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Chair's presentation

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

3rd Appraisal Committee meeting

Committee D

Lead team: Rebecca Harmston, Sumithra Maheswaran and David Meads

ERG: Southampton HTA Centre

NICE technical team: Ross Dent, Ian Watson

Company: Roche

Date: 6 February 2018

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 (TA492)

ACD preliminary recommendation:
Not recommended for mUC after platinum chemotherapy

Clinical effectiveness	• Data from IMvigor 211 comparing atezolizumab with chemotherapy (docetaxel, paclitaxel or vinflunine)
	  ○ Median OS in overall population higher than with chemotherapy (8.6 months vs. 8.0 months, HR 0.85, p<0.05)
	• Vinflunine not used in NHS, company presented taxane comparison
	  ○ Median OS 8.3 months vs. 7.5 months (HR 0.73, p<0.05)
	• Committee concluded that comparison with taxanes relevant for decision-making and atezolizumab is an effective treatment option

Economic model	• PFS: taxane PFS data mature and do not need to be extrapolated • OS: K–M curves extrapolated with a log-logistic distribution produce more plausible estimates for taxanes ○ 2.4% alive at 5 years vs. 0.4% in company base case • Time to treatment discontinuation: log-logistic distribution should be used to extrapolate atezolizumab data as it fits best
End of life criteria	• Life expectancy around 12 months; company's and ERG's models predict atezolizumab extends life by a mean of around 8 months
ICERs	• Company base case: £100,844 (with-PAS: [redacted]) • ERG's preferred ICER: £154,282 (with-PAS: [redacted])

Committee conclusions

- ERG's analysis reflects committee's preferred assumptions
- Most plausible ICER higher than those usually considered a cost-effective use of NHS resources, even for end of life treatments
- The committee could not make recommendations for subgroups based on PD-L1 expression because cost-effectiveness analyses were not provided
- Atezolizumab did not meet the criteria for use in CDF – no plausible potential that it could be cost-effective after previous platinum-containing chemotherapy

ACD consultation response: company

- **Committee concluded it could not consider any stopping rules**
  - such a rule would be arbitrary, as there were no stopping rule in the clinical trial and no evidence that a stopping rule benefits patients
- **Committee was concerned there was no standard definition of loss of clinical efficacy**
  - loss of clinical efficacy clearly defined in the clinical trial
  - e.g. stabilisation/improvement of disease-related symptoms, no symptoms and signs of disease progression, no decline in ECOG
- **Committee concerned HRs may not reflect the effectiveness of atezolizumab as OS K-M curves cross so hazards not proportional**
  - economic model does not rely on proportional hazards, separate parametric models used to account for non-proportional hazards

ACD consultation response: company
Modelling overall survival

Committee conclusion: ERG's approach to modelling OS produces estimates for the taxanes more in line with clinical expert expectation (2-3% alive at 5 years)

- company approach: 0.4% of patients alive in taxane arm at 5 years
- ERG approach: 2.4% of patients alive in taxane arm at 5 years

- ERG approach is based only on validation against expert opinion
- Disregards IMvigor 211 data and no assessment of statistical or visual fit
- Selects the most optimistic distribution for the taxane data
- Company approach makes best use of the available trial data and follows DSU guidance on fitting survival models
- Using committee's preferred assumptions about PFS and time to treatment discontinuation with company's original OS extrapolation:
  - ICER £131,427 at list price and [redacted] at PAS price

