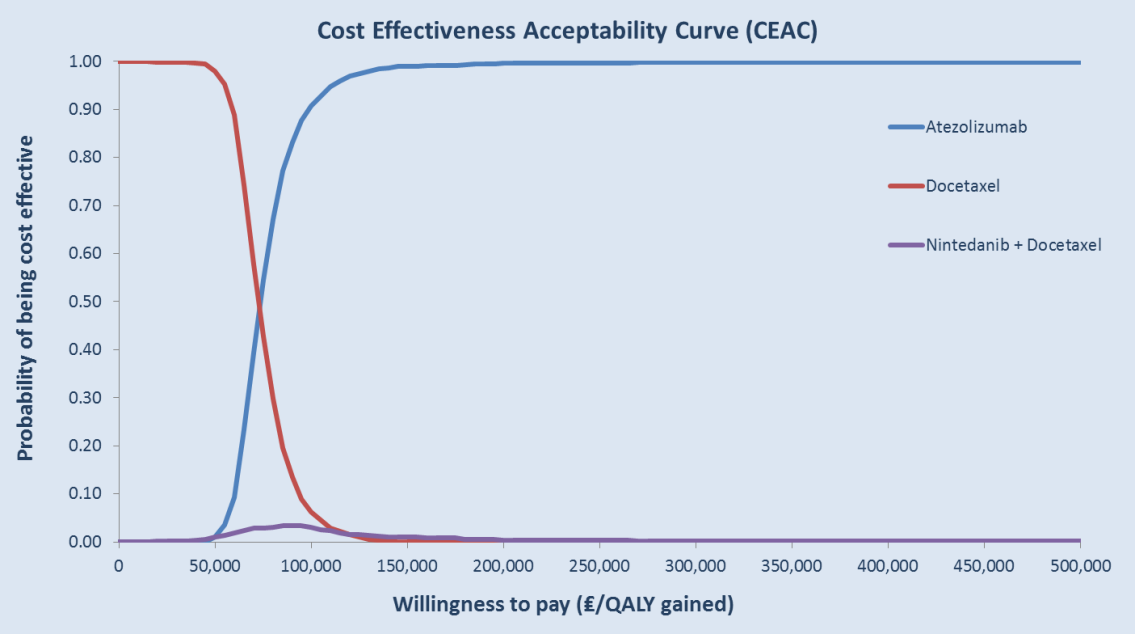

Figure 12 Cost effectiveness acceptability curve

Source: CS, Figure 60

5.4.11 Model validation and face validity check

The company reports that the model approach and inputs were validated by a number of external health economists and clinical experts on two separate occasions to ensure that the model reflected UK clinical practice. In particular, resource use, health state methodologies,

OS projections and extrapolation techniques were checked and verified. In addition, external consultants carried out internal quality control and validation of the model.

5.5 Detailed critique of company's economic model

The company provided a model built in MS Excel. The ERG's assessment of the structure of the company model and the data used to populate it are provided in Section 5.5.1 to 5.5.4 of this ERG report. The ERG considers that the model is generally well constructed and welcomes the following model design choices made by the company:

- use of utilities based on time to death rather than disease state
- use of data as the basis for estimating the cost of treating patients with atezolizumab.

5.5.1 ERG corrections to company model

Health-related quality of life

The ERG considers that, as patients with metastatic NSCLC face significant HRQoL issues, the utility values used in the company model to represent the HRQoL of patients who are more than 30 weeks to death seems high (0.77). This conclusion is based on the fact that the UK population norm for people aged 63, the age of the population at the start of the model time horizon, is 0.79. As part of the clarification process, the ERG asked the company to provide utility values for all patients in the OAK trial, calculated using the UK valuation set. On examination of these results the ERG was satisfied that the utility values used by the company fairly reflect the values suggested by the EQ-5D questionnaires completed by patients who participated in the trial. However, the ERG notes that the people who completed the questionnaires were trial participants and, therefore, may not be wholly representative of all patients in NHS clinical practice who are eligible for treatment with atezolizumab.

Within the company model, different utility values are applied depending on whether patients are 'on' or 'off' treatment. The ERG is not convinced that the separation of 'on' and 'off' treatment utilities is necessary. However, as the off-treatment utility value for patients who are more than 30 weeks to death is 0.68, the ERG considers that this value likely reflects the actual utility of patients during this phase and, therefore, has not amended this aspect of the company model.

Correction C1: inaccurate application of the discount rate

Due to an algorithmic error, the company has incorrectly applied discounting in the model by starting to discount from week 1, rather than from the start of year 2. The ERG has amended this error with the result that the company's base case ICER for the comparison of atezolizumab versus docetaxel increases by £408 to £72,764 per QALY gained. This

amendment decreases the company's base case ICER for the comparison of atezolizumab versus nintedanib+docetaxel by £117 to £55,959 per QALY gained.

Correction C2: failure to apply an age-related utility decrement

The ERG considers that the company model was misspecified as it does not take into account declining utility with age. Within the company model, a patient with the same time to death at age 63 years (the start of the model time horizon) has the same utility as a patient with the same time to death at age 88 years (the end of the model time horizon). To correct this error, the ERG has incorporated age-related decrements drawn from the publication by Kind[75] (0.02 at age 65 years and 0.07 at age 74 years) to reflect the lower HRQOL that patients experience as they get older.

Applying age-related decrements increases the company's base case ICER for the comparison of atezolizumab versus docetaxel by £2,960 to £75,316 per QALY gained. This amendment also increases the company's base case ICER for the comparison of atezolizumab versus nintedanib+docetaxel by £2,532 to £58,608 per QALY gained.

Correction C3: inappropriate half-cycle correction to modelling of time on treatment

The company has applied a half-cycle correction to their modelling of time on treatment TTD for all treatment arms. As treatment is administered at the start of each cycle, rather than during it, a half-cycle correction was unnecessary for this parameter. This approach also created the implausible situation whereby 4.3% of patients in the atezolizumab arm of the model did not receive their first cycle of atezolizumab i.e., these patients stopped treatment before they even started it. The ERG has, therefore, removed the half-cycle correction applied to TTD data. This amendment increases the company's base case ICER for the comparison of atezolizumab versus docetaxel by £1,736 to £74,092 per QALY gained. For the comparison of atezolizumab versus nintedanib+docetaxel, this amendment increases the ICER by £1,873 to £57,949 per QALY gained.

The ERG notes that the data used in the model to represent TTD for patients receiving nintedanib+docetaxel have been generated from an adjustment of the PFS data from the OAK trial. The PFS estimate for nintedanib+docetaxel is, therefore, not drawn from an analysis of direct trial data and so the ERG considers that the costs of treatment with nintedanib+docetaxel within the model have a level of uncertainty that means any ICERs based upon these costs should be considered as uncertain and indicative only.

Corrected company base case

The combined effect of introducing an age-related decrement to patients' HRQoL and removing the half-cycle correction applied to TTD data increases the size of company's base case ICER for the comparison of atezolizumab versus docetaxel by £5,213 to £77,569 per QALY gained. The effect of these changes on the ICER for the comparison of treatment with atezolizumab versus nintedanib+docetaxel is to increases it by £4,290 to £60,366 per QALY gained.

5.5.2 Company's approach to modelling overall survival: atezolizumab

The company has used a mixed cure-rate model to reflect survival for patients treated with atezolizumab. The ERG considers that, within the CS, the company has failed to justify the need for the application of a 'cure rate'. Even if a case had been made, the choice of cure rate used (2%) appears to be arbitrary as it is not supported by the evidence presented in the CS. The ERG considers that cost effectiveness results generated by the company's mixed cure-rate model are an inappropriate basis for decision-making.

Company justification for application of a cure rate

The company states (CS, p161) that the rate of death of patients with cancer declines over time if patients are treated with immunotherapies, and that:

> *"Long term evidence is not available from clinical trials, and with relatively immature data from the OAK study - use of traditional parametric survival analysis which relies on the observed data for atezolizumab will fail to account for this change in mortality rate and 'flattening' of the tail of the survival curve."* (Source: CS, p160)

The company concludes that the way to account for this is to use a mixed cure-rate model. The company references TA414[76] (Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma) as a previous example of the need to use a mixed cure-rate model in a cancer population receiving immunotherapy treatments.

In TA414,[76] the company described registry data from patients with advanced melanoma and explained that these data indicated that there was a subpopulation of patients who, having survived for 5 years, had a noticeably lower mortality rate than the population of patients who did not survive to 5 years. The ERG notes that the use of a mixed cure-rate model in the TA414[76] appraisal was not due to evidence of any prolonged treatment effect, or because of a lowering of the long-term mortality rate due to the effect of an immunotherapy. Rather, the

mixed cure-rate model was used because of a peculiarity in the survival trajectory of a population with malignant melanoma that could not be captured by the available trial data.

The ERG is unaware of any NSCLC registry data that suggest that a subgroup of patients exists where differential mortality rates occur once a specific survival point has been reached. The ERG considers that the company's reference to TA414[76] as a justification for applying a mixed cure-rate model to represent the survival trajectory of patients with NSCLC receiving atezolizumab is inappropriate.

The company states (CS, pp159-160) that the mixed cure-rate model is required because treatment with atezolizumab (a drug that is similar to other immunotherapies) may have a sustained effect for a subgroup of patients with Stage IV NSCLC. The company suggests that mortality rates for this subgroup are equal to population mortality rates. The ERG considers that this statement needs to be evidenced, and not simply assumed. In the absence of an evidence base, the ERG suggests that the application of a potential cure rate should be applied within the framework of a scenario analysis rather than used in the base case analysis.

In addition, the ERG notes that, for the comparison of treatment with atezolizumab versus docetaxel or nintedanib+docetaxel, application of a cure rate effectively generates a differential hazard at all time-points. The ERG considers that if there is evidence for such a difference it could be modelled by appropriately chosen distributions, based upon available trial data, and without recourse to a hypothetical cure rate.

Cure rate, OAK trial data and the National Lung Cancer Audit registry data

During the TA414[76] appraisal, the company identified a cure rate by adjusting registry data based on the characteristics of patients in the trial that provided evidence for the company's cost effectiveness analyses. The resulting extrapolation using the cure rate was then compared to survival data from a second trial, in which patients also received the study drug, to ensure it was appropriate. In the current appraisal, the company has justified the cure rate used in the model by comparing the mixed cure-rate model OS prediction against OS data from the OAK and POPLAR trials. However, when the mixed cure-rate OS model is compared with OAK trial data at 24 months, the chosen cure rate (2%) produces an overestimate of survival for patients treated with atezolizumab by 2.8% whilst underestimating OS for patients receiving docetaxel by 1.6% (recognising that the docetaxel OS curve is dependent on the atezolizumab curve although no cure rate is assumed for docetaxel). The mixed cure-rate model applied by the company, therefore, generates survival gains for patients treated with atezolizumab and docetaxel, over the first 24 months of the model time horizon, that are not supported by data from the OAK trials.

Whilst the company has presented NLCA registry data from 2006-2010 to support their choice of cure rate for patients receiving atezolizumab (CS, Table 59), the company has not undertaken any adjusted statistical analysis of the NLCA registry data. Without rebasing the data to take into account the time since diagnosis, number of prior treatments, and progression status, the company's use of the registry data as a justification of the need for, or value of, a cure rate is spurious.

The ERG, therefore, considers that the company's choice of cure rate is arbitrary; it is unsupported by the company's own trial data and cannot be verified with registry data.

Clinical opinion on 5-year survival for patients with NSCLC

To assess the clinical plausibility of any projection, the company explored potential 5-year survival rates for patients treated with atezolizumab by eliciting opinions from clinicians. In the CS (p161), the company states that unanimous clinical opinion is that a value of 10% for the 5-year OS rate of patients receiving immunotherapy "…would not be implausible". The company did not provide any context to explain how this number was elicited from clinicians. The ERG considers that the phrase "…would not be implausible" should not be interpreted as 'likely'.

To support the 5-year OS rate of 10%, the company then referenced the final appraisal determination for TA428[15] (Pembrolizumab for treating PD-L1-positive NSCLC after chemotherapy) and states that, "…under the Committee's preferred assumptions, the resulting 5-year OS estimate was 10.4%" (CS, p161). The company has acknowledged, in response to an ERG clarification question, that the quoted value was inaccurate and should have been 9.6%. However, it is not just the number that is inaccurate; it is also the statement that this value was the **Committee's** preferred assumption. During TA428,[15] this 9.6% survival rate was generated using the **company's** preferred assumptions. The Committee and the ERG for that appraisal were particularly concerned about the company's assumption that treatment with pembrolizumab would generate a lifetime treatment effect; this **company** assumption generated the 9.6% 5-year OS rate. The Committee considered a more clinically plausible duration of treatment effect would be 3 years after treatment stopped, at which point the Committee considered that the mortality hazard for patients treated with pembrolizumab would be equal to the mortality hazard for patients treated with docetaxel.

The company assumed that 10% would be a plausible 5-year OS rate for patients treated with atezolizumab. However, the company's mixed cure-rate log-logistic model used in the base case analysis leads to an estimated 12.6% of patients receiving atezolizumab being alive at 5 years. The company's mixed cure-rate log logistic model, therefore, produces more optimistic

5-year survival estimates than the 'plausible' (but not 'most likely') estimate provided as clinical advice to the company, and is higher than an estimate thought 'optimistic' by a previous NICE Appraisal Committee who had evaluated immunotherapy in a population with NSCLC.

Implausibility of long-term projection

Due to the resultant long tail that is a characteristic of any log-logistic distribution, coupled with the lifetime duration of treatment effect, results from the company model suggest that 5.6% of patients treated with atezolizumab will be alive at 10 years, and 1.4% will be alive at 25 years. The company projection generates a 5-year mortality rate of 36.9% between years 20 and 25 of the model, when patients are aged between 83 and 88 years. However, the 5-year mortality rate for all people aged between 83 and 88 years, based on UK life tables[77] provided within the company model is 39.5%. The ERG considers the company projection is implausible as it leads to a situation where treatment with atezolizumab is not just keeping people with advanced NSCLC alive for 20 years and longer after progressing on their first treatment, it is also preventing them from dying from other, non-NSCLC, causes. Therefore, the ERG considers that i) the ICERs that are generated by this approach should not be used to inform decision-making and ii) that the log-logistic distribution is a poor choice of distribution for modelling the OS trial data.

5.5.3 ERG preferred approach to modelling OS: atezolizumab versus docetaxel

Kaplan-Meier data and extrapolation of overall survival

The ERG's preferred method is to model OS for both atezolizumab and docetaxel by using K-M data from the OAK trial for as long as possible, then append curves to project OS for the remainder of the model time horizon.

The minimum period for which follow-up OS data from the OAK trial are available for all patients is 19 months (83 weeks). After this point the number of patients at risk starts to decrease rapidly through censoring. Whilst deciding the point at which K-M data are no longer robust due to censoring is a subjective judgement, the ERG considers that, given that there is limited censoring up to 83 weeks, the data up to this point may be considered to be robust.

Inspection of the OS K-M data from the OAK trial suggests that there are three clear phases in the data between trial start and week 83, with different mortality ratios between atezolizumab and docetaxel for each phase. For the first 11 weeks, the hazard rates for patients in both arms of the trial are indistinguishable (Figure 13) implying a HR of one. Between weeks 11 and 56, if the population is rebased, a clear separation of survival between patients receiving atezolizumab and patients receiving docetaxel can be seen (

Figure 14) implying a HR for atezolizumab compared to docetaxel of less than one. If the population is again rebased at weeks 56, then between weeks 56 and 83 (the point after which follow-up data cease to be available for the full trial population) the picture is unclear (

Figure 15).

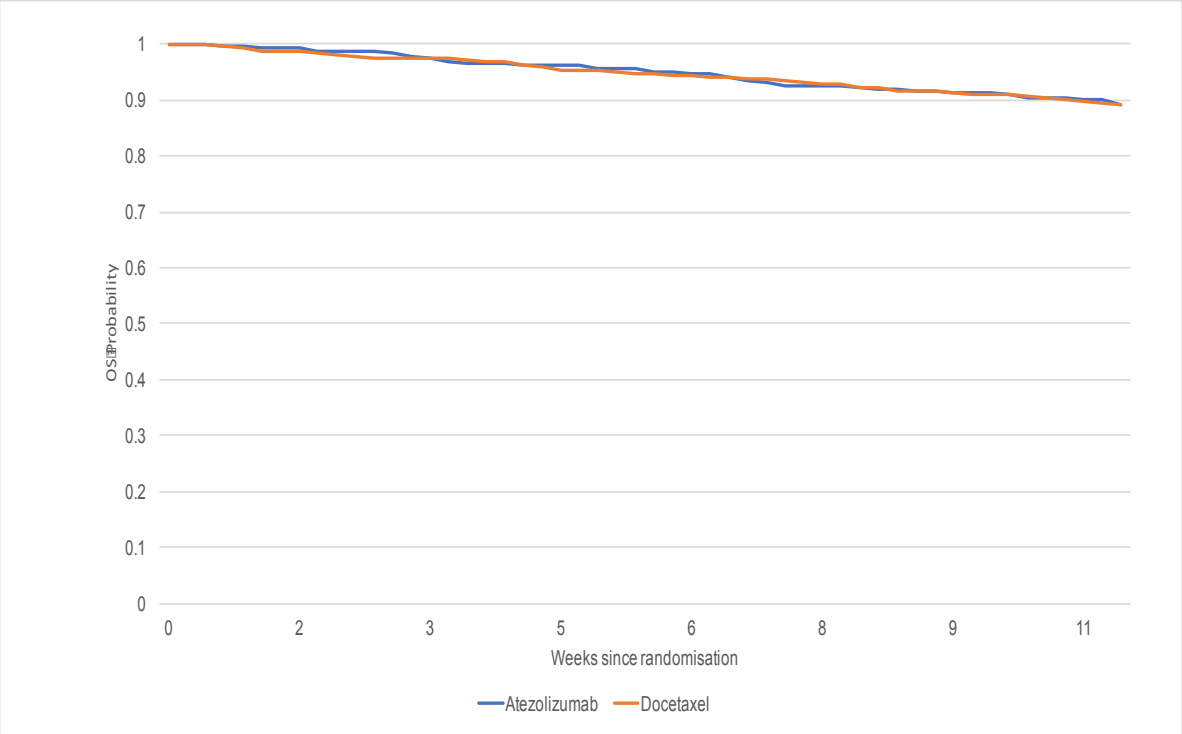

Figure 13 OS K-M data from the OAK trial for the first 11 weeks

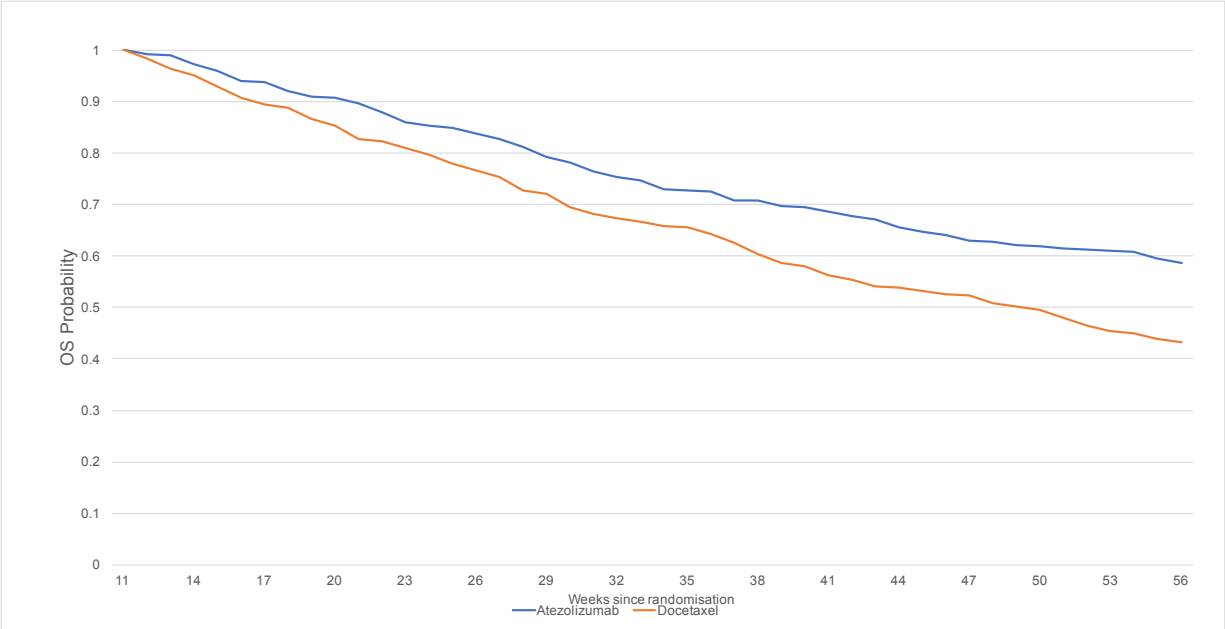

Figure 14 OS K-M data from the OAK trial, weeks 11 to 56 (rebased at week 11)

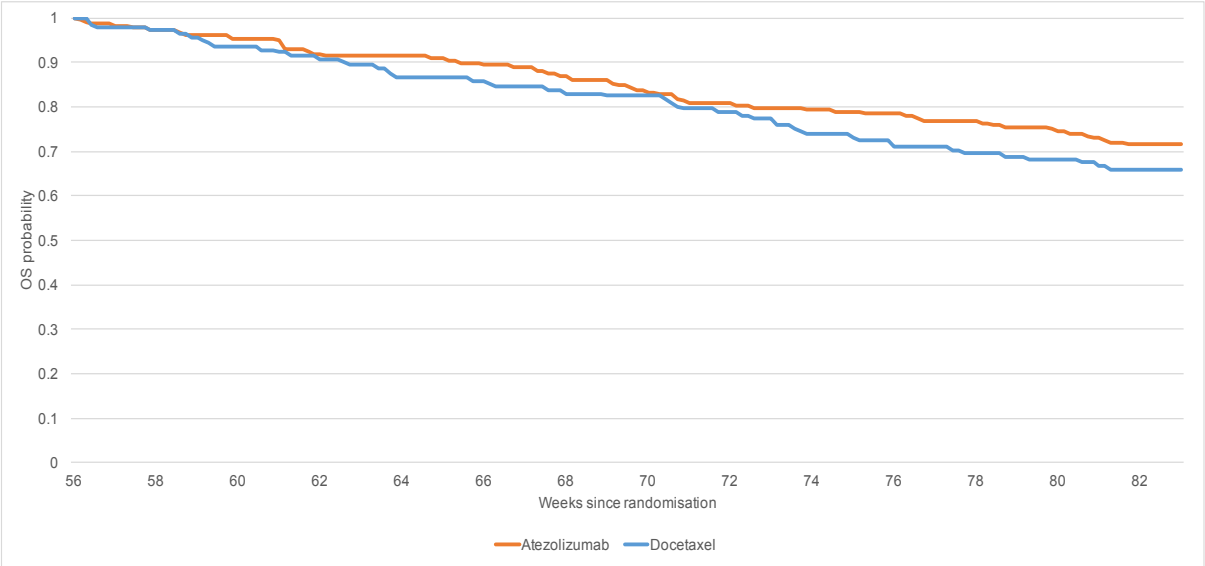

Figure 15 OS K-M data from the OAK trial, weeks 56 to 83 (rebased at week 56)

Between weeks 56 and 83 (

Figure 15) there may be some separation between the two arms of the OAK trial, but the K-M curves touch twice and visual inspection suggests that the HR between atezolizumab and docetaxel may have returned to one. Whilst the ERG is not convinced there is compelling evidence to support applying a differential hazard rate after week 56, the ERG estimated

distributions for extrapolation from week 56 onwards based on K-M data from weeks 56 to 83 separately for atezolizumab and docetaxel (see Figure 16 and Figure 17 respectively).

Inspection of the cumulative hazard plots for atezolizumab and docetaxel suggests that, between weeks 56 and 83, the cumulative hazards are linear and exponential distributions could fit both data sets over this period and could be used to extrapolate OS for both atezolizumab and docetaxel past week 56.

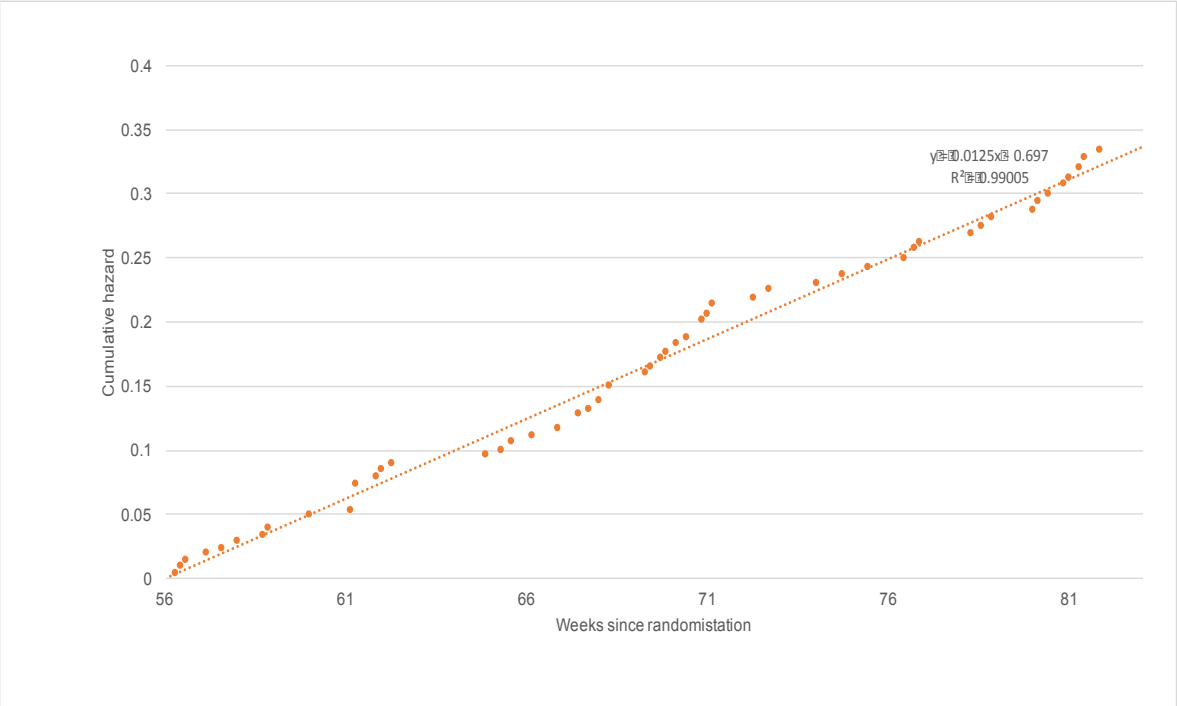

Figure 16 OS cumulative hazard plot for atezolizumab between weeks 56 and 83

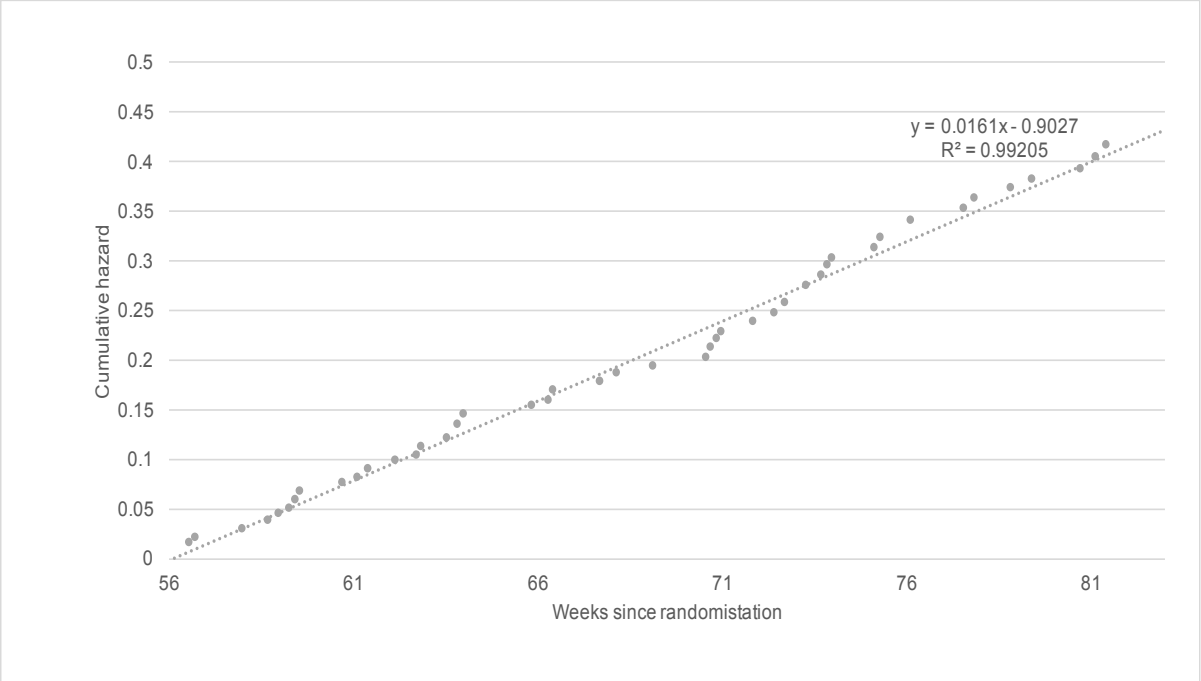

Figure 17 OS cumulative hazard plot for docetaxel between weeks 56 and 83

Duration of treatment effect

The company has assumed a lifetime duration of treatment effect for atezolizumab, this results in a lower mortality rate for patients who received atezolizumab versus docetaxel or nintedanib+docetaxel for the duration of the model. The NICE Appraisal Committee raised concerns during TA428[15] (Pembrolizumab for treating PD-L1positive NSCLC after chemotherapy) relating to the duration of treatment effect (after treatment had ended) associated with receiving an immunotherapy. Consequently, the ERG looked to cap the duration of treatment effect of atezolizumab at 3 years in line with the (TA428[15]) Committee's view on what could be considered a reasonable duration of treatment effect.

