NICE National Institute for Health and Care Excellence

Public handouts (ACIC fully redacted)

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy

Chairs' presentation

ERG: Health Economics Research Unit and Health Services Research Unit, University of Aberdeen

Chair: Lindsay Smith

Technical team: Vicky Gillis-Elliott, Sally Doss, Ross Dent

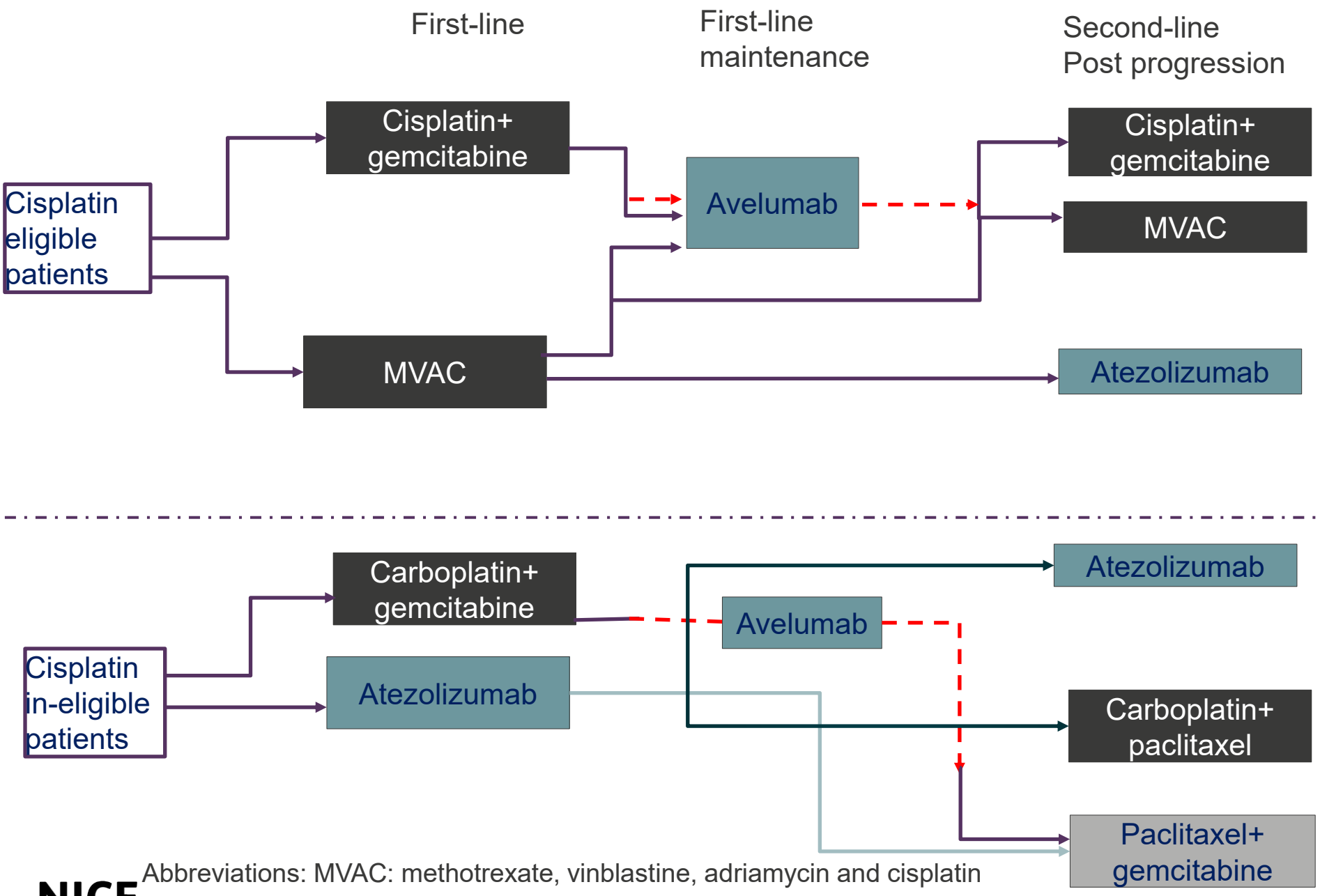
Company: Merck Serono

Second committee meeting 17th June 2021

Key issues

