NICE National Institute for Health and Care Excellence

PART 1

Slides for public – no confidential information

Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]

ACM3 presentation – post-appeal

10 February 2022

Avelumab (Bavencio, Merck Serono)

Marketing authorisation	Avelumab is indicated 'as monotherapy 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	Intravenous infusion, flat dosing schedule 800 mg every 2 weeks
Cost of treatment	List price is £768.00 per 200 mg vial, (£3,072 for 800 mg dose) Existing confidential patient access scheme discount (updated post appeal).
Key clinical trial	• **JAVELIN Bladder 100 trial**: phase 3, randomised, open-label study in adults with locally advanced or metastatic urothelial cancer that did not get worse during, or 4 to 10 weeks after, first-line platinum-based chemotherapy. • People either had avelumab plus best supportive care or best supportive care alone.

Appraisal history (1)

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.

April 2021	June 2021	September 2021	February 2022
ACM1 → ACD issued	**ACM2 → FAD issued**	**Appeal**	**ACM3 → consider appeal outcome**

ACD: appraisal consultation document; ACM: appraisal committee meeting; FAD: final appraisal document

Appraisal history (2)

Key considerations by committee:

Stopping treatment	• Time to stopping treatment with avelumab should reflect the trial data, company's proposed 2-year stopping rule should not be included in the model: ○ waning of treatment effect should not be included in the model
End of life	• Extension to life criterion met • Short life expectancy criterion not met based on modelled estimates of mean life-expectancy.
Cost-effectiveness	• Most plausible ICER with committee preferred assumptions: £72,933 per QALY/gained (includes previous avelumab discount only, ICER higher with confidential discounts for subsequent treatments)

Time to stopping treatment and waning of treatment effect = model drivers

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year

Appeal summary

- Appeals submitted by the company, Fight Bladder Cancer, Association of Cancer Physicians, British Uro-oncology Group, and Action Bladder Cancer UK.
- Appeal points were considered under Ground 2 - the recommendation is unreasonable in the light of the evidence submitted to NICE.
- The points considered all related to 2 issues, both appeal points were upheld.

Appeal point	Appraisal remitted to committee to:
1. It is unreasonable to conclude that a stopping rule for avelumab is inappropriate.	Either consider the application of a stopping rule for avelumab or explicitly detail why in contrast to TA525 and TA692 a stopping rule is either methodologically problematic or practically difficult.
2. It is unreasonable to conclude that the short life expectancy criterion of the end of life policy is not met.	Appraise avelumab on the basis that the end of life criteria applies.

- NICE TA525 = Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy
- NICE TA692 = Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy

Upheld appeal points

Upheld appeal points

Appeal point	Summary
Point 1	Either consider the application of a stopping rule for avelumab or explicitly detail why in contrast to TA525 and TA692 a stopping rule is either methodologically problematic or practically difficult.
Point 2	Appraise avelumab on the basis that the end of life criteria applies.

Upheld appeal point 1 – stopping rule (1)

Committee considerations in FAD (section 3.8)

- The model captures the benefits that people had from continuing avelumab treatment beyond 2 years ([redacted] in trial), but the costs were not included.
- Concern that it would be difficult for people to accept that they would no longer be able to have treatment after 2 years if they were free from disease.
- People whose disease had not progressed before needing to stop avelumab would not be able to have another immunotherapy in the NHS.
- In TA525 and TA692 where the committee accepted a stopping rule, it was either included in the trial, or the committee was able to generalise these results to other treatments in the same class used in the same population and settings.
- No similar evidence to support a stopping rule for this appraisal:
  - No stopping rule in JAVELIN Bladder 100 and the setting and population (adults who are progression-free following chemotherapy) in this appraisal is different to TA525 and TA692 (adults who have progressed following chemotherapy).
  - Other technology appraisals of avelumab in other disease areas have preferred no stopping rules.

Conclusion: Time to stopping treatment should reflect the trial evidence and a stopping rule should not be included in the model.

