Public observer slides (redacted)

NICE National Institute for Health and Care Excellence

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

Lead team presentation

Lead team: Rachel Elliott, Chris Parker, Rebecca Harmston

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

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Key issues

Issues resolved after Technical engagement	
Issue 2: Treatment effectiveness parameters (extrapolation of overall survival curves for avelumab and watchful waiting)	**Resolved**
Issues discussed at Technical engagement	
Issue 3: Definition of progression (Blinded Independent Central Review vs. Investigator assessed)	**To discuss**
Issue 4: Time to treatment discontinuation on avelumab and duration of continued progression-free and overall survival benefit	**To discuss**
Issue 5: Proportion of patients receiving subsequent (post progression) treatment in the model	**To discuss**
Issue 6: The mix of subsequent (post progression) treatments included in the model	**To discuss**
Issue 7: Uncertainty about whether end of life criteria are met	**To discuss**

Urothelial cancer

- Urothelial carcinoma is cancer of the cells that form the inner lining of bladder, urethra, ureter, or renal pelvis
  - accounts for around 90% of bladder cancers
- Bladder cancer accounts for 1 in every 30 new cancer diagnoses each year in the UK, and is the 10th most common cancer in the UK
- Majority of new cases occur in people aged over 75
- 72% of bladder cancer cases in the UK are in men
- Common symptoms include blood in urine, pain or discomfort during urination.
- People with advanced disease may have symptoms caused by the spread of the disease such as muscle-invasive disease or bone-pain

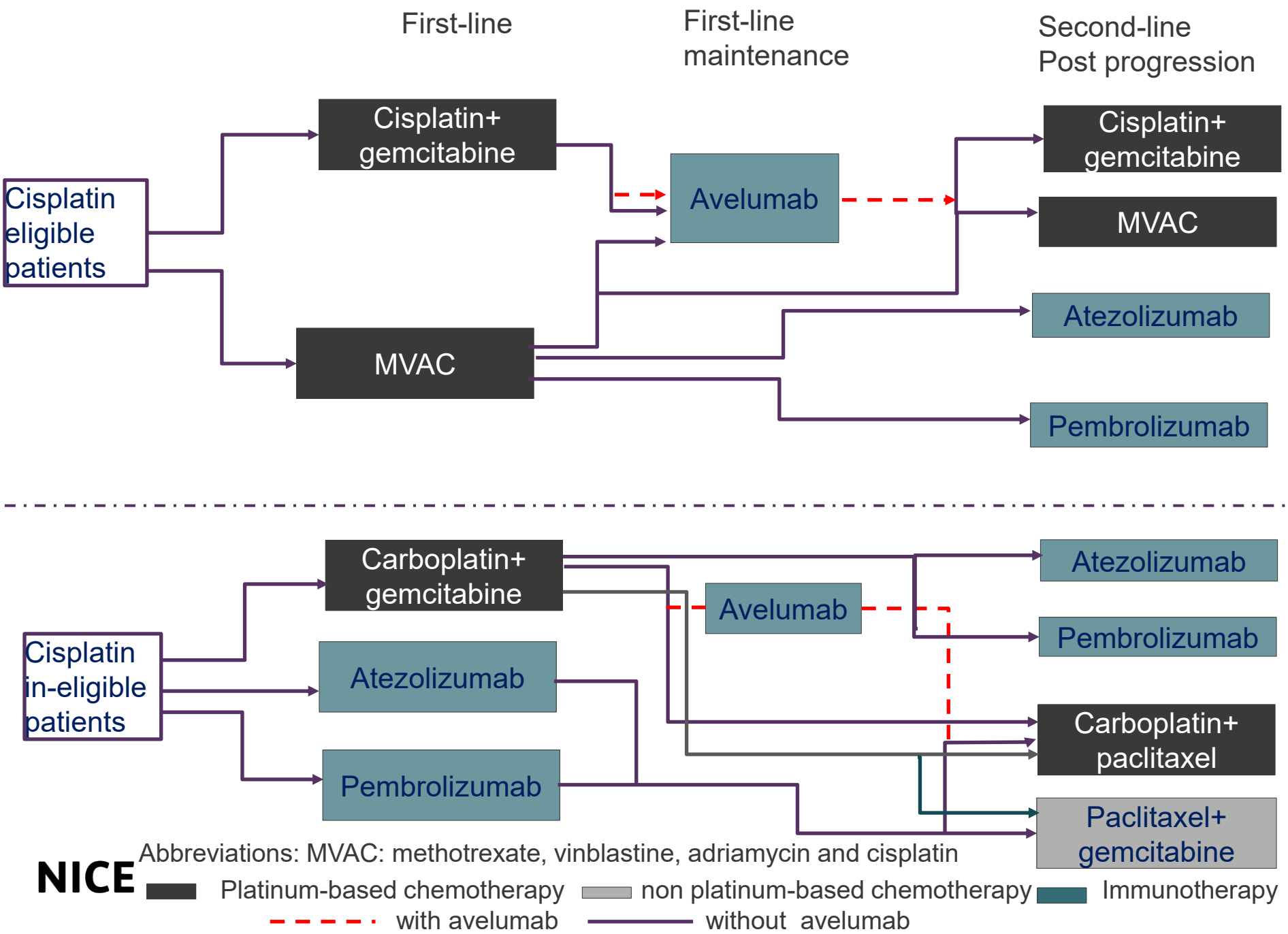
Avelumab (Bavencio, Merck Serono)

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

Proposed position of avelumab in pathway



Patient perspectives

Submission from Action Bladder Cancer, UK

- Patient groups and survey responses reflect similar experiences -
  "*Patients struggle to come to terms with the very poor outcomes when they are told their bladder cancer has spread …In addition to coming to terms with the very poor outlook they must also endure the adverse side effects of currently available treatments, leaving patients both emotionally and physically exhausted"*
  "Family members and carers struggle between providing optimistic support and hoping that the ordeal they are forced to witness gets no worse, or lasts too long, giving rise in many cases to feelings of guilt at their own mixed emotions".
- Data from trial shows positive outcomes and generally acceptable side effects of avelumab which would be welcomed by patients, providing them with greater optimism and hope for the future.