Whilst the company model allows the duration of treatment effect to be fixed, the approach that is used to stop the treatment effect in the model is simplistic. If the duration of treatment effect is set to be 'x' months in the model, then the hazard rate for atezolizumab is set to be equal to docetaxel at 'x' months after the **start** of the model. Any patients that stop atezolizumab in month 't' will have a duration of treatment effect for atezolizumab of x-t. This means the duration of treatment effect of atezolizumab in the model varies for patients and is not fixed and underestimates the true duration of treatment effect for atezolizumab of 'x' months if this is believed to exist in reality.

For example, if duration of treatment effect for atezolizumab is actually 3 years, then, in the model, setting the duration of treatment effect to 3 years would mean the duration of treatment effect of atezolizumab would be 2.5 years for a patient who stopped treatment after 6 months, but zero for a patient who is still on treatment at 3 years.

The method used in the model for dealing with duration of treatment effect for atezolizumab underestimates OS for atezolizumab if a treatment effect of 3 years actually exists and 36 months is entered into the model as the duration of treatment effect. Without restructuring the model, which is beyond the remit of the ERG, it is not possible to implement a more sophisticated approach to modelling the duration of treatment effect.

Taking the company model limitations into account but still attempting to implement a 3-year duration of treatment effect, the ERG set the *company model* duration of treatment effect to 5 years. As 8.5% of patients are predicted by the company's TTD extrapolation to be receiving atezolizumab at 2 years, this means that for those patients, if they are alive at 5 years, the duration of treatment effect will still be less than 3 years even though the duration of treatment effect is set to 5 years in the company model. However, patients who stopped treatment before 2 years and are still alive at 5 years will have a greater than 3 year treatment effect.

On balance, whilst there is no accurate way within the company model to set the duration of treatment effect for atezolizumab to 3 years, the ERG, therefore, considers that setting the *company model* duration of treatment effect to 5 years rather than 3 years probably produces more accurate ICERs per QALY gained if the real duration of treatment effect for atezolizumab is actually 3 years.

ERG remodelled OS for atezolizumab and docetaxel

The ERG's preferred OS curves for atezolizumab and docetaxel, taking into account the use of K-M data, exponential extrapolations and the ERG's preferred duration of treatment effect for atezolizumab are shown in Figure 18, with survival rates at different time points shown in Table 42.

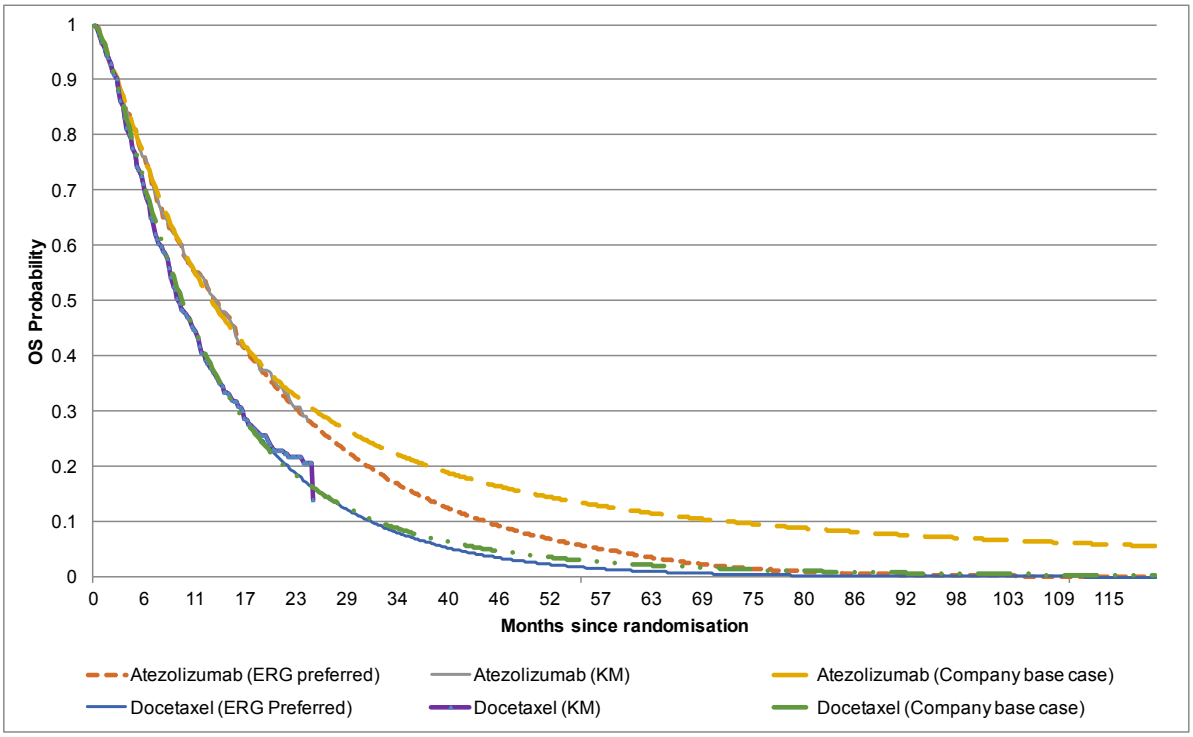

Figure 18 ERG preferred OS distributions compared to company modelled OS and K-M data

Table 42 Estimates, generated using different survival data or projections, of proportions of patients alive at different time points since randomisation

OS curve	Time since randomisation					
	1 year	2 years	5 years	10 years	20 years	25 years
Atezolizumab (K-M)	54.7%	28.1%	-	-	-	-
Atezolizumab (company base case)	53.6%	31.1%	12.2%	5.5%	2.2%	1.4%
Atezolizumab (ERG preferred)	54.7%	28.5%	4.4%	0.1%	0.0%	0.0%
Docetaxel (K-M)	41.7%	20.6%	-	-	-	-
Docetaxel (company base case)	42.5%	16.8%	2.4%	0.0%	0.0%	0.0%
Docetaxel (ERG preferred)	41.7%	17.0%	1.2%	0.0%	0.0%	0.0%

ERG=Evidence Review Group; K-M=Kaplan-Meier

Applying the ERG's preferred OS distribution and preferred duration of treatment effect to the ERG's corrected company base case reduces the incremental QALY gain from atezolizumab compared to docetaxel from 0.746 to 0.302. This increases the ERG's corrected company base case ICER by £92,928 to £170,497 per QALY gained.

5.5.4 ERG preferred approach to modelling OS: atezolizumab versus nintedanib+docetaxel

The ERG asked the company to indirectly compare atezolizumab versus nintedanib+docetaxel in the adenocarcinoma population only. However, these results were

not provided by the company. Instead, the company provided the results of atezolizumab (total population, OAK and POPLAR trials) versus nintedanib+docetaxel (adenocarcinoma population, LUME-Lung 1 trial). It may be that if only the adenocarcinoma populations were compared, then a statistically significant difference in OS would have emerged. In the absence of this analysis, the ERG considers that the company has concluded that the effectiveness of atezolizumab on OS is independent of whether a patient does or does not have adenocarcinoma. As such, the OS for patients with adenocarcinoma and treated with nintedanib+docetaxel can be compared fairly to all patients treated with atezolizumab. Consequently, as this comparison shows there is no statistically significant difference in OS, the ERG concludes that there is no justification for modelling a different OS curves for atezolizumab and nintedanib+docetaxel.

Setting OS equal for atezolizumab and nintedanib+docetaxel results in the QALY gain for atezolizumab falling to 0.027 with the ERG corrected company base case ICER for atezolizumab versus nintedanib+docetaxel increasing to £1,170,260 per QALY gained, assuming a lifetime duration of treatment effect for both treatments. If the duration of treatment effect is limited to approximately 3 years using the method described previously, the ICER would increase to £1,170,793 per QALY gained for atezolizumab versus nintedanib+docetaxel.

5.6 Conclusions of the cost effectiveness section

The ERG considers that there are three errors in the company model. These relate to discounting, age-related disutility and the half-cycle correction applied to TTD data. The ERG considers that these errors must be corrected to allow accurate estimates of the cost effectiveness of atezolizumab versus docetaxel, or atezolizumab versus nintedanib+docetaxel, under the company base case assumptions. Once these errors have been corrected, the ERG's major concerns relate to the assumptions made by the company in relation to modelling OS for patients receiving all treatments.

Treatment with atezolizumab was modelled by the company using a mixed cure-rate model that was not fully justified as being necessary, was arbitrarily specified and ultimately produced implausible projections of the mortality hazard rate associated with treatment with atezolizumab. The ERG considers that the use of a mixed cure-rate model was unnecessary and that the OS of patients receiving atezolizumab could have been modelled simply by using K-M data from the OAK trial for as long as the data are robust and then extrapolating the trial data by appending an exponential distribution. Similarly, modelling OS for patients receiving docetaxel could be carried out using the same approach.

The ERG notes that inspection of the K-M data from week 56 of the OAK trial does not necessarily justify the application of a different mortality hazard rate from this point onwards for atezolizumab and docetaxel. However, given the OAK trial was not powered to identify a difference in OS from week 56, the ERG applied different exponential distributions from week 56 for the two therapies. Nevertheless, the cost effectiveness results generated from these ERG models of OS can be interpreted as optimistically favouring treatment with atezolizumab as the ERG does not consider it implausible that the mortality hazard from week 56 may be the same for both atezolizumab and docetaxel.

The company model allowed the duration of treatment effect for atezolizumab to be fixed, albeit in a simplistic way. The ERG fixed the duration of treatment effect such that is approximately 3 years in line with the duration thought plausible for immunotherapy by the NICE Appraisal Committee assessing pembrolizumab as second-line treatment for patients with advanced or metastatic PD-L1 positive NSCLC.

The ERG does not consider that, from analysis of the clinical trial data that are currently available, there is statistically significant evidence to justify a differential OS for atezolizumab compared to nintedanib+docetaxel for the adenocarcinoma population for which nintedanib is licensed and an OS gain should not be included in the company model.

6 SUMMARY OF ADDITIONAL WORK UNDERTAKEN BY THE ERG

Details of the ERG's revisions to the company model may be found in the appendices (Section 10.8). A summary of the effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of atezolizumab versus docetaxel and for the comparison of atezolizumab versus nintedanib+docetaxel are provided in Table 43 and Table 44 respectively.

The ERG considers the first three changes (C1 to C3) to be corrections to the company model. The changes have been implemented as a result of identifying errors or omissions and, therefore, reflect inaccuracies rather than differences of opinion between the ERG and the company. The ERG considers that making these corrections allows the generation of ICERs per QALY gained that fairly reflect the company base case assumptions. Applying the three corrections increases the size of company's base case ICER for the comparison of atezolizumab versus docetaxel by £5,213 to £77,569 per QALY gained. For the comparison of treatment with atezolizumab versus nintedanib+docetaxel, applying the three corrections increases the company's ICER by £4,290 to £60,366 per QALY gained.

The major amendments made by the ERG to the corrected company base case model relate to modelling OS. The ERG considers the company's approach to modelling OS for patients receiving atezolizumab to be insufficiently justified. The ERG considers that, not only was the approach used by the company not supported by the available OAK trial data, but that it also led to a risk of death, in the long-term, that was higher than the risk for the general population. The ERG considers that OS for atezolizumab can be more accurately and simply modelled using the OAK trial data and, once a constant hazard had been observed in the data, appending an exponential function.

In addition, the ERG also adjusted the model so as to limit the duration of treatment effect of atezolizumab to approximately 3 years from the lifetime duration of treatment effect assumed in the company base case.

In terms of modelling the survival of patients treated with docetaxel, the ERG considers that an adequate model could be created without the need for the FP ITC in a similar manner as for atezolizumab. The ERG considers that OS for atezolizumab can be more accurately and simply modelled using the OAK trial data and, once a constant hazard had been observed in the data, appending an exponential function.

Applying the ERG's preferred OS projections for patients receiving atezolizumab and docetaxel, increases the ERG's corrected company base case ICER by £87,741 to £165,310 per QALY gained (R1). While implementing the ERG's preferred projections for the atezolizumab and docetaxel arms **and** setting the treatment duration effect for atezolizumab to approximately 3 years, increases the ERG's corrected company base case ICER for the comparison of atezolizumab versus docetaxel by £92,928 to £170,497 per QALY gained (R2).

There is no statistically significant evidence to support the claim that atezolizumab generates an OS gain compared to nintedanib+docetaxel. Assuming the same OS for patients treated with atezolizumab and nintedanib+docetaxel and a lifetime duration of treatment effect, results in the ERG corrected company base case ICER for atezolizumab versus nintedanib+docetaxel increasing by £1,109,894 to £1,170,260 per QALY gained (R3). Assuming the same OS for patients treated with atezolizumab and nintedanib+docetaxel and an approximate 3 year duration of treatment effect for both treatments results in the ERG corrected company base case ICER for atezolizumab versus nintedanib+docetaxel increasing by £1,110,427 to £1,170,793 per QALY gained (R4).

Table 43 Cost effectiveness results for atezolizumab versus docetaxel with ERG revisions to company base case (list prices)

Model scenario & ERG revisions	Atezolizumab			Docetaxel			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change
Company base case	**£73,911**	**1.471**	**2.224**	**£19,941**	**0.725**	**1.188**	**£53,970**	**0.746**	**1.036**	**£72,356**	-
C1) Discounting algorithms	£74,479	1.479	2.236	£20,111	0.732	1.198	£54,367	0.747	1.038	£72,764	**+£408**
C2) Age-related utility decrement	£73,911	1.437	2.224	£19,941	0.720	1.188	£53,970	0.717	1.036	£75,316	**+£2,960**
C3) TTD half-cycle correction	£75,468	1.472	2.224	£20,197	0.726	1.188	£55,271	0.746	1.036	£74,092	**+£1,736**
ERG corrected company base case (C1-C3)	**£76,046**	**1.446**	**2.236**	**£20,369**	**0.728**	**1.198**	**£55,677**	**0.718**	**1.038**	**£77,569**	**+£5,213**
R1) ERG preferred OS for atezolizumab and docetaxel	£71,525	0.998	1.544	£19,951	0.686	1.134	£51,574	0.312	0.409	£165,310	**+£92,954**
R2) ERG preferred OS for atezolizumab and docetaxel, and atezolizumab treatment duration effect set to 3 years	£71,418	0.988	1.527	£19,951	0.686	1.134	£51,467	0.302	0.393	£170,497	**+£98,141**

Costs and QALYs discounted; life years undiscounted
OS=overall survival; QALYs=quality adjusted life years; TTD=time to treatment discontinuation; ICER=incremental cost effectiveness ratio

Table 44 Cost effectiveness results for atezolizumab versus nintedanib+docetaxel with ERG revisions to company base case (list prices)

Model scenario & ERG revisions	Atezolizumab			Nintedanib+docetaxel			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change
Company base case	**£73,911**	**1.471**	**2.224**	**£37,702**	**0.826**	**1.315**	**£36,209**	**0.646**	**0.910**	**£56,076**	**-**
C1) Discounting algorithms	£74,479	1.479	2.236	£37,582	0.820	1.306	£36,896	0.659	0.930	£55,959	**-£117**
C2) Age-related utility decrement	£73,911	1.437	2.224	£37,702	0.819	1.315	£36,209	0.618	0.910	£58,608	**+£2,532**
C3) TTD half-cycle correction	£75,468	1.472	2.224	£37,999	0.826	1.315	£37,470	0.647	0.910	£57,949	**+£1,873**
ERG corrected company base case (C1-C3)	**£76,046**	**1.446**	**2.236**	**£37,879**	**0.813**	**1.306**	**£38,168**	**0.632**	**0.930**	**£60,366**	**+£4,290**
R3) ERG preferred OS for atezolizumab and assumed equal for nintedanib+docetaxel	£71,525	0.998	1.544	£39,420	0.970	1,544	£32,105	0.027	0.000	£1,170,260	**+£1,114,185**
R4) ERG preferred OS for atezolizumab and assumed equal for nintedanib+docetaxel, and treatment duration effect for both set to 3 years	£71,418	0.988	1.527	£39,313	0.961	1.527	£32,105	0.027	0.000	£1,170,793	**+£1,114,718**

Costs and QALYs discounted; life years undiscounted
OS=overall survival; QALYs=quality adjusted life years; TTD=time to treatment discontinuation; ICER=incremental cost effectiveness ratio

7 END OF LIFE

The NICE End of Life criteria, and the data presented by the company to show that these have been met, are presented in Table 45.

Table 45 End of life criteria

<table>
<tr><th>NICE End of Life criteria</th><th>Data presented by the company</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>The company considers this criterion to be met and quotes values from Beckett 2013[78] that show median survival for patients with Stage IIIb and Stage IV NSCLC is 7.5 months and 3.4 months, respectively (CS, Section 3.4)</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>The company considers this criterion to be met and quotes data (CS, Figure 8) from the OAK trial that show that treatment with atezolizumab is associated with a statistically significant improvement in OS compared with docetaxel in the ITT population (HR 0.73, 95% CI: 0.62 to 0.87).
The company also highlights that results from the OAK trial (CS, Section 4.7) show that median OS in the ITT population is 9.6 months (95% CI: 8.6 to 11.2) in the docetaxel arm and 13.8 months (95% CI: 11.8 to 15.7) in the atezolizumab arm
<u>Company economic model results</u>
Results from the company model (CS, Section 5.7) show that mean OS of patients treated with atezolizumab is >3 months versus all comparators, and median OS results are >3 months versus docetaxel:
<table>
<tr><td></td><td>Mean (months)</td><td>Median (months)</td></tr>
<tr><td>Atezolizumab</td><td>31.1</td><td>13.3</td></tr>
<tr><td>Docetaxel</td><td>14.1</td><td>9.8</td></tr>
<tr><td>Nintedanib+docetaxel</td><td>16.4</td><td>10.6</td></tr>
</table>
</td></tr>
</table>

ITT=intention to treat; HR=hazard ratio; CS=company submission; OS=overall survival
Source: CS, Table 50

Short life expectancy

The ERG agrees with the company that patients with advanced or metastatic NSCLC have a life expectancy of less than 24 months, although the survival estimates quoted by the company relate to **all** patients with Stage IIIb and Stage IV NSCLC and the population being considered in this appraisal is restricted to patients who have progressed after prior chemotherapy. However, as the K-M data from the OAK trial suggest that median life expectancy for patients receiving docetaxel is 9.6 months, the NICE End of Life criteria for short life expectancy criteria is met.

Extension to life

An examination of the ERG's remodelled OS suggests that treatment with atezolizumab generates a mean survival gain of 4.7 months compared to docetaxel. Suggesting that when the whole trial population is considered patient life expectancy is extended by more than 3 months when treatment with atezolizumab is compared with docetaxel.

However, when treatment with atezolizumab is compared with nintedanib+docetaxel, the size of the survival gain is uncertain. The company provided evidence during the clarification

process which suggests there is no statistically significant difference in OS for atezolizumab (total population) compared to nintedanib+docetaxel (adenocarcinoma patients only). If there is no statistically significant difference in OS, then, for the adenocarcinoma population, atezolizumab does not offer an extension of life of at least 3 months and so does not meet the NICE End of Life criteria for life extension.

8 OVERALL CONCLUSIONS

Discrepancies between the decision and the final scope issued by NICE

The ERG considers that the submitted evidence largely reflects the decision problem defined in the final scope issued by NICE, except that pembrolizumab was not considered as a comparator and the comparison of the efficacy of treatment with atezolizumab versus nintedanib+docetaxel should have been carried out using data from only the nintedanib+docetaxel licensed population, i.e. patients with adenocarcinoma. Furthermore, the ERG considers that full subgroup analyses based on levels of PD-L1 expression should have been undertaken.

Direct evidence

The direct clinical effectiveness evidence for the treatment of atezolizumab versus docetaxel was derived from the OAK and POPLAR trials. The ERG considers that both these trials were of good quality and were well conducted; patient characteristics were balanced across the groups, and statistical methods were generally appropriate. The ERG agrees with the company that the AE data from the OAK trial are consistent with the known AE profile of atezolizumab and that no new safety concerns have been highlighted. In terms of survival results (OS and PFS), the ERG considers that the company's median HR values from the OAK and POPLAR trials should be viewed with caution as the method used to calculate them relies on an assumption of PH which does not hold.

Results from both the OAK and POPLAR trials show that treatment with atezolizumab is associated with a statistically significant and clinically meaningful improvement in median OS (4.2 months in the OAK trial and 2.9 months in the POPLAR trial) compared to docetaxel in patients with ECOG PS 0 and 1. In the OAK trial, this statistically significant gain in OS is observed regardless of histology and PD-L1 status. However, in the POPLAR trial, statistically significant improvement is observed only in the non-squamous histology subgroup and for individuals with NSCLC of ≥1% PD-L1 expression.

Indirect evidence

The ERG considers that the company applied the ITC methodology using FP models appropriately but does not support the original ITC approach taken by the company as the:

- main network includes comparators that are not listed in the final scope issued by NICE and excludes pembrolizumab, which is listed in the final scope
- comparison of the effectiveness of atezolizumab versus nintedanib+docetaxel was carried out using data from the whole populations included in the trials and not just the population with adenocarcinoma histology (the nintedanib+docetaxel licensed population).

The ERG considers that the company's approach to the FP ITC is influenced by a range of factors (e.g., comparators and population selected, type of FP model chosen and the use of FE or RE) and that this means that it is difficult to identify the most appropriate combination of factors to use to generate ITC results. Furthermore, the ERG considers that the expected survival results generated by the ITC are difficult to interpret.

Economic evidence

The ERG considered that the mixed cure-rate model used to represent OS of patients receiving atezolizumab led to implausible OS estimates; this is due to the use of a log-logistic distribution, the cure-rate fraction, and an optimistic assumption that treatment with atezolizumab confers a lifetime effect. The ERG highlights that, at some time points, the company's OS model for atezolizumab produces survival estimates that are higher than the respective UK age-related population values.

The approach taken by the company to model OS for patients receiving docetaxel and nintedanib+docetaxel was to adjust the survival curve created to represent OS for patients receiving atezolizumab using hazard rates generated by their FP ITCs. Due to the implausibility of the company's atezolizumab OS model and methodological challenges related to the company's ITCs, the ERG considers that these OS models are unreliable.

Application of the ERG model amendments results in an ICER for the comparison of treatment with atezolizumab versus nintedanib+docetaxel of £1,170,793 per QALY gained. The ERG notes that this is a huge increase from the £56,076 per QALY gained estimated by the company and that this increase is largely due to the results of the company's ITC which showed that expected OS for patients receiving atezolizumab (total population) is not statistically significantly different from that of patients receiving nintedanib+docetaxel (adenocarcinoma population).

8.1 Implications for research

Grigg[79] et al highlight that currently published tissue studies have found PD-L1 positivity to indicate favourable, unfavourable, as well as variable correlations with histology and mutation status in NSCLC and other tumour types. Cree et al[32] identify a number of issues that they consider should be addressed to ensure that PD-L1 testing is introduced effectively into routine practice:

- relevance of tissue source and sample quality
- heterogeneity of PD-L1 expression within the tumour, between primary and metastatic lesions and over time
- impact of prior lines of treatment on PD-L1 expression

- optimal cut-offs identifying appropriate patient populations for treatment
- national and regional rates of PD-L1 positivity
- reproducibility and concordance of companion diagnostic kits and platforms
- validation of tumour infiltrating lymphocytes (LDTs) laboratory developed tests
- role of TILs and/or staining intensity in interpretation
- role of digital pathology.

The ERG considers that further research is required to address the issues identified by Cree et al.[32]

There is no direct clinical evidence to allow a comparison of the effectiveness of treatment, following chemotherapy, with atezolizumab versus nintedanib+docetaxel in patients with adenocarcinoma histology or versus pembrolizumab in patients with ≥1% PD-L1 expression. The results of head-to-head trials of atezolizumab versus these comparators in restricted patient populations would be useful.

