Chair's presentation

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

3rd Appraisal Committee meeting

Committee C

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ERG: LRiG

NICE technical team: Jessica Maloney (ACM1-2) Victoria Kelly, Alex Filby

Company: Roche

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Appraisal History

MA	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before atezolizumab.
ACD 1	• Atezolizumab is **not recommended** • Pivotal trial (both PD-L1 positives and negative) showed overall survival with atezolizumab is longer than with docetaxel alone • Most plausible ICERs > £50,000 per QALY gained for atezolizumab vs docetaxel and atezolizumab vs nintedanib + docetaxel. • no evidence directly comparing atezolizumab with nintedanib plus docetaxel or with pembrolizumab • Could not make a judgement on CE of PD-L1 positive group as company did not present this data
ACD 2	• Atezolizumab is **not recommended** • ICERs for ITT population vs docetaxel & nintedanib + docetaxel still > £50,000 • EOL met for docetaxel but not nintedanib + docetaxel • Clinical evidence for atezolizumab vs pembrolizumab in the PD-L1 positive group is highly uncertain – could not say if atezolizumab clinically similar to pembrolizumab • company provided a cost minimisation analysis for the comparison with pembrolizumab which committee did not accept for decision making.

Committee's ACD2 conclusions (I)

Issue	Committee's conclusion
PD-L1 expression	Disappointed company did not present all relevant PD-L1 subgroup results.
Comparators	Would like comparison in PD-L1 positive subgroup of atezolizumab with pembrolizumab. Rejected cost-minimisation analysis for ATEZ vs PEMBRO as not suitable for decision making and this comparator was not considered further
Atez v docetaxel	Atezolizumab is more effective than docetaxel regardless of PD-L1 expression
Atez v nintedanib plus docetaxel	Atezolizumab may not increase overall survival compared with docetaxel plus nintedanib difference in OS estimate 3.33 months (95% CI -0.15 to 6.81). Wide confidence intervals which would increase if a random effects model was used.
Atez v pembrolizumab	The committee could not conclude with any certainty that atezolizumab is clinically equivalent to pembrolizumab. Atezolizumab (whole population) compared with pembrolizumab (PD-L1 expression ≥1%) difference of overall survival –0.18 months (95% CI –5.58 to 4.60).
Indirect treatment comparisons are uncertain	Results of ITC not robust, statistical heterogeneity influenced by; choice of comparators included in the network, the populations used, use of fixed effects or random effects models, and the type of fractional polynomial model chosen

Committee's ACD2 conclusions (II)

Issue	Committee's conclusion
Adjusting for subsequent treatment	The rank-preserving structural failure time method was not suitable for adjusting for subsequent therapies (it is normally used to adjust for treatment crossover). Committee used the estimates from the unadjusted trial data.
Stopping rule	Would like to see 2-year stopping rule implemented in the economic model
Cost minimisation analysis	Survival benefit for atezolizumab compared with pembrolizumab is uncertain, therefore the CMA is not suitable for decision making
Extrapolation of overall survival	Company's log-logistic model produces implausibly long survival tail. Prefer ERG extrapolation: • KM data for atezolizumab up to week 83 followed by extrapolation using exponential model
Lifetime treatment effect	Lifetime treatment effect for atezolizumab is implausible, unlikely to last more than 5 years after treatment had stopped.
End of life criteria	Compared with docetaxel: • meets EoL criteria. Compared with nintedanib plus docetaxel: • 3 month OS extension not met, considerable uncertainty in fractional polynomial method used by the company. • Based on committee preferred assumptions estimated OS gain for atezolizumab compared with nin+doc is between 0 and 2.65 months.

Related appraisal considerations

	Pembrolizumab (TA428)	Nivolumab; (TA483 non-squamous); (TA484 squamous)	Atezolizumab conclusions in ACD2
Recommendation	PD-L1-positive, only if stopped at 2 years of uninterrupted treatment.	Recommended in CDF only if: • tumours are PD-L1 (non-squamous only) positive and • nivolumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression	Not recommended
PD-L1 subgroup	Trial data only on PD-L1 +ve	Plausible nivolumab has different level of effectiveness by PDL1 expression	Company case based on benefit regardless of PD-L1 expression
Duration of treatment effect	Lifetime treatment effect implausible	treatment effect up to 3 years after stopping treatment. Based on 36 month results from the CheckMate 057 trial	Company prefer lifetime treatment effect. Cmte suggest lifetime treatment effect implausible. Suggest max 5 years after treatment stops.
Treatment stopping rule	2 year stopping assumption based on KEYNOTE-010 protocol	2 year stopping assumption • not applied in main clinical trial CheckMate 037, • not specified in SmPC	No stopping rule in OAK ACD2 ‘Cmte would prefer 2-year stopping rule’

