

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

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee C

Lead team: Gail Coster, Paul Tappenden, Judith Wardle

ERG: LRiG

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14 June 2017

Private part 1, no public

Key issues – clinical effectiveness

- Pembrolizumab was not included as a comparator
- Atezolizumab targets PD-L1 but the focus of the company submission is on PD-L1 positive and negative patients
- Calculation of hazard ratios in the atezolizumab trials assumed proportional hazards holds, but they do not, so HRs should be interpreted with caution.
- 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 shows 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).

Non-small cell lung cancer

- In the UK, more than 45,000 people are diagnosed with lung cancer. 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] $\geq 50\%$)

NSCLC TA guidance

Published

- Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after platinum-based chemotherapy (January 2017).
- Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (Jul 2015).
- Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (August 2016).
- Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (Dec 2015).
- Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (Mar 2014).
- Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (Sept 2013).
- Pemetrexed for the treatment of non-small-cell lung cancer (Nov 2007).

In development

- Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer. (Publication TBC)

Atezolizumab

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	<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• List price: £3807.69 per 20mL vial.• PAS: Simple discount agreed by the company (Roche) and DoH as confidential.
Cost of a course of treatment	<ul style="list-style-type: none">• The average cost per treatment course is £42,913.66 at list price.

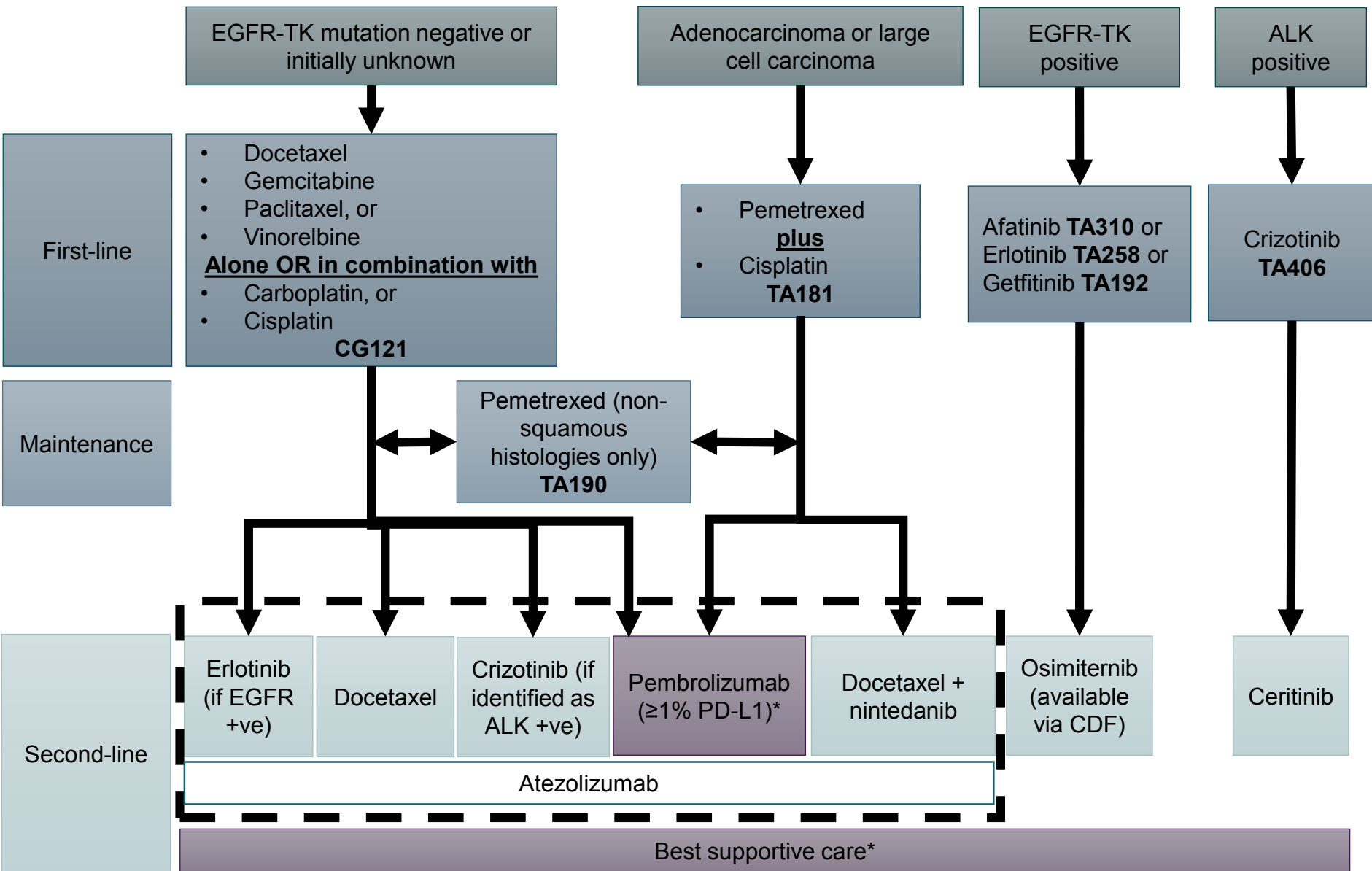
Impact on Patients and Carers

- People with relapsed NSCLC have multiple and distressing symptoms, e.g. breathlessness
 - Symptoms can be difficult to manage
 - Options that reduce tumours have best effect on symptoms
- Until recently, further chemotherapy was only option
- Immunotherapy has been major development which can significantly extend survival
- Since outlook for these patients is poor, improved QoL and even small extension of life is significant for patients & family

Patient/carer views on Atezolizumab

- Provides an additional option that can significantly extend life
- Side effects appear to be well tolerated, especially when compared with chemotherapy
- Patients group highlights the importance of End of Life considerations for these patients

Company treatment pathway



*Excluded from company submission

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	<ol style="list-style-type: none"> 1. Docetaxel 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 	<ol style="list-style-type: none"> 1. Docetaxel 2. Nintedanib with docetaxel 	<p>Pembrolizumab</p> <ul style="list-style-type: none"> • licenced for PDL1 positive only. • not likely to represent standard care (recommended January 2017). <p>Nivolumab</p> <ul style="list-style-type: none"> • not recommended by NICE in ACD (October 2016). <p>Best supportive care</p> <ul style="list-style-type: none"> • clinical expert opinion suggests people eligible for atezolizumab are fit enough for other 	<p>Pembrolizumab</p> <ul style="list-style-type: none"> • Relevant comparator for PD-L1 expressors • Effectiveness of atezolizumab is similar in PD-L1 -ve and PD-L1 +ve <p>Agrees with exclusion of Nivolumab and BSC</p>

COMPANY'S DECISION PROBLEM & DEVIATIONS FROM FINAL SCOPE (1)

	Final NICE scope	Company submission	Rationale	ERG comments
Outcomes	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • baseline characteristics and • histology subgroups (squamous and non-squamous) • PD-L1 expression presented from OAK trial for <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • TC3 or IC3, and • TC2/3 or IC2/3.

Clinical expert's statement

- NCCN guidelines recommend atezolizumab for PS0-2 patients after progression on 1st line systemic therapy.
- Optimal duration of therapy uncertain. Currently there is no data to support modifying the treatment regimen.
- PD-L1 expression may identify a subgroup of patients who benefit more from treatment.
 - Patients with high levels of PD-L1 expression showed improvement in OS of 12.4 months (median) compared with docetaxel.
- PD-L1 testing for atezolizumab is more complex than other PD-L1 assays and may not be interchangeable.
- Atezolizumab could reduce hospital admissions due to chemotherapy associated toxicity, and improve quality of life for patients.

NHSE statement

- Disagree with exclusion of pembrolizumab as a comparator by the company
- ‘Disappointed’ that nivolumab was not included as a comparator as there was potential for NICE to recommend it (currently has preliminary negative recommendation).
- More mature data will be available for OAK, currently reported on first 850 patients out of 1225. Currently few patients at risk after 24 months.
- Awaiting results from large study assessing the performance of 4 major PD-L1 assays, the transferability of results of one assay to another is important as different trials use different tests.
- Docetaxel treatment in OAK continued until disease progression or unacceptable toxicity.
 - In NHS, treatment duration with docetaxel is 4-6 cycles, most often 4 cycles.
- Atezolizumab treatment continued until loss of clinical benefit or unacceptable toxicity in OAK.
 - Mean time on treatment with atezolizumab 7.8 months and median PFS was 4.0 months
- OAK trial included patients with activated EGFR mutations with progressive disease on erlotinib/gefitinib/afatinib, 10% of the trial population.
 - HR for EGFR mutant: 1.24
 - EGFR wildtype: 0.69

NHSE statement

- Atezolizumab toxicities are wide ranging, uncommon, unusual and potentially severe. Disutility has not been incorporated into the cost effective analysis for these toxicities.
- 2 year stopping rule was recommended by NICE for pembrolizumab. NHSE could implement a similar arrangement for atezolizumab if necessary.
- If recommended NHSE treatment criteria are likely to be:
 - First cycle of systemic anti-cancer therapy prescribed by a consultant specialist accredited in the use of systemic anti-cancer therapy
 - Prescribing clinician aware of treatment modifications needed for immune related adverse reactions
 - Use of validated PD-L1 test and for this patient, the result is ...%.
 - 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
 - ECOG performance score of 0 or 1
 - Patients must not have untreated or active metastases in the central nervous system
 - No prior treatment with an anti-PD1, anti-PDL1, anti-PDL-2, anti-CD137 or anti-CTLA-4 antibody treatment
 - No treatment breaks of more than 4 weeks (unless to allow immune toxicities to settle)