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10 APPENDICES

10.1 Proportional Hazards Testing of the POPLAR trial

The company provided three diagnostic plots for OS and PFS indicating non PH between the treatment arms. The ERG agrees with the judgement of the company that the PH assumption does not hold for both OS and PFS in the POPLAR trial

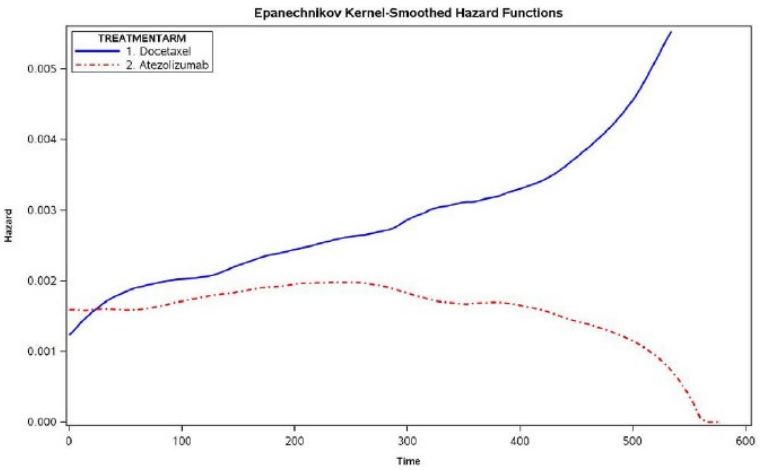
10.1.1 Overall survival

The company interpreted the three plots as follows:

For the OS hazard function plot, the two hazard curves crossed over at around 1 month and started to separate from each other around 8 months (Figure 19), the two curves of the log of negative log plots for OS overlapped at various time points and were clearly not parallel (

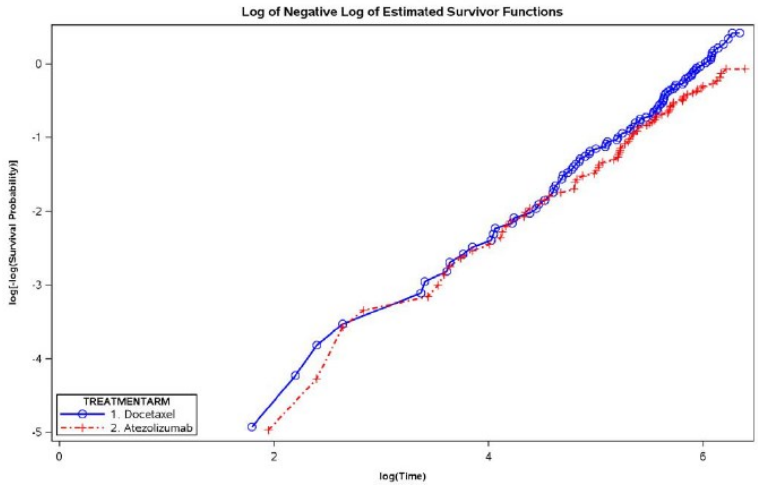
Figure 20) and for the log of survival plots, a trend of two lines passing the origin was observed, with one on top of the other, the overlap from randomization to approximately 3 months revealed a potential non-proportionality between the hazards of the two arms (Figure 21)

Figure 19 OS hazard function plot



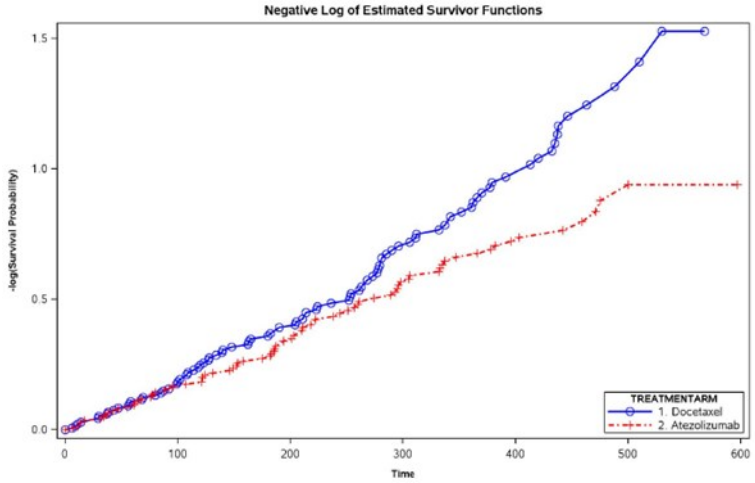
Source: Company response to ERG clarification letter

Figure 20 OS log of negative log plots



Source: Company response to clarification letter

Figure 21 OS log of survival plot



Source: Company response to ERG clarification letter

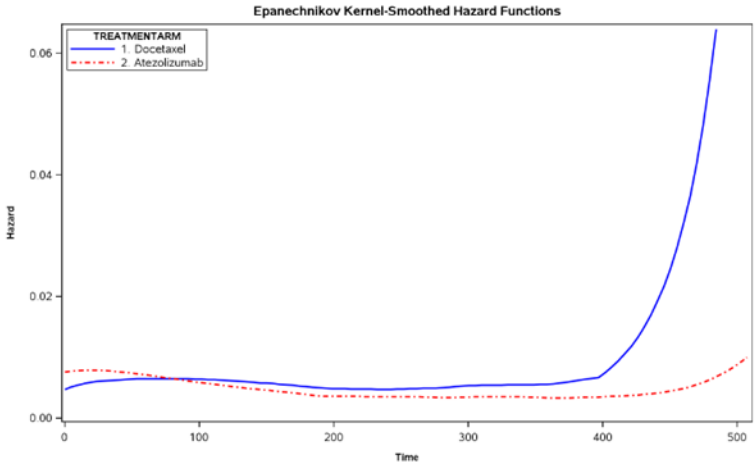
10.1.2 Progression-free survival

The company interpreted the three plots as follows:

For the PFS hazard function plot, the two curves were approximately parallel until around 13 months, corresponding to the minimum follow-up time (

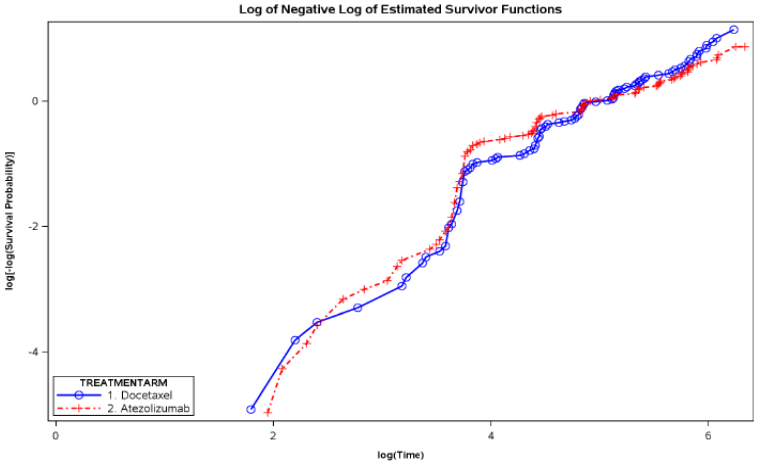
Figure 22), the two curves of the log of negative log plots for PFS overlapped (Figure 23) and the log of survival plots showed a cross-over pattern between the atezolizumab and docetaxel arms, where the crossing occurred approximately at 4-5 months (Figure 24).

Figure 22 PFS hazard function plot



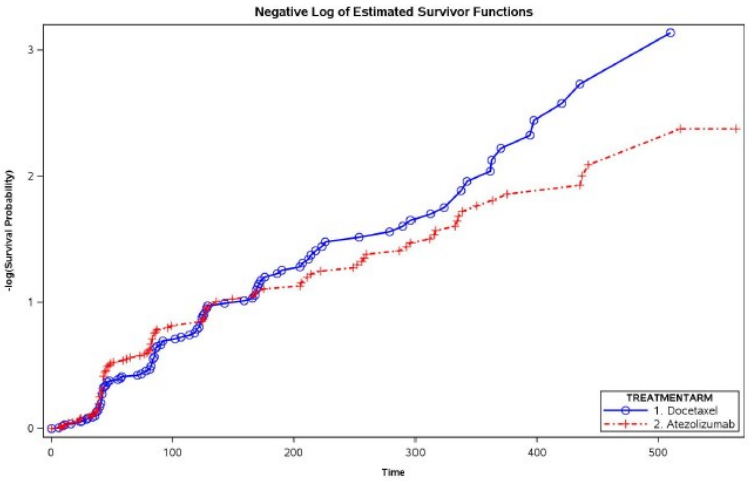
Source: Company response to ERG clarification letter

Figure 23 PFS log of negative log plots



Source: Company response to ERG clarification letter

Figure 24 PFS log of survival plot



Source: Company response to clarification letter

10.2 Additional secondary efficacy endpoints reported in the OAK and POPLAR trials

The main efficacy outcomes for the OAK and POPLAR trials were OS (primary outcome) and PFS (secondary outcome); the definitions and methods of analysis for these outcomes are presented in Table 9 of this report. ORR and DOR were also reported as secondary efficacy outcomes in the OAK and POPLAR trials, the definitions and methods of analysis for these outcomes are presented in Table 46.

Table 46 Description and method of analysis for secondary efficacy outcomes (other than time to progression and overall survival) reported in the OAK and POPLAR trials

Outcome	Outcome definition	Censoring definition	Statistical analysis
OAK			
ORR	Proportion of patients achieving confirmed best response of CR or PR per RECIST v1.1	Patients without any post baseline tumour assessments were considered non-responders	Clopper-Pearson methods for 95% CI of response rates and Mantel-Haenszel test for difference in rates
DOR	Interval between first documented objective response (CR or PR) and first documented PD or death	Date of last tumour measurement	Kaplan-Meier methodology, stratified in the 1°P and TC1/2/3 or IC1/2/3 subgroup , unstratified for all other subgroups
POPLAR			
ORR	Proportion of patients achieving confirmed best response of CR or PR per RECIST v1.1	n/a	Clopper-Pearson methods for 95% CI of response rates and Mantel-Haenszel test for difference in rates
DOR	Interval between first documented objective response (CR or PR) and first documented PD or death	Date of last tumour measurement	Kaplan-Meier methodology

1°P=primary population; CI=confidence interval; CR=complete response; DOR=duration of response; IC=tumour-infiltrating immune cell; ITT=intention-to-treat; ORR=objective response rate OS=overall survival, PD=progressive disease; PFS=progression-free survival; PR=partial response; RECIST=response evaluation criteria in solid tumours; TC=tumour cell
Source: CS, adapted from Table 21 and Table 22

The ERG is satisfied that the analysis method for each of these efficacy outcomes was pre-specified in the TSAPs, but notes a slightly different censoring definition for DOR in the OAK trial in the TSAP from the CS; the date of the first occurrence of a complete or partial response plus one day. The ERG is satisfied that all results were reported fully in the CSRs.

10.3 Additional analyses of overall survival reported in the POPLAR trial

The results for primary outcome OS for the POPLAR trial were presented from the updated analysis in the CS; these results are summarised in Section 4.3.2 of this report. OS was also analysed at two previous time points in the POPLAR trial for an interim analysis and the primary analysis and the extended follow-up in the POPLAR trial demonstrates increased benefit with atezolizumab compared to docetaxel. Results of OS in the POPLAR trial with increasing data maturity are presented in Table 47.

Table 47 OS in the POPLAR trial with increasing data maturity

Outcome	Atezolizumab (n=144)	Docetaxel (n=143)
Interim analysis[a]		
Median OS, months (95% CI)	11.4 (9.7 to NE)	9.5 (8.6 to 11.9)
HR (95% CI) – stratified for ITT population	0.77 (0.56 to 1.06, log-rank p-value=0.1145)	
Primary analysis[b]		
Median OS, months (95% CI)	12.6 (9.7 to 16.4)	9.7 (8.6 to 12.0)
HR (95% CI) – stratified for ITT population	0.73 (0.53 to 0.99, log-rank p-value=0.0404)	
Updated analysis[c]		
Median OS, months (95% CI)	12.6 (9.7 to 16.0)	9.7 (8.6 to 12.0)
HR (95% CI) – stratified for ITT population	0.69 (0.52 to 0.92, log rank p-value=0.011)	

[a] The data cut-off for the interim analysis was 30th January 2015
[b] The data cut-off date for the primary analysis was 8th May 2015
[c] The data cut-off date for the updated analysis was 1st December 2015
CI=confidence interval; ITT=intention-to-treat; NE=not evaluable; OS=overall survival
Source: CS, adapted from Section 4.7, Figure 12; POPLAR CSR adapted from Table 2, Table 21.

Overall survival results from the primary and updated analyses of the POPLAR trial according to histology and to PD-L1 status are presented in Table 48. The results presented in this table are discussed in Section 4.3.2 of this report.

Table 48 Overall survival results in the POPLAR trial according to histology and to PD-L1 status (primary and updated analyses)

Outcome	Primary analysis (data cut-off: 8st May 2015)		Updated analysis (data cut-off: 1st December 2015)	
	Atezolizumab	Docetaxel	Atezolizumab	Docetaxel
ITT population				
Number of participants analysed	144	143	144	143
Median OS, months (95% CI)	12.6 (9.7 to 16.4)	9.7 (8.6 to 12.0)	12.6 (9.7 to 16.0)	9.7 (8.6 to 12.0)
HR (95% CI) - stratified for ITT population	0.73 (0.53 to 0.99, log-rank p-value=0.0404)		0.69 (0.52 to 0.92, log-rank p-value=0.011)	
Histology: Non-squamous NSCLC				
Number of participants analysed	95	95	95	95
Median OS, months (95% CI)	15.5 (9.8 to NE)	10.9 (8.8 to 13.6)	14.8 (9.8 to 19.5)	10.9 (8.8 to 13.6)
HR (95% CI) – unstratified	0.69 (0.47 to 1.01, log-rank p-value=0.0562)		0.69 (0.49 to 0.98, log-rank p-value=0.039)	
Histology: Squamous NSCLC				
Number of participants analysed	49	48	49	48
Median OS, months (95% CI)	10.1 (6.7 to 14.5)	8.6 (5.4 to 11.6)	10.1 (6.7 to 14.5)	8.6 (5.4 to 11.6)
HR (95% CI) – unstratified	0.80 (0.49 to 1.30, log-rank p-value=0.3617)		0.66 (0.41 to 1.05, log-rank p-value=0.075)	
PD-L1 subgroup: TC3 or IC3				
Number of participants analysed	24	23	24	23
Median OS, months (95% CI)	15.5 (9.8 to NE)	11.1 (6.7 to 14.4)	NE (9.8 to NE)	11.1 (6.7 to 14.4)
HR (95% CI) – unstratified	0.49 (0.22 to 1.07, log-rank p-value=0.0684)		0.45 (0.22 to 0.95, log-rank p-value=0.033)	
PD-L1 subgroup: TC2/3 or IC2/3				
Number of participants analysed	50	55	50	55
Median OS, months (95% CI)	15.1 (8.4 to NE)	7.4 (6.0 to 12.5)	15.1 (8.4 to NE)	7.4 (6.0 to 12.5)
HR (95% CI) – unstratified	0.54 (0.33 to 0.89, log-rank p-value =0.0146)		0.50 (0.31 to 0.88, log-rank p-value=0.003)	
PD-L1 subgroup: TC2/3 or IC2/3 excluding TC3 or IC3				
Number of participants analysed	26	32	NR	NR
Median OS, months (95% CI)	9.0 (NR to NR)	6.2 (NR to NR)	NR	NR
HR (95% CI) – unstratified	0.59 (0.31 to 1.12, log-rank p-value =NR)		NR	
PD-L1 subgroup: TC1/2/3 or IC1/2/3				
Number of participants analysed	93	102	93	102
Median OS, months (95% CI)	15.5 (11.0 to NE)	9.2 (7.3 to 12.8)	15.1 (11.0 to NE)	9.2 (7.3 to 12.8)

HR (95% CI) – stratified for PD-L1 status	0.59 (0.40 to 0.85, log-rank p-value=0.0050)		0.59 (0.41 to 0.83, log-rank p-value=0.003)	
PD-L1 subgroup: TC1/2/3 or IC1/2/3 excluding TC2/3 or IC/23				
Number of participants analysed	43	47	NR	NR
Median OS, months (95% CI)	15.6 (NR to NR)	12.4 (NR to NR)	NR	NR
HR (95% CI) – unstratified	0.65 (0.37 to 1.16, log-rank p-value =NR)		NR	
PD-L1 subgroup: TC0 or IC0				
Number of participants analysed	51	41	51	41
Median OS, months (95% CI)	9.7 (6.7 to 12)	9.7 (6.8 to 12)	9.7 (6.7 to 12.0)	9.7 (8.6 to 12.0)
HR (95% CI) – unstratified	1.04 (0.62 to 1.75, log-rank p-value =0.8713)		0.88 (0.55 to 1.42, log-rank p-value=0.601)	

CI=confidence interval; IC=tumour-infiltrating immune cell; ITT=intention-to-treat; NE=not evaluable; NR=not reported NSCLC=non-small cell lung cancer; OS=overall survival; PD-L1=programmed death-ligand 1; TC=tumour cell
Source: adapted from Smith et al 2016; CS adapted from Section 4.7, Section 4.8, Figure 11 and Figure 16; POPLAR CSR, adapted from Table 23 and Table 34.

10.4 POPLAR trial: additional analyses of progression-free survival

The results for secondary outcome investigator assessed PFS for the POPLAR trial were presented from the updated analysis in the CS; these results are summarised in Section 4.3.3 of this report. PFS was also analysed at two previous time points in the POPLAR trial for an interim analysis and the primary analysis and the extended follow-up in the POPLAR trial; no statistically significant difference between treatment arms was observed at any time. Results of PFS in the POPLAR trial with increasing data maturity are presented in Table 49.

Table 49 POPLAR trial investigator-assessed PFS

Outcome	**Atezolizumab (n=144)**	**Docetaxel (n=143)**
Interim analysis[a]		
Median PFS, months (95% CI)	2.8 (2.1 to 4.1)	3.4 (2.8 to 4.1)
Hazard ratio (95% CI) – stratified for ITT population	0.98 (0.74 to 1.28, log-rank p-value=0.8606)	
Primary analysis[b]		
Median PFS, months (95% CI)	2.7 (2.0 to 4.1)	3.0 (2.8 to 4.1)
Hazard ratio (95% CI) – stratified for ITT population	0.94 (0.72 to 1.20, log-rank p-value=0.6450)	
Updated analysis[c]		
Median PFS, months (95% CI)	2.7 (2.0 to 4.1)	3.4 (2.8 to 4.1)
Hazard ratio (95% CI) – stratified for ITT population	0.92 (0.71 to 1.20, log-rank p-value=0.5560)	

[a] The data cut-off for the interim analysis was 30th January 2015
[b] The data cut-off date for the primary analysis was 8th May 2015
[c] The data cut-off date for the updated analysis was 1st December 2015
CI=confidence interval; ITT=intention-to-treat; PFS=progression-free survival
Source: CS, adapted from Section 4.7, Figure 13; POPLAR CSR adapted from Table 25; Table 48.

10.5 OAK and POPLAR trials: additional analyses of secondary endpoints

The results of the analyses for the secondary outcomes of the OAK and POPLAR trials not reported in the main body of this ERG report are provided in Table 50. ORR and DOR determined by the investigator per RECIST v1.1 were analysed for the 1°P of the OAK trial and the ITT population of the POPLAR trial. The company confirmed that no blinded independent central review of any endpoints explored in either of the OAK or POPLAR trials.

Table 50 ORR and DOR among responders (OAK and POPLAR trials)

Outcome	OAK (primary analysis)		POPLAR (updated analysis)	
	Atezolizumab	Docetaxel	Atezolizumab	Docetaxel
ORR per RECIST v1.1				
Number of participants analysed	425	425	144	143
Responders, n (%) (95% CI)	58 (13.6) (10.53 to 17.28)	57 (13.4) (10.32 to 17.02)	22 (15.3) (9.8 to 22)	21 (14.7) (9.3 to 21.6)
Complete response, n (%) (95% CI)	6 (1.4) (0.52 to 3.05)	1 (0.2) (0.01 to 1.30)	1 (0.7) (NR to NR)	0 (0) (NR to NR)
Partial response, n (%) (95% CI)	52 (12.2) (9.27 to 15.73)	56 (13.2) (10.11 to 16.77)	21 (14.6) (NR to NR)	21 (14.7) (9.3 to 21.6)
Stable disease, n (%) (95% CI)	150 (35.3) (30.75 to 40.05)	177 (41.6) (36.92 to 46.50)	43 (30.0) (NR to NR)	NR (NR to NR)
Progressive disease, n (%) (95% CI)	187 (44.0) (39.22 to 48.86)	117 (27.5) (23.33 to 32.04)	NR (NR to NR)	NR (NR to NR)
DOR among responders				
Number of participants (responders) analysed	58	57	22	21
Patients without event, n (%)	30 (51.7)	10 (17.5)	11 (50)	3 (14)
Median duration of response, months (95% CI)	16.3 (10.0 to NE)	6.2 (4.9 to 7.6)	18.6 (11.6 to NE)	7.2 (5.6 to 12.5)
Unstratified HR, (95% CI)	0.34 (0.21 to 0.55)		0.32 (0.15 to 0.70)	

CI=confidence interval; DOR=duration of response; HR=hazard ratio; NE=not evaluable; NR= not reported; ORR=objective response rate; RECIST=response evaluation criteria in solid tumours
Source: CS adapted from Section 4.7, Table 29, Table 30, Table 31.

In the OAK trial, the proportion of patients with complete response per RECIST v1.1 was similar across the treatment arms. Limited numerical results for ORR were available in the CS for the updated analysis of the POPLAR trial; ORR results for the primary analysis of the POPLAR trial are available in Table 27 of the POPLAR CSR. The company states that the proportion of patients with confirmed response was similar in the atezolizumab and docetaxel arms and that results of updated analysis did not significantly change compared to the primary analysis.

In both the OAK and POPLAR trials, the median DOR was more than doubled in the atezolizumab arms compared with the docetaxel arms in the ITT population of the trials; OAK:

16.3 compared to 6.2 months, HR 0.34 (95% CI 0.21 to 0.55) and POPLAR 18.6 compared to 7.2 months, HR 0.32 (95% CI 0.15 to 0.70).

10.6 Additional characteristics of trials included in the indirect treatment comparison

Three trials were identified for inclusion in the ITC; design characteristics of the OAK and POPLAR trials are summarised in Table 6 and an assessment of the risk of bias of the OAK and POPLAR trials is provided in Section 4.2.5 of this report.

Design characteristics of the LUME-Lung 1 trial are summarised in Table 51 and an assessment of the risk of bias of the LUME-Lung 1 trial is provided in

Table 52.

Table 51 Key characteristics of the LUME-Lung 1 trial

Characteristic	LUME-Lung 1
Location	International (27 countries, 211 centres)
Design	Randomised (1:1), phase III, double blind, placebo controlled
Population	A total of 1314 patients were randomised and analysed as the ITT population, 655 to docetaxel plus nintedanib and 659 to docetaxel plus placebo
Intervention	Docetaxel (75mg/m^2) by intravenous infusion on day 1 plus nintedanib 200mg orally BID on days 2-21 every 3 weeks, until unacceptable side effects or disease progression.
Comparator	Docetaxel (75mg/m^2) by intravenous infusion on day 1 plus matching placebo orally BID on days 2-21 every 3 weeks, until unacceptable side effects or disease progression.
Primary outcome	PFS (defined as time from randomisation to progression or death) by central independent review
Secondary outcomes	OS, investigator assessed PFS, tumour response by central review and investigator assessment
Safety endpoints	Safety and tolerability of treatment with docetaxel plus nintedanib compared to docetaxel plus placebo
Duration of trial	Patients were enrolled between 23rd December 2008 and 9th February 2011
Data analyses	Data cut-off for analysis of the ITT population: 15th February 2013
Median duration of follow-up (primary analysis)	PFS: 7.1 months (IQR 3.8 to 11.0 months) OS: 31.7 months (IQR 27.8 to 36.1 months)

BID=twice daily; IQR=interquartile range; ITT=intention to treat; OS=overall survival; PFS=progression-free survival
Source Reck et al 2014; CS Appendix 4.

Table 52 Risk of bias assessment of the LUME-lung 1 trial

Risk of bias question	Company assessment	ERG comment
Was randomisation carried out appropriately?	Low risk of bias	Agree; web-based block randomisation (by country) via web-based interactive response system
Was the concealment of treatment allocation adequate?	Low risk of bias	Agree; treatment assigned by an interactive third party (web-based response system)
Were the groups similar at the outset of the trial in terms of prognostic factors, for example, severity of disease?	Low risk of bias	Agree; demographic and baseline characteristics were well balanced between the treatment groups
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Low risk of bias	Agree; blinding of care providers and participants achieved by matching placebo. Primary outcome (PFS) primarily assessed by central review.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Low risk of bias	Agree; Reasons for withdrawal from treatment adequately reported, all randomised participants included as the ITT population for analyses of primary and secondary outcomes.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk of bias	Agree; Results for all outcomes specified in the published protocol and clinical trial registry are available
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low risk of bias	Agree; all randomised participants included as the ITT population for analyses of primary and secondary outcomes.

ITT=intention to treat; PFS=progression-free survival
Source Reck et al 2014; CS Appendix 4.

10.7 Additional survivor plots of fractional polynomial models

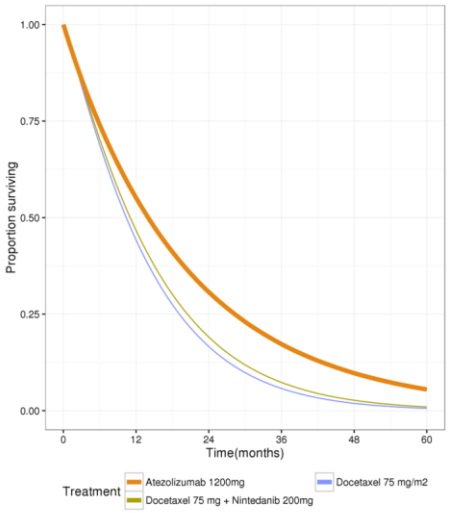
The company provided survivor plots as an output of each FE FP ITC model fitted in the response letter to ERG clarification questions. Survivor plots were not made available to the ERG by the company for each RE FP ITC model fitted.

Visual inspection of these fitted survival curves, along with the DIC statistic, was used by the company to determine the best fitting model for OS and PFS. Visual inspection of these curves conducted by the ERG is discussed in Section 4.6.3 of this report.

The company also provided graphical plots of the resulting HR functions for the best fitting model for each outcome; the Weibull FE FP model for both OS and PFS.