Upheld appeal point 1 – stopping rule (2)

Appeal panel conclusions (1)

- *"Stopping rules are widely applied in the NICE technology appraisals for systemic cancer therapy, including for comparable therapies for apparently similar populations..."*
- *"Whilst there is no obligation for the appraisal committee to apply a stopping rule in the case of avelumab because they have been widely applied previously, it is reasonable to expect that the appraisal committee should fully explain their rationale for not doing so."*
- *"…This could include an explanation of why application of a stopping rule would be flawed based on new information addressing the difficulties in the health service with the practical application of stopping rules in clinical practice, or their theoretical basis, that was not considered during the development of TA525 and TA692."*
- *"Alternatively, the panel consider that it could be reasonable for the appraisal committee to explain why avelumab represents a sufficiently different technology from atezolizumab or pembrolizumab; that the proposed application in this technology appraisal is different from TA525 and TA692; or that the population is distinct in this appraisal from that envisaged in TA525 and TA692, in order to explain why a stopping rule is not applicable for this technology appraisal."*

Upheld appeal point 1 – stopping rule (3)

Appeal panel conclusions (2)

- *"…The committee were increasingly aware about the broader difficulty in applying stopping rules in particular the acceptance of stopping rules by patients at two-years following the start of treatment. However, no evidence was presented in the FAD or the documents associated with the appraisal committee meetings to support the reasonableness of a change in approach to the application of stopping rules in NICE technology appraisals."*
- *"…The appeal panel accepted that modelling a stopping rule in the case of avelumab is problematic, in particular modelling what if any effect avelumab continues to have after cessation of treatment…..Whilst it might be reasonable to adopt a conservative modelling approach in view of the uncertainty, the appeal panel do not feel that it is reasonable to reject a stopping rule only on the basis of the difficulties associated with modelling the effect of avelumab following the cessation of treatment."*

The appeal panel concluded that insufficient justification was given in the FAD for adoption of an approach in the appraisal of avelumab that was not broadly consistent with previous comparable technology appraisals.

RECAP

Upheld appeal point 1 – stopping rule (4)

Related appraisals for locally advanced/ metastatic urothelial carcinoma

TA692 Pembrolizumab (April 2021) - CDF review of TA519 (April 2018)	

Indication	• Pembrolizumab monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults:
	  ○ who have received prior platinum-containing chemotherapy, or
	  ○ who are considered cisplatin ineligible, and whose tumours have a PD-L1 with a combined positive score ≥ 10

Trial population and follow-up	• People whose disease progressed or reoccurred following platinum-containing chemotherapy • Median follow-up of 40.9 months (range 36.6 to 48.9 months)
Stopping rule in trial or SmPC?	• No stopping rule in SmPC • Maximum treatment duration was 2 years from the first dose in trial
Company analyses	• 2-year stopping rule + 5-year treatment effect duration from the start of treatment in company base case. • Scenarios exploring 3 and 10 years of treatment effect from the start of treatment.
Key committee conclusions	**2 year stopping rule appropriate, lifetime treatment effect implausible:** • No strong evidence to support 5-year or longer treatment effect, but robust evidence to support 3-year treatment effect after starting treatment. • Treatment effect duration uncertain, but a 3-year to 5-year treatment effect from start of treatment could be plausible. • Considered ICERs with 3-year and 5-year treatment effect durations.

CDF = Cancer Drugs Fund; SmPC = summary of product characteristics

RECAP

Upheld appeal point 1 – stopping rule (5)

Related appraisals for locally advanced/ metastatic urothelial carcinoma

TA525 Atezolizumab (June 2018)	

Indication	• Atezolizumab monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma:
	  ○ after prior platinum-containing chemotherapy, or
	  ○ who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%

Trial population and follow-up	• People whose disease progressed during or following a platinum-containing chemotherapy regimen • Median follow-up of 17.3 months (range 0 – 24.5 months)
Stopping rule in trial or SmPC?	• No stopping rule (remain on treatment until loss of clinical benefit or unmanageable toxicity)
Company analyses	• 2-year stopping rule in company base case. • Provided scenario analyses capping treatment effect at 3 or 5 years after stopping treatment
Key committee conclusions	**2 year stopping rule appropriate, lifetime treatment effect implausible:** • In previous appraisals clinicians concerned about using IOs beyond 2 years • CDF lead: 2 year stopping rule acceptable • Other guidance in area has 2 year stopping rule • Noted the effect of 3-year treatment effect cap after stopping treatment on ICERs but not enough evidence to support a specific duration of benefit.