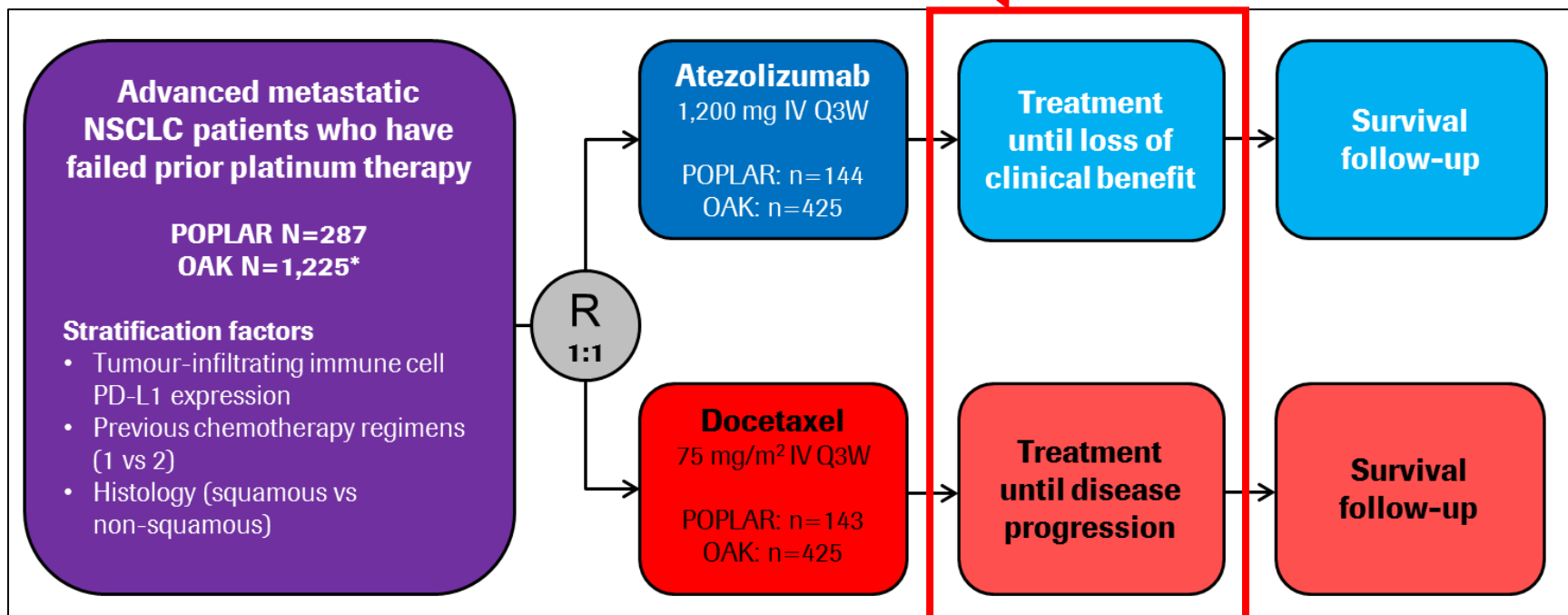
Clinical evidence

	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	<ul style="list-style-type: none"> Locally advanced or metastatic NSCLC ≥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, gefitinib) 	
Recruited regardless of PD-L1 expression		
Outcomes	<p>Primary: Overall survival</p> <p>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)</p>	<p>Primary: Overall survival</p> <p>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)</p>

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

OAK and POPLAR study design

ERG comments: Stopping rule for atezolizumab and docetaxel differed in both trials. Clinical expert opinion suggests that in practice patients receive 4-6 cycles of docetaxel.



*A pre-specified 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. Proportion of cells stained at any intensity:

TC3: ≥50% TC2/3: ≥5% TC1/2/3: ≥1% TC0: <1%
IC3: ≥10% IC2/3: ≥5% IC1/2/3: ≥1% IC0: <1%

POPLAR results – 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

ERG comments:

- PFS is investigator assessed, potential for bias
- Interpret OS and PFS HRs with caution, hazards aren't proportional and were calculated with a prespecified method that assumes they are proportional

OAK results – 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)	2.8 (2.6, 3.0)	4.0 (3.3, 4.2)
	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

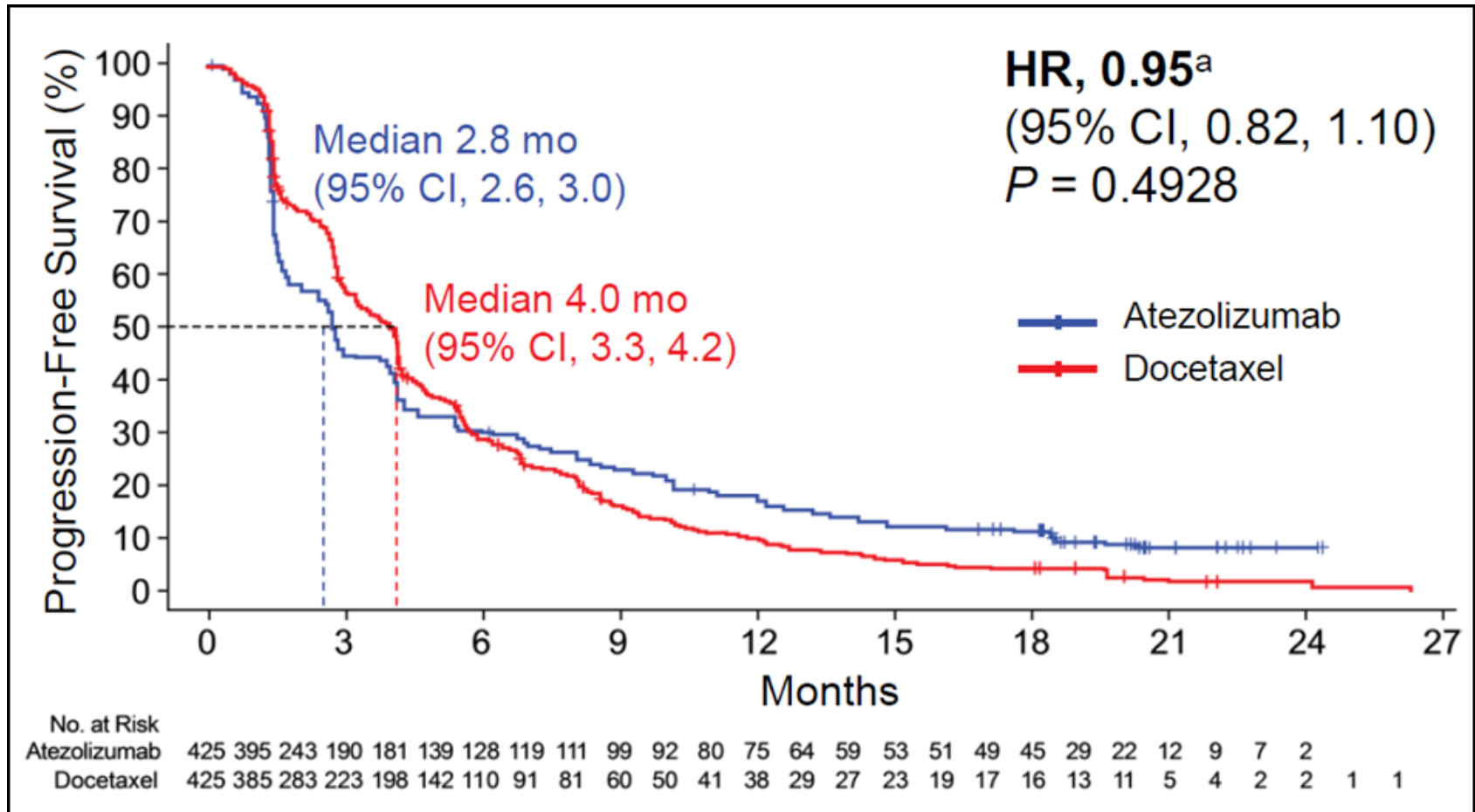
*Note duration of response is based on atezolizumab n=58; docetaxel n=57

ERG comments:

- PFS investigator assessed, potential for bias.
- Interpret OS and PFS HRs with caution, hazards aren't proportional and were calculated with a prespecified method that assumes they are proportional