ACD 2 consultation responses

- Consultee comments from:
  - Roche
  - Clinical expert (Consultant Oncologist)/Royal colleges NCRI-ACP-RCP-RCR
- 2 web comments (NHS professionals)
- No comments from Department of Health

Note: Roche have submitted an updated PAS

ACD2 consultation(I)

Issue	Consultation comments	Company new evidence
Extrapolation of OS in the ITT population	Company and clinical experts: ERG extrapolation unduly pessimistic. Committee did not consider the results from pembrolizumab or nivolumab trials which suggest survival at 5 years is > 4%.	Evidence from FlatIron study which suggests patients receiving docetaxel would have a 5 year survival of 4%.
Adjusting for subsequent treatment	Company: Use the RPFST. 2-stage adjustment not suitable	-
Stopping rule and lifetime treatment effect	Company and clinical experts: Unreasonable to apply stopping rule and limit treatment effect in light of evidence.	Evidence from checkmate trial (patients who stopped treatment with nivolumab at 1 year had higher risk of progression)

ACD2 consultation (II)

Issue	Consultation comments	Company new evidence
PD-L1 expression	Higher response rate with higher levels PD-L1 likely but correlates less well with long term survival benefit	Company have presented a CE analysis by: • TC/IC 0 (PD-L1 negative) and • TC/IC 1/2/3 (PD-L1 positive)
Comparison with pembrolizumab		The company's PD-L1 positive CE analysis includes pembrolizumab as the comparator
ITC		Company resubmitted a reduced network containing; atezolizumab, docetaxel and pembrolizumab
EOL	For the ITT: • Met EOL with docetaxel • Not met with nintedanib + docetaxel. In light of the subgroup analysis results; committee will need to discuss if criteria is met for the PD-L1 positive (atezolizumab vs pembrolizumab) group and PD-L1 negative group (atezolizumab vs docetaxel and nintedanib + docetaxel)	

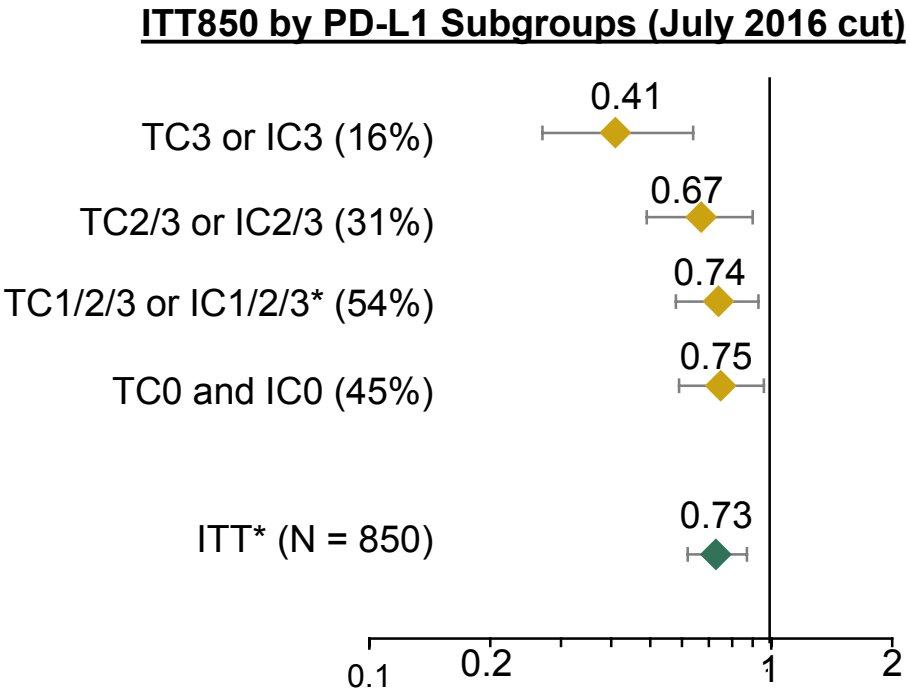
Company new evidence: OAK trial updated data cut (1)

- NICE and the ERG asked the company to provide updated results from their pivotal trial (OAK) using data from 375 additional patients (January 2017 cut)
- Company provided top-level clinical results only and the new data cut was not included in the company's updated models
- New data cut included n=1225 patients.