- Should a 2 year stopping rule be applied?
- Should a treatment benefit cap be applied?
- Should the mean or median be used to assess short life expectancy?
- Does avelumab meet the short-life expectancy criterion?
- Should health state utility values be pooled across treatment arms?
- Is avelumab innovative – are there any benefits not captured in the modelling?

Proposed position of avelumab in pathway



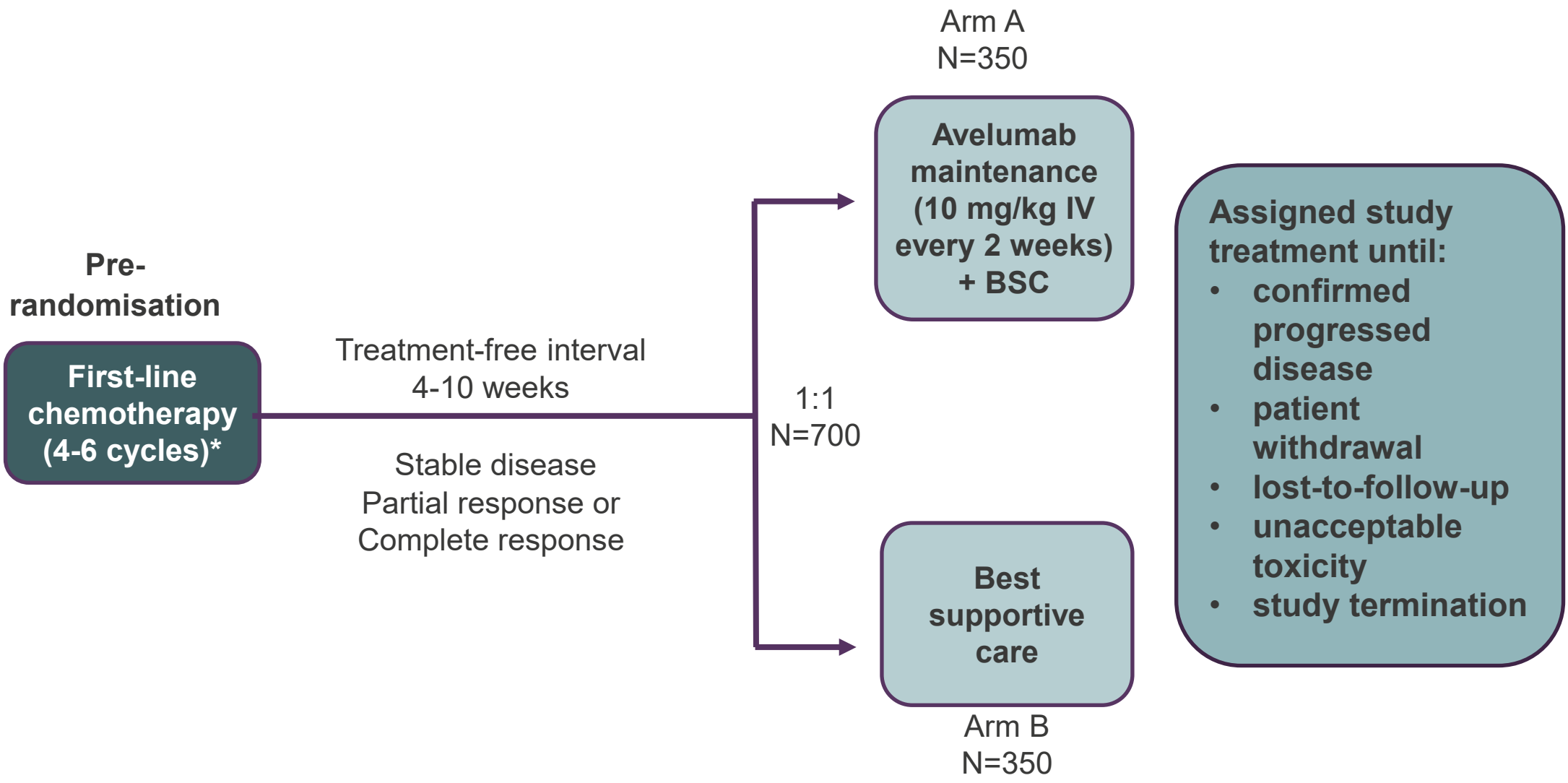
Avelumab (Bavencio, Merck Serono)