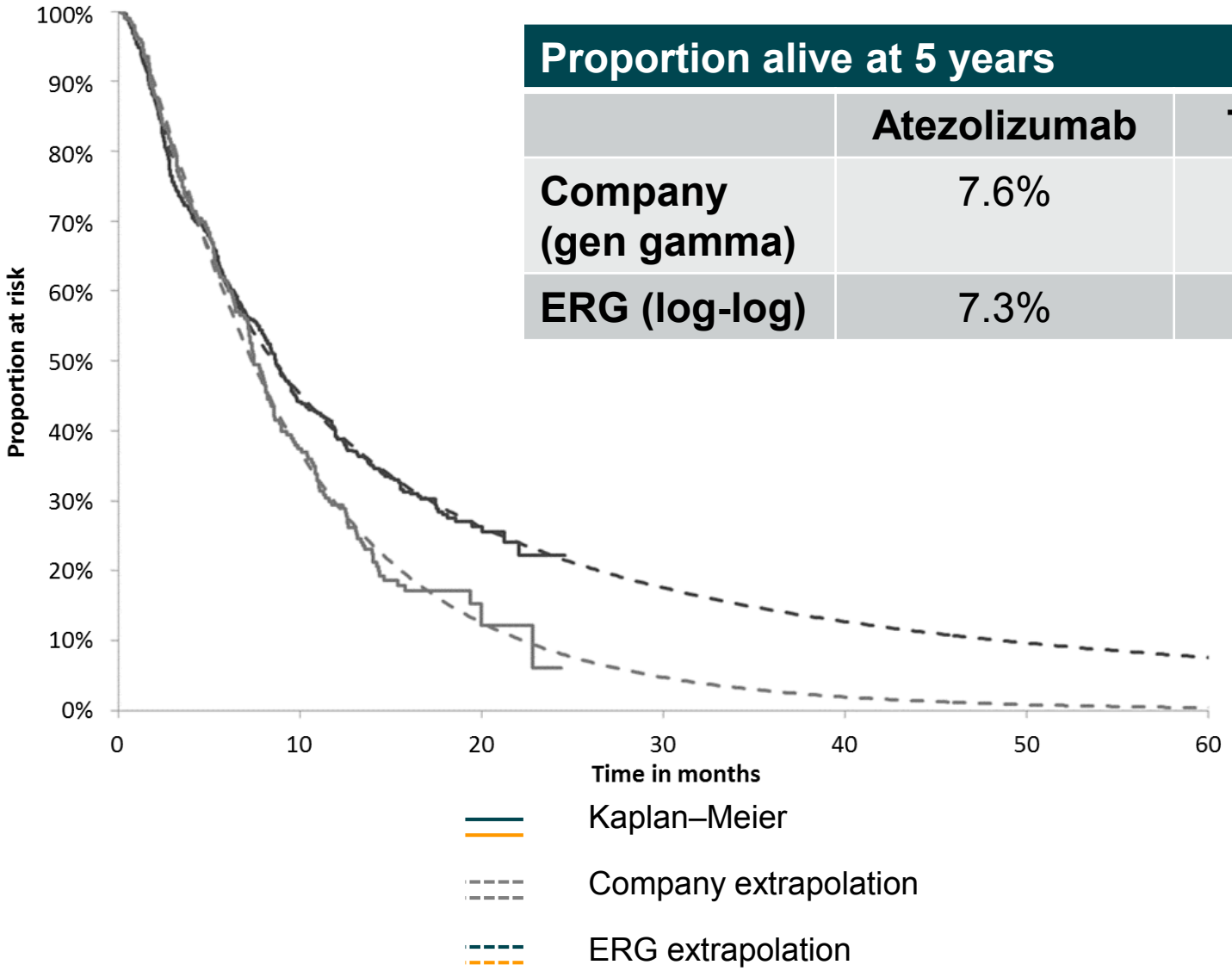
OS extrapolation

- **Company**: generalised gamma best fit for atezolizumab and taxanes

	Atezolizumab		Taxanes	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	715.13 (7)	719.28 (7)	563.20 (6)	566.57 (5)
Weibull	715.10 (6)	719.25 (6)	553.41 (4)	560.14 (3)
Log-logistic	**696.08 (3)**	**700.23 (3)**	**550.81 (2)**	**557.54 (1)**
Log-normal	687.67 (2)	691.82 (2)	552.01 (3)	558.74 (2)
Gompertz	710.58 (4)	714.73 (4)	561.07 (5)	567.81 (6)
Gamma	714.36 (5)	718.50 (5)	NR	NR
Generalised gamma	**686.89 (1)**	**691.04 (1)**	**550.75 (1)**	**560.85 (4)**