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

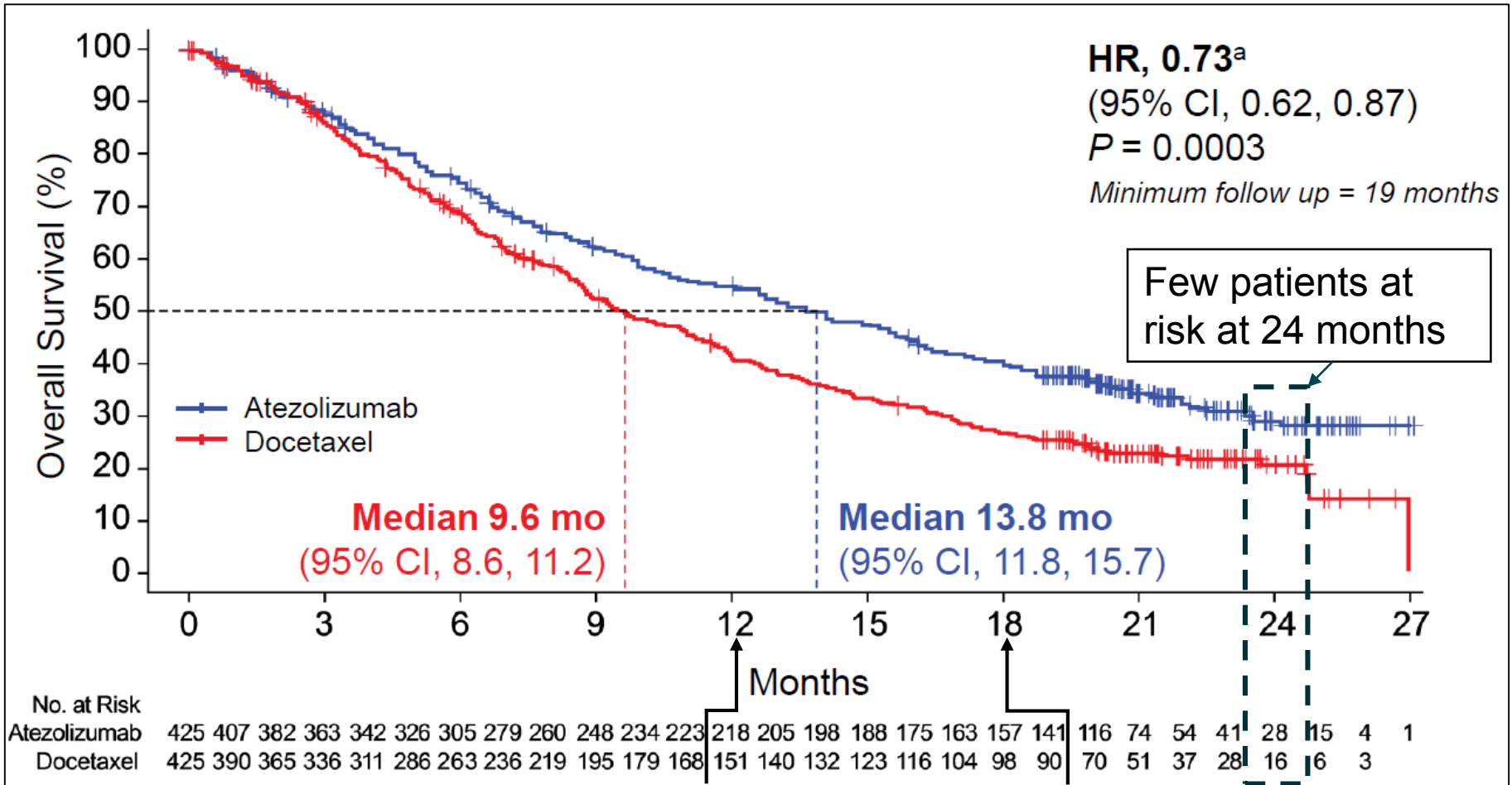
no statistically significant difference in PFS between atezolizumab and docetaxel



^a Stratified HR

OAK Kaplan-Meier plot of overall survival (ITT)

statistically significant improvement in OS for atezolizumab compared with docetaxel in all subgroups



^a Stratified HR

At 12 months:

- 55% alive in atezolizumab arm
- 41% alive docetaxel arm

At 18 months:

- 40% alive in atezolizumab arm
- 27% alive in docetaxel arm

OAK subsequent therapies

- Crossover from the docetaxel arm to the atezolizumab arm was not originally permitted in OAK, however this was allowed after 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 only made a marginal impact, so 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)

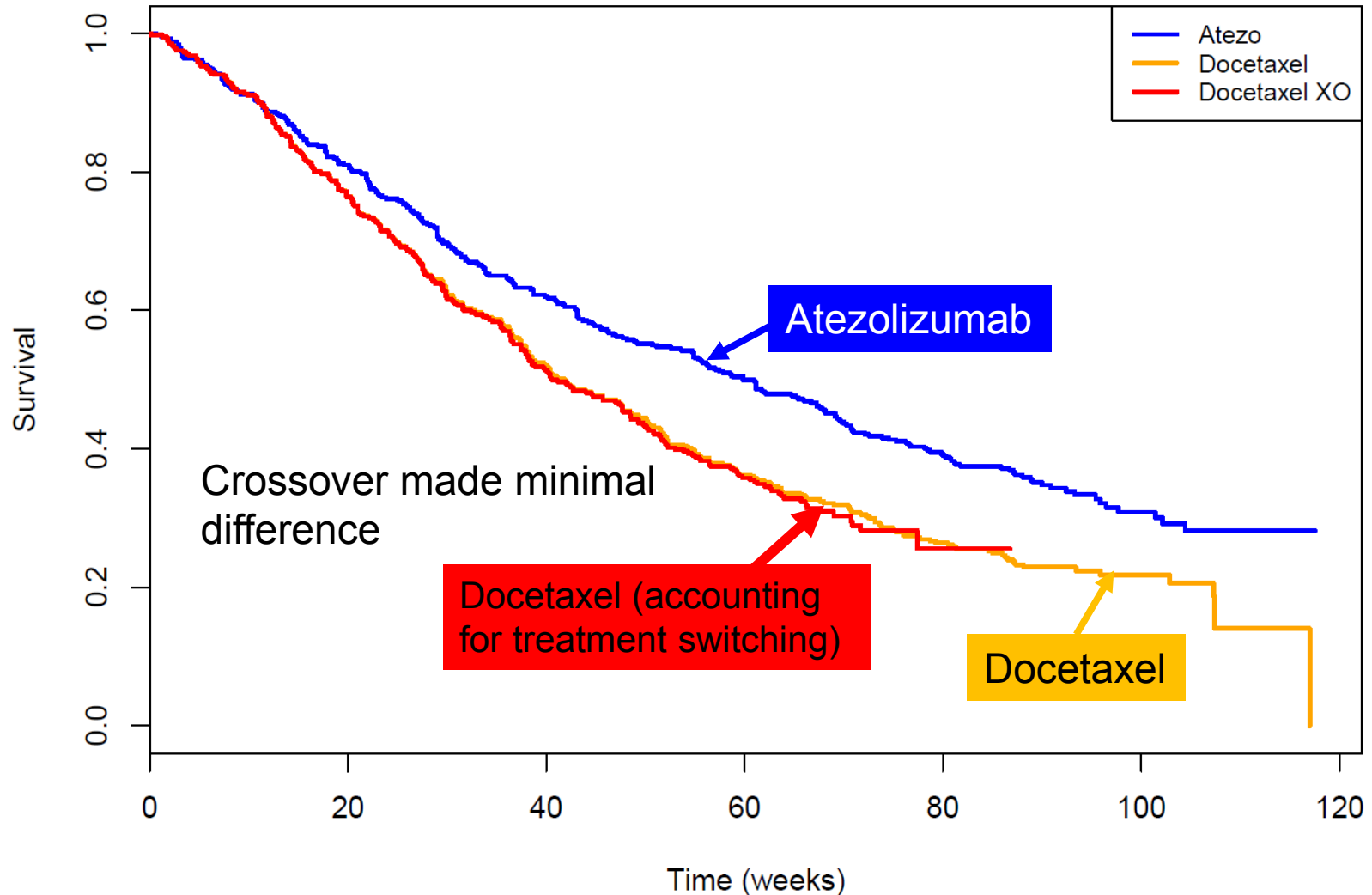


Subsequent immunotherapies (mostly nivolumab) were received by:

- 5% of patients in the atezolizumab arm, and
- 17% of patients in the docetaxel arm

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

Subgroup analyses

- 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
 - **OS by PD-L1 expression for TC3 or IC3, TC2/3 or IC 2/3**

OAK overall survival by 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)
- EGFR subgroup (ERG notes: small numbers, should be treated with caution)
 - EGFR mutant HR 1.24
 - EGFR wildtype HR 0.69

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

Indirect and mixed treatment comparisons

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

- No data providing direct comparative evidence for atezolizumab compared with nintedanib+docetaxel.
- 19 studies for comparators were identified through a systematic literature review and included in the network meta-analysis
- Company included: 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 has a marketing authorisation for people with adenocarcinoma histology, that is narrower than the anticipated marketing authorisation for atezolizumab

Results of the indirect and mixed treatment comparison

- Company presented results from full network (including comparators not listed in the scope)

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)

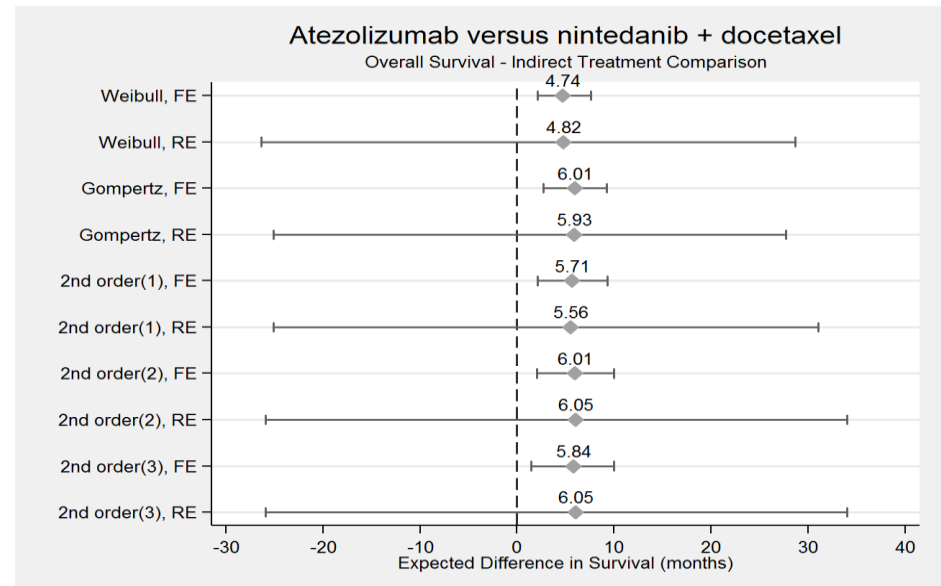
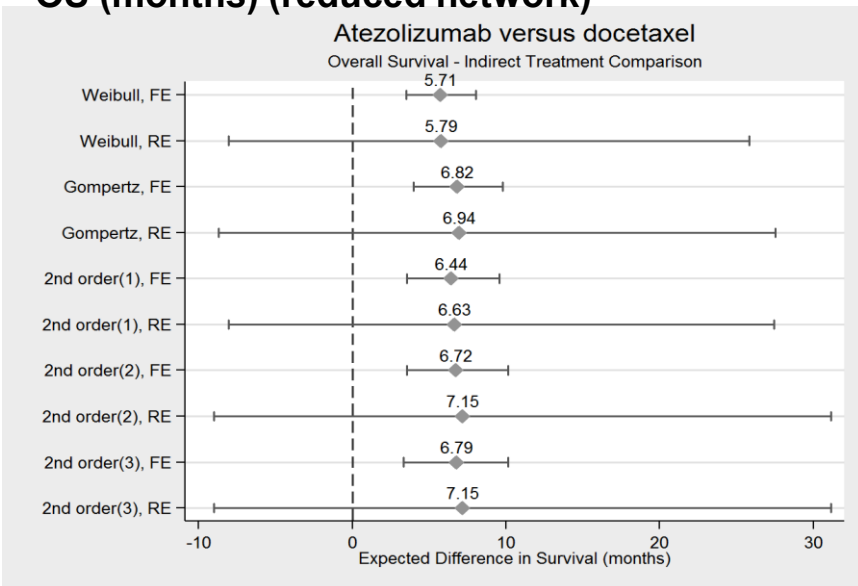
*Results came from the 'best fitting' Weibull fixed effects fractional polynomial model
PFS=progression-free survival; OS=overall survival