Marketing authorisation	Avelumab was granted marketing authorisation on 21st January 2021 for the 'first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum based chemotherapy'
Mechanism	A human immunoglobulin G1 monoclonal antibody against the programme-death-ligand L1 (PD-L1) protein

Administration and dose	• Licensed dose: intravenous **flat dosing schedule** 800 mg every 2 weeks → used in cost effectiveness analysis
	  • Note: main trial used **weight-based dose** 10 mg/kg every 2 weeks
	  • Identical dose change has been accepted in TA645
	  • ERG noted average total treatment dose administered (750mg) is similar to flat dose

Place in pathway	Monotherapy for first-line treatment of adults with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy.
Cost of treatment	List price is £768.00 per 200 mg vial, (£3,072 for 800 mg dose) Existing confidential patient access scheme discount

JAVELIN Bladder 100 - design



Abbreviations: BSC: best supportive care, * first-line chemotherapy comprised gemcitabine +cisplatin and/or gemcitabine+ carboplatin

Clinical evidence - Overall survival

All randomised patients (n=700)	Avelumab + BSC (N=350)	BSC (N=350)
Median OS (95% CI), months	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)
HR (95% CI)	0.69 (0.556, 0.863) p=0.001	
PD-L1 positive patients (n= 358)*	**Avelumab + BSC (N=189)**	**BSC (N=169)**
Median OS (95% CI), months	NR (20.3, NR)	17.1 (13.5, 23.7)
HR (95% CI)	0.56 (0.404, 0.787), p<0.001	
PD-L1 negative patients (n= 271)*	**Avelumab + BSC (N=139)**	**BSC (N=132)**
Median OS (95% CI), months	18.8 (13.3, 22.5)	13.7 (10.8, 17.8)
HR (95% CI)	0.85 (0.615, 1.181) p= not reported	

Abbreviations: BSC; best supportive care; CI: confidence interval; HR: Hazard ratio; NR = not reached; OS = overall survival; PD-L1 = programmed death-ligand

*Based on number reporting PD-L1 status. PD-L1 status unknown for small number taking part in trial

Clinical evidence - Progression free survival

All randomised patients (n=700)	Avelumab + BSC (N=350)	BSC (N=350)
Median PFS (95% CI), months*	3.7 (3.5, 5.5)	2.0 (1.9, 2.7)
HR (95% CI)	0.62 (0.519, 0.751) p<0.0001	
PD-L1 positive patients (n= 358)**	**Avelumab + BSC (N=189)**	**BSC (N=169)**
Median PFS (95% CI), months*	5.7 (3.7, 7.4)	2.1 (1.9, 3.5)
HR (95% CI)	0.56 (0.431, 0.728) p<0.0001	
PD-L1 negative patients (n= 271)**	**Avelumab + BSC (N=139)**	**BSC (N=132)**
Median PFS (95% CI), months*	3.0 (2.0, 3.7)	1.9 (1.9, 2.0)
HR (95% CI)	0.63 (0.476, 0.845) P= not reported	

Abbreviations: BSC; best supportive care; CI: confidence interval; HR: Hazard ratio; NR = not reached; PD-L1 = programmed death-ligand; PFS= progression free survival

