Chair's presentation

Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-based chemotherapy

2nd Appraisal Committee meeting

Committee D

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ERG: Southampton HTA Centre

NICE technical team: Ross Dent, Ian Watson

Company: Roche

Date: 23 November 2017

For projector and public observers

Atezolizumab (Tecentriq), Roche

Mechanism of action	Monoclonal antibody that binds to and inactivates PD-L1 leading to activation of immune response
Marketing authorisation	• For the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy or who are considered cisplatin ineligible • Had early access to medicines scheme status for use in people who have had platinum-based chemotherapy
Administration and dose	• 1,200 mg intravenous infusion every 3 weeks until loss of clinical benefit or unmanageable toxicity

Comparators:

- Docetaxel, paclitaxel and best supportive care

Population for whom cisplatin is unsuitable considered separately – recommended as an option in the CDF

ACD preliminary recommendation:
Not recommended for mUC after platinum chemotherapy

Clinical effectiveness	• IMvigor 210 – Median overall survival: 7.9 months
	  ○ Difficult to assess relative treatment benefit as no control arm
	• Clinical experts: some people sustain a lasting response
	• Indirect comparison highly uncertain:
	  ○ STC did not account for all prognostic factors
	  ○ NMA based on sparse evidence networks
	• Atezolizumab appears to be effective but considerable uncertainty

Economic model	• OS extrapolation highly uncertain ○ Could fall between the company's generalised gamma (fitted to atezolizumab) and ERG's K–M + Weibull (fitted to comparator) – ERG's more clinically plausible • Treatment duration: more appropriate to use distribution which best fit the data • Treatment effect: not plausible to assume same treatment effect for people continuing atezolizumab after disease progression • Utilities: company base-case estimate implausibly high
End of life criteria	• Life expectancy <24 months, uncertain whether atezolizumab extends life by >3 months – most likely end of life criteria met

Most plausible ICERs

- Company base case: £98k to £131k (with-PAS: [redacted])
- ERG's preferred ICERs: £166k to £288k (with-PAS: [redacted])

- Most plausible ICERs higher than ERG's preferred ICERs, as they did not include all the committee's preferred assumptions:
  - ERG used a utility value of 0.71 for progressed disease (company scenario analysis with lower utility value increased ICERs)
  - people taking atezolizumab after disease progression assumed to have the same treatment benefit as those whose disease has not progressed (a lower treatment benefit would increase the ICERs)
  - problems with probabilistic sensitivity analysis meant that the ERG's ICERs were deterministic and did not appropriately reflect all the uncertainty (company's PSA increased ICERs by up to 20%)

Committee conclusions

- Most plausible ICERs higher than those usually considered a cost-effective use of NHS resources, even for end of life treatments
- No cost-effectiveness analyses based on PD-L1 expression
  - committee would have liked to see analyses to assess if there are any subgroups for whom atezolizumab could be cost-effective
- Did not meet the criteria for use in CDF – no plausible potential that atezolizumab could be cost-effective for previous chemotherapy (2nd line) population

ACD consultation responses

- Consultee comments from:
  - Roche – including new evidence and updated PAS
  - Action Bladder Cancer UK

Comments from patient and professional organisations

- There is an urgent need for new treatments for urothelial carcinoma, as 5-year survival rates are low and have not increased since 1980
- Atezolizumab has the potential to increase survival and offers the prospect of long term remission for around 20% of people with urothelial carcinoma
- Cost effectiveness modelling is unduly pessimistic and does not take into account atezolizumab's mechanism of action
- If atezolizumab is made available in the NHS, additional data collection could reduce the uncertainty about its effectiveness

Company: additional evidence
IMvigor 211

Description	• Multicentre, open-label, phase III trial • Atezolizumab (n=467) vs chemotherapy (n=464) • Investigator's choice of chemotherapy: vinflunine (n=242), docetaxel (n=148) or paclitaxel (n=53) • Stratification by factors including PD-L1 expression and chemotherapy: vinflunine vs. taxanes (docetaxel or paclitaxel)
Eligibility criteria	• Locally advanced or metastatic urothelial carcinoma with progression during or following a platinum-containing regimen • ≤2 prior lines of therapy • ECOG 0-1
Outcomes	1º: Overall survival, 2º: Objective response rate, progression-free survival, duration of response

Primary endpoint tested hierarchically:

- PD-L1≥5%, followed by PD-L1≥1%, then overall population
- Based on observation in uncontrolled studies that patients with higher PD-L1 expression experienced longer survival when taking atezolizumab