ERG comments: 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)



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 anticipated marketing authorisation 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**

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:

- Disagree with ITC approach as it includes comparators not listed in the final scope
- 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
- ITC approach influenced by range of factors (comparators, population, type of FP model), results are difficult to interpret
- Pembrolizumab should have been included in the ITC network.
- Company has compared nintedanib outside of its MA using the total trial population (includes non-adenocarcinoma histologies).

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.

PD-L1 assays

Atezolizumab (OAK)

- Used VENTANA (SP142) immunohistochemistry assay
 - Measures PD-L1 expression in TCs and ICs
 - TC3 or IC3: $\geq 50\%$ of TCs or $\geq 10\%$ of ICs
 - TC2/3 or IC2/3: $\geq 5\%$ of TCs or ICs
 - TC1/2/3 or IC1/2/3: $\geq 1\%$ of TCs or ICs
 - TC0 and IC0: $< 1\%$ of TCs and ICs

Pembrolizumab (KEYNOTE-010)

- Used DAKO22C3 immunohistochemistry assay
 - Measures PD-L1 expression in TCs only using tumour proportion score
 - Expressers: staining of $\geq 1\%$ TCs (previously treated), $\geq 50\%$ (treatment-naïve)
 - Non-expressers: staining $< 1\%$ TCs

- Waiting for results of large study assessing performance of 4 major assays (funded by FDA ASCO AACR)
- Small published study (n=90) comparing 4 assays showed results were statistically similar for 3 tests (including DAKO22C3).
 - VENTANA (SP142) identified less PD-L1 expression in tumour cells and immune cells than other assays.

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

1st Appraisal Committee meeting

Cost Effectiveness

Committee C

Lead team: Gail Coster, Paul Tappenden, Judith Wardle

ERG: LRiG

NICE technical team: Jessica Maloney, Fay McCracken

14 June 2017

Private part 1, no public

Key issues - cost effectiveness

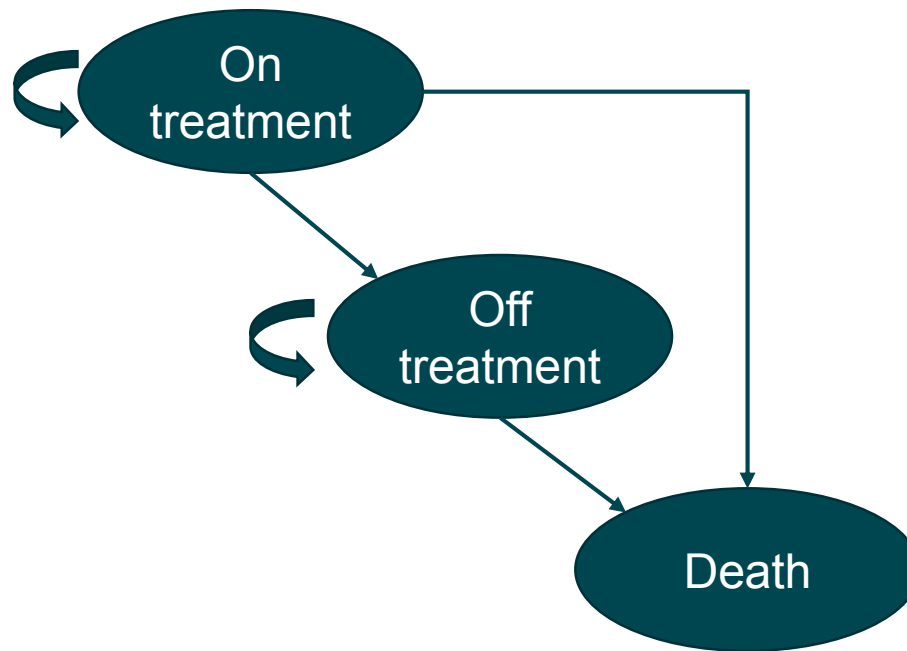
- The company's economic analysis excludes three comparators included in the scope (nivolumab, pembrolizumab and BSC)
- The company's model assumes atezolizumab has a lifetime protective effect
 - ERG's preferred assumptions are to use KM data for as long as possible and then extrapolate with a HR of 1
- Mixed cure-rate used to model OS for patients receiving atezolizumab
 - Insufficient evidence to apply cure-rate
 - Cure fraction 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

Population	Patients with locally advanced or metastatic NSCLC after prior chemotherapy
Intervention	<ul style="list-style-type: none">• Atezolizumab
Comparators*	<ul style="list-style-type: none">• Docetaxel• Nintedanib+docetaxel (adenocarcinoma histology)
Outcome	Incremental cost per QALY gained
Time horizon	25 years
Cycle length	1 week
Half cycle correction	Yes
Discount rate	3.5% for costs and utilities
Perspective	UK NHS

* NICE scope also included nivolumab, pembrolizumab and BSC as comparators

Company's model structure



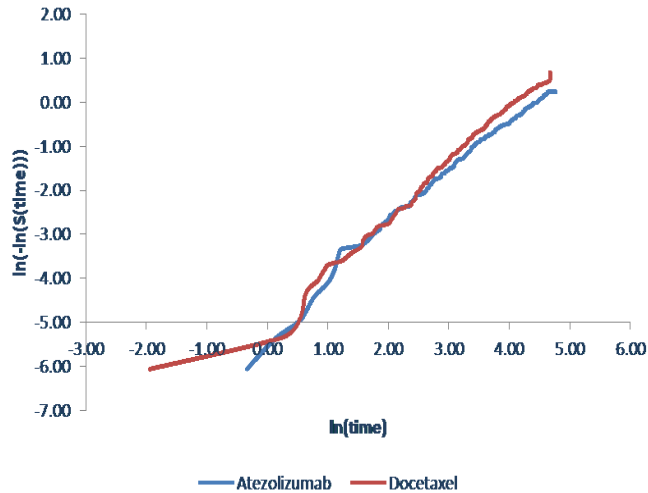
- Partitioned survival model based on TTD and OS
- ATEZ patients treated until loss of benefit of treatment.
- PFS data are used for NIN+DOC comparison for treatment duration, supportive care costs and utilities as TTD not available. Also used for DOC supportive care costs.
- Time-to-event outcomes modelled using OAK for ATEZ and fractional polynomial (FP) network meta-analysis (NMA) for DOC and NIN+DOC
- PAS agreed for ATEZ and NIN

Company's model

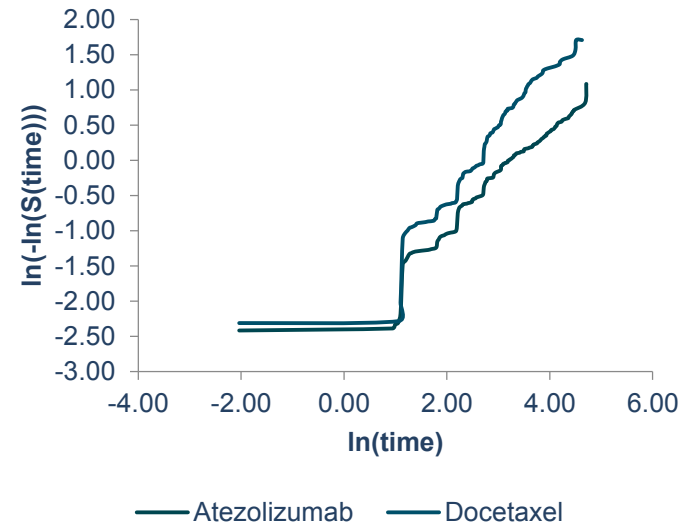
Assumption	Company approach
Treatment duration	ATEZ: Treated until loss of clinical benefit (TTD from OAK). DOC: Capped at 18 weeks. NIN+DOC: Based on PFS in LUME-Lung 1.
TTD	ATEZ: K-M curve + gamma tail when 15% patients still at risk. DOC: K-M curve + gamma tail when 1% patients still at risk. NIN+DOC: FP NMA of PFS as proxy (ATEZ reference).
PFS	As per TTD
OS	ATEZ: Mixed cure-rate model. 2% cure rate. Log logistic distribution fitted to OAK data. Lifetime protective effect assumed. DOC: Based on FP NMA. NIN+DOC: Based on FP NMA.
Utilities	Based on health state and time to death using EQ-5D-3L from OAK.
AE	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 $\geq 2\%$ of patients.
PD-L1 testing	Not included for ATEZ.
Resources & costs	Includes drug acquisition, administration, AEs, subsequent treatments, radiotherapy, monitoring, visits, tests, imaging, palliative treatment and end-of-life care.