Comments from Roche:

- the primary analysis of OAK (n=850) has consistently been used in the economic models submitted by Roche on the basis that it was:
  - the pre-specified analysis of the first 850 patients that provided sufficient power to test the co-primary endpoints of the OAK study,
  - the regulatory approval for the marketing authorisation of atezolizumab in this indication
  - the results in the pre-specified analysis are more appropriate for decision-making because they are less confounded by treatment crossover:
    - Treatment crossover was more prevalent in the additional patients enrolled in OAK after the primary analysis and included in the secondary analysis population.
    - The rate of subsequent immunotherapy in the docetaxel arm for the last 375 patients enrolled was [redacted]

Company new evidence: OAK trial updated data cut (2)



*Stratified HR for ITT850, TC1/2/3 or IC1/2/3 of ITT850, ITT1225, TC1/2/3 or IC1/2/3 of ITT1225, TC2/3 or IC2/3 of ITT1225, TC3 or IC3 of ITT1225; unstratified for all other subgroups

Committee considerations: does the new data cut reflect the results from the pre-specified analyses presented by the company previously and used to inform the CE analyses?

Comparators

Committee conclusions in ACD2	
Comparator	**Population**
Docetaxel	ITT
Nintedanib + docetaxel	ITT (adenocarcinoma)
Pembrolizumab	PD-L1 positive

Comments from Roche and 2 web comments:

- nintedanib + docetaxel is not a useful comparator because of small populations and it is rarely used in clinical practice
- Docetaxel for PD-L1 negative and pembrolizumab for PD-L1 positive should be the appropriate comparators for decision making purposes in this appraisal

Comparators: ERG comments

- The ERG considers that comparison of atezolizumab versus docetaxel for the OAK trial all-comers (ITT) population is not relevant to this appraisal due to >50% of patient in the trial having some level of PD-L1 expression *(in current clinical practice PD-L1 expressers would receive pembrolizumab not docetaxel)*

- The ERG considers docetaxel would only be prescribed to patients in the TC/IC 1/2/3 subgroup (54% of the all-comers population) if immunotherapy was **not** an appropriate treatment.

- Pembrolizumab (TA428) is recommended for the treatment of patients with PD-L1 positive NSCLC who have had at least one prior chemotherapy.

All comers overall survival extrapolation (1)

Committee conclusions ACD2: Using a log-logistic model creates an implausibly long survival tail; Kaplan–Meier data plus an exponential curve remains optimistic

Comments from Roche, clinical expert, Royal Colleges and 2 web comments: Committee preferred OS extrapolation unduly pessimistic and not supported by available data

	Proportion of patients alive at 5 years	
	Atezolizumab	**Docetaxel**
KM+Exponential*	4.9%	0.2%
KM+Weibull	3.1%	0.1%
KM+Log normal	10.3%	1.1%
KM+Gamma	5.8%	0.3%
KM+Log logistic**	10.1%	1.0%
KM+Gompertz	2.9%	0.1%

***Committee preferred. **Company preferred**

All comers overall survival extrapolation (2)

Roche submitted evidence to support its preferred OS extrapolations:

- Relevant clinical trial evidence for atezolizumab and other immunotherapies:
  - OAK and POPLAR (pivotal trials for atezolizumab)
  - KEYNOTE-010 (pembrolizumab vs docetaxel in TPS>1%)
  - Checkmate-017 (nivolumab vs docetaxel in squamous)
  - Checkmate-057 (nivolumab vs docetaxel in non squamous)
  - TA428 Pembrolizumab (9.6% 5-year OS)
- Natural history data sets for OS with docetaxel:
  - NLCA (stage 4, chemo eligible/ineligible, 2013)
  - NCLA (stage 3b, previously treated, 2013)
  - SEER (distant, 2014)
  - SEER (regional/distant, 2014)
  - **New evidence**: Flatiron (Atez eligible population with stage 3b/4, second-line NSCLC treated with docetaxel, Jan 2011- Mar 2017)

All comers overall survival extrapolation (3)

		Docetaxel OS (%)				Atezolizumab OS (%)			
	Data source	**2 yr**	**3 yr**	**4 yr**	**5 yr**	**2 yr**	**3 yr**	**4 yr**	**5 yr**
Model data	**Company base case OS: KM+ log logistic**	**16**	**7**	**4**	**2**	**30**	**19**	**13**	**10**
	ERG and committee preferred OS: KM+ exponential	**17**	**7**	**3**	**1**	**29**	**16**	**8**	**4**
Other immunotherapies	KEYNOTE-010 [TPS ≥1%] (pembrolizumab)	15				30			
	Checkmate-017 (Squamous nivolumab)	8	6			3	16		
	Checkmate-057 (Non-squamous nivolumab)	16	9			29	18		
	CA209-003 (nivolumab)					24	18		16
	Pembrolizumab (TA428)								9.6
Natural history	NLCA (Stage IV; docetaxel 1st line)	7	4		3				
	NLCA (stage IIIB/IV; docetaxel 1st line)	20	13		7				
	SEER (distant; docetaxel 1st line)				5				
	SEER (regional/distant; docetaxel 1st line)				32				
	Flatiron-database*	14	10	6	4				