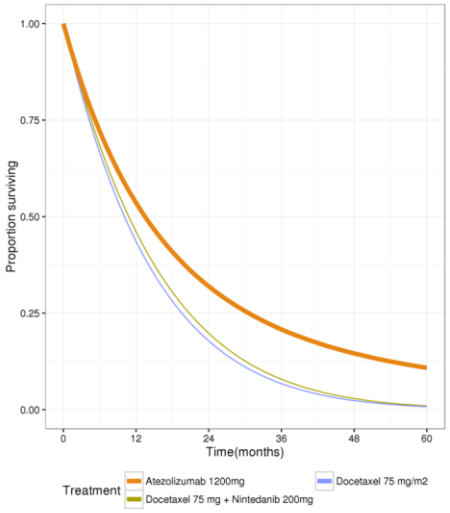
10.7.1 Overall survival

Figure 25 Survivor plot (1st order, p1=0 [Weibull])



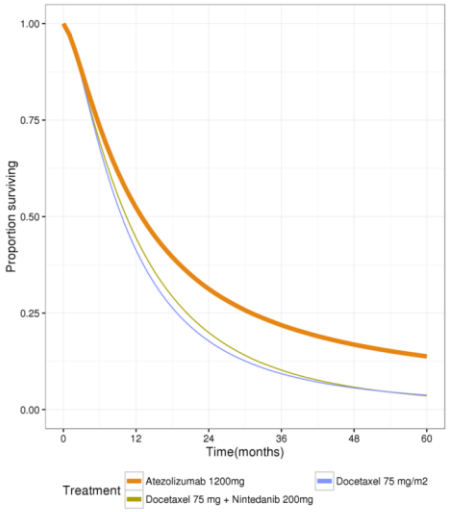
Source: Company response to clarification letter

Figure 26 Survivor plot (1st order, p1=0 [Gompertz])



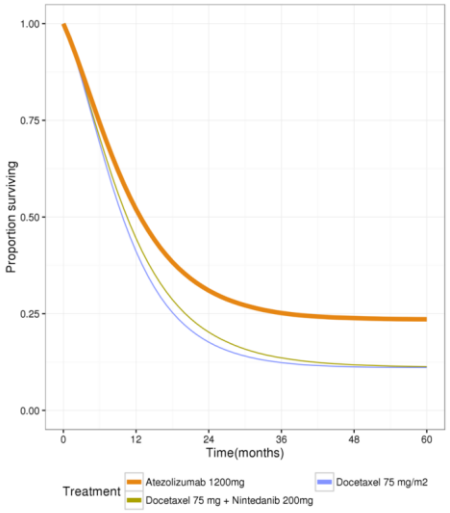
Source: Company response to clarification letter

Figure 27 Survivor plots (2nd order (1), p1=0, p2=0)



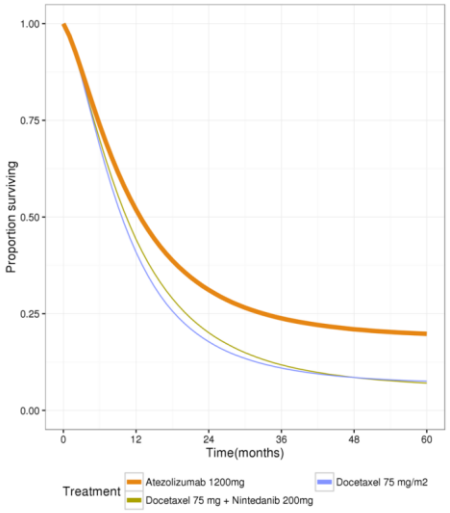
Source: Company response to clarification letter

Figure 28 Survivor plots (2nd order (2), p1=0, p2=1)



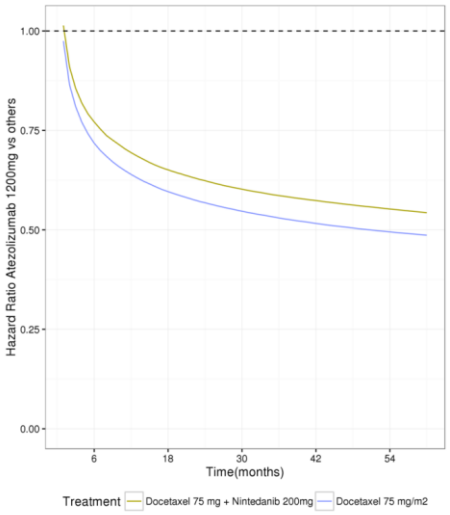
Source: Company response to clarification letter

Figure 29 Survivor plots (2nd order (3), p1=1, p2=1)



Source: Company response to clarification letter

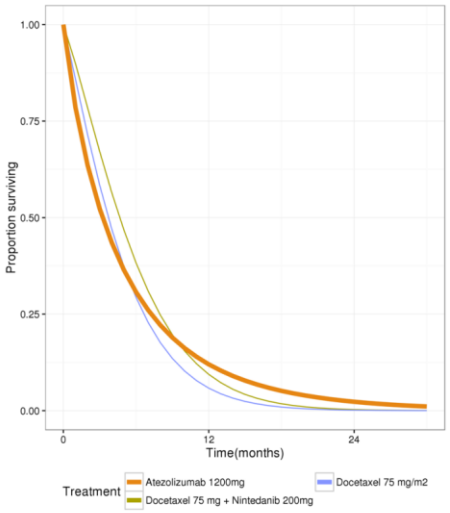
Figure 30 Hazard ratio functions of best fitting model (1st order, Weibull)



Source: Company response to clarification letter

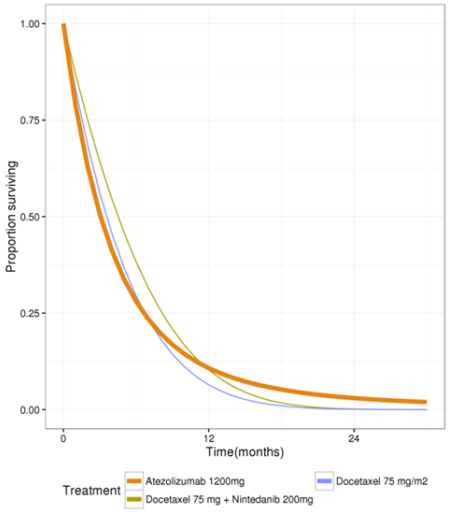
10.7.2 Progression-free survival

Figure 31 Survivor plot (1st order, p1=0 [Weibull])



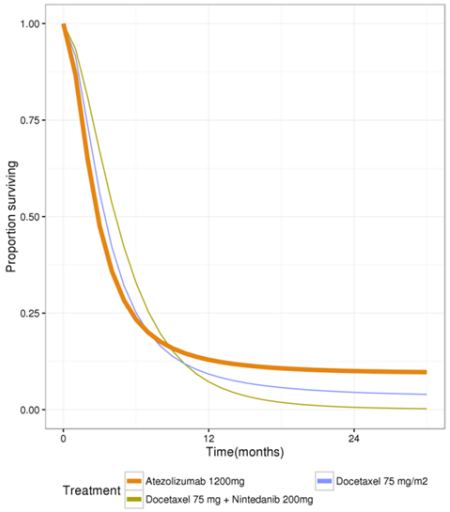
Source: Company response to clarification letter

Figure 32 Survivor plot (1st order, p1=1 [Gompertz])



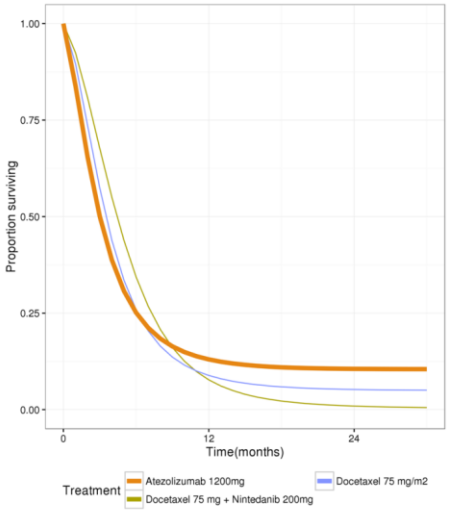
Source: Company response to clarification letter

Figure 33 Survivor plot (2nd order (1), p1=0, p2=0)



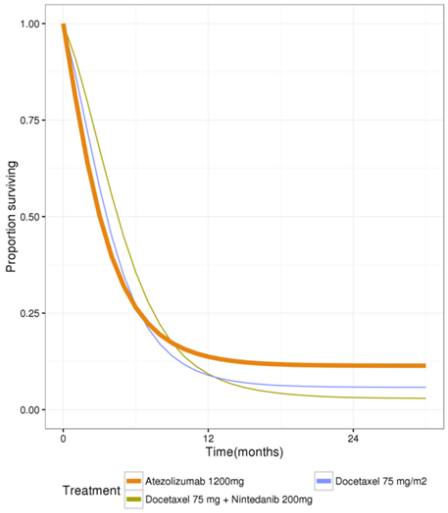
Source: Company response to clarification letter

Figure 34 Survivor plot (2nd order (2), p1=0, p2=1)



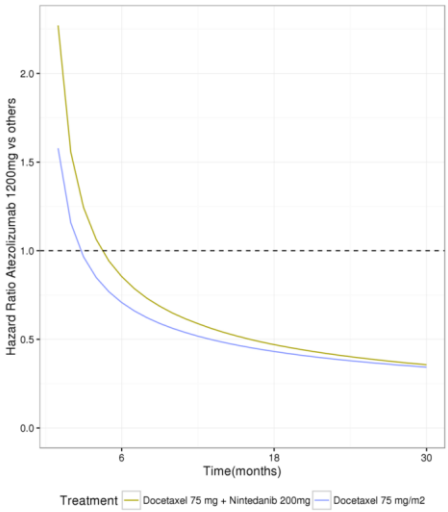
Source: Company response to clarification letter

Figure 35 Survivor plot (2nd order (3), p1=1, p2=1)



Source: Company response to clarification letter

Figure 36 Hazard ratio functions of best fitting model (1st order, Weibull)

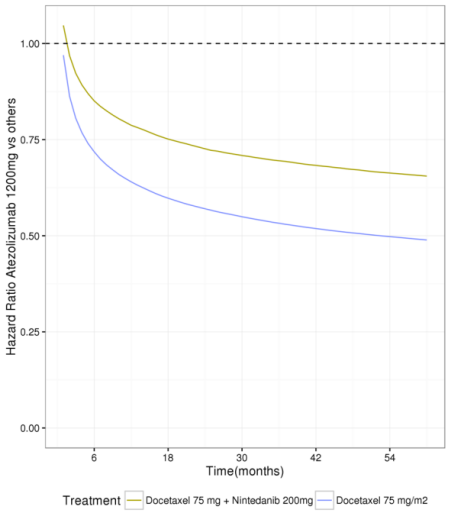


Source: Company response to clarification letter

10.7.3 Adenocarcinoma histology

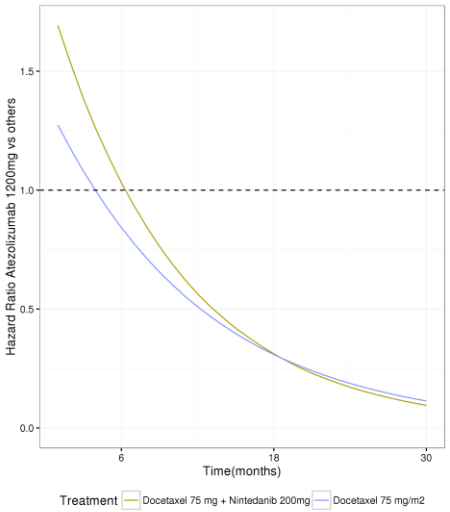
The ERG requested that the company perform additional ITCs to account for the population for which nintedanib+docetaxel is licenced for (i.e. patients with adenocarcinoma histology only) and the company provided results which compared atezolizumab within its intended licence to nintedanib+docetaxel (adenocarcinoma subgroup), see Section 4.6.4 for further discussion of this additional ITC and the results for the expected difference in OS and PFS. The company also provided graphical plots of the resulting HR functions for the best fitting model for each outcome; the Weibull FE FP model for both OS and PFS.

Figure 37 Hazard ratio functions of best fitting model (1st order, Weibull) for overall survival; atezolizumab (total population) and nintedanib+docetaxel (adenocarcinoma subgroup)



Source: Company response to clarification letter

Figure 38 Hazard ratio functions of best fitting model (1st order, Weibull) for PFS, atezolizumab (total population) and nintedanib+docetaxel (adenocarcinoma subgroup)

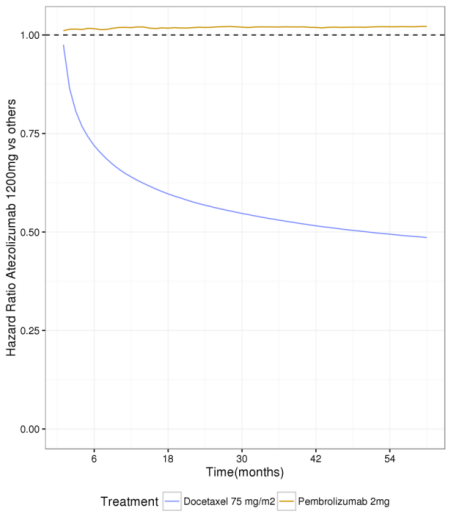


Source: Company response to clarification letter

10.7.4 Inclusion of pembrolizumab

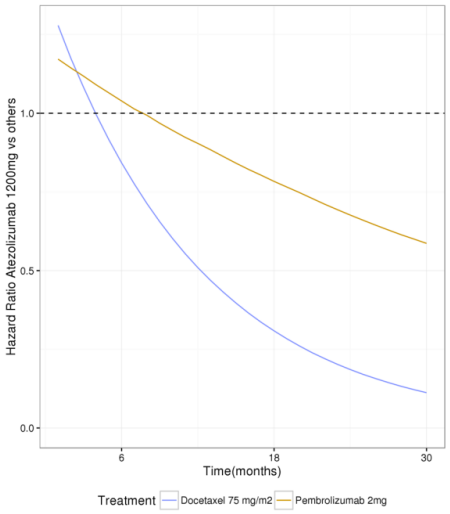
The ERG requested that the company perform additional ITCs to extend the scope of the submission to pembrolizumab, which had previously been excluded from the appraisal, see Section 4.6.4 for further discussion of this additional ITC and the results for the expected difference in OS and PFS. The company also provided graphical plots of the resulting HR functions for the best fitting model for each outcome; the Weibull FE FP model for both OS and PFS.

Figure 39 Hazard ratio functions of best fitting model (1st order, Weibull) for OS



Source: Company response to clarification letter

Figure 40 Hazard ratio functions of best fitting model (1st order, Weibull) for PFS



Source: Company response to clarification letter

10.8 ERG revisions to the company model

This appendix contains details of the changes that the ERG made to the company model. Information contained with the file named 'ID970 ERG corrected OS.xlsx' is needed to replicate the ERG's cost effectiveness results.

ERG Section 6 results table revision	Implementation instructions
C1 Discounting algorithms	In Sheets 'Atezo', 'Doce' and 'Ninted + Doce – ITC' Set value in cell **C13**= 0 Copy cell **C13** to **C14:C65** In Sheet 'Ninted + Doce – ITC' Insert formula in cell **C66** = ROUNDDOWN(F66/wk2yr,2) Copy cell **C66** to **C67:C1578**

C2 Age related utility decrement	In Sheet 'Atezo' Set formula in cell **CM118** =IF(util_optn=4,((BB118*u_Pre5On-0.02)+BC118*(u_Pre15On-0.02)+BD118*(u_Pre30On-0.02)+BE118*(u_Post30On-0.02))*(BV118*AV118),IF(util_optn=1,BV118*AV118*(u_pfs_new-0.02),AW118*(u_pfs_new-0.02))) Copy cell **CM118** to **CM119:CM586** Set formula in cell **CM587** =IF(util_optn=4,((BB587*u_Pre5On-0.07)+BC587*(u_Pre15On-0.07)+BD587*(u_Pre30On-0.07)+BE587*(u_Post30On-0.07))*(BV587*AV587),IF(util_optn=1,BV587*AV587*(u_pfs_new-0.07),AW587*(u_pfs_new-0.07))) Copy cell **CM587** to **CM588:CM1578** Set formula in cell **CO118** =IF(util_optn=4,(BB118*(u_Pre5Off-0.02)+BC118*(u_Pre15Off-0.02)+BD118*(u_Pre30Off-0.02)+BE118*(u_Post30Off-0.02))*(AY118-BV118*AV118),IF(util_optn=1,(AY118-BV118*AV118)*(u_prog-0.02),AX118*(u_prog-0.02))) Copy cell **CO118** to **CO119:CO586** Set formula in cell **CO587** =IF(util_optn=4,(BB587*(u_Pre5Off-0.07)+BC587*(u_Pre15Off-0.07)+BD587*(u_Pre30Off-0.07)+BE587*(u_Post30Off-0.07))*(AY587-BV587*AV587),IF(util_optn=1,(AY587-BV587*AV587)*(u_prog-0.07),AX587*(u_prog-0.07))) Copy cell **CO587** to **CO588:CO1578** In Sheet 'Doce' Set formula in cell **CJ118 =**IF(util_optn=4,(AZ118*(u_Pre5On-0.02)+BA118*(u_Pre15On-0.02)+BB118*(u_Pre30On-0.02)+BC118*(u_Post30On-0.02))*(BT118*AT118),IF(util_optn=1,BT118*AT118*u_pfs_com,AU118*u_pfs_com)) Copy cell **CJ118** to **CJ119:CJ586** Set formula in cell **CJ587 =** IF(util_optn=4,(AZ587*(u_Pre5On-0.07)+BA587*(u_Pre15On-0.07)+BB587*(u_Pre30On-0.07)+BC587*(u_Post30On-0.07))*(BT587*AT587),IF(util_optn=1,BT587*AT587*u_pfs_com,AU587*u_pfs_com)) Copy cell **CJ587** to **CJ588:CJ1578** Set formula in cell **CL118** =IF(util_optn=4,(AZ118*(u_Pre5Off-0.02)+BA118*(u_Pre15Off-0.02)+BB118*(u_Pre30Off-0.02)+BC118*(u_Post30Off-0.02))*(AW118-BT118*AT118),IF(util_optn=1,(AW118-BT118*AT118)*u_prog,AV118*u_prog)) Copy cell **CL118** to **CL119:CL586** Set formula in cell **CL587** =IF(util_optn=4,(AZ587*(u_Pre5Off-0.07)+BA587*(u_Pre15Off-0.07)+BB587*(u_Pre30Off-0.07)+BC587*(u_Post30Off-0.07))*(AW587-BT587*AT587),IF(util_optn=1,(AW587-BT587*AT587)*u_prog,AV587*u_prog)) Copy cell **CL587** to **CL588:CL1578** In Sheet 'Ninted + Doce – ITC'

ERG Section 6 results table revision	Implementation instructions
	Set formula in cell **AR118** =IF(util_optn=4,(U118*(u_Pre5On-0.02)+V118*(u_Pre15On-0.02)+W118*(u_Pre30On-0.02)+X118*(u_Post30On-0.02))*P118,P118*u_pfs_com3) Copy cell **AR118** to **AR119:AR586** Set formula in cell **AR587** =IF(util_optn=4,(U587*(u_Pre5On-0.07)+V587*(u_Pre15On-0.07)+W587*(u_Pre30On-0.07)+X587*(u_Post30On-0.07))*P587,P587*u_pfs_com3) Copy cell **AR587** to **AR588:AR1578** Set formula in cell **AT118** =IF(util_optn=4,(U118*(u_Pre5Off-0.02)+V118*(u_Pre15Off-0.02)+W118*(u_Pre30Off-0.02)+X118*(u_Post30Off-0.02))*Q118,Q118*u_prog) Copy cell **AT118** to **AT119:AT586** Set formula in cell **AT587** =IF(util_optn=4,(U587*(u_Pre5Off-0.07)+V587*(u_Pre15Off-0.07)+W587*(u_Pre30Off-0.07)+X587*(u_Post30Off-0.07))*Q587,Q587*u_prog) Copy cell **AT587** to **AT588:AT1578**

ERG Section 6 results table revision	Implementation instructions
C3 ToT half cycle correction	In Sheet 'Atezo' Set formula in cell **BV13 =** BU13 Copy cell **BV13** to **BV14:BV1578** In Sheet 'Doce'' Set formula in cell **BT13 =** BS13 Copy cell **BT13** to **BT14:BT1578** In Sheet 'Ninted + Doce – ITC' Set formula in cell **Z13 =** Y13 Copy cell **Z13** to **Z14:Z1578** Set formula in cell **AB13=** IF(MOD(F13,(1/cyc2wk))=0,1,0)*Y13*AA13*IF(F13=0,c_adm1_com3,c_adm_com3) Copy cell **AB13** to **AB14:AB1578** Set formula in cell **AD13=** **I**F(F13<doc_cap,IF(MOD(F13,(1/cyc2wk))=0,1,0)*Y13*AA13*IF(F13=0,c_adm1_com,c_adm_com),0) Copy cell **AD13** to **AD14:AD1578**
R1. ERG preferred OS for atezolizumab and docetaxel	Open Worksheet **'OS'** from ID970 ERG corrected OS.xlsx Copy cells A2:A1567 In sheet 'Atezo' Paste in cells AQ13:AQ1578 Open Worksheet **'OS'** from ID970 ERG corrected OS.xlsx Copy cells C2:C1567 In Sheet 'Doce' Paste in cells AO13:AO1578

ERG Section 6 results table revision	Implementation instructions
R2. ERG preferred OS for atezolizumab and docetaxel and atezolizumab treatment duration effect set to 5 years	Open Worksheet **'OS'** from ID970 ERG corrected OS.xlsx Copy cells B2:B1567 In sheet 'Atezo' Paste in cells AQ13:AQ1578 Open Worksheet **'OS'** from ID970 ERG corrected OS.xlsx Copy cells C2:C1567 In Sheet 'Doce' Paste in cells AO13:AO1578
R3 ERG preferred OS for atezolizumab applied to both atezolizumab and nintedanib+docetaxel	Open Worksheet **'OS'** from ID970 ERG corrected OS.xlsx Copy cells A2:A1567 In sheet 'Atezo' Paste in cells AQ13:AQ1578 Open Worksheet **'OS'** from ID970 ERG corrected OS.xlsx Copy cells A2:A1657 In Sheet 'Ninted + Doce – ITC' Paste in cells J13:J1578
R4 ERG preferred OS for atezolizumab applied to both atezolizumab and nintedanib+docetaxel and treatment duration effect for both set to 5 years	Open Worksheet **'OS'** from ID970 ERG corrected OS.xlsx Copy cells B2:B1567 In sheet 'Atezo' Paste in cells AQ13:AQ1578 Open Worksheet **'OS'** from ID970 ERG corrected OS.xlsx Copy cells B2:B1567 In Sheet 'Ninted + Doce – ITC' Paste in cells J13:J1578

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]

You are asked to check the ERG report from Liverpool Reviews and Implementation Group (LRiG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 10 May 2017** 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Inappropriate comparison of mean and median OS estimates

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 11, section 1.3; paragraph 3 Related to the statement: "Results from the company's indirect treatment comparison (ITC) suggest that the best estimate of the expected difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (compared to a median OS gain of 4.2 months and 2.9 months in the OAK and POPLAR trials respectively). Results from the company's ITC suggest that the best estimate of the expected difference in OS is around 5 to 6 months for the comparison of atezolizumab versus nintedanib+docetaxel." This is a misleading and inappropriate statement. The FP point estimates are referring to mean OS over a 5 year time horizon, as compared to a median OS from the trial. When implemented in the model over a 25 year TH, the equivalent change in median OS is 3.4 months versus docetaxel, and 2.8 months versus nintedanib+docetaxel. A statement such as this implies an exaggerated over-estimate of survival benefit versus the clinical data. This is not accurate, and a comparison of mean and median OS results is inappropriate	"Results from the company's indirect treatment comparison (ITC) suggest that the best estimate of the expected mean difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (equating to 3.4 months median survival benefit). Results from the company's ITC suggest that the best estimate of the expected mean difference in OS is around 5 to 6 months for the comparison of atezolizumab versus nintedanib+docetaxel (equating to 2.8 months median survival benefit)."	Misleading statement, and inappropriate comparison of mean and median OS results	For clarity, text reworded as follows: "Results from the company's indirect treatment comparison (ITC) suggest that the best estimate of the expected mean difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (~~compared to a~~ median OS gains were 4.2 months and 2.9 months in the OAK and POPLAR trials respectively). Results from the company's ITC suggest that the best estimate of the expected mean difference in OS is around 5 to 6 months for the comparison of atezolizumab versus nintedanib+docetaxel"
Page 15, paragraph 3 Relating to the statement: "The ERG highlights that the expected docetaxel survival results	Remove paragraph	Misleading statement, and inappropriate comparison of mean and median OS results	For clarity, text reworded as follows:

produced by the company's FP ITC are optimistic when compared with median OS from the OAK trial." This is misleading as the ERG are citing a mean OS benefit from the ITC as compared to median OS benefit from the trial. Rather, the median OS benefit once the FP ITC is implemented in the economic model is 3.4 months and 2.8 months versus docetaxel and nintedanib+ docetaxel, respectively. Compared to a median OS gain of 4.2 months from the OAK trial, the outcome of the FP ITC can be considered pessimistic, rather than optimistic.			"The ERG considers that the expected docetaxel survival results produced by the company's FP ITC may be optimistic ~~when compared with median OS from the OAK trial~~. "
Page 72; paragraph 2 Related to the statement: "Table 24, Figure 3 and Figure 4 show expected difference in survival (months) according to all FP models fitted in the FE and RE ITCs. The ERG notes that across all ten models fitted, the expected difference in survival is very similar, ranging between 5.7 and 7.2 months for atezolizumab compared to docetaxel and between 4.7 and 6.1 months for atezolizumab compared to nintedanib+docetaxel." This is misleading as the ERG are not specifying mean or median: two very different measures that can be misinterpreted in the context of median OS from OAK. The figures presented are mean OS benefit from the ITC which is not comparable to the median OS benefit from the trial. Rather, the median OS benefit once the FP ITC is implemented in the economic model is 3.4 months and 2.8 months	"Table 24, Figure 3 and Figure 4 show expected mean difference in survival (months) according to all FP models fitted in the FE and RE ITCs. The ERG notes that across all ten models fitted, the expected mean difference in survival is very similar, ranging between 5.7 and 7.2 months for atezolizumab compared to docetaxel and between 4.7 and 6.1 months for atezolizumab compared to nintedanib+docetaxel. When implemented in the economic analysis, this equates to a median OS benefit of 3.4 months, and 2.8 months for the comparison versus docetaxel and nintedanib+docetaxel, respectively"	Misleading statement, and inappropriate comparison of mean and median OS results	For clarity, text reworded as follows: "Related to the statement: "Table 24, Figure 3 and Figure 4 show expected mean difference in survival (months) according to all FP models fitted in the FE and RE ITCs. The ERG notes that across all ten models fitted, the expected mean difference in survival is very similar, ranging between 5.7 and 7.2 months for atezolizumab compared to docetaxel and between 4.7 and 6.1 months for atezolizumab compared to nintedanib+docetaxel"

versus docetaxel and nintedanib+ docetaxel, respectively.			
Page 74, paragraph 3 Related to the statement: "The results suggest that the best estimate of the expected difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (compared to a median OS gain of 4.2 months and 2.9 months in the OAK and POPLAR trials from direct evidence) and around 5 to 6 months for atezolizumab versus nintedanib+docetaxel" This is a misleading and inappropriate statement. The FP point estimates are referring to mean OS over a 5 year time horizon, as compared to a median OS from the trial. When implemented in the model over a 25 year TH, the equivalent change in median OS is 3.4 months versus docetaxel, and 2.8 months versus nintedanib+docetaxel. A statement such as this implies an exaggerated over-estimate of survival benefit versus the clinical data. This is not accurate, and a comparison of mean and median OS results is inappropriate	"Results from the company's indirect treatment comparison (ITC) suggest that the best estimate of the expected mean difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (equating to 3.4 months median survival benefit). Results from the company's ITC suggest that the best estimate of the expected mean difference in OS is around 5 to 6 months for the comparison of atezolizumab versus nintedanib+docetaxel (equating to 2.8 months median survival benefit)."	Misleading statement, and inappropriate comparison of mean and median OS results	For clarity, text reworded as follows: "The results suggest that the best estimate of the expected mean difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (~~compared to a~~ median OS gains were 4.2 months and 2.9 months in the OAK and POPLAR trials respectively from direct evidence) and the expected mean difference in OS is around 5 to 6 months for atezolizumab versus nintedanib+docetaxel"
Page 78, Table 26 Related to the statement: "Expected survival differences: atezolizumab (total population) and nintedanib+docetaxel (adenocarcinoma subgroup)" This is misleading as the ERG are not specifying mean or median: two very different	"Expected mean survival differences: atezolizumab (total population) and nintedanib+docetaxel (adenocarcinoma subgroup)"	Misleading statement, and inappropriate comparison of mean and median OS results	For clarity, text reworded as follows: "Expected mean survival differences: atezolizumab (total population) and nintedanib+docetaxel (adenocarcinoma subgroup)"

measures that can be misinterpreted in the context of median OS from OAK. The figures presented are mean OS benefit from the ITC which is not comparable to the median OS benefit from the trial. Rather, the median OS benefit once the FP ITC is implemented in the economic model is 3.4 months and 2.8 months versus docetaxel and nintedanib+ docetaxel, respectively.			
Page 83, bullet point 2 and 3 Relating to the statements: 1) "The company's best estimate of expected difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (compared to median OS gains of 4.2 months and 2.9 months from the OAK and POPLAR trials respectively). 2) The company's best estimate of expected difference in OS is around 5 to 6 months for atezolizumab versus nintedanib+docetaxel" This is a misleading and inappropriate statement. The FP point estimates are referring to mean OS over a 5 year time horizon, as compared to a median OS from the trial. When implemented in the model over a 25 year TH, the equivalent change in median OS is 3.4 months versus docetaxel, and 2.8 months versus nintedanib+docetaxel. A statement such as this implies an exaggerated over-estimate of survival benefit versus the clinical data. This is not accurate, and a comparison of mean and median OS results is inappropriate	1) "The company's best estimate of expected mean difference in OS is around 6 to 7 months for atezolizumab versus docetaxel, equating to a median OS benefit of 3.4 months. 2) The company's best estimate of expected mean difference in OS is around 5 to 6 months for atezolizumab versus nintedanib+docetaxel, equating to a median OS benefit of 2.8 months"	Misleading statement, and inappropriate comparison of mean and median OS results	For clarity, text reworded as follows: 1) "The company's best estimate of expected mean difference in OS is around 6 to 7 months for atezolizumab versus docetaxel (~~compared to~~ median OS gains were 4.2 months and 2.9 months from the OAK and POPLAR trials respectively) 2) The company's best estimate of expected mean difference in OS is around 5 to 6 months for atezolizumab versus nintedanib+docetaxel