Clinician perspectives

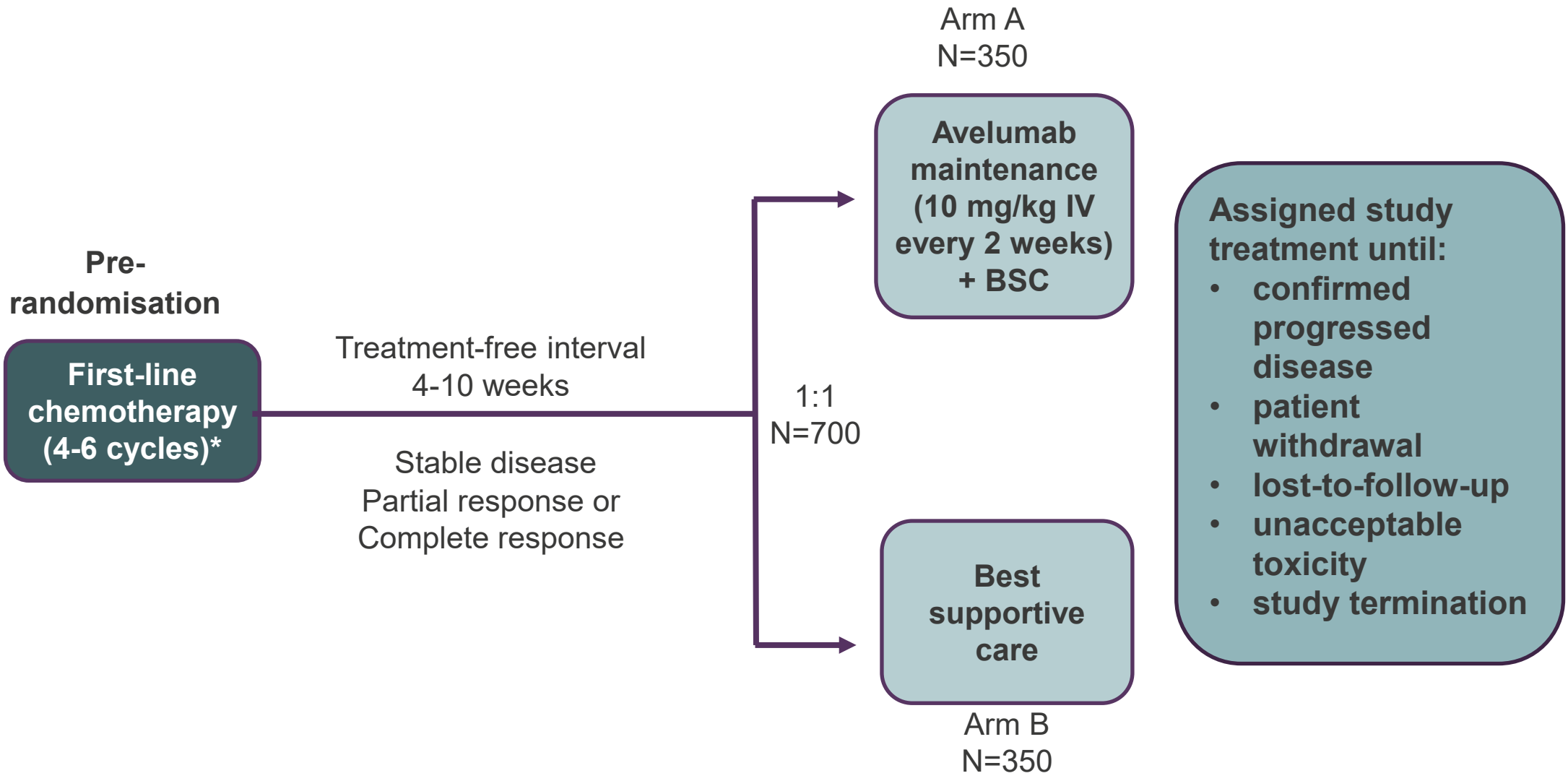
Submissions from Consultant Oncologist and Professor of Medical Oncology

- Advanced bladder cancer has poor overall survival and progressive disease has a huge impact on quality of life
- Many patients develop complications including ureteric obstruction, renal failure, haematuria, and significant pain from both local and metastatic disease, anaemia, and fatigue
- Second line chemotherapy response rate is around 18% and second line immunotherapy response rate is 23%. Approximately half of patients do not go onto receive second line treatment as they relapse too quickly for it to be initiated
- Current treatments are costly, time consuming and uncomfortable for patients and outcomes are poor
- Avelumab improves survival and reduces the number of people receiving second line immunotherapy. Staying in early or stable disease state for longer will allow for a vastly improved quality of life, improved survival and reduce healthcare resources