OAK non-proportional hazards

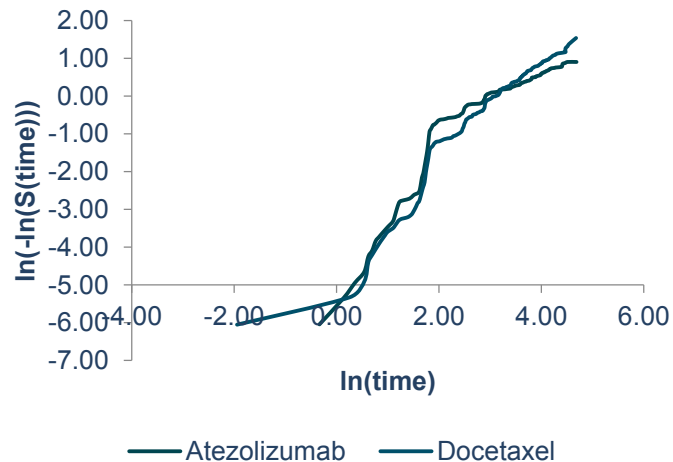
OS log-cumulative hazard plot



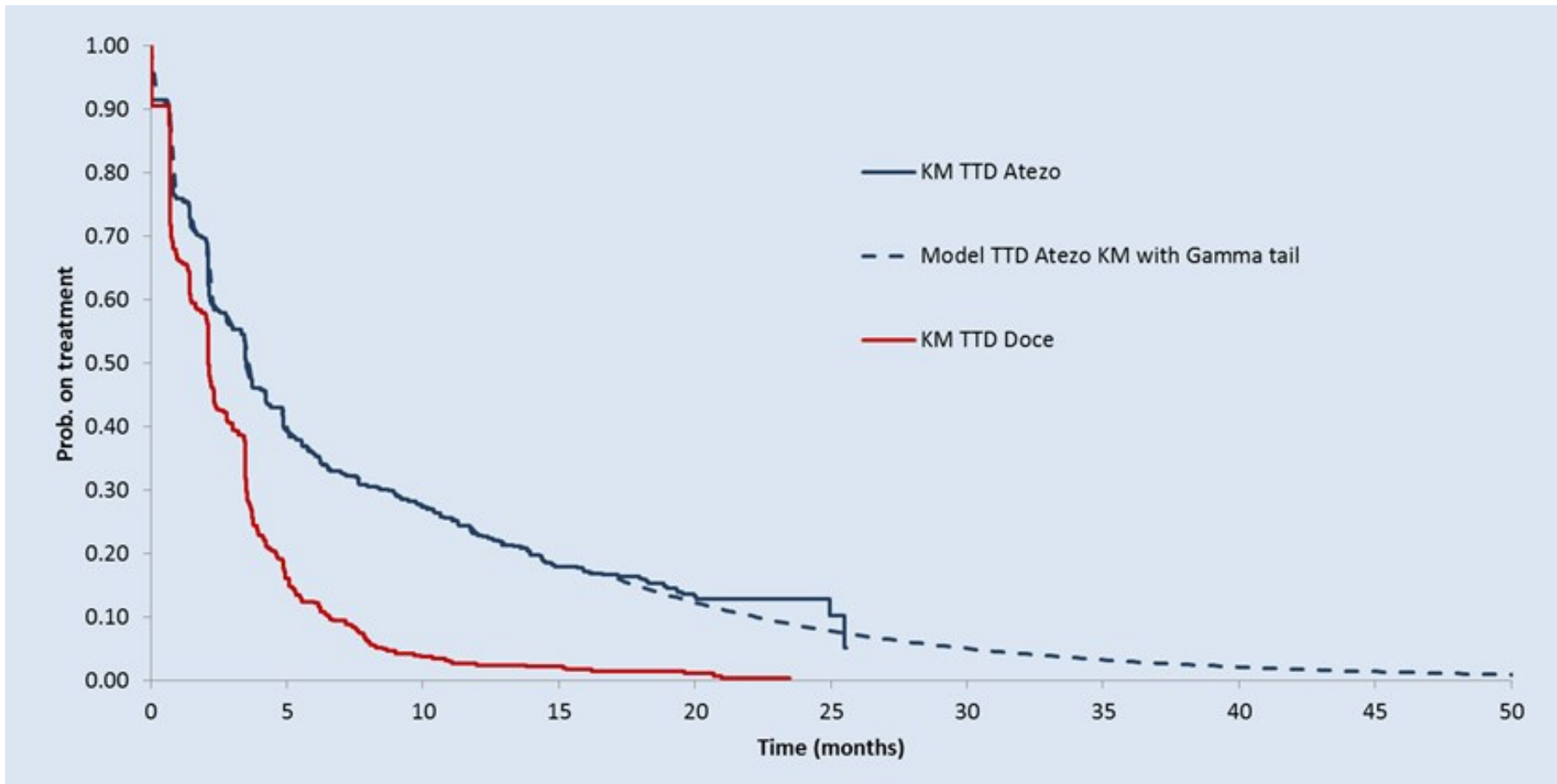
TTD log-cumulative hazard plot



PFS log-cumulative hazard plot



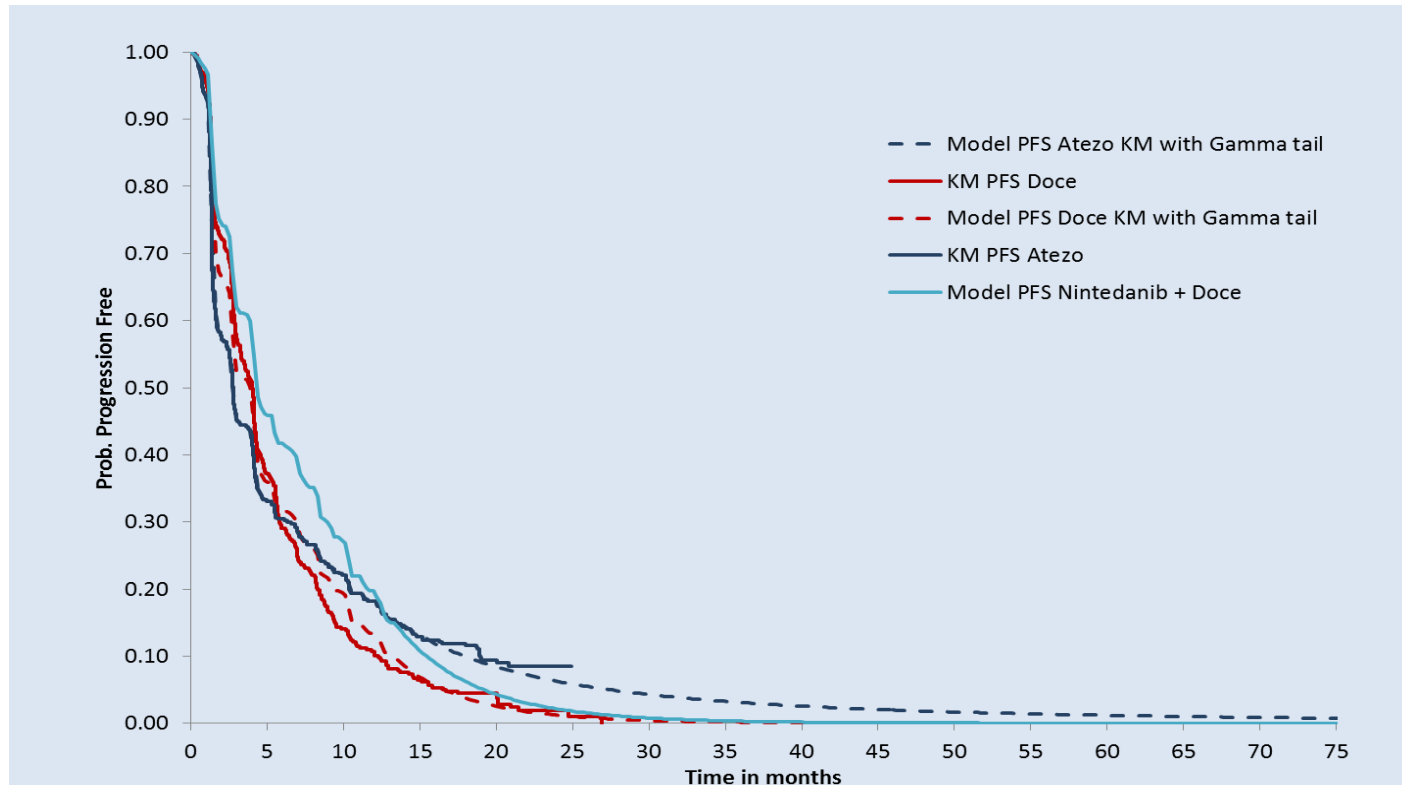
Company's model: TTD - atezolizumab vs docetaxel