IMvigor 211 – Baseline characteristics

	Atezolizumab n=467	Chemotherapy n=464
Median age, years (range)	67 (33–88)	67 (31–84)
Male, %	76	78
ECOG 0, %	47	45
Haemoglobin <10 g/dL, %	14	16
Liver metastases, %	30	28
Primary tumour site, % Bladder Renal pelvis/ureter	69 27	73 24
0 prognostic risk factors, %	31	30
PD-L1 ≥5%, % 1≤ PD-L1 <5%, % PD-L1 <1%, %	25 43 32	25 41 33
Chemotherapy type: Docetaxel, % Paclitaxel, % Vinflunine, %	 - - -	 12 33 55

Prognostic risk factors: ECOG≥1, prior chemo <3 months, haemoglobin <10 g/dL

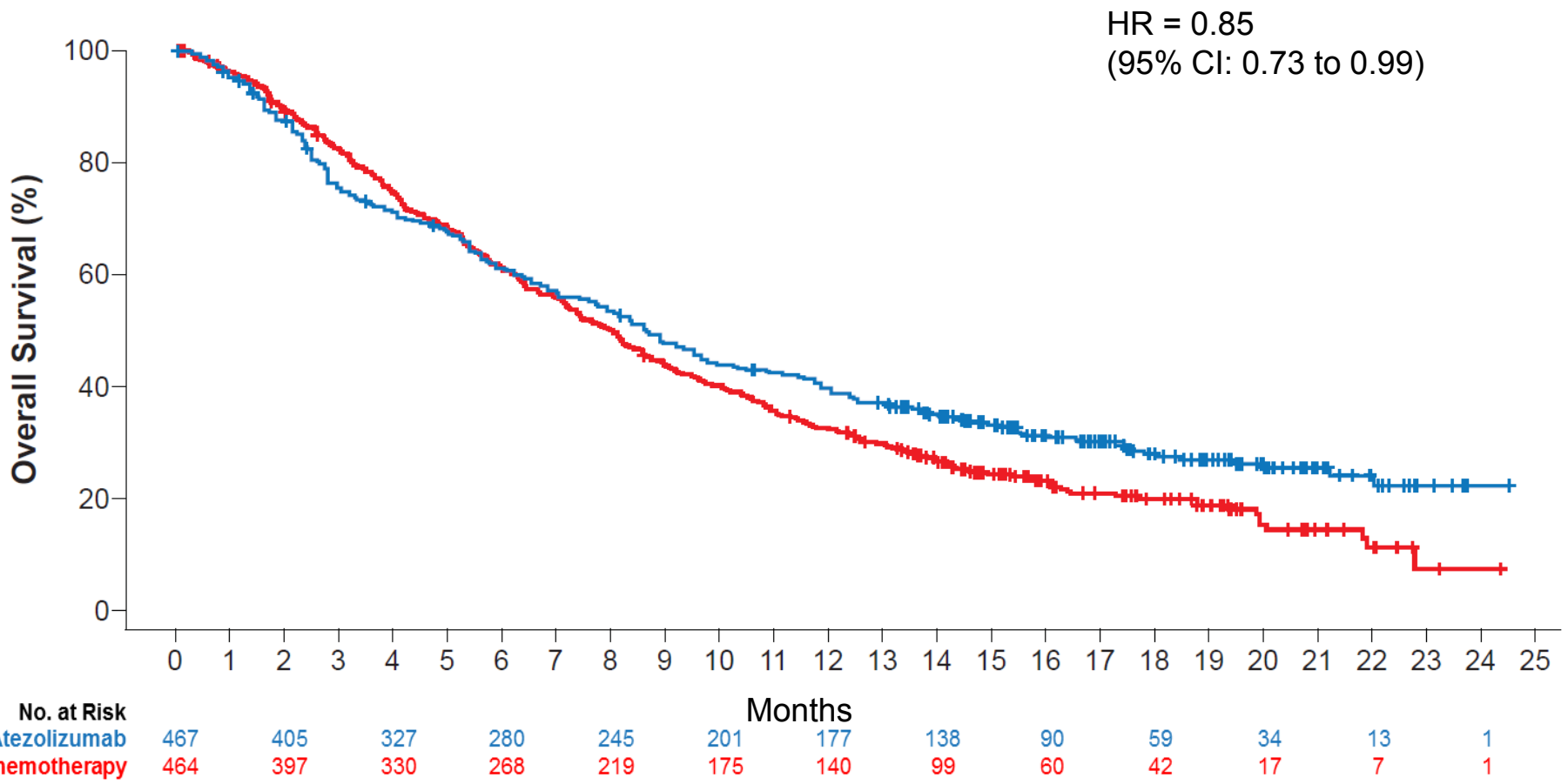
Results of IMvigor 211 (1)