Decision problem

	Final scope	Company submission	ERG comment
P	Adults with locally advanced or metastatic urothelial cancer whose disease did not progress while on or after completion of first-line platinum-based chemotherapy	As per scope	• Matches final scope • Javelin Bladder 100 trial reflects patient population eligible for treatment in UK
C	Established clinical management without avelumab (including but not limited to routine surveillance, symptom control and pain management [including palliative radiotherapy])	As per scope	• Company use BSC (antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (inc. palliative radiotherapy*) but not* active anti-tumour therapy • ERG view: BSC generally reflects current UK practice
O	• Overall survival • Progression-free survival • Response rates • Time to relapse or progression • Adverse effects of treatment	As per scope	Outcomes match scope
No sub-groups identified			

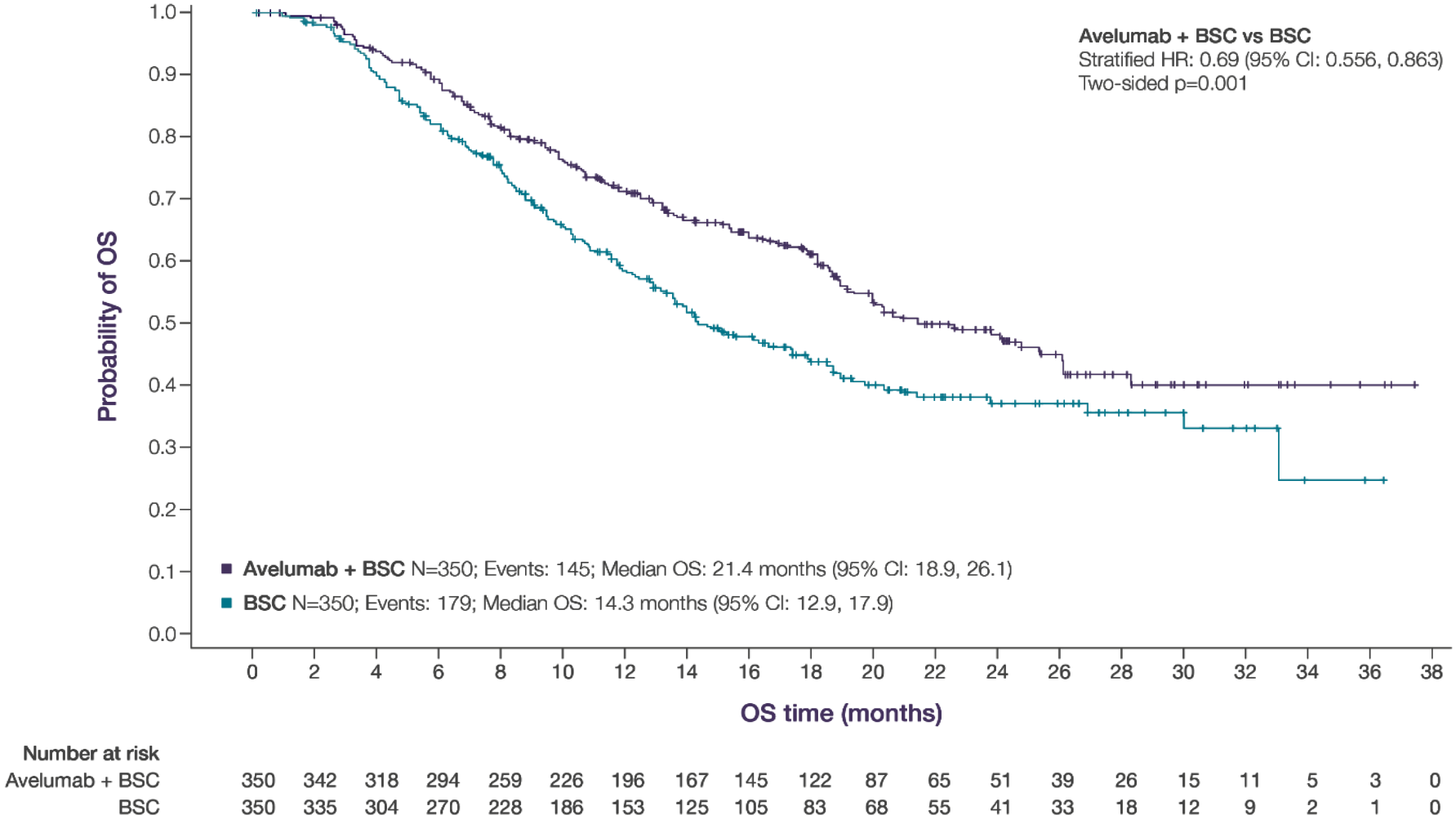
JAVELIN Bladder 100 - design



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

Key results: Overall survival

Kaplan-Meier plot of OS in all randomised patients



NICE Abbreviations: BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; N = number of patients evaluable; OS = overall survival