*** New evidence: page 2-6 of company new evidence appendix**

Subsequent treatment adjustment

Committee conclusions ACD2: the unadjusted data in the company's original submission should be considered for decision-making

Roche:

- 5% of patients randomised to atezolizumab and 17% in docetaxel arm received subsequent cancer immunotherapies.
- two-stage adjustment for treatment switching (used in TA428) cannot be implemented for the OAK dataset, since this adjustment method requires new baseline values of previously selected variables to be defined at the time of switch
- Rank-preserving structural failure time (RPSFT) method was used and previously accepted by the NICE committee as an appropriate method in the appraisal of pembrolizumab (TA428)*

***TA428 pembrolizumab** the RPSFT method does not have a test for a common treatment effect and it preferred the 2-stage adjustment method to account for the effects of crossover'… The committee concluded that the **2-stage adjustment method was reasonable.**

Stopping rule & duration of treatment effect

Committee conclusion ACD 2:

- concern among clinicians about use of immunotherapies beyond 2 years.
- Lifetime treatment effect for atezolizumab is implausible, unlikely to last more than 5 years after treatment had stopped.

Roche:

- Arbitrary stopping rule is unreasonable in light of MA and evidence submitted by company:
  - CheckMate 153 trial: patients on ***nivolumab*** who stopped treatment after 1 year had a statistically significant higher risk of progressing (HR: 0.42, 95% CI: 0.25 to 0.71), and a higher risk of dying (HR: 0.63, 95% CI: 0.33 to 1.20).
- 2-year stopping rule has minimal effect on the ICER
- appreciate the uncertainty regarding the long term duration of treatment effect but highlight that a cap on duration-of-treatment effect are not based on clinical evidence.

Updated cost-effectiveness results* atezolizumab **vs docetaxel**: ITT Company analyses (with atezolizumab PAS)

	Total costs	Total QALYS	Inc. costs	Inc. QALYs	ICER
Company basecase (no stopping rule, on-going treatment effect, with switching adjustment, company-preferred extrapolation)					
Docetaxel	£19,536	0.64			-
Atezolizumab	[redacted]	1.31	[redacted]	0.66	[redacted]
1. 2 year stopping rule					
Docetaxel	£19,536	0.64			-
Atezolizumab	[redacted]	1.31	[redacted]	0.66	[redacted]
2. 3-year treatment effect					
Docetaxel	£19,517	0.64			-
Atezolizumab	[redacted]	1.29	[redacted]	0.65	[redacted]
3. without switching adjustment					
Docetaxel	£20,181	0.71			-
Atezolizumab	[redacted]	1.31	[redacted]	0.60	[redacted]
4. Committee preferred OS extrapolation (for all comers)*					
Docetaxel	£19,279	0.62			-
Atezolizumab	[redacted]	1.02	[redacted]	0.41	[redacted]
Committee preferred assumptions (1+2+3+4)**					
Docetaxel	£19,644	0.66			-
Atezolizumab	[redacted]	0.98	[redacted]	0.33	[redacted]

**Uses piecewise distribution in the company economic model, KM until 52 weeks, as preferred, end of piece: 69 weeks (atezo) and 80 weeks (doce).

Updated cost effectiveness results* atezolizumab **vs nintedanib plus docetaxel**: ITT Company analyses

	Total costs	Total QALYS	Inc. costs	Inc. QALYs	ICER
Company basecase (no stopping rule, on-going treatment effect, with switching adjustment, company-preferred extrapolation)					
Nin + Doc	£37,265	0.81			-
Atezolizumab	[redacted]	1.31	[redacted]	0.49	[redacted]
1. 2 year stopping rule					
Nin + Doc	£37,265	0.81			-
Atezolizumab	[redacted]	1.31	[redacted]	0.49	[redacted]
2b. 3-year treatment effect					
Nin + Doc	£37,220	0.81			-
Atezolizumab	[redacted]	1.29	[redacted]	0.48	[redacted]
3. without switching adjustment					
Nin + Doc	£38,261	0.91			-
Atezolizumab	[redacted]	1.31	[redacted]	0.39	[redacted]
4. Committee preferred OS extrapolation (for all comers)*					
Nin + Doc	£36,623	0.75			-
Atezolizumab	[redacted]	1.02	[redacted]	0.27	[redacted]
Committee preferred assumptions (1+2+3+4)*					
Nin + Doc	£37,022	0.79			-
Atezolizumab	[redacted]	0.98	[redacted]	0.19	[redacted]

*Same model from company original submission updated with atez PAS only

Note: there is a PAS for nintedanib, results will be presented in part 2

PD-L1 Expression: Subgroup analyses

The committee noted in ACD2 that:

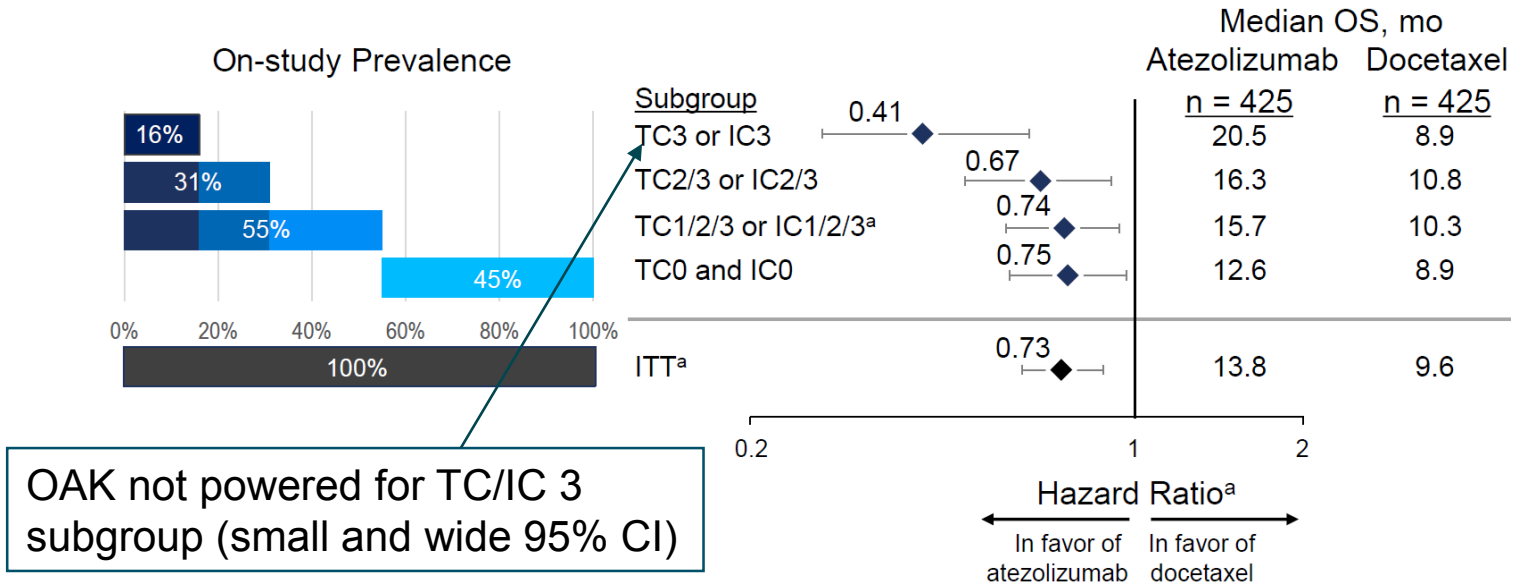
- the MA does not specify treatment based on PD-L1 expression however the trial results suggested that higher levels of PD-L1 expression led to greater clinical response
- for PD-L1-positive NSCLC pembrolizumab is the appropriate comparator
- agreed atezolizumab is more effective than docetaxel regardless of PD-L1 expression and it becomes more effective as PD-L1 expression rises
- the company did not provide analyses by PD-L1 expression because the trials for atezolizumab (OAK) and pembrolizumab (KEYNOTE-010) used different PD-L1 tests.
- it was disappointed that the company did not present clinical and cost-effectiveness results for all of the relevant PD-L1 subgroups (including TC3 or IC3 and TC2/3 or IC 2/3

PD-L1 subgroups – company clinical data

Roche and 1 web comment: higher response rate with higher levels PD-L1 likely but correlates less well with long term survival benefit.

Roche:

- All-comers population should be used for decision making
- Unethical to restrict access to PD-L1 expressers, when atezolizumab shows similar OS benefit for low and negative PD-L1 expressers (greatest unmet need).



Company updated model for PD-L1 subgroup analyses

- Company new base-case
  - Updated atezolizumab PAS
  - Corrections of ERG-identified errors from ITT economic model
  - No cost of testing for PD-L1 expression for atezolizumab
  - Separate parameterisation of OAK data as proportional hazards assumption is violated
  - No stopping rule
  - Lifetime treatment effect
  - Adjusted for subsequent treatment using RFSPT (apart from PD-L1 negative subgroup TC/IC 0)
  - Updated costs for adverse events, terminal care and drug acquisition in the PD-L1 positive group
  - Results presented for:
    - PD-L1 Negative (*comparators: Docetaxel & nintedanib + docetaxel*)
    - PD-L1 Positive (*comparator: Pembrolizumab*)