	PD-L1≥5%		PD-L1≥1%		Overall population	
	Atezo n=116	Chemo n=118	Atezo n=316	Chemo n=309	Atezo n=467	Chemo n=464
Median OS, months 95% CI	11.1 8.6 to 15.5	10.6 8.4 to 12.2	8.9 8.2 to 10.9	8.2 7.4 to 9.5	8.6 7.8 to 9.6	8.0 7.2 to 8.6
OS HR 95% CI	0.87 0.63 to 1.21, p=0.41		0.87 0.71 to 1.05, p=0.14		0.85 0.73 to 0.99, p=0.038	
Median PFS, months 95% CI	2.4 2.1 to 4.2	4.2 3.7 to 5.0	2.1 2.1 to 2.2	4.1 3.6 to 4.2	2.1 2.1 to 2.2	4.0 3.4 to 4.2
ORR	23%	22%	14%	15%	13%	13%
Median DOR, months	15.9	8.3	15.9	8.3	21.7	7.4
Ongoing responders	[redacted]	[redacted]	[redacted]	[redacted]	63%	21%

Abbreviations: OS, overall survival; CI, confidence interval; HR, hazard ratio; PFS, progression free survival; ORR, objective response rate DOR, duration of response

1º endpoint: difference in median OS in PD-L1≥5% arm not stats. significant (p=0.41)

IMvigor 211 OS: overall population



Results of IMvigor 211 (2)

Company:

- Primary endpoint an underpowered comparison of 2 groups with good prognosis
- Overall population more meaningful: OS HR is similar to that for the PD-L1 sub-groups but larger population gives greater statistical power
- Although anticipated predictive value of PD-L1 was not seen in trial, results are similar to earlier studies (12 month overall survival 39% vs. 37% in IMvigor 210)

ERG comments on trial:

- Well-conducted trial, although note that it was open-label
- No obvious imbalances that are likely to be of prognostic importance
- The hazard ratios are unlikely to accurately represent the underlying hazard functions, as hazards are not proportional (K-M curves cross)
- Objective response rate similar between the atezolizumab and chemotherapy arms, but median duration of response longer with atezolizumab
- Responses to atezolizumab durable regardless of PD-L1 status

Results of IMvigor 211 (3)

Exploratory analyses: atezolizumab vs taxanes and vs vinflunine

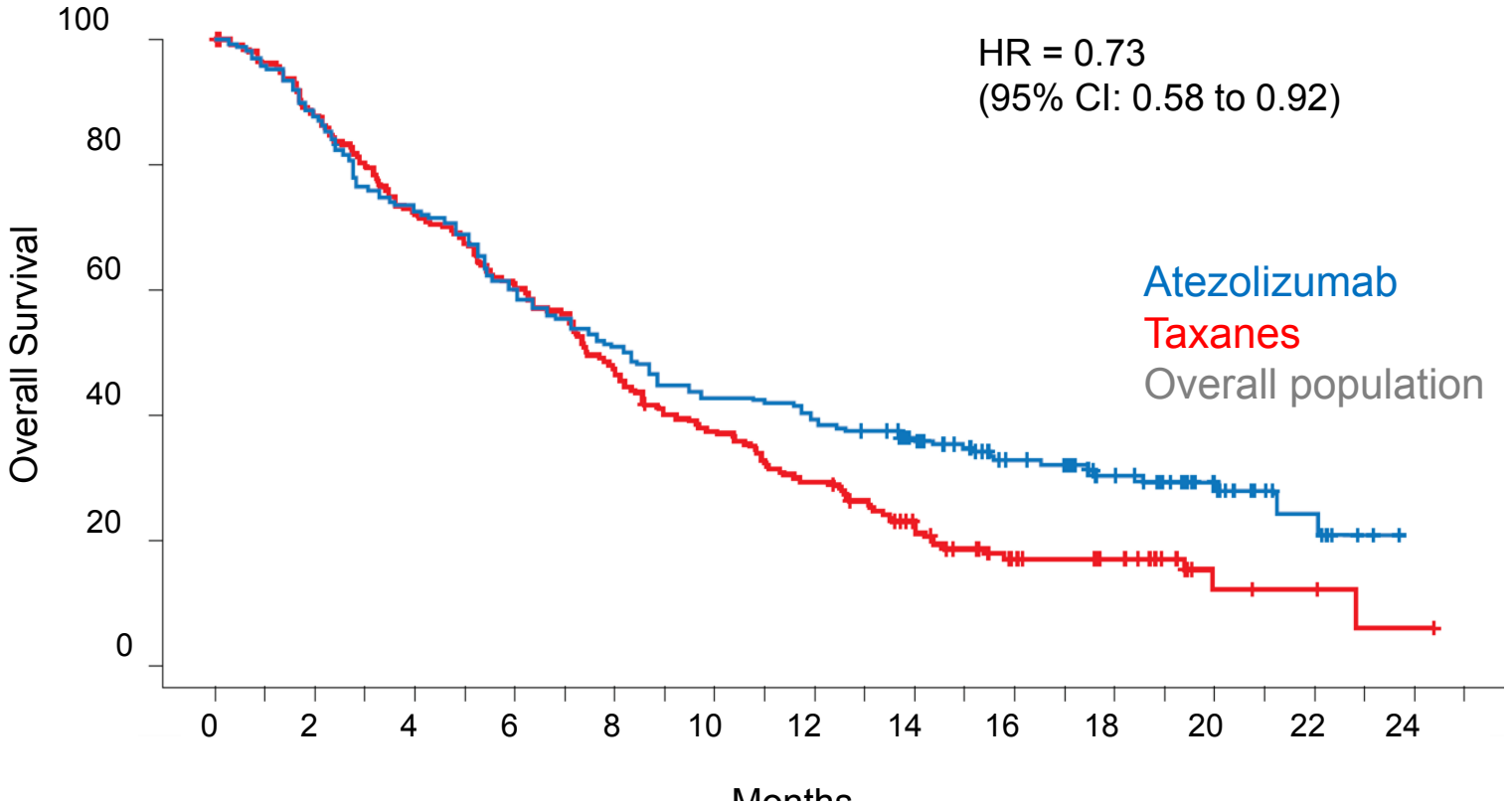
	Atezolizumab n=215	Taxanes n=214
Median OS, months **95% CI**	8.3 6.6 to 9.8	7.5 6.7 to 8.6
OS HR **95% CI**	0.73 0.58 to 0.92	
Median PFS, months **95% CI**	2.1 2.1 to 2.3	3.7 2.2 to 4.1
PFS HR **95% CI**	1.00 0.81 to 1.23	