Key results: Overall survival

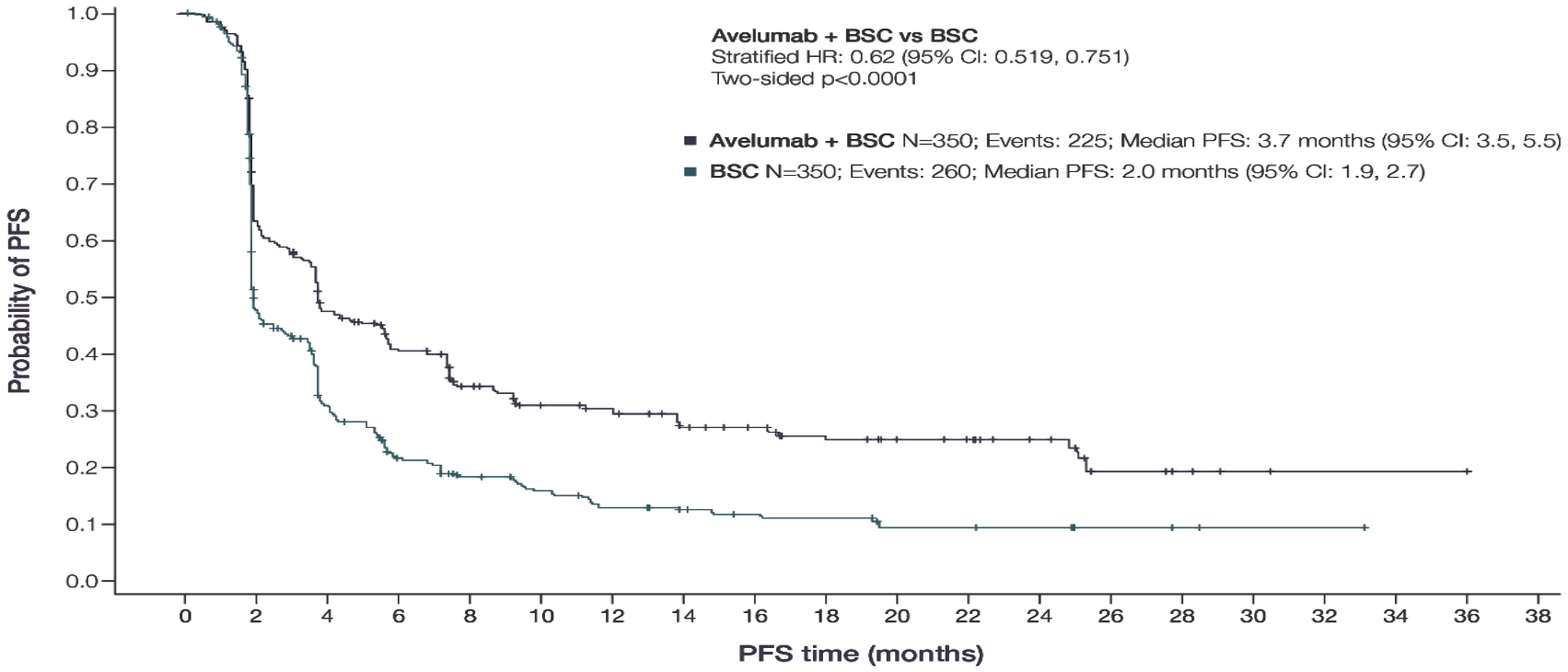
All randomised patients (n=700)	Avelumab + BSC (N=350)	BSC (N=350)
Median OS (95% CI), months	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)
HR (95% CI)	0.69 (0.556, 0.863) p=0.001	
PD-L1 positive patients (n= 358)*	**Avelumab + BSC (N=189)**	**BSC (N=169)**
Median OS (95% CI), months	NR (20.3, NR)	17.1 (13.5, 23.7)
HR (95% CI)	0.56 (0.404, 0.787), p<0.001	
PD-L1 negative patients (n= 270)*	**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

Key results: Progression-free survival

Kaplan-Meier plot of PFS* in all randomised patients



Number at risk																		
Avelumab + BSC	350	198	145	118	90	72	59	49	45	34	27	25	17	9	4	2	1	1	0
BSC	350	144	87	52	39	31	24	20	17	16	10	10	7	3	2	1	1	0	

Abbreviations: BICR = blinded independent central review; BSC = best supportive care; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; N= number of patients evaluable; PFS = progression-free survival

*Based on BICR assessment

NICE

Key results: 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= 270)**	**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

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Issues discussed at technical engagement

Issue No	Summary	Company response	Comments
2	- ERG considered overall survival extrapolation curves (generalised gamma) chosen by company may over-estimate overall survival for avelumab and watchful waiting (WW) arms of the model - ERG preferred log-normal curves	- Accepted generalised gamma may be considered optimistic for WW. - Revised base-case uses lognormal model (aligned with ERG's preferred base-case) for OS for both avelumab and WW	- Company updated base case following Technical Engagement - ERG considered this issue has resolved

Issues to discuss after technical engagement

Outstanding issues unresolved post technical engagement	Impact on ICERs	Slide
Issue 3: Definition of progression (BICR vs. INV)		16
Issue 4: Part 1 - Time to treatment discontinuation on avelumab Part 2 - Duration of continued PFS and OS benefit	 	17 to 23
Issue 5: Proportion of patients receiving subsequent (post progression) treatment in the model		24 to 25
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Issue 7: Uncertainty about whether end of life criteria are met		28

Issue 3: Definition of progression (BICR vs. INV)

Background:

- PFS curves fitted for 2 alternative definitions of progression in company economic model
- Company base case assumes blinded independent central review (BICR) definition of progression but provided sensitivity analyses for investigator assessed (INV)
- ERG prefer INV- assessed progression in model, based on clinical opinion that INV-assessed progression more likely to be used to guide treatment decisions in clinical practice
  - JB100 BICR assessments carried out every 8 weeks up to 1 year and every 12 weeks until progression