PD-L1 Positive subgroup group (TC/IC 1/2/3):

- Relevant comparators:
  - Pembrolizumab

Company's updated indirect treatment comparison in the PD-L1 positive subgroup

		Estimated OS difference (95% CI), months
Atezolizumab (TC/IC 1/2/3) vs pembrolizumab (>1% TPS)	Adjusted for subsequent treatment (RPSFT method)*	1.98 (-4.05, 7.32)
	No adjustment for subsequent treatment**	-0.18 (-6.36, 5.22)

*used in economic model as base case
**used in scenario analyses in economic model

Note: ITC results were calculated using a reduced network containing; atezolizumab, docetaxel and pembrolizumab

Updated ITC: ERG comments

- Results show, for both PFS and OS, that treatment with atezolizumab is non-inferior to pembrolizumab irrespective of adjusting for treatment switching.
- The ERG highlights that a range of input parameters could be used in the analyses and it is difficult to identify the most appropriate combination of factors and, therefore, it is difficult to interpret results from the ITCs.
- It is not currently possible to directly (or, with any confidence, indirectly) compare the effectiveness of atezolizumab versus pembrolizumab in patients whose tumours exhibit a level of PD-L1 expression.

ERG comparative analysis of atezolizumab and pembrolizumab

Results from the OAK trial Jan 2017 data cut (TC/IC 1/2/3 subgroup) and the KEYNOTE-010 (pembrolizumab) trial:

- suggest better OS in the atezolizumab arm of the OAK trial (TC/IC 1/2/3 subgroup) than in the pembrolizumab arm of the KEYNOTE-010
- However, compared with results from the OAK trial, median PFS was higher, and median OS was lower, in the docetaxel arm of the KEYNOTE-010 trial
- Treatment related adverse events similar ([redacted]% in atezolizumab vs 63.4% in pembrolilzumab).

- OS

- PFS

PD-L1 positive (TC/IC123): Company's OS extrapolation (I)

- Company propose that KM + log-logistic is best fit based on clinical plausibility (12% survival at 5 years with Atez and 9% with pembro)

Atezolizumab clinical plausibility model predictions vs available data (table 32, page 45 company new evidence appendix)					
		2 years	3 years	4 years	5 years
Trial data	OAK (atezolizumab) – TC/IC 1/2/3	32%	-	-	-
	POPLAR (atezolizumab) – TC/IC 1/2/3	35%	18%	-	-
	CA209-003 (nivolumab) - >1% PD-L1	25%	23%	23%	23%
	CA209-003 (nivolumab) – all patients	24%	18%	17%	16%
	Keynote-001 - >1% TPS (pembrolizumab)	30%	19%	-	-
Parametric distributions	KM+Exponential	30%	17%	8%	4%
	KM+Weibull	30%	16%	7%	3%
	KM+Log normal	31%	21%	15%	12%
	KM+Gamma	30%	18%	11%	7%
	KM+Log logistic*	31%	21%	15%	12%
	KM+Gompertz	30%	16%	6%	2%

* Company preferred extrapolation

PD-L1 positive (TC/IC123): Company's OS extrapolation (II)

Pembrolizumab clinical plausibility assessment: model predictions versus available data (table 33, page 47 company new evidence appendix)

		2 years	3 years	4 years	5 years
Pembrolizumab NICE committee appraisal *		30% *	19% *	13% *	9% *
CA209-003 (nivolumab) - >1% PD-L1		25%	23%	23%	23%
CA209-003 (nivolumab) – all patients		24%	18%	17%	16%
Parametric distributions	KM+Exponential	27%	14%	8%	4%
	KM+Weibull	26%	13%	6%	3%
	KM+Log normal	27%	18%	13%	9%
	KM+Gamma	27%	15%	9%	5%
	KM+Log logistic	27%	17%	12%	9%
	KM+Gompertz	26%	13%	6%	3%

* Digitised curve, subject to a degree of uncertainty

Company preferred extrapolation

Company results for PD-L1 positive population (TC/IC 1/2/3)

	Total costs	Total QALYS	Inc. costs	Inc. QALYs	ICER
Company basecase (no stopping rule, on-going treatment effect, with switching adjustment)					
Pembrolizumab*	£76,720	1.25			-
Atezolizumab	[redacted]	1.44	[redacted]	0.28	[redacted]
1. 2 year stopping rule					
Pembrolizumab	£76,720	1.25			-
Atezolizumab	[redacted]	1.44	[redacted]	0.28	[redacted]
2. 3-year treatment effect					
Pembrolizumab	£76,536	1.23			
Atezolizumab	[redacted]	1.41	[redacted]	0.18	[redacted]
3. without switching adjustment					
Pembrolizumab	£80,021	1.58			
Atezolizumab	[redacted]	1.44	[redacted]	-0.14	[redacted]
4. Include cost of testing in atezolizumab arm					
Pembrolizumab	£76,720	1.25			
Atezolizumab	[redacted]	1.44	[redacted]	0.18	[redacted]