- Compared with vinflunine:
  - median OS 9.2 months vs 8.3 months, HR 0.97 (0.78 to 1.19)
  - median PFS 2.1 months vs 4.1 months, HR 1.19 (0.98 to 1.44)
- Company: vinflunine OS higher than expected – vinflunine phase III trial, 6.9 months and no statistically significant improvement compared to BSC

Adverse events

- No new safety issues
- Fewer patients in the atezolizumab arm had Grade 3/4 treatment-related AEs (20% vs 43%) or discontinued due to AEs (7% vs 18%)
- **ERG**: atezolizumab has a more favourable safety profile than the taxanes

IMvigor 211 – overall survival
Exploratory analyses atezolizumab vs. taxanes



No. at Risk													
Atezolizumab	215	186	153	125	106	89	81	66	45	34	19	7	0
Taxane	214	179	147	122	94	74	58	35	20	16	4	3	1

Revised economic model (1)

- Analyses vs. pooled taxanes only using data from IMvigor 211
  - company: vinflunine not used in NHS, comparison with taxanes most relevant
  - no comparison with best supportive care
  - no analyses by PD-L1 status presented
- To extrapolate OS and PFS, separate models fitted to each arm, as proportional hazards assumption does not hold

Extrapolation	Justification
PFS: K–M curves + tails extrapolated using generalised gamma	• best fit to atezolizumab data • 2nd best fit to taxane data, but observed PFS data almost complete, so distribution has limited effect
OS: generalised gamma distribution, mix-cure rate model for atezolizumab	• best fit for atezolizumab and taxanes • mix-cure rate model means extrapolated tail never higher than background mortality
Treatment duration: K–M curves + tails extrapolated using generalised gamma	• best fit to overall data and taxanes • log-logistic best fit to atezolizumab data, but extrapolation crosses OS curve

Revised economic model (2)