Company response to Technical engagement

- Feedback from 8 clinicians suggest INV-assessed progression is most likely used in clinical practice
- Company supports use of INV-assessed progression in base case

ERG response to Technical Engagement

- ERG note advantages and disadvantages to both BICR and INV-assessed progression
- Retains preference for INV-assessed progression based on alignment to real-world decision making

Lead team comment

- BICR-assessed progression less susceptible to bias, has been preferred in other appraisals

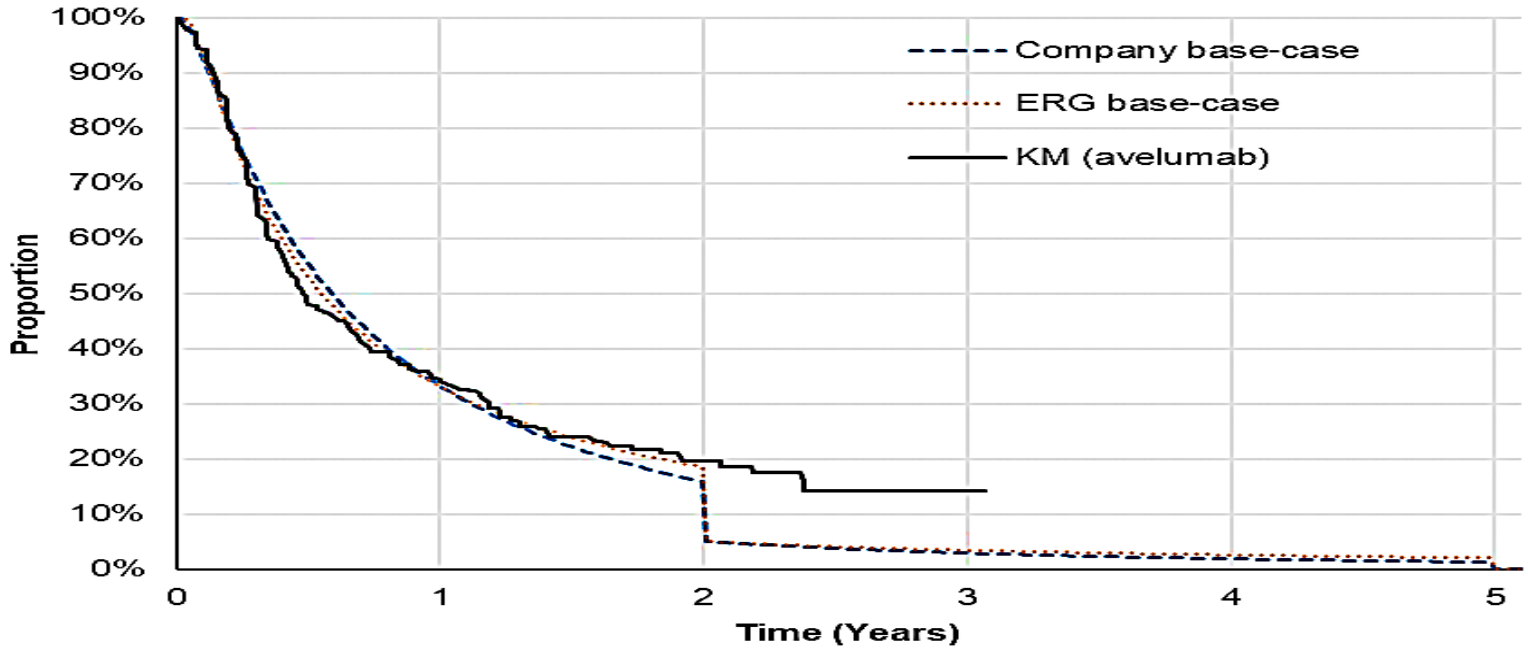
Does committee prefer BICR or INV- assessment of progression?

Issue 4: TTD and duration of continued benefit

Background:

- In JB100 no formal stopping rule was applied, and treatment continued at discretion of investigator. Hazard ratios and ICERs are based on unadjusted trial data.
- Company base case assumes treatment discontinuation in NHS will occur earlier than in JB100 (5% continuing treatment at 2 years and all stopping treatment by 5 years)
- K-M data from trial shows that XXXX were having treatment at 2 years
- The summary of product characteristics states "*Administration …. should continue according to the recommended schedule until disease progression or unacceptable toxicity*"
- Company fitted a log-normal and ERG preferred generalised gamma to extrapolate data

Comparison of Company and ERG-preferred extrapolations of time to treatment discontinuation



Issue 4: TTD and duration of continued benefit

- Both Company and ERG base case assume 95% stop avelumab at 2 years and 100% stop at 5 years but have explored changes to stopping rules in scenarios
- Company sought feedback from UK oncologists:
  - indicated that after 2 years, some patients may stop treatment with avelumab
  - in clinical practice, anticipate treatment for majority of patients will stop by 2 yrs
- ERG suggests 2-year stopping rules are common for immunotherapy treatments for cancer
  - Applying TTD assumptions as per the company's economic model would be acceptable but there is uncertainty about duration of treatment benefit
  - An ERG scenario considers removal of stopping rule which matches JB100 trial

	Base case	Scenarios
Company	• 95% stop at 2 yrs, 100% stop by 5 yrs	-
ERG		• No drop at 2 yrs, 100% stop by 5 yrs • No drop at 2 yrs, no stop at 5 yrs