- **ERG:** Log-logistic gives more plausible estimate for taxanes: 2.4% at year 5
- Atezolizumab OS extrapolation using log-logistic distribution has similar visual fit and predicts similar proportion alive at 5 years as company
- Company did not challenge committee's preferred distribution for TTD extrapolation (log-logistic), but previously noted atezolizumab curves meet when this is combined with generalised gamma for OS, which is implausible

Company vs ERG extrapolations
Overall survival



Proportion alive at 5 years		
	Atezolizumab	**Taxanes**
Company (gen gamma)	7.6%	0.4%
ERG (log-log)	7.3%	2.4%

Key issues

- Has the committee seen any evidence to change its view about the most appropriate OS extrapolation?

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Chair's presentation

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

4th Appraisal Committee meeting

Committee D

Lead team: Rebecca Harmston, Sumithra Maheswaran and David Meads

ERG: Southampton HTA Centre

NICE technical team: Ross Dent, Lulieth Torres

Company: Roche

Date: 11 April 2018

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 • 1,200 mg IV every 3 weeks until loss of clinical benefit or unmanageable toxicity

- ACM1- April 2017 Atezolizumab is not recommended
- Sept 2017 Additional clinical evidence submitted
- ACM2- Nov 2017 Atezolizumab is not recommended
- ACM3- Feb 2018 FAD suspended because company requested to submit new evidence.
- ACM4- Apr 2018

Population for whom cisplatin is unsuitable considered separately – recommended as an option in the CDF (TA492)

ACD preliminary recommendation:
Not recommended for mUC after platinum chemotherapy

Clinical effectiveness	• IMvigor 211 compared atezolizumab with chemotherapy • Atezolizumab vs taxanes: median OS 8.3 months vs. 7.5 months (HR 0.73, p<0.05) – effective treatment option
Economic model	• Key issues: extrapolation of PFS, OS and time to discontinuation
End of life	• Life expectancy around 12 months; mean life extension ~8 months
ICERs	• Company base case: £100,844 (with-PAS: [redacted]) • ERG's preferred ICER: £154,282 (with-PAS: [redacted])

- ERG's analysis reflects committee's preferred assumptions
- Most plausible ICER higher than those usually considered cost-effective, even for end of life treatments
- Unable to consider a 'stopping rule' – not included in clinical evidence and not proposed by company
- Did not meet the criteria for use in CDF – no plausible potential that it could be cost-effective

New evidence

- Updated confidential simple discount
- Cost-effectiveness estimates based on committee's preferred assumptions
- 2-year stopping rule
  - Consistent with the appraisal of atezolizumab in second-line NSCLC [ID970] and other immunotherapies
  - Noted the lack of clinical evidence for benefit to patients in the long term
  - However, it would allow patients to access atezolizumab – valuable alternative to taxane chemotherapy
- Cap on duration of treatment benefit
  - Previous recommendations have concluded that it is inappropriate to implement a stopping rule while assuming lifetime treatment benefit

Cost-effectiveness estimates

	Total Cost	Incr. Costs	Total QALYs	Incr. QALYs	ICER
Committee-preferred analysis; updated discount					
Atezolizumab	[redacted]	[redacted]	0.97	0.40	[redacted]
Taxanes	[redacted]	-	0.57	-	-
Scenarios: Committee-preferred analysis; updated discount, 2-year stopping rule; cap on duration of treatment effect					
Life time treatment effect	[redacted]	[redacted]	0.97	0.40	[redacted]
Taxanes	[redacted]	-	0.57	-	-
3 year treatment effect after stopping rule	[redacted]	[redacted]	0.94	0.36	[redacted]
Taxanes	[redacted]	-	0.57	-	-
5 year treatment effect after stopping rule	[redacted]	[redacted]	0.95	0.38	[redacted]
Taxanes	[redacted]	-	0.57	-	-
Company considered the analysis with 2- year stopping rule and 3- year cap to be its preferred base case, ICER [redacted]					
Source: Adapted from table 1 to 4, page 2 and 3, company's additional analyses					