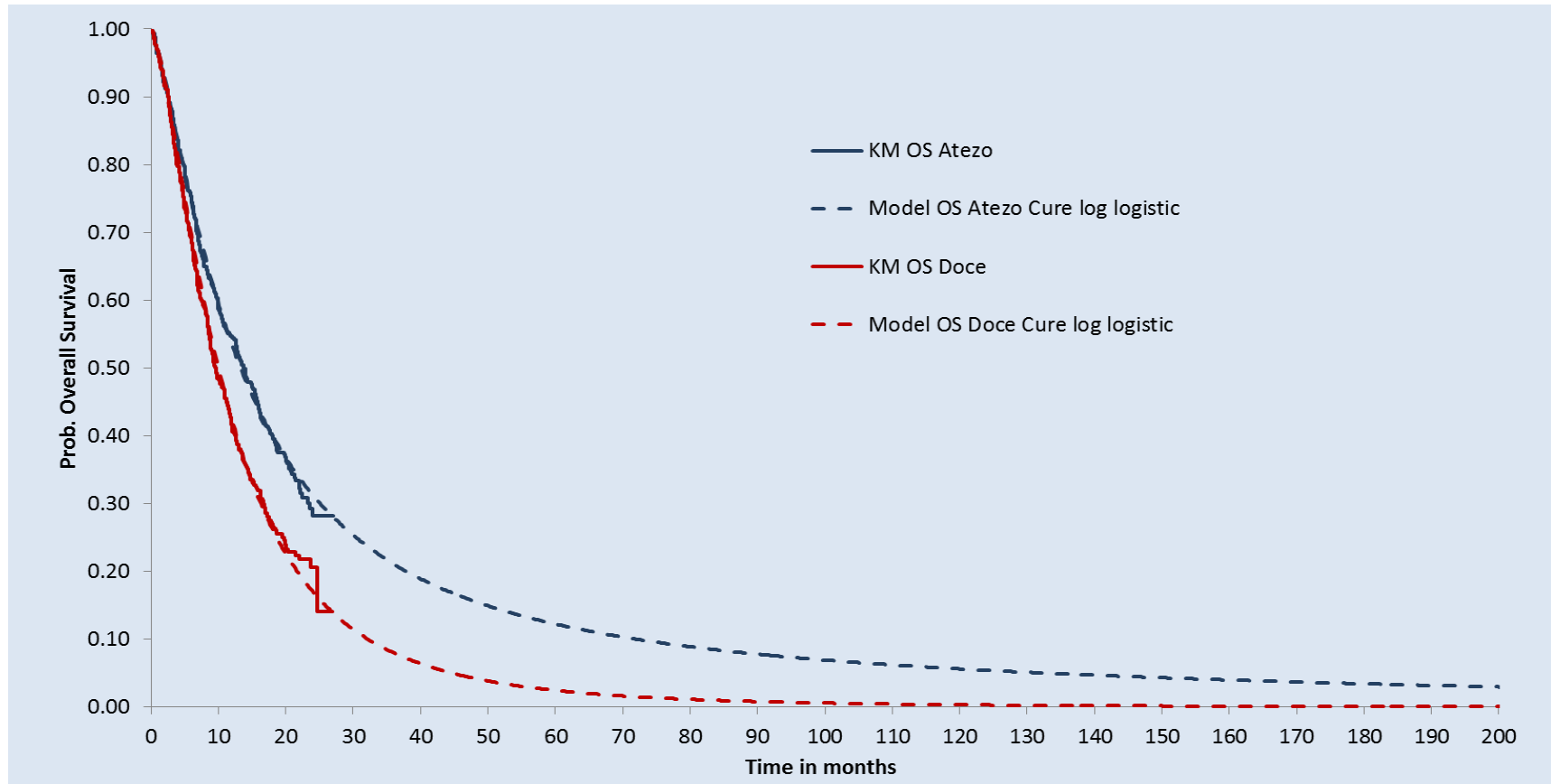
- Company fitted exponential, Weibull, log normal, gamma, log logistic, and Gompertz curves.
- None provided good visual fit hence KM+parametric tails explored.
- Gamma function selected based on goodness of fit and plausibility
- Tail cut points: ATEZ=15%, DOC=1%

Company's model: TTD - nintedanib+docetaxel

- TTD data not available for NIN+DOC so PFS data used as proxy via FP NMA
- Time-dependent log hazard ratios are applied to ATEZ reference curve
- Gamma model selected based on statistical fit (AIC, BIC criteria), however the company did not consider any of the distributions to be a good visual fit

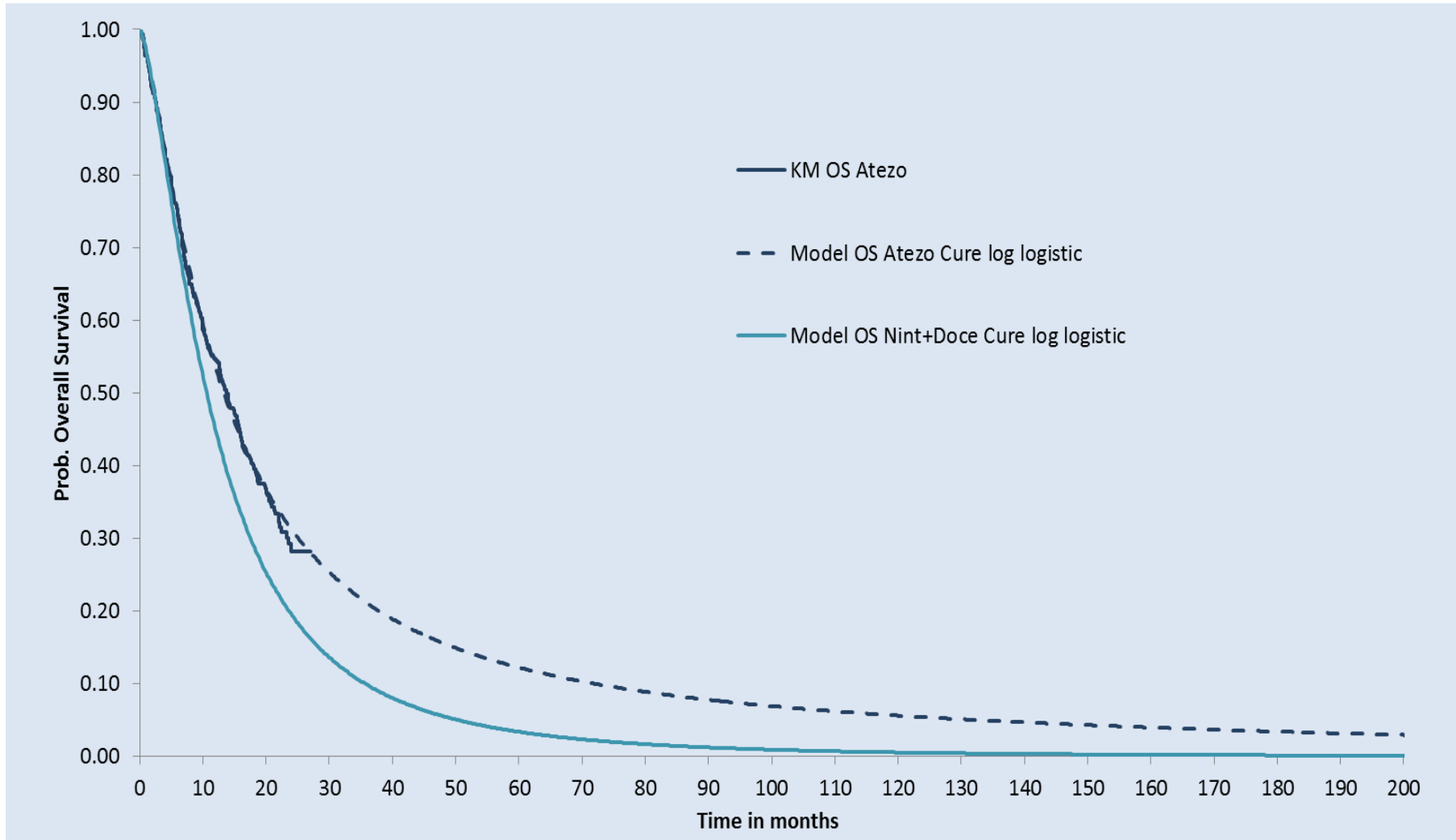


Company's model: OS atezolizumab vs docetaxel



- Mixture cure model assuming 2% cure rate.
- Exponential, Weibull, log logistic, log normal, Gompertz, gamma and generalised gamma models considered
- Log logistic function selected based on goodness of fit and plausibility.
- Company justifies extrapolation based on TA428 and states that under the Committee's preferred assumptions the 5 year OS rate was 9.6%.

Company's model: OS nintedanib



- Comparator curves estimated using FP NMA

Health-related quality of life

- HRQoL derived from EQ-5D-3L utilities collected in OAK
- ‘On treatment’ and ‘off treatment’ states used 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	Mean utility (95% C.I.)
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)

Adverse event disutilities

- Model includes disutility for all Grade 3-5 AEs which occurred in $\geq 2\%$ of patients for intervention and comparator arms
- Applied to each group whilst on treatment

Adverse Event	Disutility	Source
Anaemia	-0.07346	(Nafees <i>et al.</i> , 2008)
Fatigue	-0.07346	(Nafees <i>et al.</i> , 2008)
Febrile Neutropenia	-0.09002	(Nafees <i>et al.</i> , 2008)
Neutropenia	-0.08973	(Nafees <i>et al.</i> , 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 <i>et al.</i> , 2013)
Respiratory Tract Infection	-0.096	Assumption adapted from Hunter 2015
White blood cell count decreased	-0.05	(NICE TA347)

Costs

- Includes drug acquisition, administration, AEs, subsequent treatments, radiotherapy, monitoring, visits, tests, imaging, palliative treatment and end-of-life care
- New review not undertaken – resources and costs based on previous appraisals of nivolumab and pembrolizumab
- List price: atezolizumab=£3807.69 per vial
- PAS in place for atezolizumab and nintedanib. Company did not have access to PAS price for nintedanib