Is it appropriate to assume 95% stop treatment at 2 years and all stop treatment by 5 years

Issue 4 (part 1): Extrapolating TTD

	Extrapolation model	Rationale and critique	Outcome and impact on ICER
Company	Log-normal fitted to TTD data from JB100 up to 2 year timepoint	• Good visual and statistical fit to KM curve (2nd best AIC and BIC score) • Predicts lowest proportion on treatment at 5 years (4%, prior to adjustment at 2 years) **ERG suggest not robust rationale → survival curves are already adjusted to reduce proportion on treatment to 5%**	Proportion remaining on treatment at 5 years [redacted]%
ERG	Generalised gamma fitted to TTD data from JB100 up to 2 year timepoint	• Better visual fit to all stages of KM curve and best statistical fit (lowest AIC and BIC) • Predicts large proportion on treatment at 5 years (7.5%, prior to adjustment at 2 years)	Proportion remaining on treatment at 5 years [redacted]% Small impact on ICER

Does committee prefer log-normal or generalised-gamma to model time to treatment discontinuation?

Issue 4 (part 2): Duration of PFS and OS benefit

- ERG and company base case assume continued treatment benefit over lifetime horizon despite 95% stopping treatment at 2 years
- ERG provides scenarios in which treatment effect wants at 2, 5 or 10 years
- Company: inappropriate to apply treatment waning effect from year 2 as model assumes people remain on treatment up to year 5. Provides scenarios based on 5, 6, 7 and 8 years.
  - Consider 5-year waning conservative scenario
  - Prefer gradual waning to ERG's instantaneous waning (better replicates real-world setting) → next slide

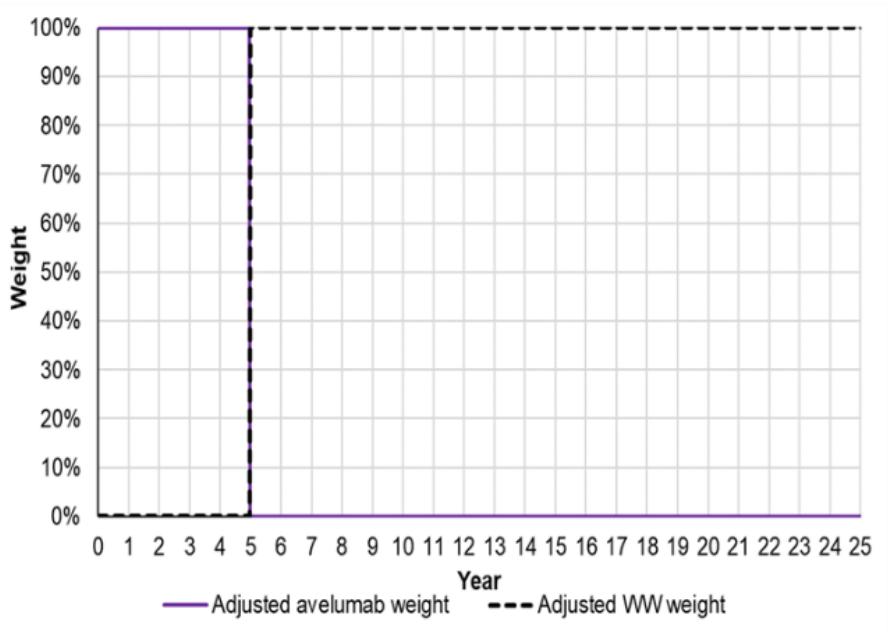
	Cap on duration of PFS & OS	Rationale
Company	Base case: no cap Scenario: cap at 5, 6, 7 or 8 years • 8 year scenario means 3 years of benefit after stopping before waning of effect applied • Waning applied as instant loss when all stop treatment (HR=1)	• Maximum 8-year treatment waning effect was based on the prior NICE appraisal TA525 (Atezolizumab for mUC)
ERG	Base case: no cap Scenario: cap at 2, 5 or 10 years	• Scenarios at 2 and 5 years align with when 95% and 100% of people are assumed to stop treatment

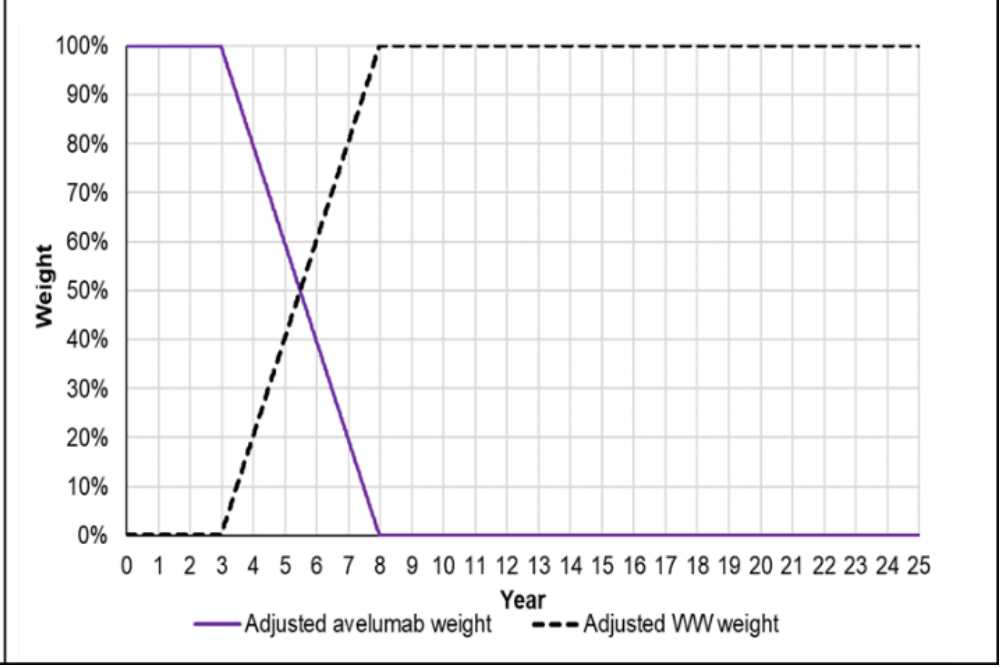
Issue 4 (part 2) Duration of PFS and OS benefit