IO = immunoncology therapies; SmPC = summary of product characteristics

Upheld appeal point 1 – stopping rule (6)

Treatment effect waning – committee considerations in FAD (section 3.9)

- The company's revised base case applied a treatment benefit capping at 5 years (instant loss of treatment benefit 3 years after stopping treatment with avelumab, aligned with its proposed 2-year stopping rule).
- In other technology appraisals of immunotherapies, a treatment cap between 2 and 5 years had been applied when a stopping rule was applied.
- ERG scenario analyses varied from no benefit after stopping treatment to 5 years after stopping treatment and a gradual waning of treatment effect.
- There is substantial uncertainty about the most appropriate treatment benefit capping assumptions.

Conclusion: Since a stopping rule had not been accepted, a waning of treatment effect should not be included in the model.

- ***Why, in contrast to TA525 and TA692, do the committee think that a stopping rule is methodologically problematic or practically difficult?***
- ***Does avelumab represent a sufficiently different technology from atezolizumab or pembrolizumab? Is the proposed application of avelumab or population in this appraisal distinct from that in TA525 and TA692?***
- ***If the committee reconsiders modelling with a 2 year stopping rule, how should the effect of avelumab after stopping treatment be modelled?***

Upheld appeal points

Appeal point	Summary
Point 1	Either consider the application of a stopping rule for avelumab or explicitly detail why in contrast to TA525 and TA692 a stopping rule is either methodologically problematic or practically difficult.
Point 2	Appraise avelumab on the basis that the end of life criteria applies.

Upheld appeal point 2 – short life expectancy (1)

Committee considerations in FAD (sections 3.13 to 3.14)

- Avelumab meets the criterion for a life-extending treatment.
- Median survival from JAVELIN trial for people on best supportive care (BSC) was 14.3 months.
- Mean estimates of survival from the model were higher than 24 months → cost-effectiveness results and decisions are based on mean QALYs and costs.
- Model (using trial data) predicts that 37% (generalised gamma) and 35% (log-normal) of people on BSC live longer than 2 years, which did not suggest that only a few people survive and that the mean is skewed.
- Wider literature and survey of clinicians suggest that median survival is ≤18 months but these estimates may include people whose disease has not responded to chemotherapy – different to the population in this appraisal
- Concern about differences between median survival and mean estimates from the model.

Conclusion: avelumab did not meet the short life expectancy criterion

BSC: best supportive care

Upheld appeal point 2 – short life expectancy (2)

Data considered at ACM2

- Median survival for BSC in avelumab trial was 14.3 months
- Estimates from literature showing median survival ranging from 9.3 to 18 months
  - only 1 study related specifically to people whose disease had responded well to chemotherapy, the indication for avelumab
- Feedback from 8 clinicians who said that overall survival for people whose disease responds to chemotherapy was between 12 and 18 months
  - a patient organisation also provided similar estimates from 2 clinicians
- Data from model – both the generalised gamma and log-normal considered plausible by committee for extrapolating overall survival

Model	Median survival for BSC	Mean survival for BSC
Generalised gamma (original company base case)	15.9 months	35.4 months
Log-normal (ERG and company base case after TE)	15.6 months	27.8 months

TE: technical engagement

Upheld appeal point 2 – short life expectancy (3)

Appeal panel conclusions (1)

- *"The NICE end of life criteria is applied when, 'The treatment is indicated for patients with a short life expectancy, normally less than 24 months'. The appeal panel note that there is no guidance in the NICE Guide to the Methods of Technology Appraisal or from the NICE Decision Support Unit on how the word 'normally' should be interpreted and the appeal panel note that historically both the mean and median have been used."*
- *"…NICE end of life criteria are founded on the principles in the NICE guide to the use of Social Value Judgements and the outcomes of the Citizens Council meeting in November 2008. Consequently, the panel feel that the paramount consideration should be what the key stakeholders of NICE: the general public, patients, clinicians, policy makers and industry would consider a reasonable interpretation of the word 'normally'."*
- *"The appeal panel, therefore, do not accept the argument advanced by the appraisal committee that the mean survival of 24 months must be used as the threshold for application of end of life criteria to maintain consistency with the methodology used to calculate the incremental cost-effectiveness ratio."*