*Does not include pembrolizumab PAS. Results with cPAS presented in part 2

Company results for PD-L1 positive population (TC/IC 1/2/3)

		Total costs	Total QALYS	Inc. costs	Inc. QALYs	ICER
KM+EXP	Pembrolizumab*	£73,840	0.98			
	Atezolizumab	[redacted]	1.08	[redacted]	0.10	[redacted]
KM+Weibull	Pembrolizumab	£73,498	0.95	[redacted]		[redacted]
	Atezolizumab	[redacted]	1.05	[redacted]	0.10	[redacted]
KM+Log normal	Pembrolizumab	£76,569	1.24	[redacted]		[redacted]
	Atezolizumab	[redacted]	1.41	[redacted]	0.18	[redacted]
KM+Gamma	Pembrolizumab	£74,283	1.02	[redacted]		[redacted]
	Atezolizumab	[redacted]	1.13	[redacted]	0.12	[redacted]
KM+Log log	Pembrolizumab	£76,720	1.25	[redacted]		[redacted]
	Atezolizumab	[redacted]	1.44	[redacted]	0.18	[redacted]
KM+Gompertz	Pembrolizumab	£73,415	0.95	[redacted]		[redacted]
	Atezolizumab	[redacted]	1.04	[redacted]	0.09	[redacted]
Piecewise	Pembrolizumab	£75,409	1.13	[redacted]		[redacted]
	Atezolizumab	[redacted]	1.26	[redacted]	0.13	[redacted]
0% cure Log log	Pembrolizumab	£77,201	1.30	[redacted]		[redacted]
	Atezolizumab	[redacted]	1.49	[redacted]	0.19	[redacted]
	Pembrolizumab	£74,379	1.03	[redacted]		[redacted]
Committee preferred assumptions (1+2+3+most plausible OS curve)						
	Pembrolizumab	£76,076	1.21			-
	Atezolizumab	[redacted]	1.17	[redacted]	-0.05	[redacted]

Company's cost comparison: atezolizumab vs pembrolizumab*

- Base case: atezolizumab TC/IC 1/2/3 vs pembrolizumab (table 48 page 58 of company new evidence)

		Atezolizumab	Pembrolizumab (list price)	Increment	% absolute increment
Mean costs in PFS/On treatment	Treatment cost	[redacted]	£48,133	[redacted]	[redacted]
	Diagnostic cost	£0	£338	-£338	[redacted]
	Drug administration	£2,769	£2,320	£449	[redacted]
	Adverse events	£117	£117	£0	[redacted]
	Supportive care	£11,392	£10,661	£732	[redacted]
Total costs in PFS/On treatment		[redacted]	£61,568	[redacted]	[redacted]
Mean costs in PD/Off treatment	Supportive care	£9,528	£1,574	£1,574	[redacted]
	Subsequent therapy cost	£3,749	£3,749	£0	[redacted]
Total costs in PD/Off treatment		£13,277	£11,703	£1,574	[redacted]
Terminal care costs		£3,404	£3,449	-£45	[redacted]
Total costs		[redacted]	£76,720	[redacted]	[redacted]

*Does not include pembrolizumab PAS. Results with cPAS presented in part 2

ERG comments on company's CMA

- Treatment with both atezolizumab and pembrolizumab is continued until disease progression or unacceptable toxicity therefore trial PFS K-M data act as a reasonable proxy for time on treatment
- Data from the ERG's comparative analysis (figure 2, page 9 of ERG report [slide 30]) suggest that time on treatment for patients treated with these drugs is likely to be similar
- treatment with pembrolizumab is only permitted for a period of 2 years; data from the OAK trial TC/IC 1/2/3 subgroup indicate that, at 128 weeks, 11.1% of that subgroup were still receiving atezolizumab
- The actual lifetime cost differential between treatment with atezolizumab and treatment with pembrolizumab is, therefore, unclear.