Company: Also provided scenarios exploring gradual instead of instantaneous treatment waning effect → gradual effect avoids sudden change in hazards (progression and death) that may occur if applying instantaneous effect

ERG: Assumes HR of OS and PFS gradually approaches 1 beyond treatment effect. ERG prefer HR set to 1 at treatment benefit capping time point as better aligns with company's assumptions about instantaneous discontinuation from treatment at years 2 and 5

Instantaneous waning effect (5 years) – hypothetical example	Gradual waning effect (3 – 8years) – hypothetical example





If a waning of treatment effect is modelled, should this be instantaneous) or gradual?

Issue 4: TTD and duration of continued benefit considerations in other NICE avelumab appraisals

TA ref	Base case/scenario considerations	Committee conclusion
TA645 (Avelumab with axitinib for untreated advanced renal cell carcinoma)	**Company base case** • Treatment stops after 2 years whether disease has progressed or not • 2/3 stopping treatment have treatment benefit over lifetime, 1/3 have waning treatment effect **Company updated base case** • At 2nd meeting removed stopping rule • Treatment continued so assumptions about continuing treatment effect after stopping treatment at a set time period were removed **ERG scenarios** • Removed treatment waning effect	**Not appropriate to include a stopping rule. If no stopping rule, appropriate to exclude treatment waning effect** • Trial did not include stopping rule • CDF lead: patients relapsing after stopping treatment would not be able to resume treatment if stopping rule accepted • No evidence to support proportion that would have long-term treatment effect after stopping treatment
TA517 (Avelumab for treating metastatic Merkel cell carcinoma)	**Company base case** • Assumed 2/3 stop treatment after 2 years and all stop after 5 years **ERG base case** • Considered TTD without stopping rule at 2 years	**Company assumptions reflect clinical practice** • Clinical experts expect 95% to stop treatment by 2 years • Few continue beyond 2 years

Issue 4: TTD and duration of continued benefit considerations in other NICE urothelial appraisals

TA ref	Base case/scenarios	Committee conclusion
TA519 (Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy)	**Company base case/scenario** • Assumed 2 year stopping rule and lifetime treatment benefit • Scenarios exploring continued treatment effect at different time points of stopping	**2 year stopping rule appropriate but lifetime treatment effect implausible** • SmPC: treatment continues until disease progression but other indications of pembrolizumab included stopping after defined period • CDF lead confirmed acceptability of 2 year stopping rule • Duration of continued treatment effect after stopping is an area of uncertainty
TA525 (Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy)	**Company base case/scenario** • Lack of clinical evidence to show long-term benefit after stopping • Provided scenario analyses capping treatment effect at 3 or 5 years after stopping treatment	**2 year stopping rule appropriate but lifetime treatment effect implausible** • In previous appraisals clinicians highlighted concern about using immunotherapies beyond 2 years • CDF lead: 2 yr stopping rule acceptable • Noted other guidance included 3-year treatment effect cap after stopping treatment, but not enough evidence to support a specific duration of benefit

Issue 5: Proportion having subsequent (post progression) treatment (1)

Background

- Company base case assumes costs of subsequent treatments following progression are based on JB100 trial (adjusted for treatments in UK clinical practice)
  - Avelumab + BSC= xxxxx%; BSC= xxxxx% will receive treatment post progression
  - ERG think proportion in JB100 trial is likely higher than in UK clinical practice
- ERG noted company provided info from SACT dataset (41.9% receive 2nd line therapy following progression in UK) and scenario based on average of proportions in each arm of JB100 and from SACT dataset
- ERG Base case: Avelumab = xxxxx% and WW= xxxxx% (from company scenario analysis)

Company response to technical engagement

- SACT does not reflect the same maintenance population as JB100
- SACT dataset collected prior to recent NICE recommendations for immunotherapies in metastatic UC

ERG critique

- JB100 cohort likely to respond better to treatment so more will be treated with additional treatments post progression than people seen in current clinical practice
- Average of datasets better reflects true usage of post progression
- Average may even be an optimistic estimate of the ICER for avelumab

Should proportion receiving subsequent treatment be based on JB100 trial data or average of datasets?

Issue 5: Proportion having subsequent (post progression) treatment (2)

Would data from the systemic anti-cancer therapy dataset be representative of the population and a useful source to inform estimates?