* Based on BICR assessment

**Based on number reporting PD-L1 status. PD-L1 status unknown for small number taking part in trial

NICE

ACD preliminary recommendation

Avelumab is not recommended, within its marketing authorisation, for maintenance treatment of locally advanced or metastatic urothelial cancer that has not progressed after platinum-based chemotherapy in adults

ACD considerations (1)

Key Issue	Committee's considerations
Extrapolating overall survival data (ACD section 3.6)	• Both generalised gamma and log-normal plausible but lead to different mean life years for comparator arm (35.4 months - generalised gamma, 27.8 months- log-normal)
Definition of progression - (ACD section 3.7)	• BICR gives most unbiased assessment of disease progression • Committee conclude progression should be defined by BICR as preferred approach used in many TAs
Time to stopping treatment (ACD section 3.8)	• Company assumption does not reflect trial • Other TAs preferred no stopping rules • Committee concluded no evidence to support stopping rule • Committee would like PFS data and time to stopping treatment data presented on 1 graph
Duration of treatment benefit (ACD section 3.9)	• Company base case assume continued lifetime benefit even after stopping treatment • Committee considered lifetime benefit after stopping implausible

ACD considerations (2)

Issue	Committee's considerations
Proportion having subsequent treatments (ACD section 3.10)	• Committee note SACT does not reflect maintenance setting for avelumab and data should be based on trial
Costs of subsequent treatment (ACD section 3.11)	• Committee note recent TA guidance set precedent - if subsequent treatment had been received in trial (and efficacy data is not adjusted to reflect this) then costs should also be included in model
Pooling health state utilities (ACD section 3.12)	• Company model used pooled health state utility values • Before progression utilities higher in avelumab arm but, after progression lower for avelumab compared with BSC alone • Committee - reasonable to consider separate health state utilities for each arm

End of life criteria (ACD sections 3.13 & 3.14)	• Agree avelumab meets extends life by at least 3 months
	• Unclear if life expectancy for people not having avelumab is less than 24 months.
	  • mean estimates of OS from JB100 were higher than 24 months
	  • unsure if OS from existing trials and estimates from clinical experts accurately reflect people who are eligible for maintenance treatment

Consultation responses

ACD consultation responses

Consultation comments

- Fight Bladder Cancer
- Action Bladder UK
- Merck Serono (company)

- **Web comments**

- 2 public responses (note 1 response was from a patient organisation in addition to the comments from their stakeholder response form)

Key themes have been summarised over the next few slides

Summary of consultation comments from Fight Bladder Cancer

End of life:

- No clear use of mean or median - Other Appraisal committees have considered median life expectancy
- Median survival more appropriate because small number of long-term survivors can skew distribution
- Data from National Cancer Registration and Analysis Service found median overall survival of 14.0 months
- Clinical feedback suggests most people live for average of 14 months (median of 12 to 18 months) and less than 20% live longer than 2 years
- ERG base case predict mean overall survival 27.82 months (median 15.6 months)
- Using an ICER threshold lower than maximum available is unreasonable
- People in clinical trials generally healthier than clinical practice, so unreasonable to extrapolate overall survival from economic model

Summary of consultation comments from Fight Bladder Cancer

Time to treatment discontinuation

- Currently no maintenance immunotherapy available as part of routine commissioning for group of people with bladder cancer
- Feedback from people with bladder cancer is they would be comfortable with a 2 year stopping rule if informed at start of treatment and also given information on mechanism of action

Summary of consultation comments from Action Bladder Cancer UK

End of life:

- Difficulty in extrapolating JB100 data to fit UK clinical practice but real world data shows end of life criteria met in UK clinical practice
- Survival should not be measured from start of chemotherapy but from start of receiving avelumab
- Other appraisal committees have considered short life expectancy for end of life criteria has been met for people with advanced or metastatic urothelial cancer who have had platinum based chemotherapy (see TA692 pembrolizumab para 3.29)