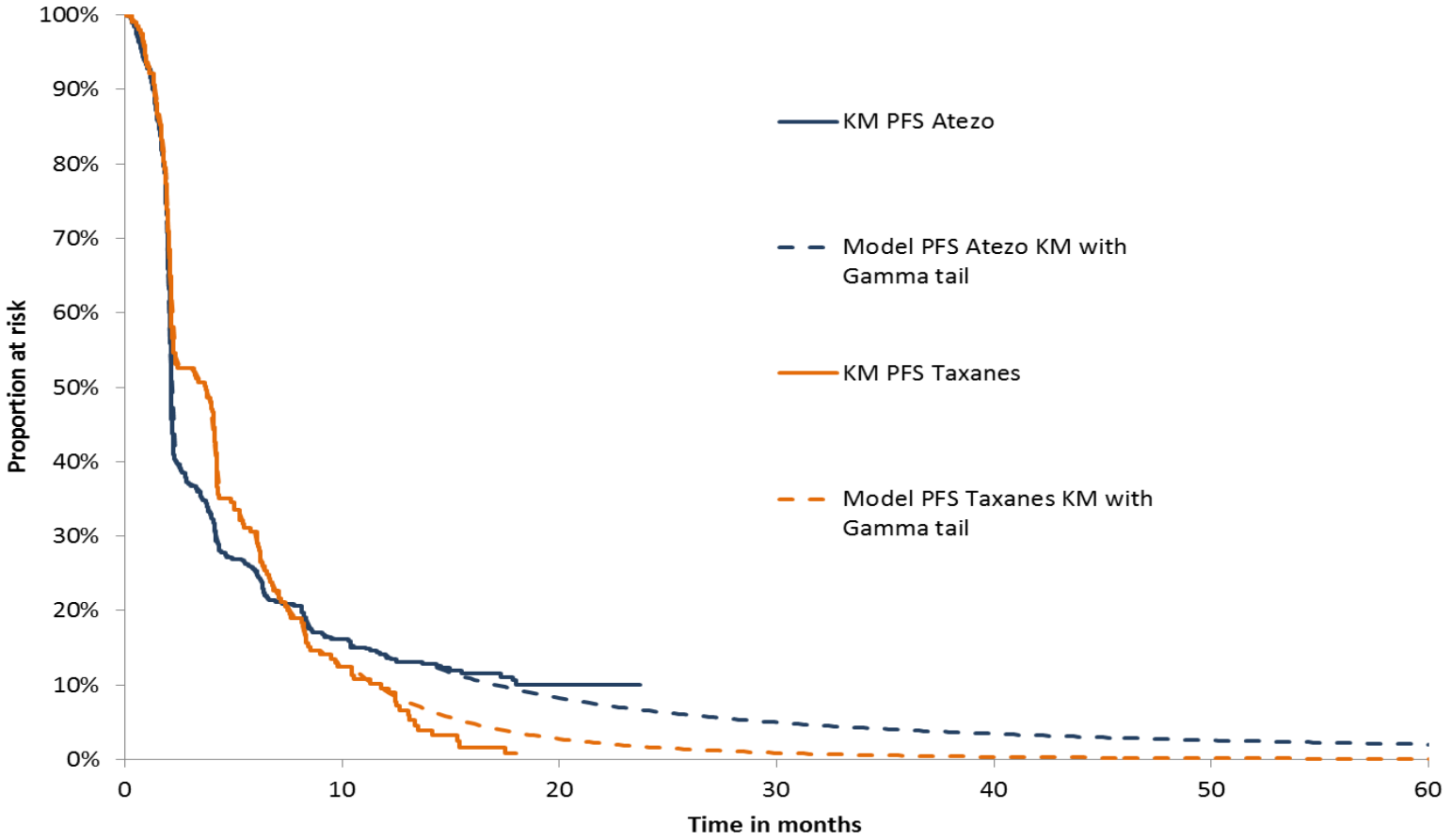
- Adverse event and health-related quality of life data from IMvigor 211
  - grade 3+ treatment related adverse events with an incidence ≥2% included
  - treatment can continue beyond progression, so utilities relate to on- or off-treatment rather than progression-free and progressed disease

	IMvigor 211		Original submission	
Utilities	**Atezolizumab**	**Taxanes**	**Atezolizumab**	**Comparators**
On treatment	0.68	0.66	0.75	0.75
Off treatment	0.55	0.55	0.71	0.75