Upheld appeal point 2 – short life expectancy (4)

Appeal panel conclusions (2)

- *"Key stakeholders of NICE would consider it unreasonable to state that life-expectancy was not 'normally less than 24 months', even if the mean life expectancy was greater than 24 months, if 65% of patients, the significant majority, in the modelled cohort had died prior to 24 months."*
- *"The appeal panel agreed that a totality of the data and analysis have to be looked at when considering if life expectancy is 'normally less than 24 months'. It does not wish to suggest that there is a general rule that median is preferable to mean or vice versa. The question is, is it reasonable to conclude that life expectancy is below 24 months, and the mean, the median, and clinical opinion all inform that..."*
- *"The panel did not feel it would be possible to explain to patients or clinicians why it was said these patients would have a life expectancy in excess of 24 months, and therefore this conclusion was unreasonable."*
- *"The panel understood the concern about using means in one context and medians in another, but the end of life criteria are a stand-alone test…"*
- *"Agreed that 'normally' allowed a committee a discretion to apply end of life criteria even if it felt on some measures of life expectancy might be somewhat over 24 months."*

- **The appeal panel concluded that in this case it would be unreasonable to conclude that this end of life criterion was not met.**
- **The appraisal committee should appraise the technology on the basis that the NICE end of life criteria applies.**

Upheld appeal point 2 – short life expectancy (5)

Clarification sought from appeal panel (published alongside appeal decision):
"Is the panel's view that having found it unreasonable to reject end of life criteria, based on the totality of the evidence available to the panel:

- The consideration for the application of end of life criteria is now fundamentally binary and that the only option for any reasonable committee, given the facts your panel heard in this appeal, would be limited to moving on to deciding the impact of the criteria.

Or

- The consideration for the application of end of life criteria still has the potential for deliberation and judgement by a committee based on the evidence."

Response from appeal panel:

- Conceptually it will be open for the committee, having reconsidered the question with an open mind, to come again to the view that the end of life criteria are not met.
- There would be a very high bar for the committee to persist in that view.

- ***Having reconsidered the evidence, what is the committee's view on whether the end of life criteria are met?***
- ***Overall, what is an acceptable ICER in this appraisal?***

Cost-effectiveness estimates

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

Analyses committee will consider in part 2

Results include updated avelumab PAS

Analysis	Key features (assumptions in bold differ between company revised base case and committee's preferences in FAD)
Company revised base case	• Treatment-specific utility values (updated post-appeal) • OS curves: log-normal • Progression assessed by BICR • TTD curve: generalised gamma • Subsequent treatments based on the JAVELIN Bladder 100 trial • **2-year stopping rule for avelumab + 3-year benefit cap after stopping tx**
Committee's preferences in FAD	• Treatment-specific utility values • OS curves: log-normal **or generalised gamma** • Progression assessed by BICR • TTD curve: generalised gamma • Subsequent treatments based on the JAVELIN Bladder 100 trial • **No stopping rule and no waning of treatment benefit**
Additional ERG scenarios applied to committee's preferences in FAD	• Separate scenarios for log-normal and generalised gamma OS (unless stated): ○ 2-year stopping rule + 3-year benefit cap after stopping tx (company revised base case with generalised gamma OS curve) ○ 2-year stopping rule + 2-year benefit cap after stopping tx ○ 2-year stopping rule + 1-year benefit cap after stopping tx ○ 2-year stopping rule + gradual waning between years 1 to 3 after stopping tx

BICR = blinded independent central review; OS = overall survival; TTD = time to treatment discontinuation; tx = treatment with avelumab

Innovation, unmet need and equality

Committee's considerations in FAD

Innovation and unmet need

- There is an unmet need for effective treatments for people with locally advanced or metastatic urothelial cancer that has not progressed after platinum-based chemotherapy.
- Avelumab is innovative as a maintenance treatment for people whose disease has not progressed 4 to 10 weeks after having first-line chemotherapy.
- The treatment benefit from avelumab has been adequately incorporated into the model.

Equality:

- No equality or social value judgement issues were identified.

⊙ ***Have all the committee's considerations relating to innovation, unmet need and equality been captured in the FAD?***