CDF-Lead:

- 2nd line cytotoxic chemotherapy after 1 cytotoxic chemotherapy (cisplatin + gemcitabine or carboplatin + gemcitabine) has limited efficacy, such that the 2nd line treatment rate is low
- Part relates to relatively poor efficacy of 2nd line therapy, part is due to significant toxicity and/or inconvenience of receiving treatment and part is a consequence of reducing fitness to receive chemotherapy in a population of patients
- SACT dataset could give the numbers of patients receiving a 2nd line therapy in urothelial cancer
- SACT could give the proportion of avelumab failures having 2nd line chemotherapy and the outcomes associated with that treatment

Should proportion receiving subsequent treatment be based on JB100 trial data or average of datasets?

Issue 6: Costs of post-progression treatments (1)

Background:

- Treatments included post-progression based on subsequent active treatments received in JB100 adjusted to reflect clinical practice
- Company model assumes atezolizumab covers all anti-PD-1/PD-L1 treatment costs (exc other immunotherapies)
  - Avelumab: [redacted]% = 2nd line anti-PD-1/PD-L1 treatment (most had 2nd-line chemo)
  - WW: [redacted]% = 2nd line anti-PD-1/PD-L1 treatment (except avelumab)
- ERG - patients would have chemotherapy not another immunotherapy after avelumab, so don't need to include immunotherapy costs after avelumab
- Company scenario analysis - atezolizumab cost removed for avelumab

Company response to technical engagement

- Consulted 8 clinicians. All agreed following avelumanb maintenance patients would not have another immunotherapy but have chemotherapy instead
- Company agree costs of atezolizumab following avelumab should be removed from base case and assume patients have chemotherapy on progression after avelumab maintenance

ERG response to technical engagement

- Clinical advice aligns with ERG view → ERG and company agree immunotherapy costs should be removed from avelumab arm

Issue 6: Mix of post-progression treatments (2)

Lead team: In NHS patients would not receive a 2nd line immunotherapy after progression on avelumab. However in JB100 a small number did receive immunotherapies post-progression and may have received some benefit. The clinical data in model has not been adjusted to account for this

How post-progression treatments have been addressed in other Technology appraisals:

- ID1536 (Pembrolizumab for locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy) - if active treatments are received then these should be included in the costs:
- *Draft FAD: Section 3.25:*
  - *Company noted retreatment with pembrolizumab did not reflect clinical practice in the NHS in England so preferred analysis without costs*
  - *Committee found it inconsistent to include the potential benefits of retreatment without the costs, so both should either be included or excluded.*
  - *In the absence of an analysis removing the benefits of retreatment, it concluded that the costs should be applied at 3 years.*

Should the costs of treatments used after progression on avelumab include the cost of immunotherapies?

Issue 7: Are the end-of-life criteria met?

Eligibility for end of life criteria:

Avelumab meets improvement in OS greater than 3 months

- JB100 unadjusted improvement in median OS 7.1 months
- Company model increase in mean OS 12 months (median 6.9 months);

Uncertain whether expected OS without avelumab is more or less than 24 months

- Company submission: Studies report life expectancy range median 9.3 to 18.5 months
- JB 100 trial: median survival BSC arm = 14.3 months (95% CI: 12.9 to 17.9 months).
- Company base case predicts WW mean OS: 35.4 months (median: 15.9 months)
- ERG base case predicts WW mean OS of 27.82 months (median = 15.6 months)

Company response to technical engagement

- Alternative approach = Proportion of patients expected to survive more than 24 months in WW arm
- Company base case = 36.58%; ERG base-case = 35.05% showing that the majority do not survive longer than 2 years

ERG response to technical engagement:

Company response still reports *median OS* below 24 months (supported) but still uncertainty whether *mean OS* without avelumab (i.e. BSC) is above or below 24 months

Note: ICERs are based on mean survival estimates but mean OS from JB100 was not provided in company submission

Does avelumab meet the EOL criteria?

Additional area of uncertainty

Issue 1	Description of issue
Health related quality of life	• The company provided utility data for each arm of the study, split by pre-progression and post-progression states. • The utilities for pre-progression are *higher* xxxxxxxx in the avelumab + BSC arm compared to BSC alone but post-progression are *lower* xxxxxxxx in avelumab + BSC arm compared to BSC alone. • ERG: difficult to know why utilities would be lower post progression in one group than another. However, agrees with company it is appropriate to pool health state utilities across treatment arms

Points for Committee consideration

- Innovation?
  - Company consider maintenance treatment with avelumab following first-line platinum-based chemotherapy is a novel and innovative treatment approach in urothelial cancer
- Quality of life?
  - Overall health status and health related quality of life (HRQoL) were similar between the arms of the JB100 trial
- Robust data?
  - Is the data robust for decision making?

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

Analyses committee will consider in part 2

Analysis	Key features
Company base case	• Log-normal for OS (both arms) • INV-assessed PFS • No immunotherapy costs after avelumab • 95% stop at 2 years, 100% at 5 years • No waning of treatment effect
Company waning scenarios	• Scenarios exploring waning of treatment effect - Instantaneous and gradual waning
ERG base case	As company base case + • Generalised gamma extrapolation for TTD • ERG preferred proportion on post-progression treatment
ERG waning scenarios	• Scenarios exploring waning of treatment effect
ERG scenario maximising trial data	• BICR-assessed PFS • Immunotherapy costs after avelumab • Trial post-progression treatment proportions • No stopping rules

Issues to discuss after technical engagement

Outstanding issues unresolved post technical engagement	Impact on ICERs	Slide
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