Issue 2 Misrepresentation of opinion on cure-rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 104, paragraph 5 Relating to statement: "However, when the mixed cure-rate OS model is compared with OAK trial data at 24 months, the chosen cure rate (2%) produces an overestimate of survival for patients treated with atezolizumab by 2.8% whilst underestimating OS for patients receiving docetaxel by 1.6% (recognising that the docetaxel OS curve is dependent on the atezolizumab curve although no cure rate is assumed for docetaxel). The mixed cure-rate model applied by the company, therefore, generates survival gains for patients treated with atezolizumab and docetaxel, over the first 24 months of the model time horizon that are not supported by data from the OAK trials." It is inappropriate to only take one point estimate from the extrapolation: Whilst at 2 years there is a slight overestimation, this effect of this is moderated by an underestimation 1 year, which balances the area under the curve. In addition, there are more patients in each arm at 12 months vs. 24 months, so the overall effect cannot be assumed to favour atezolizumab. By not presenting overall view, the ERG are	When the mixed cure-rate OS model is compared with OAK trial data at 12 months, the chosen cure rate (2%) produces an underestimation of survival for patients treated with atezolizumab by 1.1% whilst overestimating OS for patients receiving docetaxel by 0.8% (recognising that the docetaxel OS curve is dependent on the atezolizumab curve although no cure rate is assumed for docetaxel). Conversely, when the mixed cure-rate OS model is compared with OAK trial data at 24 months, the chosen cure rate (2%) produces an overestimate of survival for patients treated with atezolizumab by 2.8% whilst underestimating OS for patients receiving docetaxel by 1.6%."	Statement is not an accurate reflection of the data or the company submission	This is not a factual error, no change made The ERG considers that what matters most is the disparity at the end of the trial data as this is projected into the future. Adding in the difference in the first 12 months does not change the conclusion that the mixed cure-rate model does not produce results that are supported by the trial data

providing an imbalanced view of the approach to the reader.			
Page 113, paragraph 4 Related to: "Treatment with atezolizumab was modelled by the company using a mixed cure-rate model that was not fully justified as being necessary, was arbitrarily specified and ultimately produced implausible projections of the mortality hazard rate associated with treatment with atezolizumab." This is an opinion of the ERG which is an inaccurate reflection of the company submission. The cure-rate model was justified in section 5.3.4 (page 155-162) of the submission. By utilising a mixed-cure model, background mortality is incorporated in to the survival function which ensures survival for atezolizumab never crosses mortality of the general population. In addition, there is a well justified assumption that a proportion of patients treated with immunotherapy achieve a sustained response. This is supported by the number of complete responses achieved in the OAK trial, as well as the recent publication from BMS, stating a 5-year OS of 16% for the PD-1 inhibitor, nivolumab in previously treated NSCLC patients (Bristol Myers Squibb, 2017). Thus, for an immunotherapy with similar effects, mortality hazards which generate 12.2% OS projections are not "implausible".	"Treatment with atezolizumab was modelled by the company using a mixed cure-rate model that the ERG believes was not fully justified as being necessary was arbitrarily specified and ultimately produced projections of the mortality hazard rate associated with treatment with atezolizumab that the ERG believes are unlikely.	This statement is an opinion of the ERG which does not accurately reflect the company submission, or published data available and hence can mislead the reader	This is not a factual error, no change made As the company states this is the ERG's opinion. An opinion that is fully explained in the report. The paper referenced relates to an analysis from April 2017 of a phase I trial of 129 patients and the findings from such a study should be treated with caution.

Page 122, paragraph 2 Related to statement: "The ERG considered that the mixed cure-rate model used to represent OS of patients receiving atezolizumab led to implausible OS estimates" This is an opinion of the ERG. BMS have recently published 5 year OS data of 16% for the PD-1 inhibitor nivolumab in previously treated NSCLC patients (Bristol Myers Squibb, 2017). Thus, for an immunotherapy with similar effects, an OS prediction of 12.2% OS is not "implausible".	"The ERG do not believe the OS estimates generated from the mixed cure-rate model used to represent OS of patients receiving atezolizumab"	This statement is an opinion of the ERG which does not accurately reflect published data available and hence can mislead the reader	This is not a factual error, no change made. See above for details
Page 15, third bullet point Relating to statement: "the value for the cure-rate used by the company was not justified by the company." This is an opinion of the ERG which is an inaccurate reflection of the company submission, and which can mislead the reader: External data and clinical validation was provided to support the cure fraction, and the OS predictions as a result of the cure fraction in section 5.3.4 of the submission, pages 157-160.	"The ERG does not believe the value for the cure-rate used has been sufficiently justified by the company."	This statement is an opinion of the ERG which does not accurately reflect the company submission and hence can mislead the reader	For clarity, text reworded as follows: “the value for the cure-rate ~~used by the company~~ was not sufficiently justified by the company“

Issue 3 Inaccurate interpretation of background mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 15, paragraph 2 Relating to statement: "In addition, the ERG highlights that the company's approach to modelling OS for patients receiving atezolizumab results in mortality rates that are, at some points, lower than the mortality rates of the UK general population of the same age." This is an incorrect statement: The only example provided by the ERG was between 20-25 years follow up, where a mistake was made by the ERG in calculating the survival probabilities of atezolizumab. The ERG have used the mortality table presented in the "Life tables" sheet of the economic model to present the residual mortality for a cohort of patients all aged 63 at the beginning of the study. The ERG calculated the 5-year mortality rate between ages 83 and 88 for this table. However, this is not the approach Roche have used to determine background mortality, which is then incorporated in to the mixed-cure fraction equation. Background mortality can be found in the "Cure s(t)" sheet of the economic model, column P.	Remove statement	Statement is incorrect	This is not a factual error, no change made The calculation as described by the company in this FIC proforma was not provided in the model. The life tables analysis in the model starts at the average OAK trial patient age of 63 years. Furthermore, the text in the CS does not clearly describe the cure-fraction model as being constructed in the way that is described in this FIC proforma The ERG accepts that the background mortality rate in the S(t) sheet of the model is lower than that in the life tables sheet – albeit as a column of numbers rather than formulas, meaning that the ERG has no way of checking that it has been calculated accurately The ERG does not consider that this is an appropriate approach for a Markov model that deals with an average patient. In addition, the cure-

Background mortality is calculated using the residual mortality for every patient enrolled in OAK. Individual mortality curves are constructed for each patient based on their age. The background mortality curve is therefore the mean of all individual mortality curves. As all patients have a different baseline age, it is not possible to determine one survival probability for a set age (e.g 83-88 years as the ERG have). Rather, this methodology allows you to account for all ages of patients over the time horizon of the economic model, and therefore includes the younger patients enrolled in the trial who continue to survive to the follow up period one is interested in assessing. Thus, the background mortality rate between a follow up of 20-25 years is 28%, not the 39.5% the ERG state. Thus, atezolizumab does not generate a mortality rate lower than the general population. Finally, this statement also seems to be mathematically incorrect: One of the benefits of the mixed-cure methodology is that it incorporates background mortality to ensure the mortality rate of the treatment never exceeds that of the general population.			rate has been implemented under the assumption that background mortality is a function of age but cancer specific mortality is not. The ERG does not consider that the report should be changed in light of the information presented in the FIC proforma or in the CS. The ERG's preferred approach would have been to use background mortality for people from the age of 63 years (the model start age), in which case mortality rates could not have been higher than the background mortality at any point for a population with an average start age of 63 years. However, ultimately, the ERG's substantive concern about the mixed cure-rate model is the lack of robust justification for its use with the justification provided being speculative or based upon other disease areas (notably melanoma) where there is a known population that does have a mortality rate essentially the same as the population without the condition, which is not the

			case for the population with NSCLC.
Page 17, bullet point 10 Relating to statement: "the company's approach to modelling OS for patients treated with atezolizumab is implausible as it resulted in survival rates that, at some points, were higher than that of the UK general population." See point above	Remove statement	Statement is incorrect	This is not a factual error, no change made See above for details
Page 106, paragraph 2 Relating to statement: "The company projection generates a 5-year mortality rate of 36.9% between years 20 and 25 of the model, when patients are aged between 83 and 88 years. However, the 5-year mortality rate for all people aged between 83 and 88 years, based on UK life tables provided within the company model is 39.5%. The ERG considers the company projection is implausible as it leads to a situation where treatment with atezolizumab is not just keeping people with advanced NSCLC alive for 20 years and longer after progressing on their first treatment, it is also preventing them from dying from other, non-NSCLC, causes. Therefore, the ERG considers that i) the ICERs that are generated by this approach should not be used to inform decision-making and ii) that the log-logistic distribution is a poor choice of distribution for modelling the	Remove statement	Statement is incorrect	This is not a factual error, no change made See above for details

OS trial data." See point above			
Page 115, paragraph 3 Relating to statement: "The ERG considers that, not only was the approach used by the company not supported by the available OAK trial data, but that it also led to a risk of death, in the long-term, that was higher than the risk for the general population." See point above	Remove statement	Statement is incorrect	This is not a factual error, no change made See above for details
Page 122, paragraph 2 Relating to statement: "The ERG highlights that, at some time points, the company's OS model for atezolizumab produces survival estimates that are higher than the respective UK age-related population values." See point above	Remove statement	Statement is incorrect	This is not a factual error, no change made See above for details

Issue 4 Inappropriate OS extapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 112, Table 42 Related to the OS estimates The ERG has opted for an extrapolation which	Additional evidence required to support the OS extrapolation recommendation	Unjustified OS extrapolation	This is not a factual error, no change made The registry data are for patients from time of diagnosis, not for patients

demonstrates consistently low OS estimates for both treatment arms. Roche utilised registry data and expert opinion to determine the most plausible OS estimates. However the ERG has not validated any of the assumptions made in their extrapolation. Based on the NLCA registry data, OS for patients with stage IV NSCLC have a 5-year OS rate of 2%. Roche used a generous 2.4%, whereas the ERG has opted for an OS rate of 1.2%. In contrast, the ERG has assumed a 5 year OS rate for atezolizumab of 4.4%. This is in stark contrast to the recent BMS publication demonstrating 5 year OS data of 16% for the PD-1 inhibitor nivolumab in previously treated NSCLC patients (Bristol Myers Squibb, 2017), an immunotherapy expected to have similar benefits to atezolizumab. There is no data to suggest the extrapolation methodology employed by the ERG is a good visual or statistical fit to the atezolizumab data. The unrealistically low estimates of survival generated by these curves, in contrast to published data, validates the implausibility.			having progressed following treatment. These data are therefore not informative unless they are rebased for patients at progression following treatment. As stated above, if the 12% OS difference between the OS for OAK patients and the phase 1 trial quoted persists, then the 4.4% suggested by the ERG is reasonable. The ERG's position is that there is no reliable information to project what 'reasonable' survival for this group may be. The ERG therefore focussed on projecting using only the available data rather than hypothecating based upon opinion and a flawed analysis of registry data rather than evidence

Issue 5 Misrepresentation of Nintedanib+Docetaxel ITC results

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 11, section 1.3, paragraph 3 Related to the statement: "Also, results from the company's ITC analyses suggest that there is no statistically significant difference in PFS survival for the comparison of atezolizumab versus docetaxel and for atezolizumab versus nintedanib+docetaxel." This is misleading, as it implies this is a challenge with atezolizumab only. Rather, this is a well-known outcome associated with immunotherapies - not just for atezolizumab.	"Also, results from the company's ITC analyses suggest that there is no statistically significant difference in PFS survival for the comparison of atezolizumab versus docetaxel and for atezolizumab versus nintedanib+docetaxel. This is consistent with data that has been presented with other immunotherapies in this space."	Misleading statement implies flaw of atezolizumab only	This is not a factual error, no change made
Page 16, section 1.8, paragraph 2 Related to the statement: "The company has provided evidence that suggests there is no statistically significant difference in OS for atezolizumab (total population) compared to nintedanib+docetaxel (adenocarcinoma patients only). If this result is reliable, then, for the adenocarcinoma population, atezolizumab does not meet the NICE End of Life criteria for life extension." This is misrepresentative of the data provided: The point estimate is 3.33 months with a 95% CI which only just crosses 0 (-0.16, 6.74) which could be due to a multitude of reasons, including increased uncertainty associated	Remove statement	Misrepresentative of the data provided	This is not a factual error, no change made

with reducing the network to 3 trials (which was specifically requested by the ERG).			
Page 18, section 1.10; paragraph 2 Related to the statement: "The FP ITC results generated by the company showed that when treatment with atezolizumab (whole population) was compared with nintedanib+docetaxel (adenocarcinoma population) using the reduced network (i.e., comparators of relevance to this appraisal) there was no statistically significant difference in expected OS between the two therapies." See point above	"The FP ITC results generated by the company showed that when treatment with atezolizumab (whole population) was compared with nintedanib+docetaxel (adenocarcinoma population) using the reduced network (i.e., comparators of relevance to this appraisal) there was no statistically significant difference in expected mean OS between the two therapies (3.33 months [-0.16,6.74])"	Misrepresentative of the data provided	Additional text added as suggested "The FP ITC results generated by the company showed that when treatment with atezolizumab (whole population) was compared with nintedanib+docetaxel (adenocarcinoma population) using the reduced network (i.e., comparators of relevance to this appraisal) there was no statistically significant difference in expected mean OS between the two therapies (3.33 months [-0.16 to 6.74])"
Page 113, paragraph 1 Related to the statement: "Consequently, as this comparison shows there is no statistically significant difference in OS, the ERG concludes that there is no justification for modelling a different OS curves for atezolizumab and nintedanib+docetaxel." See point above	"Consequently, as this comparison shows there is no statistically significant difference in OS, the ERG deems it acceptable to assume equivalence, and hence model the same OS curves for atezolizumab and nintedanib+docetaxel. This assumption has not been clinically validated."	Misrepresentative of the data provided. Misleading to the reader: this is an ERG opinion which has not been clinically validated as acceptable	This is not a factual error, no change made
Page 116, paragraph 2: Related to the statement: "There is no statistically significant evidence to support the claim that atezolizumab generates an OS gain compared to nintedanib+docetaxel."	"There is no statistically significant evidence to support the claim that atezolizumab generates an OS gain compared to nintedanib+docetaxel. However the point estimate of 3.33	Misrepresentative of the data provided	This is not a factual error, no change made

See point above	months mean OS difference is clinically meaningful"		
Page 119-120 Related to the statement: "The company provided evidence during the clarification process which suggests there is no statistically significant difference in OS for atezolizumab (total population) compared to nintedanib+docetaxel (adenocarcinoma patients only). If there is no statistically significant difference in OS, then, for the adenocarcinoma population, atezolizumab does not offer an extension of life of at least 3 months and so does not meet the NICE End of Life criteria for life extension." See point above	"The company provided evidence during the clarification process which suggests there is no statistically significant difference in OS for atezolizumab (total population) compared to nintedanib+docetaxel (adenocarcinoma patients only), but a clinically meaningful point estimate of 3.33 months mean OS benefit. If there is no statistically significant difference in OS, then, the ERG believes that for the adenocarcinoma population, atezolizumab does not offer an extension of life of at least 3 months and so does not meet the NICE End of Life criteria for life extension"	Misrepresentative of the data provided	This is not a factual error, no change made
Page 122, paragraph 4 Related to the statement: "The ERG notes that this is a huge increase from the £56,076 per QALY gained estimated by the company and that this increase is largely due to the results of the company's ITC which showed that expected OS for patients receiving atezolizumab (total population) is not statistically significantly different from that of patients receiving nintedanib+docetaxel (adenocarcinoma population)." This is misleading: The increase in ICER is not due to the results of the ITC, it is due to the	"The ERG notes that this is a significant increase from the £56,076 per QALY gained estimated by the company and that this increase is largely due to the assumptions the ERG have made of clinical equivalence based on the results of the company's ITC, which showed that expected OS for patients receiving atezolizumab (total population) is not statistically significantly different (but provides a clinically meaningful point estimate of mean difference in OS) from that of patients receiving	Misleading statement that does not reflect the true reason for the increase in ICER Misrepresentative of the data provided	This is not a factual error, no change made

assumption the ERG have made based on the ITC. The ERG has assumed that there is clinical equivalence between the two treatments due to the 95% CI. This assumption has not been clinically validated. The point estimate is 3.33 months with a 95% CI which only just crosses 0 (-0.16, 6.74) which could be due to a multitude of reasons including increased uncertainty associated with reducing the network to 3 trials (which was specifically requested by the ERG). There is no data to suggest equivalence of atezolizumab and nintedanib+docetaxel, particularly when the point estimate is a 3.33 months OS benefit: a clinically meaningful difference.	nintedanib+docetaxel (adenocarcinoma population).		

Issue 6 Misrepresentation of company ITC populations

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 12, section 1.4, paragraph 2 Relating to the statement: "However, the company undertook these using non-equivalent populations and results should be viewed with extreme caution:" The statement is misleading as it suggests Roche have been untransparent and uncooperative in our approaches: In priority question A7c of clarification questions (see page 17 of the company response) the ERG	"For consistency purposes in how analyses were conducted with these two ITC analyses, non-equivalent populations have been used and results should be viewed with extreme caution"	Statement is misleading and implies Roche have been uncooperative and untransparent in our approach	This is not a factual error, no change made

requested a non-equivalent population comparison for the analysis versus pembrolizumab, thus for consistency purposes the same approach was taken (and communicated on page 11-12 of the company response) for the analysis versus nintedanib + docetaxel. It was highlighted in the submission (page 20, 22-23, 29, 94, 143, 197) as well as the clarification questions (page 17) that there were challenges and risks associated with comparing non-equivalent populations, and that all analyses should be interpreted with caution. However, in order to provide an assessment of clinical benefit of atezolizumab in its licensed population, like-with-like comparisons were conducted where possible, whilst maintaining consistency with our approaches across comparators			
Page 15, paragraph 3 Related to the statement: "The ERG also highlights that the FP ITC used by the company to model OS for patients receiving nintedanib+docetaxel was not restricted to the nintedanib+docetaxel licensed population (patients with adenocarcinoma), meaning that the company's ITC results for this treatment are not relevant to this appraisal." See point above	"The ERG also highlights that the FP ITC used by the company to model OS for patients receiving nintedanib+docetaxel in the CS was not restricted to the nintedanib+docetaxel licensed population (patients with adenocarcinoma), in order to conduct a like-with-like comparison, meaning results should be interpreted with caution. The company provided an updated ITC to the appropriate population as part of clarification questions which they believe reduced the ICER to £26,181. This is a more relevant comparison for this appraisal, but is still conducted using non-equivalent	Statement is misleading and implies Roche have been uncooperative and untransparent in our approach	This is not a factual error, no change made

	populations, therefore again should be interpreted with caution.		
Page 30, paragraph 5 Related to the statement: "The company states that, to allow for a like-with-like comparison versus atezolizumab according to its anticipated licence, the ITC used data from the intention to treat (ITT) populations of the OAK, POPLAR and LUME-Lung-1 trials." See point above	"The company acknowledges the issues in the comparison, but states that, to allow for a like-with-like comparison versus atezolizumab according to its anticipated licence, the ITC used data from the intention to treat (ITT) populations of the OAK, POPLAR and LUME-Lung-1 trials"	Statement is misleading and implies Roche have been uncooperative and untransparent in our approach	This is not a factual error, no change made. This statement is almost word for word the same as a sentence in the company submission (CS, p96). The ERG disagrees with the company's interpretation of this statement
Page 32, paragraph 3 Related to the statement: "In addition, the ERG highlights that the company has included nintedanib+docetaxel as a comparator even though this treatment is only recommended by NICE for the population with adenocarcinoma histology." See point above	Remove statement	Statement is misleading and implies Roche have been uncooperative and untransparent in our approach	This is not a factual error, no change made. The ERG disagrees with the company's interpretation of this statement
Page 83 paragraph 1 Relating to the statement: "However, the company undertook these using non-equivalent populations and results should be viewed with extreme caution:" See point above	"For consistency purposes in how analyses were conducted with these two ITC analyses, non-equivalent populations have been used and results should be viewed with extreme caution"	Statement is misleading and implies Roche have been uncooperative and untransparent in our approach	This is not a factual error, no change made
Page 112-113: Relating to statement: "The ERG asked the company to indirectly compare atezolizumab versus nintedanib+docetaxel in the	"The ERG asked the company to indirectly compare atezolizumab versus nintedanib+docetaxel in the adenocarcinoma population only. However, for consistency purposes	Statement is misleading and implies Roche have been uncooperative and untransparent in our approach	This is not a factual error, no change made

adenocarcinoma population only. However, these results were not provided by the company. Instead, the company provided the results of atezolizumab (total population, OAK and POPLAR trials) versus nintedanib+docetaxel (adenocarcinoma population, LUME-Lung 1 trial)." See point above	versus the other analysis the ERG requested, these results were not provided by the company. Instead, the company provided the results of atezolizumab (total population, OAK and POPLAR trials) versus nintedanib+docetaxel (adenocarcinoma population, LUME-Lung 1 trial).		
Page 78, paragraph 4 Related to statement: "The company states that using the 'total population' of the LUME-Lung 1 trial to conduct a 'like for like' comparison between atezolizumab and nintedanib+docetaxel is 'not anticipated to significantly affect overall results' (CS, Section 4.10). However, this statement is not supported by the additional results provided by the company (Table 26) which show that, when restricting the ITC to the adenocarcinoma subgroup of the LUME-Lung 1 trial, treatment with atezolizumab no longer shows a statistically significant difference in OS compared to nintedanib+docetaxel." This is a misleading statement, which does not reflect the data provided to the ERG. Whilst it was assumed not to significantly affect overall results in the company submission, when the additional analyses were requested by the ERG this assumption changed: Whilst not statistically significant, the point estimate of a mean of 3.33 months overall survival benefit versus nintedanib+docetaxel is clinically meaningful. In addition, when the ITC results	"The company states that using the 'total population' of the LUME-Lung 1 trial to conduct a 'like for like' comparison between atezolizumab and nintedanib+docetaxel is 'not anticipated to significantly affect overall results' (CS, Section 4.10). However, when restricting the ITC to the adenocarcinoma subgroup of the LUME-Lung 1 trial, whilst the point estimate of mean OS benefit is 3.33 months, equates to a favourable impact on the ICER to atezolizumab, treatment with atezolizumab no longer shows a statistically significant difference in OS compared to nintedanib+docetaxel."	Statement is misleading to the reader and represents only a partial view of the situation	This is not a factual error, no change made

are implemented in the economic model, this equates to a substantial decrease in the ICER to £26,181. It is the ERG assumption of clinical equivalence, which is not clinically validated that is impacting the results so adversely. Such a statement, without providing all supportive data is misrepresentative of the analysis, and the situation			

Issue 7 Misrepresentation of POPLAR results

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 11, section 1.3, paragraph 2 Related to the statement: "However, in the POPLAR trial, statistically significant improvement is observed only in the non-squamous histology subgroup and for individuals with any type of NSCLC of ≥1% PD-L1 expression" This statement is misleading as it implies the overall results for all patients are not statistically significant. POPLAR was positive across the whole population. In addition POPLAR was a phase II trial with relatively small numbers of patients, and therefore was not powered to look at efficacy in subgroups.	"In the POPLAR trial, statistical significance was only powered in the ITT population. Whilst this was achieved, when observing subgroups, the non-squamous histology subgroup and individuals with any type of NSCLC of ≥1% PD-L1 expression benefited most"	Misleading statement and inappropriate interpretation of clinical data	This is not a factual error. The sentence quoted by the company has been taken out of context. No change made
Page 53; paragraph 2 Related to the following statement: "Results from the POPLAR trial also show a	"Results from the POPLAR trial also show a statistically significant improvement for individuals in the ITT, and ≥1% PD-L1 expression	Misleading statement and inappropriate interpretation of clinical data	This is not a factual error, no change made

statistically significant improvement for individuals with NSCLC of ≥1% PD-L1 expression but not for individuals with NSCLC of no measurable PD-L1 expression." This statement is misleading as it implies the overall results for all patients are not statistically significant. POPLAR was positive across the whole population. In addition POPLAR was a phase II trial with relatively small numbers of patients, and therefore was not powered to look at efficacy in subgroups.	but not for individuals with NSCLC of no measurable PD-L1 expression. The trial was not powered for statistical significance in subgroups, but there is a trend in benefit for these patients (HR:0.88 [0.55-1.42])"		
Page 82, bullet point 7 Related to the statement: "However, in the POPLAR trial, statistically significant improvement is observed only in the non-squamous histology subgroup and for individuals with NSCLC of ≥1% PD-L1 expression"	"Results from the POPLAR trial also show a statistically significant improvement for individuals in the ITT, and ≥1% PD-L1 expression but not for individuals with NSCLC of no measurable PD-L1 expression. The trial was not powered for statistical significance in subgroups, but there is a trend in benefit for these patients (HR:0.88 [0.55-1.42])"	Misleading statement and inappropriate interpretation of clinical data	This is not a factual error, no change made
Page 121, paragraph 3 Related to the statement: "However, in the POPLAR trial, statistically significant improvement is observed only in the non-squamous histology subgroup and for individuals with any type of NSCLC of ≥1% PD-L1 expression" This statement is misleading as it implies the overall results for all patients are not	"In the POPLAR trial, statistical significance was only powered in the ITT population. Whilst this was achieved, when observing subgroups, the non-squamous histology subgroup and individuals with any type of NSCLC of ≥1% PD-L1 expression benefited most"	Misleading statement and inappropriate interpretation of clinical data	This is not a factual error, no change made

statistically significant. POPLAR was positive across the whole population. In addition POPLAR was a phase II trial with relatively small numbers of patients, and therefore was not powered to look at efficacy in subgroups.			