Stopping rules: previous committee considerations (1)

- Stopping rules are included in the recommendations for 7 out of 18 published and ongoing technology appraisals for PD-1/PD-L1 inhibitors*
  - Of the remainder:
    - 2 appraisals: committee accepted a stopping rule, but the technology was not recommended
    - 3 appraisals: committee concluded that stopping rules were inappropriate or could not be considered
    - 1 appraisal: committee considered cost effectiveness both with and without a stopping rule

- Committee considerations have concentrated on:
  - Marketing authorisations for the technologies
  - Inclusion of maximum durations in clinical trial protocols
  - Impact on treatment costs
  - Impact on clinical effectiveness
  - Implementation of the stopping rule

**Includes appraisals for nivolumab, pembrolizumab, atezolizumab and avelumab for which published ACDs or FADs are available*

Stopping rules: previous committee considerations (2)

- Current appraisal: considerations in the ACD
  - Evidence did not include a stopping rule; none had been proposed
  - "[Committee] was not able to consider any such rule in decision-making"

- Other appraisals in urothelial cancer:
  - Nivolumab (FAD, suspended): "2-year treatment stopping rule reduced costs…but the impact on long-term efficacy is unknown"
  - Pembrolizumab (FAD): recommended only if pembrolizumab is stopped at 2 years
    - "2-year stopping rule…is appropriate" – consistent with trial

- Other appraisals of atezolizumab:
  - For untreated urothelial cancer (TA492): no consideration of a stopping rule
  - For non-small-cell lung cancer (FAD): recommended only if atezolizumab is stopped at 2 years
    - "No clear data showing that continuing treatment is not beneficial in the absence of disease progression" but "growing concern among clinicians about the use of immunotherapies beyond 2 years"
    - Stopping rule not in MA, but has been included in previous NICE guidance for NSCLC – "concluded that it would prefer a 2-year stopping rule"
    - "The Cancer Drugs Fund clinical lead clarified that a 2-year stopping rule is acceptable to both patients and clinicians, and would be implementable"

Duration of treatment effect after discontinuation: previous committee considerations

- 6 of the appraisals that included stopping rules included explicit consideration of the duration of treatment effect after discontinuation
- Committees consistently highlighted that the duration of effect was uncertain, and/or lifelong benefit after discontinuation is implausible
- Atezolizumab for non-small-cell lung cancer (FAD):
  - "A lifetime treatment effect for atezolizumab is implausible"
  - "Treatment effect was unlikely to last more than 5 years after treatment had stopped…the length of any continued effect was uncertain"
- Nivolumab for urothelial cancer (FAD, suspended):
  - "Assumption of a lifetime treatment benefit is implausible"
- Pembrolizumab for urothelial cancer (FAD):
  - "Aware that the duration of continued treatment effect after implementation of a stopping rule is an area of uncertainty"
  - "Concluded that a lifetime continued treatment effect was implausible"

Cancer Drugs Fund

- When the uncertainty in clinical and cost effectiveness data is too great to recommend for routine use, the committee can recommend in CDF if:
  - ICERs have plausible potential to be cost-effective
  - Clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS
  - Data collected (including research underway) will be able to inform subsequent update (normally within 24 months)
- ACD: Atezolizumab did not meet the criteria for use in CDF
  - Although ongoing data collection in IMvigor 211 could help address some uncertainties, no plausible potential that it could be cost-effective
- In its new evidence, company did not propose that atezolizumab is considered for the CDF

Key issues

- 2-year stopping rule
- Duration of continued treatment effect – 3 or 5 years after discontinuation
- Most plausible ICER
- Consideration for use in the CDF?