Summary of consultation comments from Action Bladder Cancer UK

Time to treatment discontinuation

- Prefer if avelumab is available without a stopping rule
- If alternative would deny access to avelumab then prefer a stopping rule to be in place

Committee's preferred assumptions

- Including the cost of subsequent immunotherapies rather than removing the benefit does not reflect UK clinical practice
- Concerned committee's chosen assumptions may result in an artificially high cost base

Review of guidance

- Welcome an earlier review of 12 months, due to rapidly increasing data from using immunotherapies for cancer treatment

Summary of public comments

Has all relevant evidence been taken into account?

Yes there is little evidence / research for maintenance therapy for bladder cancer

Are clinical and cost effectiveness summaries reasonable interpretations ?

Most patients who progress through first line treatment would not survive for longer than 24 months

Are recommendations sound and suitable?

Best evidence to date. Given paucity of options for metastatic bladder cancer, having maintenance therapy for this group would be an important strategy

Are there any aspects of the recommendations that need particular consideration

No

Summary of comments from company

Company's key comments:

1. **Time to stopping treatment and duration of treatment benefit:**
   - TTD assumptions did not represent stopping rule for implementation in clinical practice, but to reflect expected treatment duration in clinical practice
   - Company present scenarios which include a 2-year stopping rule and a waning of treatment effect at 5 years
2. **End of life criteria:**
   - Disagree life expectancy for people with metastatic urothelial cancer is more than 24 months

Company's additional comments

3. **Overall survival extrapolation:**
   - Company propose log-normal model to align with ERG's preferred base case
4. **Health state utility values:**
   - Company and ERG are aligned –It is reasonable to pool utility values across treatment arms as per previous TAs in metastatic urothelial cancer (see TA519 and TA612 pembrolizumab)
5. **Innovation:**
   - Avelumab is a new treatment strategy in urothelial cancer and targets patients who will benefit the most from treatment

Company comments (1)

Issue	Comment

Time to stopping treatment	• 95% patients stopping treatment at 2 years is not a stopping rule
	  • Company did not expect this to be implemented in clinical practice
	  • Incorporated to reflect likely treatment duration in clinical practice
	• Company do not agree that other TAs have preferred no stopping rules
	  • In clinical practice majority stop treatment by 2 years (noted for other immunoncology (IO) therapies)
	  • 2 year stopping rule used in TA517 (avelumab for Merkel cell carcinoma)
	  • Other TAs for IOs in metastatic urothelial cancer have accepted a 2-year stopping rule (TA525, atezolizumab and TA692 pembrolizumab)

NICE acknowledge error in drafting ACD:
Stated: other appraisals of immunotherapies for urothelial cancer preferred no stopping rules
Committee discussion: other appraisals of avelumab preferred no stopping rules (TA645 RCC)

ERG response:
- Notes company disagrees with committee and have amended original base case
- 2 year stopping rule does not address uncertainty around assumptions about duration of treatment benefit
- Provide scenario analysis with TTD curves fitted to JB100 trial data without any treatment stopping and no treatment benefit caps applied to PFS or OS curves

Company's new evidence (1)

Progression-free survival and Time to treatment discontinuation

[redacted]

Company: KM curves show people did receive treatment beyond progression up until around 15 months when the curves cross.

Should a 2 year stopping rule be applied?

Company comments (2)

Issue	Company comment

Duration of treatment benefit	• Company provided revised base case with treatment waning applied at 5 years (instant loss of treatment benefit , HR reverts to 1) linked to a 2-year stopping rule (i.e. 3 years after stopping treatment)
	  • Aligns with clinical feedback sought at TE - agreed sustained benefit for immunotherapy when treatment is stopped- also supported by clinical experts comments at ACM 1
	  • In line with previous NICE appraisals of immunotherapies in metastatic urothelial cancer where treatment waning has been explored in a range of 3-5 years post treatment stopping (see TA525, atezolizumab)

ERG response:

- True duration of continued treatment benefit after stopping treatment is unknown
- Provide scenario analyses of different treatment benefit capping assumptions, to show uncertainty around base case ICER
- Vary duration of continued treatment benefit from 0 years (HR for avalumab = WW at 2 years) and 5 years (HR for avelumab = WW at 7 years).
- Apply a gradual loss of benefit between 2 years (treatment stopping time point) and 5 years (3 years after stopping treatment

Should a treatment benefit cap be applied?