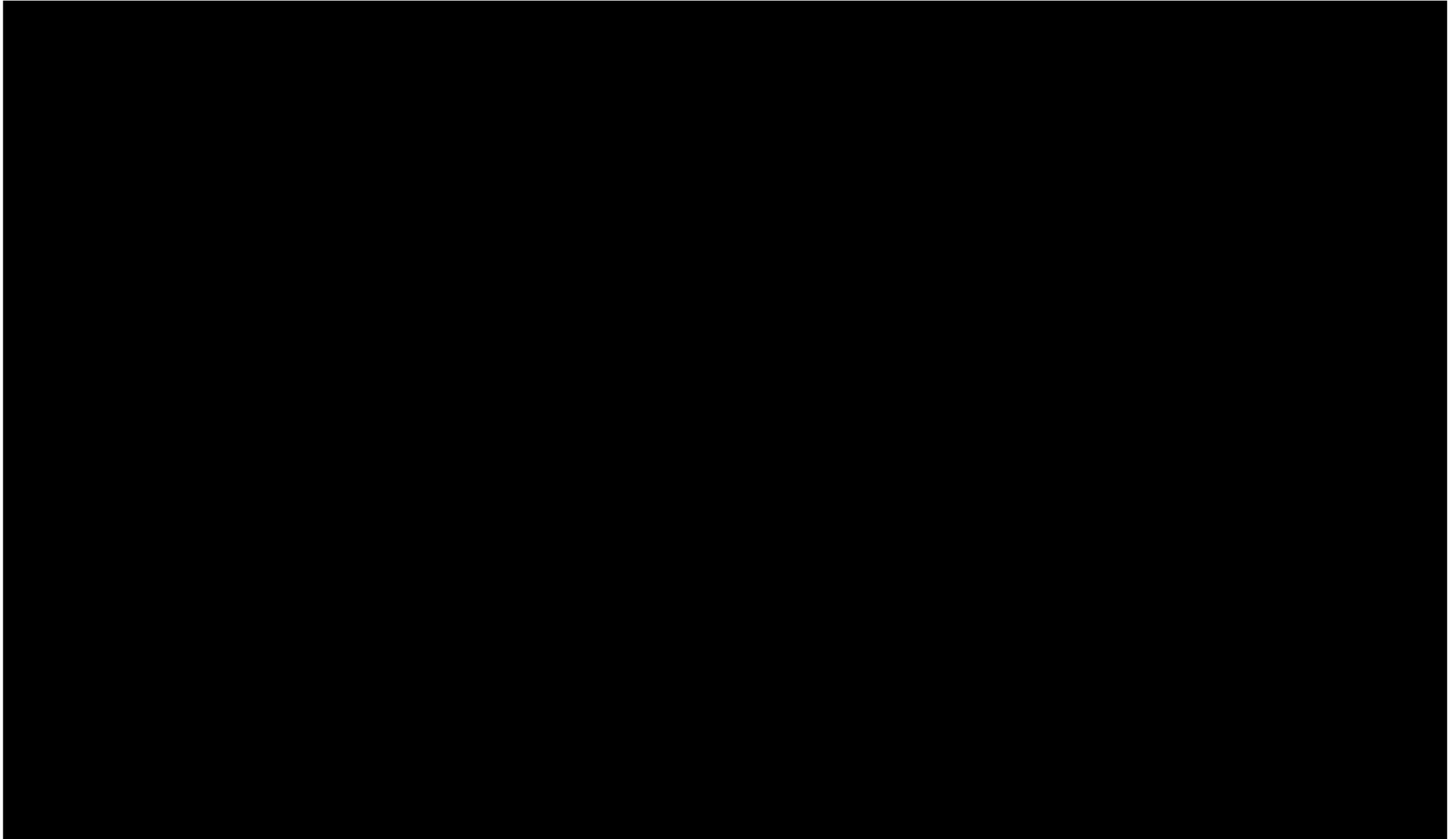
Company's base case results (atezolizumab PAS, comparator list prices)

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
ATEZ	2.22	1.47	████████	1.04	0.75	████████	████████
NIN+DOC	1.31	0.83	£37,702	-	-	-	Ext. dom*
DOC	1.19	0.73	£19,941	-	-	-	-

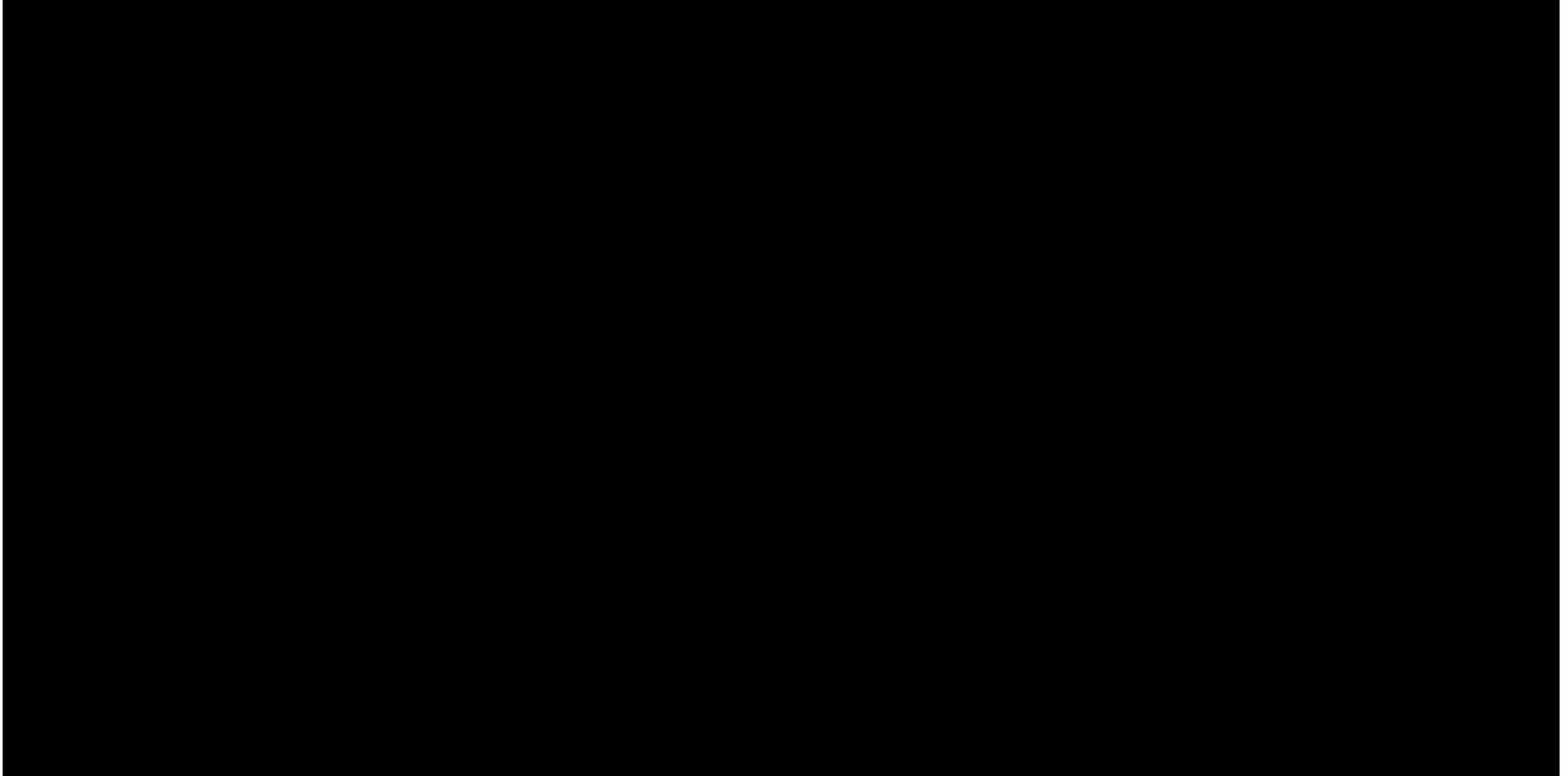
*Pairwise ICER atezolizumab versus nintedanib+docetaxel=████████ per QALY gained

- Probabilistic ICERs:
 - Atezolizumab versus docetaxel=████████ per QALY gained
 - Atezolizumab versus nintedanib+docetaxel=████████ per QALY gained

Company's PSA (atezolizumab PAS, comparator list prices)



Company's deterministic sensitivity analyses, atezolizumab vs docetaxel (with atezolizumab PAS)



Scenario analyses

- Company undertook scenario analyses to assess structural assumptions
- Results indicate that the atezolizumab versus docetaxel comparison is sensitive to:
 - OS distribution (ICER range = £72,356/QALY [base case, cure log logistic] to £156,450/QALY [Gompertz])
 - TTD distribution (ICER range = £70,531/QALY [exponential] to £104,153/QALY [log normal])
 - Utilities source (ICER range = £72.356/QALY [base case, proximity to death] to £103,681/QALY [Nafees et al])
- Cure fraction and time horizon also have some influence on ICER

ERG comments (1)

- Three model errors identified
 1. Inaccurate application of the discount rate (from week 1 not year 2)
 2. Failure to apply an age-related utility decrement
 3. Inappropriate half-cycle correction to modelling of time on treatment
 - Corrected model ICER for atezolizumab increased by ~£5,000
- HRQoL of patients who are more than 30 weeks to death (0.77) seems high but reflects trial data. May not be generalisable to NHS population.
- Company should have undertaken comparison against pembrolizumab
- Nintedanib+docetaxel comparison assumes that effectiveness of atezolizumab is independent of whether patient has adenocarcinoma