Issue 8 Inaccurate statement regarding the comparison of atezolizumab and pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 32, paragraph 1 Regarding statement: "It, therefore, appears that the company considers that it is possible to compare the output measures from the two tests used to determine level of PD-L1 expression " This is an inaccurate statement: TC1/2/3 or IC1/2/3 is defined as PD-L1 expression of 1% or more of TCs or ICs for atezolizumab. However, the pembrolizumab assay does not measure ICs, hence a different proportion of patients are captured with both tests. Thus the populations are unequivocal and cannot be compared.	Remove statement	The statement is incorrect, the two populations are unequivocal	Statement has been removed

Issue 9 Incomplete statement of PSA/CEAC results

Description of problem	Description of proposed amendment	Justification for amendment	
Page 14, paragraph 3 Related to statement: "The company's probabilistic sensitivity analysis (PSA) results show that when the cost effectiveness of treatment with atezolizumab is compared with docetaxel and nintedanib+docetaxel, there is a 1% probability of treatment with atezolizumab being cost effective at a threshold of £50,000 per QALY gained." Incomplete statement which can mislead the reader: PAS approved by DH, which greatly increases this probability	"The company's probabilistic sensitivity analysis (PSA) results show that when the cost effectiveness of treatment with atezolizumab is compared with docetaxel and nintedanib+docetaxel at list price, there is a 1% probability of treatment with atezolizumab being cost effective at a threshold of £50,000 per QALY gained."	Incomplete statement misleads reader	This is not a factual error; however, suggested additional text added for clarity "The company's probabilistic sensitivity analysis (PSA) results show that when the cost effectiveness of treatment with atezolizumab is compared with docetaxel and nintedanib+docetaxel at list price, there is a 1% probability of treatment with atezolizumab being cost effective at a threshold of £50,000 per QALY gained."
Page 99, paragraph 1 Related to statement: "Examination of the CEAC shows that the chance of atezolizumab being cost effective versus docetaxel (and versus nintedanib+docetaxel) at a threshold of £50,000 per QALY gained is approximately 45% (and 1%)." Incomplete statement which can mislead the reader: PAS approved by DH, which greatly increases this probability	"Examination of the CEAC shows that the chance of atezolizumab being cost effective versus docetaxel (and versus nintedanib+docetaxel) at a threshold of £50,000 per QALY gained is approximately 45% (and 1%) at list price"	Incomplete statement misleads reader	This is not a factual error; however, suggested additional text added for clarity "Examination of the CEAC shows that the chance of atezolizumab being cost effective versus docetaxel (and versus nintedanib+docetaxel) at a threshold of £50,000 per QALY gained is

			approximately 45% (and 1%) at list price"

Issue 10 Inaccurate interpretation of pembrolizumab appraisal

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 105, paragraph 5 Regarding statement: "However, it is not just the number that is inaccurate; it is also the statement that this value was the Committee's preferred assumption. During TA428, this 9.6% survival rate was generated using the company's preferred assumptions. The Committee and the ERG for that appraisal were particularly concerned about the company's assumption that treatment with pembrolizumab would generate a lifetime treatment effect; this company assumption generated the 9.6% 5-year OS rate. The Committee considered a more clinically plausible duration of treatment effect would be 3 years after treatment stopped, at which point the Committee considered that the mortality hazard for patients treated with pembrolizumab would be equal to the mortality hazard for patients treated with docetaxel." This is an inaccurate statement. Pembrolizumab has a treatment cap of 2 years. The March 2016 data cut of	Remove statement	The statement is incorrect	This is not a factual error, no change made The 9.6% 5-year OS relates to a lifetime treatment effect. The 3-year duration of effect for OS was not stated in the FAD but in Committee documents and can be seen to be well below 5%. (See Figure 2 of letter of 24 October 2016 in Committee papers https://www.nice.org.uk/guidance/ta428/documents/committee-papers-3) The 9.6% 5-year OS is presented by the company as being considered plausible by the Committee and is based upon their preferred assumption set. This was not the case and it is not stated in the FAD that this was the case

KEYNOTE010 supported an analysis of the proportion of patients reaching this time point. Incorporating the committee's preferred assumption of a plausible duration of treatment effect of 3 years after treatment stopped (in addition to the March 2016 data cut of KEYNOTE 010) brings the analysis to the 5-year OS figure stated. Whilst this was a company assumption, this was the most up to date analysis available to the committee which supported the positive decision made for pembrolizumab, and was specifically referenced in paragraph 4.12 (page 12) of the Final appraisal determination).			

Issue 11 Factual inaccuracy of pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 12; bullet point 2 Relating to the following statement: "first-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% tumour proportion score" This is an incorrect description of KEYNOTE 010 trial population. KEYNOTE 010 is for the second line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% tumour proportion score.	"second-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% tumour proportion score"	The statement is incorrect in describing the KEYNOTE 010 population	This is an error. Text replaced as suggested "second-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% tumour proportion score"

Page 31, paragraph 2 Relating to the following statement: "In addition, the company highlights that the European marketing authorisation for pembrolizumab is similar to the anticipated European marketing authorisation for atezolizumab in that both are targeted at adults with locally advanced or metastatic NSCLC who have received at least one prior chemotherapy treatment. However, pembrolizumab is only recommended by NICE for the treatment of people with PD-L1 positive NSCLC." Roche did not make this statement in the CS. In addition, it is an incorrect description of the pembrolizumab marketing authorisation, and implied NICE restriction. The Pembrolizumab license is in people with PD-L1 positive NSCLC: This is not a restriction imposed by NICE.	Remove statement	The statement is incorrect in many aspects: 1) This is an inaccurate reflection of the Roche CS: it was not suggested that the marketing authorisation for pembrolizumab and atezolizumab would be similar; 2) The pembrolizumab European marketing authorisation is not similar to the anticipated marketing authorisation for atezolizumab: pembrolizumab is restricted to the treatment of people with PD-L1 positive NSCLC in their license. Conversely, atezolizumab will not have a restriction as part of its license. 3) Pembrolizumab is restricted to the treatment of people with PD-L1 positive NSCLC in their license, not through the NICE recommendation.	Statement removed and replaced with the followings: "Pembrolizumab has been recommended by NICE[15] for the treatment of adults with locally advanced or metastatic PD-L1 positive (≥1%) NSCLC who have received at least one prior chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour), providing pembrolizumab is stopped at 2 years of uninterrupted treatment and that no documented disease progression is observed. The anticipated marketing authorisation for atezolizumab is not restricted by tumour PD-L1 expression."

Issue 12 Textual error: NMA statistical software

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 69, paragraph 2: Relating to the following statement "under a Bayesian framework in Win BUGS statistical	Change Win BUGS to JAGS	This statement is incorrect in describing the statistical software that was used in the NMA	Text replaced as suggested (i.e. "WinBUGS replaced with JAGS"); however, the ERG

software" The incorrect software has been stated			highlights that JAGS was not mentioned in the CS

Issue 13 Incomplete description of ITC process

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 69-70 Relating to the following statement: "ITCs were conducted with individual participant data from the OAK and POPLAR trials and survival proportions across monthly time intervals were extracted from digitalised K-M curves" There is an error in the description which misleads the reader to believe digitalised K-M curves were used rather than individial participant data from OAK and POPLAR	"ITCs were conducted with individual participant data from the OAK and POPLAR trials and survival proportions across monthly time intervals were extracted from digitalised K-M curves for other trials"	This statement is incorrect in describing how comparator survival curves were extracted. This statement is misleading as it suggests digitalised K-M curves were used rather than individial participant data from OAK and POPLAR	For clarity, suggested additional text has been added "ITCs were conducted with individual participant data from the OAK and POPLAR trials and survival proportions across monthly time intervals were extracted from digitalised K-M curves for other trials"

Issue 14 Misunderstanding of FP methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 72, paragraph 2 Relating to the following statement: "The ERG also notes that heterogeneity seems to be present in all RE FP models according to SD as defined by Jansen (i.e., SD>0)." Due to the model structure, it will be true that	Remove statement	This statement is misleading as it implies the models do not fit the data well due to heterogeneity. The statement is irrelevant because the estimate of SD will be >0 for any random effects model regardless of whether or not the heterogeneity is substantial, clinically meaningful, or	For clarity, text reworded as follows: “The ERG also notes that heterogeneity seems to be present in all RE FP models according to SD as defined by Jansen ~~(i.e., SD>0)~~ and

the estimate of SD will be >0 for any random effects model fitted in a Bayesian setting, regardless of whether or not the heterogeneity is substantial, clinically meaningful, or improves the fit of the model over fixed effects when accounted for.		improves the fit of the model over fixed effects when accounted for.	resulting in wider confidence intervals around results provided by RE FP models."

Issue 15 Incorrect statement on provisions in CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 29; paragraph 1 Relating to the following statement: "The ERG, therefore, considers that the company should have presented clinical and cost effectiveness results within the CS, or justified their absence." This statement is inaccurate and misleading. The absence of clinical and CE results by PD-L1 subgroup was justified in the CS on a number of occasions including: 1) Page 24, Table 1 2) Page 219 "Clinical benefit is observed in all subgroups of NSCLC patients treated with atezolizumab. As such no analyses are conducted on restricted populations as compared to the anticipated indication."	Remove "or justified their absence"	This statement is inaccurate and misleading as the absence of clinical and CE results by PD-L1 subgroup was justified a number of times in the CS	This is the ERG's opinion, not a factual error. For clarity, text reworded as follows: "The ERG, therefore, considers that the company should have presented clinical and cost effectiveness results within the CS, or fully justified their absence."
Page 74; paragraph 3 Relating to the following statement: "The ERG notes that the precision and, therefore, the reliability of the ITC estimates are influenced	Remove "which has not been acknowledged by the company or accounted for in any ITC analyses "	This statement is inaccurate and misleading	This is not a factual error, no change made

by the choice of FP model and by potential statistical heterogeneity in the network which has not been acknowledged by the company, or accounted for in any ITC analyses." This is inaccurate and misleading: It implies Roche have not accounted for any heterogeneity, however this was acknowledged and accounted for in the random effects analyses that were performed by the company and provided in the response to clarification questions.			
Page 83, paragraph 3 Relating to the following statement: "The ERG highlights that the precision and reliability of all additional results are influenced by the choice of FP model and greatly influenced by potential statistical heterogeneity in the network which has not been acknowledged by the company or accounted for in any ITC analyses " This is inaccurate and misleading: It implies Roche have not accounted for any heterogeneity, however this was acknowledged and accounted for in the random effects analyses that were performed by the company and provided in the response to clarification questions.	Remove "which has not been acknowledged by the company or accounted for in any ITC analyses "	This statement is inaccurate and misleading	This is not a factual error, no change made

Issue 16 Textual error in SLR description

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 35, Table 4: Relating to column 4 "End date" Incorrect statement regarding search date range end for EMBASE, MEDLINE, and MEDLINE In-Process. Currently states "Not provided" however page 94 of the CS confirms all searches were conducted in June 2016. Therefore the "end date" should be "June 2016"	Delete "Not provided" and replace with "June 2016"	Incorrect statement	This is an error. Text replaced as suggested, i.e. "Not provided" replaced with "June 2016"
Page 36; Table 5: Relating to the table title and 'additional eligibility criteria' row The table only refers to the systematic review methods, however point 2 & 3 of the "additional eligibility criteria" refer to the NMA - not the SLR. These restrictions were not applied in the SLR, and were pre-specified in the feasibility assessment before the NMA was conducted. Hence, this is incorrect and misleading to the reader	Remove points 2 and 3 from "additional eligibility criteria" column	Incorrect and misleading column.	This is an error. Text removed

Issue 17 Errors regarding OAK/POPLAR

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 37-38: Relating to the following statement: "The ERG notes that an exploratory objective of the OAK and POPLAR trials was the evaluation of the relationship between PD-L1 expression and measures of efficacy" This is inaccurate. The exploratory endpoint was to evaluate PD-L1 in blood and tissue against efficacy.	"The ERG notes that an exploratory objective of the OAK and POPLAR trials was the evaluation of the relationship between PD-L1 expression in blood and tumour tissue and measures of efficacy	Incorrect statement. Updated as per the exploratory endpoint definition in the CSR	For clarity, text added as suggested "The ERG notes that an exploratory objective of the OAK and POPLAR trials was the evaluation of the relationship between PD-L1 expression in blood and tumour tissue and measures of efficacy"
Page 39, Table 6 Relating to the 'population' row for OAK: Currently states "a total of 825 patients were randomised, 425 to the atezolizumab arm and 425 to the docetaxel arm" This is incorrect: 850 patients were randomised: 425 to the atezolizumab arm and 425 to the docetaxel arm	"a total of 850 patients were randomised, 425 to the atezolizumab arm and 425 to the docetaxel arm"	Incorrect statement. Updated as per the company submission, and OAK CSR	This is an error. Number has been corrected (i.e. 825 changed to 850)

Issue 18 Missing data in rationale for comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 10, bullet point 2 in "excluded comparators"	"Third, at the time of submission (16th February 2017) pembrolizumab had only been	Misleading statement with no justification of what constitutes "recently"	For clarity, additional text added as suggested

Related to the statement: "Third, pembrolizumab has only been recently recommended by NICE to treat patients with NSCLC and is unlikely to represent a standard of care at this time" The current statement does not account for any time horizon associated with "recently". At submission, pembrolizumab had been approved only 4 weeks beforehand. It is misleading the reader by excluding this	recently recommended by NICE to treat patients with NSCLC (guidance issued 11th January 2017) and is unlikely to represent a standard of care at this time"		"Third, at the time of submission (16th February 2017) pembrolizumab had only been recently recommended by NICE to treat patients with NSCLC (guidance issued 11th January 2017) and is unlikely to represent a standard of care at this time"

Issue 19 Inappropriate assumption of open label study impact

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 12, section 1.4; paragraph 1 Related to the statement: "However, the open-label design of these trials provides the opportunity for investigator-assessed outcomes to be biased." This statement is misleading: The primary outcome of this trial is overall survival, where results are unable to be biased.	Remove statement	Misleading statement implies bias in outcomes where the primary outcome is death	This is not a factual error, no change made
Page 49; paragraph 1 Related to the statement: "However, the open-label design of these trials provides the opportunity for investigator-assessed outcomes to be biased." This statement is misleading: The primary	Remove statement	Misleading statement implies bias in outcomes where the primary outcome is death	This is not a factual error, no change made

outcome of this trial is overall survival, where results are unable to be biased.			
Page 81, bullet point 6 Related to the statement: "However, the open-label design of these trials provides the opportunity for investigator-assessed outcomes to be biased." This statement is misleading: The primary outcome of this trial is overall survival, where results are unable to be biased.	Remove statement	Misleading statement implies bias in outcomes where the primary outcome is death	This is not a factual error, no change made

Issue 20 CIC data that has not been redacted

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
ICERs and incremental costs have not been appropriately redacted: Page 14, paragraph 1 and 5 Page 18, paragraph 3 and 4 Page 97, paragraph 2, Table 39 Page 98, paragraph 1, Table 40 Page 99, Table 41 Page 100, Figure 11, Figure 12 Page 102, paragraph 1, 3, 4 Page 103, paragraph 1 Page 112, paragraph 1 Page 113, paragraph 2 Page 115, paragraph 2 Page 116, paragraph 1 & 2 Page 117, Table 43 Page 118, Table 44 Page 122, paragraph 4	Redaction of ICERs and incremental costs	Price still confidential	NICE in discussion with the company – no change made at this stage of the process

Issue 21 Unnecessary AIC/CIC marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Data has been marked confidential unnecessarily Page 29, paragraph 3 Page 37-38 Page 39, Table 6 Page 55, paragraph 2 Page 56-57 Page 67, Table 23 Page 133, Table 47 Page 134, Table 48 Page 135, Table 48, Table 49	Un-mark as AIC/CIC	No requirement for AIC/CIC markings	NICE is in discussion with the company – no change made at this stage of the process

Issue 22 Misrepresentation of CS, and ERG requests as part of clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 70, paragraph 4 Regarding statement: "Furthermore, the company repeated the ITC with RE but only for the best fitting FE FP model and interpreted the presence of heterogeneity as a difference in the DIC of the FE and RE models if greater than five points. The company cites two	Remove statement	The statement is incorrect and misleading: the ERG did not request this reference, but Roche have provided it as part of this response	The reference that the company provides here (and previous references) discusses the interpretation of DIC relating to model fit. The latter part of the final sentence reworded as follows:

references to support this interpretation. The ERG agrees that these references suggest that DIC (along with the residual deviance statistic) can be used to compare the fit of FE and RE models, but cannot find any mention within these references of using a difference in DIC of at least five points to indicate that heterogeneity is present in analyses." This is misleading to the reader: The ERG did not request a reference specifying the use of the 5 point system to determine heterogeneity. Clarification question A7di only requested a reference for the use of DIC to assess heterogeneity, which was provided by Roche, and can be found on page 21 of the company response to clarification questions. However, we have included this reference as part of our response to this report: The University of Cambridge MRC biostatistics unit (developers of WinBUGS) state the following: "How do I compare different DICs? The minimum DIC estimates the model that will make the best short-term predictions, in the same spirit as Akaike's criterion. It is difficult to say what would constitute an important difference in DIC. Very roughly, differences of more than 10 might definitely rule out the model with the higher DIC, differences between 5 and 10 are substantial, but if the difference in DIC is, say, less than 5, and the models make very different inferences, then it could be misleading just to report the model			"…but cannot find any mention within these references ~~of using a difference in DIC of at least five points~~ to explain how to use the DIC to indicate that heterogeneity is present in analyses"

with the lowest DIC”(University of Cambridge, 2017)			

Issue 23 Incorrect citations in report

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Incorrect citations between ERG report, and company response to clarification documents Page 72, Table 24; Page 73, Figures 3&4: "Source: Company response to ERG clarification letter, adapted from Figure 18, Figure 20, Figure 22, Figure 24, Figure 26, Figure 38, Figure 39, Figure 40, Figure 41, Figure 42, Table 2"	"Source: Company response to ERG clarification letter, adapted from Figure 21, Figure 23, Figure 25, Figure 27, Figure 29, Figure 41, Figure 42, Figure 43, Figure 44, Figure 45, Table 2"	Incorrect citations	This is an error. Text changed as suggested "Source: Company response to ERG clarification letter, adapted from Figure 21, Figure 23, Figure 25, Figure 27, Figure 29, Figure 41, Figure 42, Figure 43, Figure 44, Figure 45, Table 2"
Incorrect citations between ERG report, and company response to clarification documents Page 75, Table 25: "Source: company response to ERG clarification letter, adapted from Figure 28, Figure 30, Figure 32, Figure 34, Figure 36, Figure 43, Figure 44, Figure 45, Figure 46, Figure 47, Table 3."	"Source: company response to ERG clarification letter, adapted from Figure 31, Figure 33, Figure 35, Figure 37, Figure 39, Figure 46, Figure 47, Figure 48, Figure 49, Figure 50, Table 3."	Incorrect citations	This is an error. Text changed as suggested "Source: company response to ERG clarification letter, adapted from Figure 31, Figure 33, Figure 35, Figure 37, Figure 39, Figure 46, Figure 47, Figure 48, Figure 49, Figure 50, Table 3."

Issue 24 Misrepresentation of FP outputs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 75, paragraph 1 Related to statement: "In the clarification response letter, the company states that, within the reduced network for the FE FP, the Weibull model is the best fitting model; however, within the CS, the Gompertz model was judged to be the best fitting model" The statement is misrepresentative: Roche were transparent that in reducing the network a different model became the better fit to the data. The way it is currently worded could be misinterpreted that an error was made in the original submission.	"Within the CS (extended network) the Gompertz model was judged to be the best fitting model; however, in the clarification response letter, the company states that, within the reduced network for the FE FP, this changed and rather the Weibull model was the best fitting model.	Misleading: can be perceived this was an error, rather than an acknowledgment of a better fit to the data	This is not a factual error; however, for clarity, text reworded as suggested "Within the CS (extended network) the Gompertz model was judged to be the best fitting model; however, in the clarification response letter, the company states that, within the reduced network for the FE FP, this changed and rather the Weibull model was the best fitting model."

Issue 25 Misinterpretation of cost effectiveness base case input

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 91, paragraph 1 Related to statement: "In line with clinical opinion, the company removes the costs of third-line immunotherapy from the base case analysis and considers the use of radiotherapy as a third-line treatment in a scenario analysis." This is an error: Radiotherapy as a third line	Remove "and considers the use of radiotherapy as a third-line treatment in a scenario analysis"		This is an error. Text deleted

treatment is included in the base case. However an additional scenario analysis is conducted varying the cost associated with radiotherapy based on alternative sources located.			

Issue 26 Error in status of PAS application

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 94, paragraph 1 Related to statement: "The PAS application is currently under review by the Department of Health." The PAS has been approved by the Department of Health, therefore this is no longer accurate	"The PAS has been approved by the Department of Health."		This is an error. Text changed as suggested "The PAS application ~~is currently under review~~ has been approved by the Department of Health."

Issue 27 Inappropriate statement regarding HRQoL data collected

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 101, paragraph 3 Related to statement: "However, the ERG notes that the people who completed the questionnaires were trial participants and, therefore, may not be wholly representative of all patients in NHS clinical practice who are eligible for treatment with atezolizumab."	Remove statement	Inappropriate statement for the appraisal of atezolizumab	This is not a factual error, no change made

The NICE reference case stipulates the source of data for measurement of health-related quality of life should be reported directly by patients and/or carers. Roche have met the NICE reference case with the HRQoL data, hence this criticism is inappropriate for the appraisal.			

References

BRISTOL MYERS SQUIBB. 2017. *Press release: Phase 1 study CA209-003* [Online]. Available: https://news.bms.com/press-release/bmy/five-year-survival-observed-opdivo-nivolumab-patients-previously-treated-advanced- [Accessed Accessed May 2017.

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ID970 STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Atezolizumab for treating locally advanced or metastatic non-small cell lung cancer after chemotherapy [ID970]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 16/56/11

Erratum completed 22 May 20167

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 27 overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. Not all were considered by the ERG to be factual inaccuracies but some were considered to require minor changes to the text. The pages of the ERG report that have been affected are presented here. Please note:

- Additional or replacement text added by the ERG is highlighted in grey
- Text deleted completely (as opposed to being reworded) is blacked out (for example, [redacted]).

Comparators

The comparators specified in the final scope issued by NICE are docetaxel, nintedanib+docetaxel, pembrolizumab, nivolumab and best supportive care (BSC).

- Included comparators:
    - direct evidence is available for the comparison of the effectiveness of atezolizumab versus **docetaxel** (administered at a dose of 75mg/m^2 every three weeks) from the OAK and POPLAR trials
    - treatment with **nintedanib+docetaxel** is recommended by NICE as an option for treating locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy. In the absence of direct evidence to allow a comparison of the effectiveness of treatment with atezolizumab versus nintedanib+docetaxel, the company undertook an indirect treatment comparison (ITC).
- Excluded comparators:
    - **nivolumab** was not recommended by NICE for the treatment of locally advanced or metastatic NSCLC and hence cannot be considered a standard of care
    - the company provides three reasons for excluding **pembrolizumab**. First, marketing authorisation for pembrolizumab is only for patients with PD-L1 positive NSCLC and therefore does not match the anticipated marketing authorisation for atezolizumab. Second, accurate comparisons between treatments is not possible due to the differences between tests used in clinical studies to select patients. Third, at the time of submission (16th February 2017) pembrolizumab has only been recently recommended by NICE to treat patients with NSCLC (guidance issued 11th January 2017) and is unlikely to represent a standard of care at this time
    - **BSC** was excluded due to a clinically validated assumption that patients eligible for treatment with atezolizumab would be considered fit enough to receive other treatments.

Outcomes

Clinical evidence is presented in the CS for all five outcomes specified in the final scope issued by NICE: progression-free survival (PFS), overall survival (OS), objective response rate (ORR), adverse events (AEs) and health-related quality of life (HRQoL).

Subgroups

It is specified within the final scope issued by NICE that, if evidence allows, consideration will be given to subgroups based on biological markers. Within the CS, results have been provided from the OAK trial by baseline characteristics and for histology subgroups (squamous and non-squamous disease). Results have also been presented for patients with no measurable PD-L1 expression (TC0/IC0) and for patients with ≥1% PD-L1 expression.

Other considerations

- Agreed patient access schemes (PAS) are in place for atezolizumab and nintedanib
- The company has not identified any equality issues
- The company has presented a case for atezolizumab to be assessed against the NICE End of Life criteria.

1.1 Summary of clinical effectiveness evidence submitted by the company

The direct clinical evidence for the treatment of atezolizumab versus docetaxel was derived from the OAK and POPLAR trials.

Results from the OAK and POPLAR trials

Results from both the OAK and POPLAR trials show that treatment with atezolizumab is associated with a statistically significant and clinically meaningful improvement in median OS (4.2 months in the OAK trial and 2.9 months in the POPLAR trial) compared to docetaxel in patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 and 1. In the OAK trial, this statistically significant gain in OS is observed regardless of histology and PD-L1 status. However, in the POPLAR trial, statistically significant improvement is observed only in the non-squamous histology subgroup and for individuals with any type of NSCLC of ≥1% PD-L1 expression. Improvement in OS with atezolizumab compared with docetaxel is also generally consistent across patient baseline characteristics in both trials. No statistically significant difference in investigator-assessed PFS was observed between atezolizumab and docetaxel arms in either trial.