ERG comment on utilities

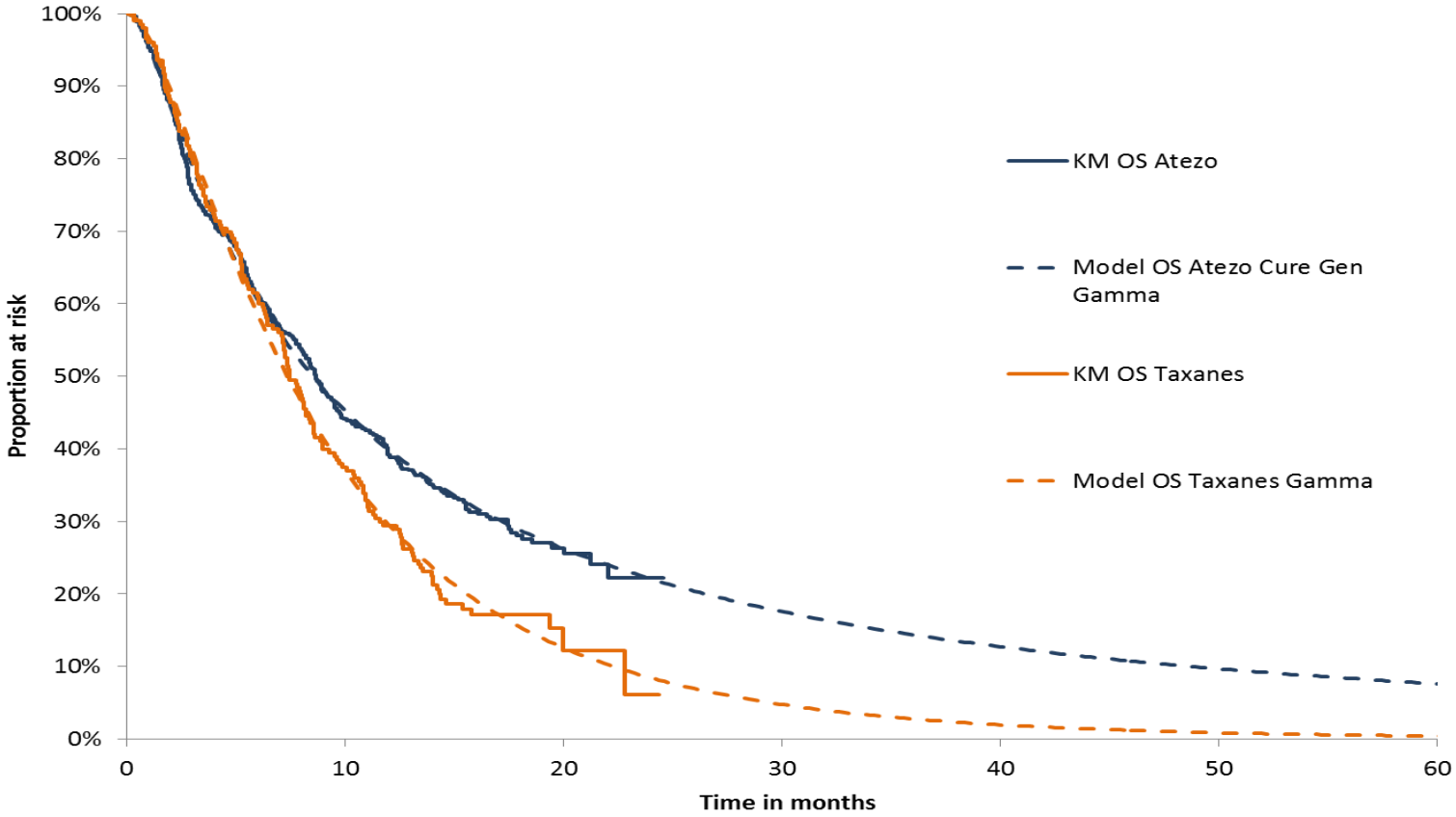
- Company presented limited data and its not clear how well the point estimates capture the EQ–5D scores – they may vary in relation to time on treatment
- More appropriate than the values used in the original submission

Company PFS extrapolation



Atezolizumab PFS	IMvigor 211 (phase III)	IMvigor 210: 2L (phase II)	Model
Median	2.1 months	2.1 months	2.06 months
12 months	Not reported	Not reported	12.0%

Company overall survival extrapolation



Atezolizumab OS	Clinical experts	Model
5 year	10–20%	7.7%
10 year	5–10%	2.7%
20 year	0–5%	0.7%

Company's results
*list price**

	Total costs	Incremental costs	Total QALYs	Incremental QALYs	Deterministic ICER
Taxanes	£10,253	-	0.49	-	-
Atezolizumab	£54,573	£44,321	0.93	0.44	£100,844
					Probabilistic ICER: £101,319

Overview of scenario analyses	Deterministic ICER
Base case	£100,844
Alternative OS extrapolations	£101,156 to £129,338
Alternative PFS extrapolations	£100,946 to £101,669
Time to treatment discontinuation extrapolations	£106,133 to £136,334
Comparison against paclitaxel alone (more commonly used in NHS than docetaxel)	£110,403
Utility values from pembrolizumab for 2L mUC appraisal (PFS, 0.73; progressed disease, 0.64)	£91,653

**The company's Patient Access Scheme is confidential; results using the PAS will be shown to committee in Part 2*

ERG critique of PFS and time to treatment discontinuation extrapolations

PFS:

- Company approach is appropriate, but taxane data is mature, so there is no need to extrapolate; the K-M data can be used alone and has little impact on ICER

Time to treatment discontinuation:

- Company use distribution that best fits overall and taxane data, and not the log-logistic which best fits atezolizumab as resulting extrapolation crosses OS curve
  - ERG do not agree that extrapolated curves cross
  - taxane data is mature, so K-M data alone can be used without extrapolation
  - log-logistic fits atezolizumab data best, so this should be used
- Effect of using log-logistic distribution is greater proportion of people on treatment in later years, increasing costs and QALYs (higher utility value for on-treatment)

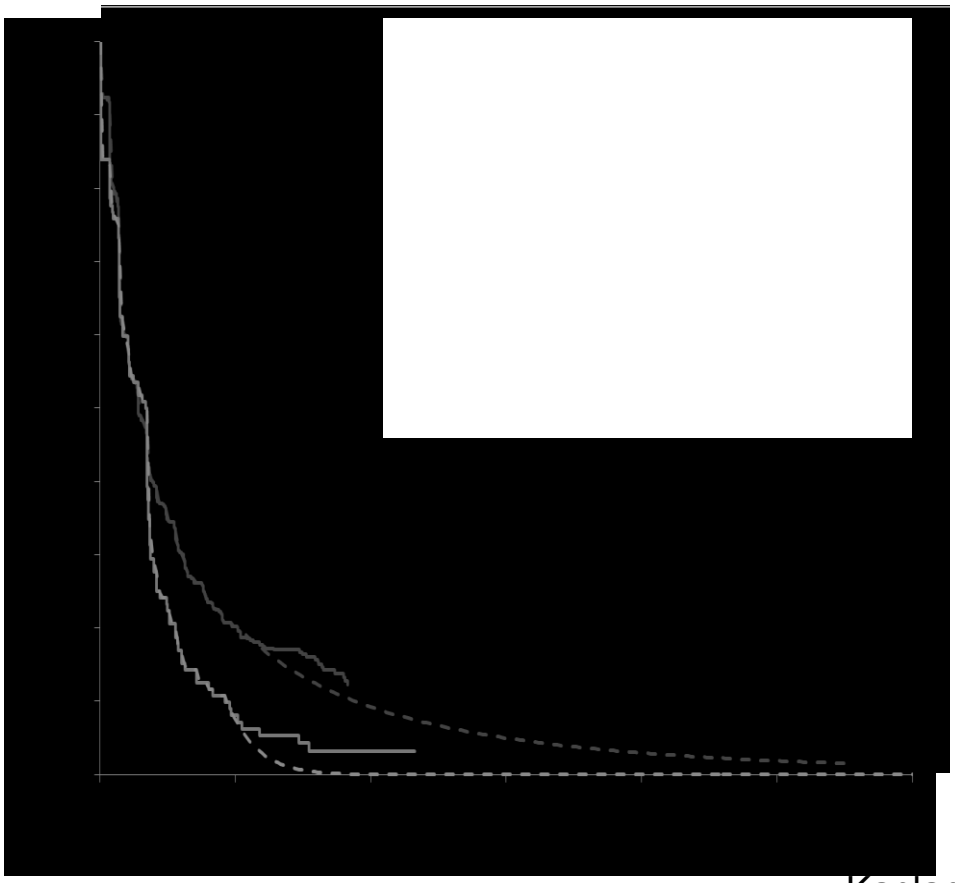
On-treatment	Company	ERG
2 years	7.1%	9.6%
3 years	3.6%	6.5%
5 years	1.2%	4.0%