Company comments (3)

Issue	Comment

End of life criteria	• Life expectancy for people having BSC should not be measured from start of chemotherapy because this does not reflect avelumab in a 1st line maintenance setting
	• Should be measured from point people are eligible for 1st line maintenance treatment (after platinum-based chemotherapy)
	• Mean should not be only statistic to inform end of life
	  • Extrapolation of JB100 and mean from trial does not show typical experience in clinical practice.
	  • Long tail in OS curve does not reflect survival for majority
	• Other NICE appraisals (TA692 pembrolizumab in UC and TA658 Isatuximab with pomalidomide and dexamethasone for multiple myeloma) used median OS for end of life criteria

ERG response:

- Satisfied median survival is less than 24 months - also consistent with results of model
- Notes company argument that a small number will have longer survival times (leading to means higher than medians)
- Notes economic model predict mean LY gains of 2.32 years for WW (based on log-normal OS extrapolation) and 2.92 years for WW (based on generalised gamma OS extrapolation)

ACM1: life expectancy data

OS in JB100	Model OS estimates (Generalised gamma)	Model OS estimates (Log-normal)	Percent alive at 2 years in WW arm
Median OS: BSC arm = 14.3 months (95% CI: 12.9 to 17.9 months)	Mean OS: 35.4 months Median OS: 15.9 months	Mean OS: 27.82 months Median OS: 15.6 months	Generalised Gamma: 36.58% Log-normal: 35.05%

Abbreviations: BSC= best supportive care; OS= overall survival; WW= watchful waiting

Company's new evidence (3)

Company consider median overall survival should qualify for end of life criteria

Evidence from literature:

- Summarise median survival based on studies of 1st line chemotherapy (approx. 4 to 6 months earlier than point people would be eligible for avelumab)
- Company note majority of people included in these studies would be eligible for avelumab

Evidence	Median OS	Population
England Cohort study	9.5 months	Adults with Stage 3 to 4 urothelial cancer between 2013 to 2017
Phase 3 RCTs	12.5 to 18.0 months 9.3 months	1st line cisplatin (7 RCTs) 1st line carboplatin + gemcitabine (1 RCT)
Meta analysis (7 phase 2 & 3 RCTs)	13.5 months	Cisplatin based regimen (1 meta analysis)
Single arm studies	11.3 to 16.3 months	1st line cisplatin-ineligible (3 studies)

Clinical feedback (8 clinicians):

- Average life expectancy of people with metastatic urothelial cancer who respond to chemotherapy and receive current standard of care in the UK = 12 to 18 months
- Feedback from clinical experts at ACM 1 in line with feedback from the 8 UK clinicians

End of life – mean or median (1)

- The trial often gives the median because the data is incomplete by the end of the trial ie. many patients may not have progressed/died. Median = results direct from trial (observed data) and reported in the medical literature as the efficacy
- Median = mean only if the statistical distribution of variable is symmetrical. In a positively skewed distribution, the mean is larger than the median
- The mean is used to calculate the QALYs gained and ICER
- In a few appraisals the discussion in the FAD focusses on median survival, but the majority focus on the mean
- Company note that TA658 and TA692 FAD discussions focus on median values

End of life – mean or median (2)