Results from the company's indirect treatment comparison (ITC) suggest that the best estimate of the expected mean difference in OS is around 6 to 7 months for atezolizumab versus docetaxel ([redacted] median OS gain of 4.2 months and 2.9 months in the OAK and POPLAR trials respectively). Results from the company's ITC suggest that the best estimate of the expected mean difference in OS is around 5 to 6 months for the comparison of atezolizumab versus nintedanib+docetaxel. Also, results from the company's ITC analyses suggest that there is no statistically significant difference in PFS survival for the comparison of atezolizumab versus docetaxel and for atezolizumab versus nintedanib+docetaxel.

The company has collected HRQoL outcome data using the European Organisation for Research and Treatment Cancer (EORTC) Quality of Life questionnaire, the EORTC Quality of Life in Lung Cancer questionnaire and the EQ-5D-3L questionnaire. Analyses of HRQoL data collected during the OAK trial show that there was no clinically meaningful worsening of

commonly reported cancer treatment-related symptoms for patients treated with atezolizumab, while there was a clinically meaningful worsening in alopecia and peripheral neuropathy throughout treatment for patients treated with docetaxel. In addition, patients treated with atezolizumab demonstrated prolonged time to deterioration of patient-reported chest pain compared with patients treated with docetaxel (hazard ratio [HR] 0.72, 95% confidence interval [CI]: 0.55 to 0.93).

1.4 Summary of the ERG's critique of submitted clinical effectiveness evidence

The ERG considers that the OAK and POPLAR trials were of good quality and well conducted; patient characteristics were balanced across the arms and the statistical methods were generally appropriate. However, the open-label design of these trials provides the opportunity for investigator-assessed outcomes to be biased. Also, the ERG notes that OS and PFS HRs must be interpreted with caution due to hazards not being proportional, as demonstrated by the company.

The ERG does not agree with the ITC approach taken by the company as the main network includes comparators that are not listed in the final scope issued by NICE. In addition, the ERG does not consider that the company was justified in excluding pembrolizumab from the ITC network of comparators relevant to this appraisal. During the clarification process, the ERG asked the company to undertake two further ITC analyses. However, the company undertook these using non-equivalent populations and results should be viewed with extreme caution:

- based on a (reduced) network using data from the intention-to-treat (ITT) populations of the OAK and POPLAR trials and the adenocarcinoma population from the LUME-Lung 1 trial, results suggest that the best estimate of expected mean difference in OS for atezolizumab versus nintedanib+docetaxel is 3.33 months (compared to median OS gain of 4.74 months when the analysis was carried out using LUME-Lung 1 trial total population) and is not statistically significant. However, this analysis was undertaken using non-equivalent populations and results should be viewed with caution.
- based on a (reduced) network using data from the ITT populations of the OAK, POPLAR and KEYNOTE-010 trials (the latter assessing the efficacy of pembrolizumab as a second-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% tumour proportion score) suggest that there is no statistically significant difference in OS or PFS for patients receiving atezolizumab when compared with pembrolizumab.

The ERG considers that the company's use of a fractional polynomial (FP) approach to conduct the ITC is appropriate. However, FP ITC results are influenced by a range of factors (e.g., comparators and population selected, type of FP model chosen and the use of FE or RE) which means that it is difficult to identify the most appropriate combination of factors to

Using list prices only, the company base case incremental cost effectiveness ratio (ICER) for the comparison of treatment with atezolizumab versus docetaxel is £72,356 per QALY gained; treatment with atezolizumab generates 0.748 additional QALYs at an additional cost of £53,970. For the comparison of treatment with atezolizumab versus nintedanib+docetaxel, the ICER is £56,076 per QALY gained; treatment with atezolizumab generates 0.646 additional QALYs at an additional cost of £36,209.

The company carried out a wide range of deterministic sensitivity analyses. The most influential parameters for both atezolizumab versus docetaxel and atezolizumab versus nintedanib+docetaxel are related to the cure fraction rate applied to atezolizumab, the monthly cost of atezolizumab and the discount rate used for effects.

The company's probabilistic sensitivity analysis (PSA) results show that when the cost effectiveness of treatment with atezolizumab is compared with docetaxel and nintedanib+docetaxel at list price, there is a 1% probability of treatment with atezolizumab being cost effective at a threshold of £50,000 per QALY gained. The company carried out 12 scenario analyses and results from these demonstrate that the cost effectiveness of treatment with atezolizumab is only sensitive to the distribution chosen to extrapolate time to treatment discontinuation (TTD) with atezolizumab and then only if a log-logistic distribution is chosen.

1.6 Summary of the ERG's critique of submitted cost effectiveness evidence

The ERG considers that there are three errors in the company model that need to be corrected if the model is to produce accurate cost effectiveness results that reflect the underlying assumptions of the company base case. These errors are:

- incorrect application of discounting
- absence of age-dependent utility decrements
- incorrect use of a half-cycle correction to TTD data.

The ERG estimates that the accurate ICER, under the company base case assumptions for the comparison of the cost effectiveness of atezolizumab versus docetaxel is £77,569 per QALY gained and for the comparison of treatment with atezolizumab versus nintedanib+docetaxel it is £60,366 per QALY gained.

The ERG considers that the company's approach to modelling OS generates overly optimistic survival gains when treatment with atezolizumab is compared with docetaxel and when atezolizumab is compared with nintedanib+docetaxel. The ERG has identified three

issues with the mixed cure-rate approach taken by the company to model OS for patients receiving atezolizumab:

- use of the log-logistic function produces an implausibly long survival tail
- there is insufficient evidence for application of a cure-rate
- the value for the cure-rate [redacted] was not sufficiently justified by the company.

A further issue with the company's atezolizumab OS model relates to the company's assumption that treatment with atezolizumab has a lifetime protective effect. This assumption has been criticised by a previous NICE Appraisal Committee when considering the use of an immunotherapy for treating patients with previously treated advanced or metastatic NSCLC. In addition, the ERG highlights that the company's approach to modelling OS for patients receiving atezolizumab results in mortality rates that are, at some points, lower than the mortality rates of the UK general population of the same age.

The company approach to modelling of OS for docetaxel and for nintedanib+docetaxel involved adjusting the company's OS atezolizumab model using the relevant hazard rates generated by the company's FP ITC. Due to concerns relating to the company's FP ITC, including the fact that the FP ITC used to generate hazard rates involved inputs that are not relevant to this appraisal, the ERG has little confidence in the results produced by this approach. The ERG considers that the expected docetaxel survival results produced by the company's FP ITC may be optimistic [redacted]. The ERG also highlights that the FP ITC used by the company to model OS for patients receiving nintedanib+docetaxel was not restricted to the nintedanib+docetaxel licensed population (patients with adenocarcinoma), meaning that the company's ITC results for this treatment are not relevant to this appraisal.

1.7 Summary of company's case for End of Life criteria being met

To meet the NICE End of Life criteria the company must demonstrate that:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months
- 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.

- confidence in modelling OS for patients receiving nintedanib+docetaxel by adjusting the OS atezolizumab model by the hazard rates generated by the company's ITC is limited by concerns relating to identifying the most relevant FP ITC, including the fact that the FP ITC used to generate hazard rates involved inputs that are not relevant to this appraisal and that the FP ITC was not limited to patients with adenocarcinoma histology.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG's preferred method was to model OS for both atezolizumab and docetaxel by using Kaplan-Meier (K-M) data from the OAK trial for as long as possible, and then to append exponential curves to project OS for the remainder of the model time horizon. The ERG also limited the duration of treatment effect of atezolizumab to approximately 3 years.

The FP ITC results generated by the company showed that when treatment with atezolizumab (whole population) was compared with nintedanib+docetaxel (adenocarcinoma population) using the reduced network (i.e., comparators of relevance to this appraisal) there was no statistically significant difference in expected OS between the two therapies (3.33 months [-0.16 to 6.74]). The ERG, therefore, undertook an analysis in which the OS of patients receiving nintedanib+docetaxel was the same as that of patients receiving atezolizumab, and the treatment effect of both interventions was limited to 3 years. Hence, the only modelled differences were therapy costs and HRQoL (utility values were adjusted for each treatment to take into account the incidence of AEs).

1.11 Cost effectiveness conclusions

Application of the ERG model amendments results in an ICER for the comparison of treatment with atezolizumab versus docetaxel of £170,497 per QALY gained.

Application of the ERG model amendments results in an ICER for the comparison of treatment with atezolizumab versus nintedanib+docetaxel of £1,170,793 per QALY gained.

Box 3 Possible reasons why atezolizumab might be effective in treating tumours that are PD-L1 negative

The first is the biological hypothesis that atezolizumab increases anticancer immunity through enhanced priming of new anticancer immune responses.[23] PD-L1 is expressed on T cells and antigen presenting cells (APCs) present in the lymph nodes. Here it binds to B7.1, which is also expressed on T cells and APCs; as with PD-1 to PD-L1 interactions, this interaction can downregulate T cell activity and subsequent immune responses. Inhibition of this interaction in the lymph node environment may therefore prevent this downregulation and stimulate an immune response in tumours that are PD-L1 negative.[29,30]

The second reason is that a PD-L1 negative tumour is defined as PD-L1 expression on less than 1% expression of tumour cells (TCs) and tumour-infiltrating immune cells (ICs), i.e. TC0 and IC0. Consequently, there could still be low levels of PD-L1 expression within the tumour environment that are sufficient to induce anti-tumoural immune responses following treatment with atezolizumab.

Finally, PD-L1 expression in tumours may be heterogeneous and variable over time in a subset of tumours. This means that a biopsies taken from different areas of a tumour may show different levels of PD-L1 expression, or that the PD-L1 expression level may have changed since the biopsy was taken and may not reflect the current PD-L1 status.[31-34]

APC=antigen presenting cells; IC=immune cells PD-1=programmed death-1; PD-L1=programmed death-ligand 1; T=tumour; TC=tumour cells
Source: Company clarification letter response

The ERG highlights that the company has provided OAK trial results comparing OS for patients treated with atezolizumab versus docetaxel (CS, Section 4.7) for patients with ≥1% (TC1/2/3 or IC1/2/3) PD-L1 expression (HR 0.74, 95% CI: 0.58 to 0.93; p=0.0102). Furthermore, OAK trial OS results by level of PD-L1 expression are in the public domain.[23] The ERG, therefore, considers that the company should have presented clinical and cost effectiveness results within the CS, or fully justified their absence.

Atezolizumab is currently being assessed by NICE for the treatment of locally advanced or metastatic urothelial carcinoma[35] (company submission: 18 January 2017) and is already available in the UK for patients with this condition under the Early Access to Medicines Scheme (EAMS). In October 2016 the US Food and Drug Administration (FDA)[36] approved atezolizumab for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. Regulatory approval for this indication has also been received in Kuwait and South Korea.

The treatment regimen for atezolizumab is a flat dose of 1200mg intravenous infusion administered in a hospital setting every 3 weeks (Q3W). The initial dose must be administered over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be administered over 30 minutes. It is stated within the draft Summary of Product Characteristics[1] (SmPC) that patients should be treated with atezolizumab until loss of clinical benefit or unmanageable toxicity.

population for which it is recommended. A full critique of the company's ITC can be found in Section 4.6 of this report.

3.3.2 Excluded comparators

Nivolumab

The ERG agrees with the company that nivolumab is not a relevant comparator. This is because, at the time the CS was sent to NICE, nivolumab had not been recommended by NICE as a treatment for the population under consideration in this appraisal. However, the ERG notes that at the time of submitting the ERG report to NICE (April 2017), two STAs considering the use of nivolumab for the treatment of locally advanced or metastatic NSCLC were on-going, one for patients with squamous disease (ID811)[41] and the other for patients with non-squamous disease (ID900).[42]

Pembrolizumab

The ERG notes that, in the CS (Figure 2) the company has placed pembrolizumab in the same position in the treatment pathway as atezolizumab. Pembrolizumab has been recommended by NICE[15] for the treatment of adults with locally advanced or metastatic PD-L1 positive (≥1%) NSCLC who have received at least one prior chemotherapy (and targeted treatment if they have an EGFR- or ALK-positive tumour), providing pembrolizumab is stopped at 2 years of uninterrupted treatment and that no documented disease progression is observed. The anticipated marketing authorisation for atezolizumab is not restricted by tumour PD-L1 expression. The company considers that this discrepancy means that a comparison of the effectiveness of treatment with atezolizumab versus pembrolizumab would not be meaningful as the relative clinical benefits of treatment with pembrolizumab would be overestimated. The ERG considers that, as results from the OAK trial (CS, p81) show that treatment with atezolizumab versus docetaxel was associated with a similar improvement in OS in the ITT population (hazard ratio [HR] 0.73, 95% CI: 062 to 0.87; p=0.0003) and in patients with ≥1% (TC1/2/3 or IC1/2/3) PD-L1 expression (HR 0.74, 95% CI: 0.58 to 0.93; p=0.0102), the company's argument is not compelling.

The company also highlights that, in studies of the effectiveness of atezolizumab and pembrolizumab, the tools used to assess PD-L1 expression differ significantly, both in how expression is measured (atezolizumab: TC and IC, pembrolizumab: TC only) and also in terms of which patients are considered positive expressors. The company considers that this means that even a subgroup analysis of PD-L1 positive patients would not be appropriate. As part of the clarification process the ERG requested an explanation from the company as to how the two tests differ. The response provided by the company focused on the differences in terms of detection antibody, immunohistochemistry (IHC) platform, cell types

scored (TC and IC versus TC) and cut-off points. However, the company states (CS, p49) that analyses of data from the OAK trial showed a statistically significant and clinically meaningful improvement in OS when treatment with atezolizumab was compared with docetaxel in patients with ≥1% PD-L1 expression (HR 0.74, 95% CI: 0.58 to 0.93, p=0.012) and, in the clarification response, the company explained that TC1/2/3 or IC1/2/3 was defined as PD-L1 expression of 1% or more of TCs or ICs. [redacted]

In addition, the company highlights that pembrolizumab has only recently been recommended by NICE[15] for use in patients with NSCLC (guidance issued 11th January 2017) and, therefore, considers it unlikely to represent a standard of care at this time (February 2017). The ERG considers that while there may not have been wide use of pembrolizumab within the NHS at the time of the CS, it is likely to have become an established option by the time the final appraisal determination (FAD) for this appraisal of atezolizumab is published. The ERG, therefore, does not find this line of argument compelling.

The ERG considers that it is difficult accept the company's argument that a difference in marketing authorisations/study populations is a barrier to undertaking a comparison between atezolizumab and pembrolizumab. In addition, the ERG highlights that the company has included nintedanib+docetaxel as a comparator even though this treatment is only recommended by NICE for the population with adenocarcinoma histology.

The ERG considers that pembrolizumab is an appropriate comparator, but only for the population for which it is currently recommended by NICE, i.e., patients whose tumours express PD-L1 (≥1%) and who have had at least one prior chemotherapy regimen (and targeted treatment if they have an EGFR- or ALK-positive tumour).

Best supportive care

Clinical advice to the company is supported by clinical advice to the ERG, namely that patients who are eligible for treatment with atezolizumab would be fit enough for other treatments and, therefore, BSC is not an appropriate comparator.

Erlotinib and crizotinib

Erlotinib and crizotinib were not included in the final scope issued by NICE but they are included in the company's treatment pathway algorithm (CS, p46). However, clinical advice to the company is that targeted therapy treatment options are likely to be preferred over

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

The company carried out a systematic search of the literature in June 2016 to identify phase II-IV randomised controlled trials (RCTs) investigating the efficacy and safety of pharmacological interventions for second- and further-line treatment for locally advanced or metastatic NSCLC. The purpose of the review was to identify studies to include in the company's ITC, which was conducted to support pricing and reimbursement submissions across all markets, and included comparators not listed in the final scope issued by NICE.

The data sources searched and the time spans for the searches are provided in Table 4, while a summary of, and ERG comments on, the review methods used by the company are presented in (Table 5).

Table 4 Data sources for the clinical systematic review

Search strategy component	Source	Search date range	
		Start	End
Electronic database searches	EMBASE	1988	June 2016
	MEDLINE	1946	
	MEDLINE In-Process	1946	
	Cochrane Central Library of Controlled Trials (CENTRAL)	January 2012	June 2016
	Cochrane Database of Systematic Reviews (CDSR)		
Congress proceedings	American Society of Clinical Oncology (ASCO) European Society for Medical Oncology (ESMO) International Association for the Study of Lung Cancer (IASLC)/World Conference on Lung Cancer (WCLC) International Lung Cancer Congress (ILCC) European Lung Cancer Conference (ELCC) British Thoracic Oncology Group (BTOG)	1 January 2013	17 June 2016
Clinical trial registries	ClinicalTrials.gov	1 January 2012	21 July 2016
	WHO's meta-registry 'International Clinical Trials Registry Platform Search Portal' (ICTRP)		
	EU Clinical Trial Registry	1 January 2012	30 August 2016

Source: CS, pp50-51

Table 5 Summary of, and ERG comment on, company systematic review methods

	Results	ERG comment
Searching		
Sources searched: • Electronic databases • Congress proceedings • Clinical trial registries	22,502 studies	• The searches were completed in summer 2016, meaning that there is a risk that some relevant studies will not have been included in the search results • The search terms were relevant but could have been expanded regarding the search terms relating to cancer • The searches only included population terms and not indication terms
Formal eligibility criteria		
Two analysts independently assessed study eligibility based on the criteria presented in Table 10 of the CS (pp52-54)	303 studies	• Use of two independent assessors improves the quality of reviews • The high number of results from the initial search tests the concentration of reviewers
Additional eligibility criteria		
1. Although no language restrictions were included in the search strategies, the company excluded Asian language publications at the data extraction stage due to the extra complexity associated with translating these articles and the limited relevant additional data these would provide [redacted]	38 Asian articles were excluded, leaving 265 publications from 184 different studies [redacted]	• The need to employ two further sets of eligibility criteria highlights the very un-focused nature of the original searches undertaken by the company
Quality assessment		
The company conducted a quality assessment exercise using the minimum criteria recommended by NICE in the company submission template. The company applied guidance from the Cochrane Handbook of Systematic Reviews to assess each of the criteria. The results of the company assessment of the OAK and the POPLAR trials are presented in the CS. The results of the assessment of the RCTs included in the company's ITC are presented in Appendix 4 of the CS.		

CS=company submission; ERG=Evidence Review Group; NSCLC=non-small cell lung cancer; RCT=randomised controlled trial
Source: CS, pp55-56 and pp96-97

4.1.1 Evidence synthesis

The company presents direct evidence to support the clinical efficacy of atezolizumab from two RCTs (the OAK trial and the POPLAR trial). The CS includes a narrative description of both of these trials. No evidence synthesis was undertaken.

4.2 ERG critique of direct clinical effectiveness evidence

4.2.1 Identified trials

Key trials: the OAK and POPLAR trials

The company presents evidence for the clinical effectiveness of atezolizumab from the OAK (phase III) and POPLAR (phase II) trials. Both are open-label multicentre RCTs that were designed to investigate the efficacy and safety of atezolizumab versus docetaxel in patients with locally advanced or metastatic NSCLC whose disease had progressed during or following a platinum-containing regimen. Patients were randomised to receive either: atezolizumab 1200mg Q3W or docetaxel 75mg/m^2 Q3W. Details relevant to the OAK and POPLAR trials are reported in the CS, in the trial clinical study reports (CSRs[22,24]) and in published papers.[23,25] Details of these trials have also been presented at a number of conferences.[44-48]

Other trials

The clinical development programme of atezolizumab in NSCLC included two single-arm phase II studies, BIRCH[49] (study GO28754) and FIR[50] (study GO28625). The company states that these trials have not been discussed in the CS as the patient populations in both trials had PD-L1 positive disease and, therefore, are not relevant to this appraisal.

The ERG is not aware of any trials that directly compare the clinical effectiveness of atezolizumab with any of the comparators, other than docetaxel, as per the final scope issued by NICE.

4.2.2 Key characteristics of the OAK and POPLAR trials

The key characteristics of the OAK and POPLAR trials are provided in the CS (pp58-77) and are summarised in Table 6.

Eligibility criteria for entry into the OAK and POPLAR trials were provided by the company (CS, pp61-63). Clinical advice to the ERG is that the eligibility criteria are reasonable. The OAK and POPLAR trials were conducted internationally (in 31 and 13 countries respectively). The OAK trial included eight UK sites (31 patients) and the POPLAR trial included four UK sites (11 patients). Patients were randomly assigned (1:1) to receive either atezolizumab or docetaxel using an interactive voice or web response system. Randomisation was stratified by previous lines of chemotherapy (one versus two) and histology (non-squamous versus squamous). In addition, randomisation was stratified by PD-L1 IC status (four categories: IC0, IC1, IC2, and IC3). The ERG notes that an exploratory

objective of the OAK and POPLAR trials was the evaluation of the relationship between PD-L1 expression in blood and tumour tissues and measures of efficacy.

Table 6 Key characteristics of the OAK and POPLAR trials

	OAK trial	POPLAR trial
Location	International (31 countries, 194 centres, including 8 in the UK [31 patients])	International (13 countries, 61 centres, including 4 in the UK [11 patients])
Design	Randomised (1:1), phase III, open-label	Randomised (1:1), phase II, open-label
Population	Primary population: a total of 850 patients were randomised, 425 to the atezolizumab arm and 425 to the docetaxel arm Secondary population: following the interim analysis of data from the POPLAR trial, the population size was increased to ensure at least 220 patients with PD-L1 TC3 or IC3 (assuming a 20% prevalence) were enrolled. In total, 1225 patients were randomised (614 to the atezolizumab arm and 611 to the docetaxel arm)	A total of 287 patients were randomised, 143 patients to the docetaxel arm and 144 patients to the atezolizumab arm
Intervention	Atezolizumab (1200mg Q3W) was administered as long as patients experienced a clinical benefit as assessed by an investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression	Atezolizumab (1200mg Q3W) was administered as long as patients experienced a clinical benefit as assessed by an investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression
Comparator	Docetaxel (75mg/m^2 Q3W) was administered until disease progression or unacceptable toxicity	Docetaxel (75mg/m^2 Q3W) was administered until disease progression or unacceptable toxicity
Primary outcome	Co-primary: • OS in the ITT population • OS in patients with ≥1% PD-L1 expression (TC1/2/3, IC1/2/3)	OS
Secondary outcomes	PFS, ORR and DOR	PFS, ORR and DOR
Safety endpoints	Safety and tolerability of treatment with atezolizumab compared with docetaxel	Safety and tolerability of treatment with atezolizumab compared with docetaxel
Patient reported outcomes	Data collected using: • EQ-5D-3L tool • EORTC-QLC-C30 and its lung cancer module (LC13)	Data collected using EORTC-QLC-C30 and its lung cancer module (LC13)
Duration of study	• First patient randomised: 11 March 2014 • Last patient randomised in the primary population: 28 November 2014 • Last patient randomised in the secondary population: 29 April 2015	• First patient randomised: 5 August 2013 • Last patient randomised: 31 March 2014
Data analyses	Primary analysis: clinical cut-off 7 July 2016	Interim analysis: clinical cut-off 30 January 2015 Primary analysis: clinical cut-off 8 May 2015 Updated efficacy analysis (OS and DOR): clinical cut-off 1 December 2015
Median duration of follow-up (primary analysis)	Atezolizumab: 21.4 months Docetaxel: 21.3 months	Atezolizumab: 14.8 months Docetaxel: 15.7 months

DOR=duration of response; EORTC-QLC-C30=European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30; EQ-5D-3L=EuroQol-5 Dimensions-3 Levels; IC=immune cell; ITT=intention to treat; OS=overall survival; ORR=objective response rate; PD-L1=programmed death-ligand 1; PFS=progression-free survival; PR=partial response; Q3W=every 3 weeks; TC=tumour cell
Source: CS, Section 4.3

relevant trials (reduced network) and for adenocarcinoma subgroups or non-squamous subgroups only. These results are discussed in Section 4.9.4.

4.6.2 Methodological approach to the indirect comparison

The company performed ITCs on OS and PFS as time-to-event outcomes, and OS at 12 months, ORR and TRAEs as binary outcomes. ITCs of ORR and TRAE did not contribute to the company's cost effectiveness analyses; therefore, the methods and results presented in this ERG report relate only to the ITCs of OS and PFS as time-to-event outcomes. Methodology and results for ITCs of binary outcomes are available in Appendix 4 of the CS.

The company demonstrated that the PH assumption does not hold for OS and PFS in either the OAK trial (CS, Figure 20 and Figure 21) or the POPLAR trial (see Section 10.1). The company therefore used an ITC methodology that does not rely on the PH assumption, namely one using fractional polynomial (FP) models under a Bayesian framework in JAGS statistical software.[59] Specifically, the company employed the method of network meta-analysis of FPs, developed by Jansen.[60]

Under the assumption of PH, the HR is represented as a single parameter (i.e. a number) that is assumed to be constant over time. This alternative approach using FPs is designed to model the hazard function with multiple parameters as a function of time, allowing the HR to change over time in the presence of non-PH. FP models of any 'order' can be fitted to time-to-event data to capture the shape of the hazard functions; 1st order FP models model time as a function with one additional parameter, 2nd order FP models model time as a function with two additional parameters, and so on. However, as the order of the FP model increases, so too does the statistical complexity required to fit the model. Therefore, the company restricted their analysis to 1st and 2nd order FP models only; a range that the company considered broad enough to model the hazard function shapes of the given example.

Fixed effects (FE) FP models were fitted in the first instance, with random effects (RE) FP models fitted subsequently, if data allowed. Five FP models were considered; two 1st order FP models (equivalent to Weibull and Gompertz models) and three 2nd order FP models, herein referred to as models 2nd order (1), 2nd order (2) and 2nd order (3). Under the Bayesian framework, uninformative prior distributions, as outlined by Jansen,[60] were used in all analyses. Further methodological details including the statistical code of the FP models are available in Appendix 4 of the CS.

ITCs were conducted with individual participant data from the OAK and POPLAR trials and survival proportions across monthly time intervals were extracted from digitalised K-M curves

for other trials. A 5-year time horizon for OS and a 2.5-year time horizon for PFS were used for presenting the time-dependent results of the ITC (expected difference in survival and functional HRs).

The ERG is satisfied that the company has applied the methods described by Jansen[60] appropriately (comparing the statistical code outlined in Appendix 4 of the CS to the template statistical code provided in the Appendix of the Jansen paper[60]) and that the restriction of analyses to 1st and 2nd order FP models was justified.

The ERG notes that due to the lack of a closed loop within the network (Figure 2), the HRs (modelled as FPs) generated by the ITCs are based on indirect evidence only. Subsequently, ITC methodological assumptions of consistency of direct and indirect evidence cannot be investigated statistically. The ERG considers that the unknown validity of this consistency assumption should be taken into account when interpreting numerical results, particularly for the indirect comparison between atezolizumab and nintedanib+docetaxel, where no direct evidence exists.