PD-L1 Negative subgroup (TC/IC0):

- Relevant comparators:
  - Docetaxel
  - Nintedanib + docetaxel (for adenocarcinoma)

PD-L1 Negative (TC/IC0): OS extrapolation

- Roche consider Log-logistic is the best statistical fit for atezolizumab and docetaxel.
- However as the committee preferred a KM+parametric distribution in the ITT population the company have explored this:
  - KM + Log-logistic predicts 5 year OS with atezolizumab as 10% but overestimates survival of patients on docetaxel (4.3%).
  - Mechanism of action of docetaxel is very different to atezolizumab.
  - In addition the proportional hazards assumption was violated therefore the company fit separate types of parametric models for each arm:
    - Atezolizumab: KM + log-logistic
    - Docetaxel: KM + log-normal

Company's docetaxel clinical plausibility assessment: model predictions versus available data

		Survival on docetaxel			
		2 years	3 years	4 years	5 years
OAK (docetaxel)		21%*			
POPLAR (docetaxel)		17%	10%*		
NLCA (Beckett P, 2013)		7%	4%	-	3%
Flatiron-database N=797 (Roche, 2017)		14.4%	10.3%	6.2%	3.7%
Parametric distributions	KM+Exponential	17.4%	7.3%	3.1%	1.3%
	KM+Weibull	16.4%	4.6%	1.2%	0.3%
	KM+Log normal	17.9%	9.8%	6.0%	3.9%
	KM+Gamma	17.1%	6.8%	2.8%	1.3%
	KM+Log logistic	17.8%	9.7%	6.2%	4.3%
	KM+Gompertz	16.5%	4.3%	0.8%	0.1%

Company preferred extrapolation for docetaxel arm

*Subject to significant cross-over

Company results for PD-L1 negative population (TC/IC0)

	Total costs	Total QALYS	Inc. costs	Inc. QALYs	ICER
Company basecase (no stopping rule, on-going treatment effect, with switching adjustment)					
Docetaxel	£20,842	0.77			-
Atezolizumab	[redacted]	1.27	[redacted]	0.50	[redacted]
1. 2 year stopping rule					
Docetaxel	£20,842	0.77			-
Atezolizumab	[redacted]	1.27	[redacted]	0.50	[redacted]
2. 3-year treatment effect					
Docetaxel	£20,842	0.77			-
Atezolizumab	[redacted]	1.09	[redacted]	0.32	[redacted]
3. Include cost of testing in atezolizumab arm					
Docetaxel	£20,842	0.77			-
Atezolizumab	[redacted]	1.27	[redacted]	0.50	[redacted]
Committee preferred assumptions (1+2+3+most plausible OS curve [piecewise])					
Docetaxel	£19,856	0.67			-
Atezolizumab	[redacted]	0.99	[redacted]	0.31	[redacted]

ERG comments on company's PD-L1 subgroup CE analyses

- company has continued to use data from the primary population of OAK in their economic model.
- all results presented by the company have been developed using the same OAK trial effectiveness data that were used to generate the cost effectiveness results presented in the February 2017 company submission
- The ERG considers that the changes made to the models to examine the PD-L1 subgroups are technically correct
- The ERG noted that for the PD-L1 **positive** subgroup CE analyses the company's ITC had showed that atezolizumab was non-inferior to pembrolizumab (in terms of survival) – therefore the ERG was surprised to note that the company's QALY estimates for this comparison generally suggest that, over a patient lifetime, treatment with atezolizumab generates more QALYs than treatment with pembrolizumab

End of life considerations

People with NSCLC have a life expectancy of less than 24 months (median survival 7.5 months for stage IIIb and 3.4 months for stage IV NSCLC)

Population	Comparator	Difference in OS	ACD 2: Criteria Met?
Company ITT	Docetaxel	3.5 months compared with docetaxel.	Yes
	Nintedanib +Docetaxel	no difference in OS from the indirect analysis (3.33 months [95% CI −0.16 to 6.74])	No.
PD-L1 positive	Pembrolizumab	Data from company's ITC suggests no difference between atezolizumab and pembrolizumab	??
PD-L1 negative	Docetaxel	3.7 months* (HR 0.75 [95% CI 0.59-0.96]) compared with docetaxel	??
	Nintedanib +Docetaxel	No new data presented	??

*The PD-L1 subgroups use different OS extrapolation to ITT

Key issues for consideration

- Nintedanib + docetaxel established use in NHS in England – comparator?
- Population comparisons and subgroups for decision-making
  - Are analyses comparing atezolizumab with docetaxel in the full ITT/all comers population appropriate given:
    - Company new evidence/analyses for PD-L1 positive and negative expressers provided using the appropriate subgroup comparators
- Most plausible OS extrapolation
- Is a treatment stopping rule needed?
- Duration of continued treatment effect after stopping atezolizumab
- ITC of atezolizumab compared with pembrolizumab
  - evidence robustness
  - similar/ improved clinical efficacy?
- Most plausible ICERs with revised atezolizumab PAS for atezolizumab compared with:Docetaxel
  - nintedanib + docetaxel
  - pembrolizumab
- End of life criteria for:
  - PD-L1 positives
  - PD-L1 negatives
- Cancer Drug Fund considerations
- Potential Equality issues