- TA692 was a CDF review of TA519 (pembrolizumab for previously treated locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy)
- As part of that review, end of life was not reconsidered, but it had been covered in the original company submission of TA519
  - Committee considered median life-expectancy from trial supported by evidence from literature from 2 references also reporting median values
  - ERG noted that median OS from the main trial was lower than 24 months
  - Both company and ERG-preferred base case OS extrapolations predicted mean life expectancy less than 24 months
    - Mean LY gains in the company base case were 1.59 years and in the ERG's preferred base case were 1.09 years

End of life – mean or median (3)

- TA658 (Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma)
  - Company reported median OS times of less than 2 years in control groups
  - Median OS in the control arm of the subgroup who had 3 previous lines of treatment was 14.4 months
  - The ERG noted modelled mean survival was higher than median ([redacted] years in the company base case) but lower than 2 years

Should the mean or median be used to assess life expectancy?

Does avelumab meet the short-life expectancy criterion?

Company comments (4)

Issue	Comment
Health state utilities	Lower values post-progression for avelumab can be accounted for by: • Higher use of IOs by people in BSC arm of JB100 • People who progressed in avelumab arm of JB100 likely sicker with lower quality of life

- **ERG response:** Agrees with company but relevant to consider uncertainty
- Provide scenario analyses exploring use of treatment specific utilities

Company's new evidence (4)

Health state utility values: some utilities differ for avelumab vs WW in progression-free and progressed health states

Sample sizes used to estimate progression-free and post-progression utility values:

	Number of patients	Number of observations	Mean EQ5D
Progressed – Avelumab + BSC	196	722	XXXXX
Progressed - BSC	234	504	XXXXX
Progression-free – Avelumab + BSC	311	2273	XXXXX
Progression-free - BSC	282	1258	XXXXX

Table shows a smaller number of observations to inform post-progression utility values for each treatment arm. Could explain lower utility value in post-progression health state for avelumab

Should health state utility values be pooled across treatment arms?

Additional company comments

Issue	Company comment
Overall survival extrapolation	Accept both generalised gamma and log-normal are plausible • Propose log-normal model selected • More conservative OS curve for avelumab • Predicts 5 and 10 year OS closer to mid-point of clinical expert expectations for WW arm

ERG response:
- ERG and company base case aligned but ERG clinical expert view is log-normal is more plausible in terms of longer-term extrapolations

Innovation	Innovation should be considered by each indication as clear differences in clinical outcomes for each tumour type • Unmet need for people with advanced bladder cancer • Avelumab is first treatment option licensed for a broad range of patients regardless of PD-L1 status and cisplatin-eligibility for many years

Key issues

- Should a 2 year stopping rule be applied?
- Should a treatment benefit cap be applied?
- Should the mean or median be used to assess short life expectancy?
- Does avelumab meet the short-life expectancy criteria?
- Should health state utility values be pooled across treatment arms?
- Is avelumab innovative – are there any benefits not captured in the modelling?

Because of confidential discounts for subsequent treatments, cost-effectiveness results will be presented in Part 2

Analyses committee will consider in part 2

Analysis	Key features
Company base case	• Log-normal OS • BICR assessed PFS • 2-year stopping rule for avelumab • 3-year waning of treatment effect after stopping avelumab treatment • Proportions post-progression from JB100 • Including cost of atezolizumab (other IOs) in avelumab arm • Pooled health state utility values
ERG scenarios aligned with ACD	1. Extrapolation of TTD, PFS and OS curves as per JB100 2. Treatment arm specific health state utility values 3. Combined scenarios 1&2 (aligned to ACD preference)
Additional ERG scenarios applied to company base case	4. Generalised Gamma OS 5. Stopping rules and benefit caps: • 2 year stopping rule + 2-year benefit cap • 2 year stopping rule + 3-year benefit cap • 2 year stopping rule + 4-year benefit cap • 2 year stopping rule + 7-year benefit cap • 2 year stopping rule + 10-year benefit cap 6. 2 year stopping rule + gradual waning between years 2 to 5 7. Combined scenarios 2 & 6 8. Combined scenarios 2, 4 & 6