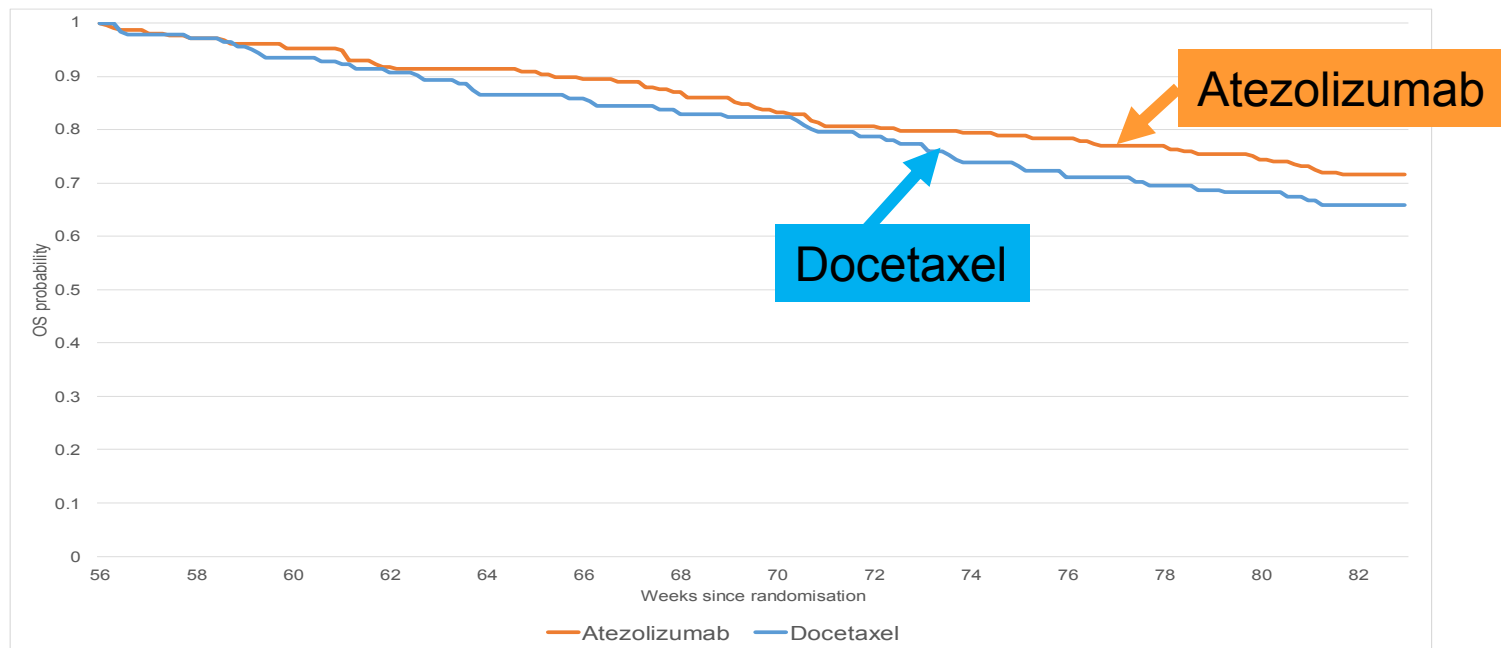
ERG comments (2)

- **Not enough evidence to apply cure rate**
 - Inappropriate justification of mixed cure-rate model using TA414
 - Mixed cure-rate model generates OS gains that are not supported by OAK.
- **Value of cure fraction (2%) not justified by the company or supported by evidence**
 - Company did not undertake any adjusted statistical analysis of the NSCLC registry 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.
 - Cure fraction overestimates the OS for atezolizumab and underestimates OS for docetaxel at 24 months.
- **Log-logistic function produces implausibly long overall survival tail**
 - “...the ICERs that are generated by this approach should not be used to inform decision-making”

ERG preferred approach to OS modelling atezolizumab vs docetaxel

- The ERG used KM data from OAK up to 19 months then extrapolated
- 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)

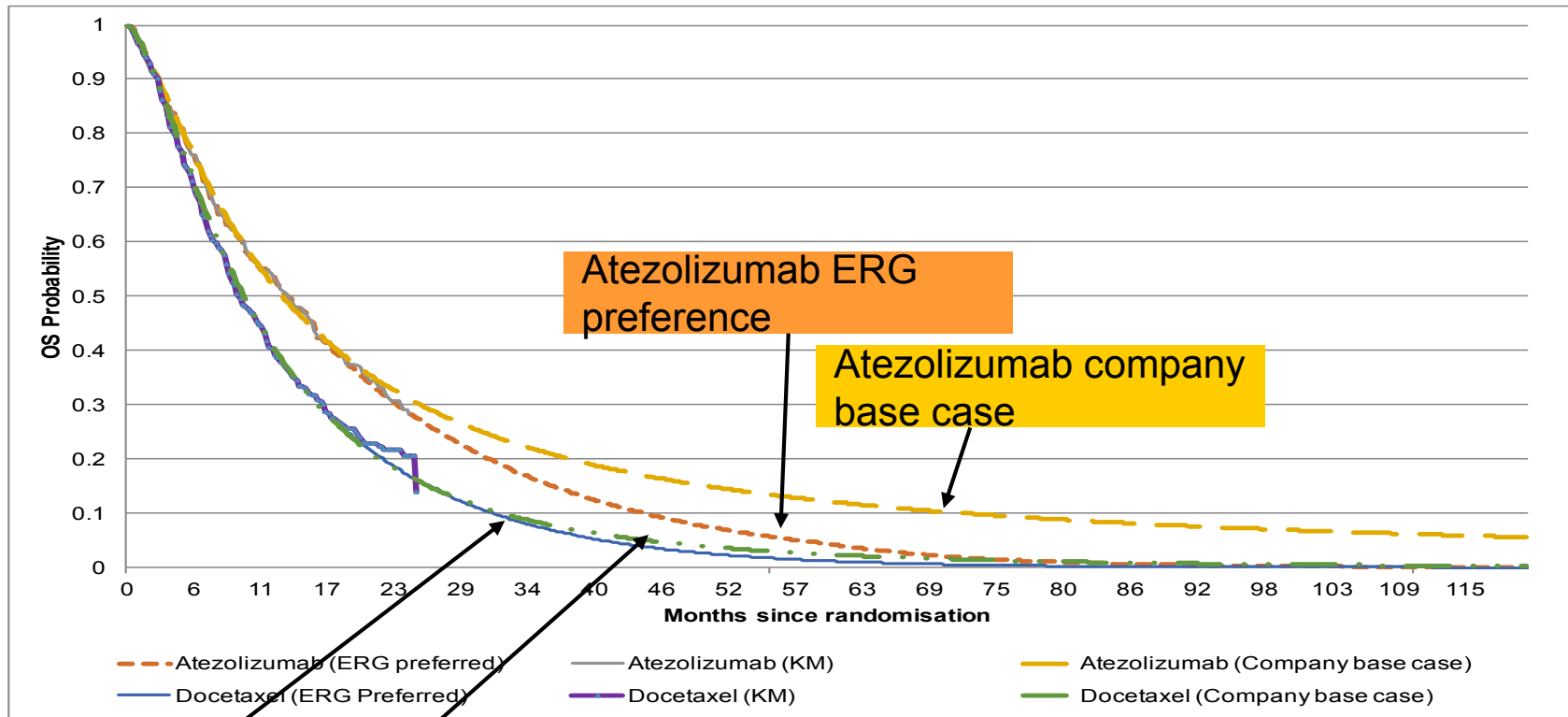
OS K-M data from the OAK trial, weeks 11 to 56 (rebased at week 11)



ERG remodelled OS atezolizumab vs docetaxel

- ERG's 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



Docetaxel ERG preference

Docetaxel company base case

ERG exploratory analyses

Atezolizumab vs docetaxel (with atezolizumab PAS)

Model scenario & ERG revisions	ICER	ICER
	£/QALY	Change
Company base case	██████████	██████████
C1) Discounting algorithms	██████████	██████████
C2) Age-related utility decrement	██████████	██████████
C3) TTD half-cycle correction	██████████	██████████
ERG corrected company base case (C1-C3)	██████████	██████████
R1) ERG preferred OS for atezolizumab and docetaxel (KM data up to 19 months, followed by exponential extrapolation with HR 1 applied for docetaxel)	██████████	██████████
R2) R1 + atezolizumab treatment duration set to 5 years (to simulate 3 years)	██████████	██████████

ERG exploratory analyses

Atezolizumab vs nintedanib + docetaxel (list prices)

Model scenario & ERG revisions	ICER	ICER
	£/QALY	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

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 (Beckett P et al., 2013)	ERG agree with company
Extension of life, normally of at least an additional 3 months, compared with current NHS treatment	<p>Mean OS estimates: Atezolizumab vs Docetaxel: 17 months Atezolizumab vs nintedanib + docetaxel: 14.7 months</p> <p>Median OS estimates: Atezolizumab vs Docetaxel: 3.5 months Atezolizumab vs nintedanib + docetaxel: 2.7 months</p>	<p>Atezolizumab vs Docetaxel: 4.7 months</p> <p>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)</p>

Innovation

- Atezolizumab anticipated to be first anti-PD-L1 antibody approved for locally advanced or metastatic NSCLC after prior chemotherapy
- 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
- Anticipated to be approved for all locally advanced or metastatic NSCLC patients with prior chemotherapy, regardless of PD-L1 expression status.
- Durable responses to atezolizumab:
 - 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)
- Unmet need

Equality and diversity

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

Key issues - cost effectiveness

- The company's economic analysis excludes three comparators included in the scope (nivolumab, pembrolizumab and BSC)
- The company's model assumes atezolizumab has a lifetime protective effect
 - ERGs preferred assumptions are to use KM data for as long as possible and then extrapolate with a HR of 1
- Mixed cure-rate used to model OS for patients receiving atezolizumab
 - Insufficient evidence to apply cure-rate
 - Cure fraction 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)