ERG critique of OS extrapolation

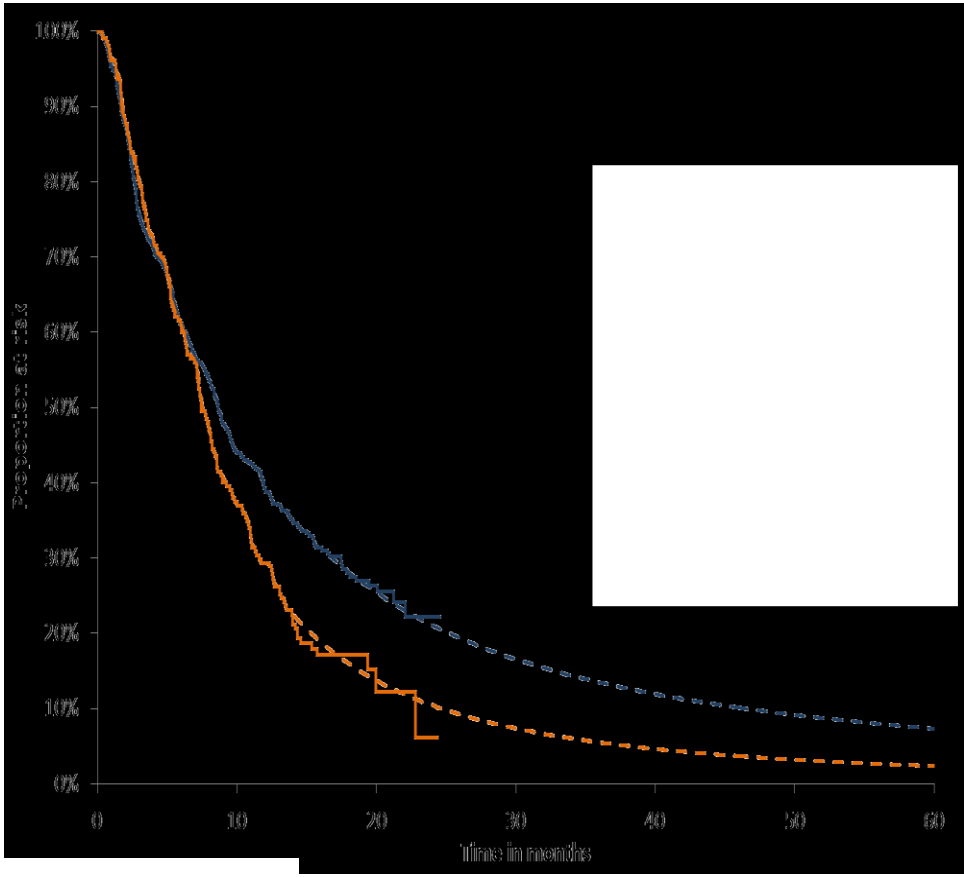
- Company's generalised gamma predicts lower OS for taxanes at year 5 than predicted by expert opinion (0.4% vs 2–3%)
- Using log-logistic distribution instead leads to a more plausible estimate at year 5 (2.4%)
- Extrapolation of atezolizumab data using K–M + log-logistic distribution has a similar visual fit to company's choice of fully parametric generalised gamma (mix cure rate model)
  - proportion alive at 5 years similar: 7.3% (log-logistic) vs. 7.6% (company base case)
  - ERG proposes to extrapolate tail from point when 20% of patients remain at risk
- Effect on atezolizumab QALYs is minimal, but taxane QALYs increase, reducing the incremental QALYs

Company vs ERG extrapolations

Time to discontinuation



Overall survival



Kaplan–Meier

Company extrapolation

ERG extrapolation

ERG's exploratory analysis and preferred analysis ***list price****, deterministic analysis

ERGs preferred analysis includes the following changes to the company's base case

a) Taxane PFS curve uses the K–M data only without extrapolation
b) Time to treatment discontinuation: uses K–M data only without extrapolation for taxanes, and the K–M with the tail extrapolated using the log-logistic distribution for atezolizumab
c) OS curves use the K–M data with the tails extrapolated using the log-logistic distribution from the point of 20% of patients at risk

	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Company base case (deterministic)	£44,321	0.44	£100,844
ERG preferred analysis	£61,492	0.40	£154,282

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End of life and CDF

End of life

- ACD conclusion:
  - life expectancy <24 months
  - uncertain whether atezolizumab extends life by >3 months
  - most likely end of life criteria met
- Data based on IMvigor 211 used in company's updated economic model

	Mean OS *(company extrapolation)*	Median OS
Atezolizumab	18.6 months	8.5 months
Taxanes	10.2 months	7.4 months

- ERG predicts that extension in survival with atezolizumab is 8.2 months

Cancer Drugs Fund

- ACD conclusion:
  - no plausible potential for atezolizumab to be cost effective
  - uncertainties could be addressed through the ongoing IMvigor 211 trial
- No CDF proposal submitted by company

Key issues

- Effectiveness of atezolizumab compared with taxanes
  - For overall population and PD-L1 subgroups
- No comparison with best supportive care
- Cost effectiveness analyses
  - Treatment duration extrapolation
  - Overall survival extrapolation
  - Most plausible ICER
- Any health-related benefits not captured

Back-up slides

ERG's exploratory analysis and preferred analysis ***with PAS***, deterministic analysis Effect of individual assumptions

- **ERG preferred assumptions**

	Incr costs	Incr QALYs	ICER (£/QALY)
Company base case	[redacted]	0.44	[redacted]
a) PFS: K–M only for taxanes	[redacted]	0.44	[redacted]
b) TTD: K–M only for taxanes, K–M + log-logistic for atezolizumab	[redacted]	0.47	[redacted]
c) OS: K–M + log-logistic tail from 20% at risk	[redacted]	0.36	[redacted]
ERG preferred analysis a+b+c	[redacted]	0.40	[redacted]

- **Overall survival (ICER, £/QALY)**

	Parametric	Tail extrapolated from 20% at risk	Tail extrapolated from 30% at risk
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]