The ERG notes that the company fitted five FE FP models but, within the CS, only provided numerical results for the best fitting model for OS and PFS. The best fitting model was judged by the company according to the Deviance Information Criteria (DIC) statistic and visual inspection of fitted HR functions. Furthermore, the company repeated the ITC with RE but only for the best fitting FE FP model and interpreted the presence of heterogeneity as a difference in the DIC of the FE and RE models if greater than five points. The company cites two references to support this interpretation.[61,62] The ERG agrees that these references suggest that DIC (along with the residual deviance statistic) can be used to compare the fit of FE and RE models, but cannot find any mention within these references [redacted] to explain how to use the DIC to indicate that heterogeneity is present in analyses.

The ERG considers that the DIC is a measure of model fit rather than of statistical heterogeneity and that choices between FE and RE models within an ITC should be made taking into account consistency of trial designs, populations and evidence sources,[61] rather than solely on model fit. The ERG also notes that the methods employed by the company allow for estimation of a heterogeneity parameter (referred to as SD by Jansen[60]) for all RE models, and considers that this SD is a more appropriate measure of statistical heterogeneity than the DIC statistic.

Table 24 OS results of FP models, model fit and heterogeneity

Weibull, FE	5.71 (3.49 to 8.03)	4.74 (2.13 to 7.60)	910.4255	NA
Weibull, RE	5.79 (-8.05 to 25.82)	4.82 (-26.37 to 28.66)	911.4979	0.368 (0.013 to 1.872)
Gompertz, FE	6.82 (3.98 to 9.77)	6.01 (2.69 to 9.26)	934.1241	NA
Gompertz, RE	6.94 (-8.69 to 27.53)	5.93 (-25.12 to 27.70)	935.3138	0.373 (0.012 to 1.838)
2nd order (1)[a], FE	6.44 (3.55 to 9.55)	5.71 (2.09 to 9.32)	837.1486	NA
2nd order (1)[a], RE	6.63 (-8.06 to 27.42)	5.56 (-25.12 to 31.03)	838.3337	0.384 (0.012 to 1.824)
2nd order (2)[b], FE	6.72 (3.54 to 10.12)	6.01 (2.06 to 9.97)	837.6918	NA
2nd order (2)[b], RE	7.15 (-9.01 to 31.12)	6.05 (-25.96 to 34.04)	839.1147	0.379 (0.011 to 1.851)
2nd order (3)[c], FE	6.79 (3.33 to 10.15)	5.84 (1.47 to 9.97)	853.9698	NA
2nd order (3)[c], RE	7.15 (-9.01 to 31.12)	6.05 (-25.96 to 34.04)	854.9049	0.365 (0.010 to 1.858)

[a] 2nd order model (1) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(log t)^2; CS, page 108
[b] 2nd order model (2) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(t); CS, page 108
[c] 2nd order model (3) corresponds to a model of the form: log hazard=beta0+beta1(t)+beta2(t*log t), CS, page 108
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; DIC=deviance information criterion; NA=not applicable OS=overall survival; RE=random effects; SD=standard deviation of the heterogeneity parameter
Source: Company response to ERG clarification letter, adapted from Figure 21, Figure 23, Figure 25, Figure 27, Figure 29, Figure 41, Figure 42, Figure 43, Figure 44, Figure 45, Table 2

The ERG suggests that according to the model fit criteria defined by the company, 2nd order model (1) could also be deemed to be the best fitting model, but notes that any judgement of model fit is subjective and that numerical results of all FE FP models are similar (Table 24, Figure 3 and Figure 4).

Table 24, Figure 3 and Figure 4 show expected mean difference in survival (months) according to all FP models fitted in the FE and RE ITCs. The ERG notes that across all ten models fitted, the expected mean difference in survival is very similar, ranging between 5.7 and 7.2 months for atezolizumab compared to docetaxel and between 4.7 and 6.1 months for atezolizumab compared to nintedanib+docetaxel. The ERG also notes that heterogeneity seems to be present in all RE FP models according to SD as defined by Jansen [redacted] and resulting in wider confidence intervals around results provided in RE FP models.[60] The SD range is estimated to be 0.36 to 0.39 across the five RE models (Table 24). Also, compared to the FE models, the resulting 95% CrI of the expected survival difference is substantially larger and crosses the line of no effect for all five RE models (Figure 3 and Figure 4).

The ERG was not provided with survivor plots for the RE FP models so was unable to visually inspect the fit of survival curves. Therefore, the ERG can only judge the fit RE models based on the DIC alone, which the ERG considers to be similar for each RE FP model fitted.

In the clarification response letter, the company states that an assessment of heterogeneity is difficult for a network as small as the reduced network and such a small network will result in RE models with wide 95% CrIs. The company considers that the model with the lowest DIC (FE or RE) depicts the best fit to the data and that the presence of heterogeneity is indicated by a difference between the model DIC scores of greater than five points. The ERG questions how, if there is no statistical heterogeneity present in the network as defined by the company (i.e. a difference in DIC of less than five points), the same model fitted with FE and RE can show a wide range of credible results. For example, when atezolizumab is compared with docetaxel, the Weibull FE model generates an expected difference in survival of 5.71 (95% CrI: 3.49 to 8.03) months while Weibull RE model generated an expected difference in survival of 5.79 (95% CrI: -8.05 to 25.82) months (Table 24).

The results suggest that the best estimate of the expected mean difference in OS is around 6 to 7 months for atezolizumab versus docetaxel ([redacted] median OS gain of 4.2 months and 2.9 months in the OAK and POPLAR trials from direct evidence) and the expected mean difference is around 5 to 6 months for atezolizumab versus nintedanib+docetaxel. The ERG notes that the precision and, therefore, the reliability of the ITC estimates are influenced by the choice of FP model and by potential statistical heterogeneity in the network which has not been acknowledged by the company, or accounted for in any ITC analyses.

Progression-free survival

Results from all FP models fitted to the reduced network (outlined in Figure 2) are shown in Table 25, Figure 5 and Figure 6. The company provided further survivor plot figures as a measure of the visual fit of the survival curves from the FE FP models; these plots are available in Section 10.7.2.

In the original ITC analysis described in the CS, the company disregards the 2nd order models based on visual inspection of the fitted curves. From visual inspection of the survivor plots of the reduced network (Section 10.7.2) the ERG notes that all models seem to 'plateau' at around 12 months, with the extent of the plateau being more prominent in the 2nd order models than the 1st order models.

Within the CS (extended network) the Gompertz model was judged to be the best fitting model; however, in the clarification response letter, the company states that, within the reduced network for the FE FP, this changed and rather the Weibull model was the best fitting model. The company provided HR functions for the Weibull FE model graphically and are available in Section 10.7.2).

Table 25 PFS results of ITC FP models, model fit and heterogeneity

FP model	Expected survival difference in months (95% CrI)		DIC	SD (95% CrI)
	Atezolizumab vs docetaxel	Atezolizumab vs nintedanib+docetaxel		
Weibull, FE	0.64 (0.01 to 1.32)	-0.30 (-1.39 to 0.70)	1123.198	NA
Weibull, RE	0.64 (-3.36 to 10.80)	-0.31 (-11.21 to 9.59)	1124.86	0.328 (0.010 to 1.832)
Gompertz, FE	0.53 (-0.12 to 1.27)	-0.43 (-1.61 to 0.66)	1157.567	NA
Gompertz, RE	0.50 (-3.30 to 9.53)	-0.42 (-12.32 to 9.03)	1159.318	0.313 (0.010 to 1.837)
2nd order (1)[a], FE	0.72 (-0.20 to 1.65)	0.77 (-1.18 to 2.15)	874.2588	NA
2nd order (1)[a], RE	0.79 (-3.83 to 11.19)	0.76 (-11.20 to 11.39)	875.9772	0.320 (0.008 to 1.838)
2nd order (2)[b], FE	0.80 (-0.12 to 1.75)	0.79 (-1.74 to 2.25)	974.306	NA
2nd order (2)[b], RE	0.78 (-4.19 to 12.53)	0.70 (-12.38 to 11.99)	975.6571	0.340 (0.012 to 1.849)
2nd order (3)[c], FE	0.88 (-0.08 to 1.90)	0.54 (-2.34 to 2.36)	1056.233	NA
2nd order (3)[c], RE	0.86 (-4.19 to 11.87)	0.49 (-13.03 to 12.35)	1057.436	0.308 (0.010 to 1.868)

[a] 2nd order model (1) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(log t)^2; CS, page 1118
[b] 2nd order model (2) corresponds to a model of the form: log hazard=beta0+beta1(log t)+beta2(t); CS, page 111
[c] 2nd order model (3) corresponds to a model of the form: log hazard=beta0+beta1(t)+beta2(t*log t), CS, page 111
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; DIC=deviance information criterion; NA=not applicable, PFS=progression-free survival; RE=random effects; SD=standard deviation of the heterogeneity parameter
Source: company response to ERG clarification letter, adapted from Figure 31, Figure 33, Figure 35, Figure 37, Figure 39, Figure 46, Figure 47, Figure 48, Figure 49, Figure 50, Table 3.

The ERG suggests that, according to the model fit criteria defined by the company, the 2nd order models with lower DIC values could be deemed to fit survival data better than the 1st order models, but notes that any judgement of model fit is subjective and that numerical results of all FE FP models are similar (Table 25, Figure 5 and Figure 6).

Table 25, Figure 5 and Figure 6 show expected difference in survival (months) according to all FP models using FE and RE. The ERG notes that, across all ten of the fitted models, the expected difference in PFS is similar, and not statistically significant for all except one result (Weibull FE model for atezolizumab compared to docetaxel, 0.64 [0.01 to 1.32] months).

In the clarification response letter, the company states that the TSAPs for the OAK and POPLAR trials did not include subgroups according to the presence of adenocarcinoma and therefore did not provide results for the ITC requested by the ERG. The ERG anticipated that adenocarcinoma subgroups may not have been defined in the OAK and POPLAR trials and therefore, if this were the case, requested alternatively that the company repeat the ITCs using data from the non-squamous subgroups of the OAK and POPLAR trials and the adenocarcinoma subgroup of the LUME-Lung 1 trial. The company, however, provided results for a comparison between atezolizumab within its intended licensed population (total OAK and POPLAR trial populations) with nintedanib+docetaxel (in the subgroup of patients with adenocarcinoma histology). The ERG notes that these results are, therefore, derived from comparing non-equivalent populations and thus should also be treated with extreme caution.

The company applied the Weibull FE FP model; results for OS and PFS are provided in Table 26 and plots of HR functions provided by the company are provided in Section 10.7.3.

Table 26 Expected mean survival differences: atezolizumab (total population) and nintedanib+docetaxel (adenocarcinoma subgroup)

Expected survival difference in months (95% CrI)*		
Outcome	**Atezolizumab vs docetaxel**	**Atezolizumab vs nintedanib+docetaxel**
OS	5.84 (3.68 to 8.07)	3.33 (-0.16 to 6.74)
PFS	0.68 (-0.04 to 1.46)	-0.07 (-1.76 to 1.28)

*Results came from the 'best fitting' Weibull FE FP model
CrI=credible interval; FE=fixed effects; FP=fractional polynomial; PFS=progression-free survival; OS=overall survival
Source: company response to ERG clarification letter, adapted from Figure 10, Figure 12

The ERG notes that when restricting the ITC to the adenocarcinoma subgroup for nintedanib+docetaxel, when comparing atezolizumab to nintedanib+docetaxel, the expected OS difference is reduced from around 4.74 months (see Table 24) to 3.33 months and the result is no longer statistically significant. The expected PFS difference when comparing atezolizumab to nintedanib+docetaxel is similar to the results showed in Table 25. The ERG also notes that OS and PFS results for the comparison of atezolizumab versus docetaxel are similar to those shown in Table 24 and Table 25.

The company states that using the 'total population' of the LUME-Lung 1 trial to conduct a 'like for like' comparison between atezolizumab and nintedanib+docetaxel is 'not anticipated to significantly affect overall results' (CS, Section 4.10). However, this statement is not supported by the additional results provided by the company (Table 26) which show that, when restricting the ITC to the adenocarcinoma subgroup of the LUME-Lung 1 trial, treatment with atezolizumab no longer shows a statistically significant difference in OS

- the company was not justified in excluding pembrolizumab from the ITC network of comparators relevant to this appraisal.

The ERG asked the company to provide ITC results from a reduced network of comparators comprising those listed in the final scope issued by NICE. Based on this (reduced) network, i.e., using data from the total populations of the OAK, POPLAR and LUME-Lung 1 trials, the company's FP ITC results suggest that:

- the company's best estimate of expected mean difference in OS is around 6 to 7 months for atezolizumab versus docetaxel ([redacted] median OS gains of 4.2 months and 2.9 months from the OAK and POPLAR trials respectively)
- the company's best estimate of expected mean difference in OS is around 5 to 6 months for atezolizumab versus nintedanib+docetaxel
- there appears to be no significant difference in PFS when comparing atezolizumab to docetaxel and when comparing atezolizumab to nintedanib+docetaxel.

The ERG also asked the company to undertake two further subgroup analyses. However, the company undertook these using non-equivalent populations and results should be viewed with extreme caution:

- based on a (reduced) network using data the ITT populations from the OAK and POPLAR trials and the adenocarcinoma population from the LUME-Lung 1 trial, the company's FP ITC results suggest that the company's best estimate of expected mean difference in OS for atezolizumab versus nintedanib+docetaxel is 3.33 months (compared to median OS gain of 4.74 months when the analysis was carried out using LUME-Lung 1 trial total population) and is no longer statistically significant
- based on a (reduced) network using data the ITT populations from the OAK and POPLAR trials, and the KEYNOTE-010 trial (a trial assessing the efficacy of pembrolizumab as a first-line treatment for metastatic NSCLC in adults whose tumours express PD-L1 with a ≥50% tumour proportion score) the company found no statistically significant difference in OS or PFS when comparing atezolizumab (total population') versus pembrolizumab (PD-L1 positive NSCLC patients).

The ERG highlights that the precision and reliability of all additional results are influenced by the choice of FP model and greatly influenced by potential statistical heterogeneity in the network which has not been acknowledged by the company or accounted for in any ITC analyses. In summary, the ERG considers that the approach to the ITC is influenced by a range of factors (e.g., comparators and population selected, type of FP model chosen and the use of FE or RE). This means that it is difficult to identify the most appropriate combination of factors to use to generate ITC results. Furthermore, the ERG considers that the expected survival results generated by the FP ITC are difficult to interpret.

nintedanib. The list price cost per cycle for nintedanib is estimated to be £1,434.07 (CS, Table 65).

Subsequent treatment

The economic model includes costs of subsequent treatment for patients who have progressed during or after initial treatment (see Table 33). At 25 months' follow-up, approximately 13% of patients were still receiving atezolizumab; this means there is no complete dataset of post-discontinuation treatments. The company states (CS, p182) that "…so as not to bias the analysis by giving a falsely low subsequent treatment cost to atezolizumab, an average has been taken by pooling the arms". As per the OAK trial, 45% of all patients were assumed to receive subsequent pharmacological treatment and 55% went on to receive radiotherapy. In line with clinical opinion, the company removes the costs of third-line immunotherapy from the base case analysis [redacted].

Table 33 Cost of subsequent treatment (drug and radiotherapy)

Cost and duration of subsequent drug and radiotherapy treatments	
Average time on subsequent drug treatment	13.59 weeks
Average cost	£1,987.06
Average number of subsequent radiotherapy doses per patient	20.58
Average cost	£1,353.08
Total cost of subsequent treatment	£3,340.14

Source: CS, Section 5.5.2.1

5.4.5 Perspective, time horizon and discounting

The company states that the economic evaluation was undertaken from the perspective of the NHS and Personal Social Services. The time horizon was set at 25 years and, in line with the NICE Guide to the Methods of Technology Appraisal,[64] both costs and outcomes were discounted at 3.5% per annum.

5.4.6 Treatment effectiveness and extrapolation

The primary data source for the company model was the OAK trial. The follow-up period over which trial data were available was shorter than the time horizon of the economic model. Therefore, modelling of OS, PFS and TTD data from OAK trial was required.

Overall survival

The company considered that the survival data available for immunotherapy agents suggest that it is plausible that some patients experience a sustained response. To model this sustained response the company constructed a mixed cure-rate model. The concept is that there is a subgroup of patients with stable disease for whom the risk of death attributable to

Table 35 Adverse event disutilities

Adverse event	Disutility	Source
Anaemia	-0.07346	Nafees 2008[66]
Fatigue	-0.07346	
Febrile neutropenia	-0.09002	
Neutropenia	-0.08973	
Leukopenia	-0.08973	Assumed equal to neutropenia Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [TA403][67] Lung cancer (non-small-cell, non-squamous, metastatic, after treatment) - nivolumab [ID900][42]
Neutropenic sepsis	-0.09002	Assumed equivalent to febrile neutropenia
Neutrophil count decreased	0	Assumption Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer [TA403][67] Lung cancer (non-small-cell, non-squamous, metastatic, after treatment) - nivolumab [ID900][42]
Pneumonia	-0.008	Marti et al (2013)[68]
Respiratory tract infection	-0.096	Assumption adapted from Hunter 2015[69]
White blood cell count decreased	-0.05	Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer [TA347][4]

Source: CS, Table 62

5.4.8 Resources and costs

Drug costs

Atezolizumab is administered at a fixed dose of 1200mg over 60 minutes for the first IV infusion and, if well tolerated, as a 30-minute IV infusion every 3 weeks. The expected list price of a 20ml vial (dose per vial is 1200mg) is £3,807.69. [redacted] The PAS application has been approved by the Department of Health.

Drug costs for docetaxel were taken from the electronic Medicines Information Tool (eMIT).[70] Drug costs for nintedanib+docetaxel were taken from the British National Formulary (BNF)[71] and eMIT[70] respectively. A PAS for nintedanib does exist; however, the company is unaware of the value of this PAS price.

The drug acquisition cost and drug cost per treatment cycle used in the company model are provided in Table 36.

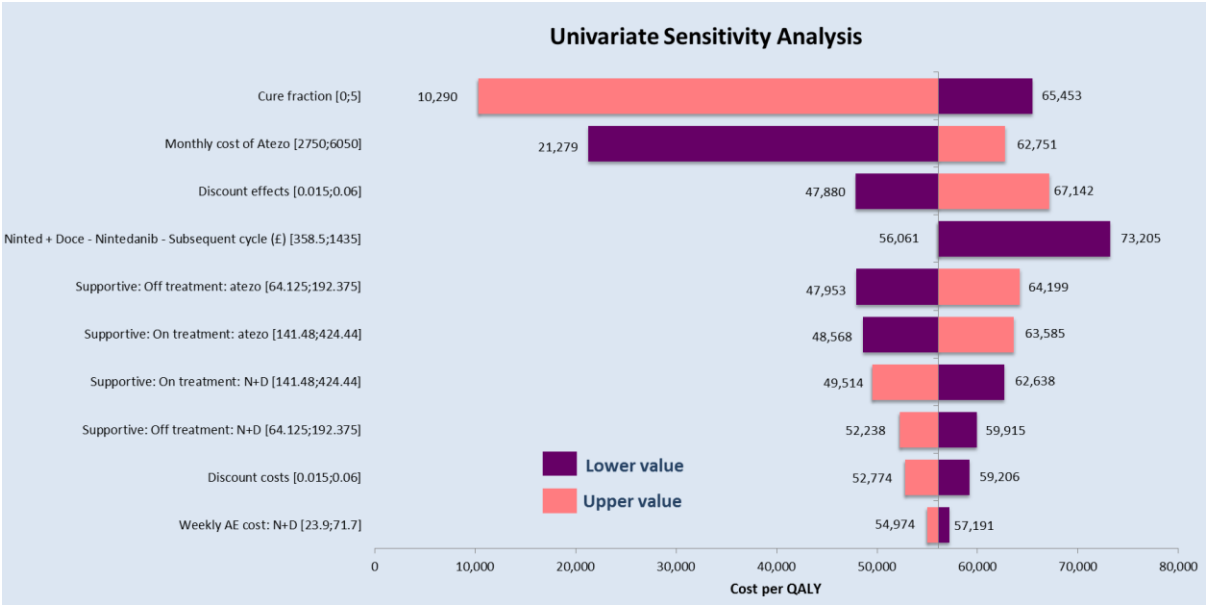

Figure 10 Univariate sensitivity analysis (atezolizumab versus nintedanib+docetaxel, list price)

Source: CS, Figure 62

Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to assess the uncertainty surrounding the parameter values used in the model. Results from this analysis are displayed in Table 41 and show ICERs per QALY gained that are slightly higher than the ICERs in the deterministic analysis. The PSA involved running the company model 1000 times. The scatterplot of PSA results and the cost effectiveness acceptability curve (CEAC) are presented in Figure 11 and Figure 12 respectively). Examination of the CEAC shows that the chance of atezolizumab being cost effective versus docetaxel (and versus nintedanib+docetaxel) at a threshold of £50,000 per QALY gained is approximately 45% (and 1%) at list price.

Table 41 PSA results compared to base-case analysis (list price)

Treatment	Costs		QALYs		ICERs (vs docetaxel)		ICERs (vs nintedanib+docetaxel)	
	Base case	PSA	Base case	PSA	Base case	PSA	Base case	PSA
Docetaxel	£19,941	£20,880	0.73	0.74	-	-	-	-
Nintedanib+ docetaxel	£37,702	£38,676	0.83	0.84	Extendedly dominated	Extendedly dominated	-	-
Atezolizumab	£73,911	£73,033	1.47	1.47	£72,356	£73,934	£56,076	£57,777

QALYs=quality adjusted life years; ICERs=incremental cost effectiveness ratios; PSA=probabilistic sensitivity analysis
Source: CS, Table 93

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ID970 STA Atezolizumab Addendum 1

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Atezolizumab for treating locally advanced or metastatic non-small cell lung cancer after chemotherapy [ID970]

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CONTAINS COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

This document provides information to inform the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process to consider the clinical and cost effectiveness of treatment with atezolizumab for treating locally advanced or metastatic non-small cell lung cancer (NSCLC) after chemotherapy [ID970]. It contains cost effectiveness results (list prices), generated by the evidence review group (ERG), as requested by the NICE lead team during the pre-meeting briefing (PMB) teleconference.

1.1 The issue

There is no direct evidence comparing the effectiveness of treatment with atezolizumab versus nintedanib+docetaxel for the treatment of NSCLC after chemotherapy. Furthermore, there is no trial evidence to allow an indirect treatment comparison (ITC) to be conducted using only data relevant to the population licensed to receive nintedanib+docetaxel (adenocarcinoma histology). However, the company has provided results from a comparison between atezolizumab within its intended licensed population (total OAK and POPLAR trial populations[1]) and nintedanib+docetaxel (in its licenced population - patients with adenocarcinoma histology) generated using the network of comparators relevant to this appraisal. Results, using the Weibull fixed effects (FE) fractional polynomial (FP) model, from this analysis show that there is no statistically significant evidence that overall survival (OS) differs between the two treatments (mean difference in expected survival: 3.33 [-0.16 to 6.64] months). The ERG, therefore, chose to model OS for patients treated with nintedanib+docetaxel by re-using their preferred atezolizumab OS curve.

During the PMB telephone conference it was advised that the appraisal committee (AC) would find it helpful to see cost effectiveness results for the comparison of atezolizumab versus nintedanib+docetaxel generated using different approaches to modelling OS for patients receiving nintedanib+docetaxel. The ERG has, therefore, presented results from two alternative methods but considers that neither of these approaches are robust and that findings should be treated with caution.

1.2 ERG alternative nintedanib+docetaxel OS curves

The ERG's first alternative approach involves constructing the nintedanib+docetaxel OS curve using the company's FE ITC time dependent hazard ratios (HRs) for atezolizumab versus nintedanib+docetaxel (whole population) applied to the ERG's preferred atezolizumab OS curve, with a 5-year duration of treatment effect applied to the nintedanib+docetaxel curve in the same way as applied to the ERG's preferred atezolizumab curve. The ERG highlights that this approach uses data from patients who are not licensed to receive nintedanib+docetaxel

and, therefore, may lead to results that favour treatment with atezolizumab. The results from this analysis show that treatment with atezolizumab generates 0.185 additional quality adjusted life years (QALYs) versus nintedanib+docetaxel at an additional cost of £34,458 (list prices). The resultant incremental cost effectiveness ratio for this comparison is £186,259 per QALY gained.

The ERG's second alternative approach involves applying the reported OS HR for the comparison of the effectiveness of nintedanib+docetaxel versus docetaxel from the LUME-Lung 1 trial[2] (0.83) to the ERG preferred docetaxel OS curve. However, the ERG highlights that analyses of LUME-Lung 1 trial[2] data show that OS hazards associated with treatment with nintedanib+docetaxel and docetaxel are not proportional and this renders such an approach statistically unsound. Results from this analysis show that treatment with atezolizumab generates 0.148 additional QALYs versus nintedanib+docetaxel at an additional cost of £33,276 (list prices). The resultant ICER for this comparison is £225,159 per QALY gained.

Detailed results from the ERG's analyses may be found in Table 1.

2 RESULTS TABLE

Table 1 Cost effectiveness results for atezolizumab versus nintedanib+docetaxel with ERG revisions to company base case (list prices)

Model scenario & ERG revisions	Atezolizumab			Nintedanib+docetaxel			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change
Company base case	**£73,911**	**1.471**	**2.224**	**£37,702**	**0.826**	**1.315**	**£36,209**	**0.646**	**0.910**	**£56,076**	**-**
C1) Discounting algorithms	£74,479	1.479	2.236	£37,582	0.820	1.306	£36,896	0.659	0.930	£55,959	**-£117**
C2) Age-related utility decrement	£73,911	1.437	2.224	£37,702	0.819	1.315	£36,209	0.618	0.910	£58,608	**+£2,532**
C3) TTD half-cycle correction	£75,468	1.472	2.224	£37,999	0.826	1.315	£37,470	0.647	0.910	£57,949	**+£1,873**
ERG corrected company base case (C1-C3)	**£76,046**	**1.446**	**2.236**	**£37,879**	**0.813**	**1.306**	**£38,168**	**0.632**	**0.930**	**£60,366**	**+£4,290**
R3) ERG preferred OS for atezolizumab and assumed equal for nintedanib+docetaxel	£71,525	0.998	1.544	£39,420	0.970	1,544	£32,105	0.027	0.000	£1,170,260	**+£1,114,185**
R4) ERG preferred OS for atezolizumab and assumed equal for nintedanib+docetaxel, and treatment duration effect for both set to 3 years	£71,418	0.988	1.527	£39,313	0.961	1.527	£32,105	0.027	0.000	£1,170,793	**+£1,114,718**
Additional analyses requested during the PMB											
R5) ERG preferred OS for atezolizumab, FP ITC for nintedanib+docetaxel OS and treatment duration effect for both set to 5 years	£71,418	0.988	1.527	£37,876	0.813	1.306	£34,458	0.185	0.238	£186,259	**+£130,183**
R6) ERG preferred OS for atezolizumab, LUME-Lung 1 HR for nintedanib+docetaxel OS and treatment duration effect for both set to 5 years	£71,418	0.988	1.527	£38,141	0.840	1.347	£33,276	0.148	0.180	£225,159	**+£169,083**

HR=hazard ratio; OS=overall survival; PMB=pre-meeting briefing; QALYs=quality adjusted life years; TTD=time to treatment discontinuation; ICER=incremental cost effectiveness ratio

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