Chair's presentation
Avelumab for metastatic Merkel cell carcinoma [ID1102]

2nd Appraisal Committee meeting

Committee A
Lead team: John Watkins, Pam Rees, and Stephen Sharp

ERG: BMJ Technology Assessment Group
NICE technical team: Marcela Haasova, Joanna Richardson, Janet Robertson

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Slides for public only – AiC information redacted

1

Preview: key issues for consideration

- Does the committee consider that the clinical effectiveness of avelumab in first line (1L) is likely to be equivalent to that in second line (2L+)?
- The company and the ERG both present ICERs for avelumab vs. BSC for 2L+ under £50K. The company argues that no further data collections are planned for Javelin part A (2L+ line) so the CDF option will not resolve uncertainty. Is the committee minded to reconsider avelumab for routine commissioning for 2L+, despite the uncertainty?
- What is the committee's view on the September 2017 data for 1L? Does it reduce uncertainty or affect the recommendation for CDF?
- The post committee ICER for 1L was £75,526 per QALY vs. BSC and £72,033 per QALY vs. chemotherapy. The company argues that the ICER is £58,315 per QALY vs. chemotherapy based on only 5% of patients at 2 years are given avelumab, and OS and PFS hazards should not be worse than 2L+ values (1L hazards capped at 2L+). Does the committee accept this as a plausible scenario?

2

ACD preliminary recommendation

- The committee is minded not to recommend avelumab for routine commissioning for treating metastatic Merkel cell carcinoma in adults. However the committee recognised the promising nature of this technology and saw its potential as a suitable candidate for use in the Cancer Drugs Fund. Therefore the company is invited to submit a proposal for including avelumab in the Cancer Drugs Fund for this indication.

- Note recommendation applied to 1st and 2nd line

3

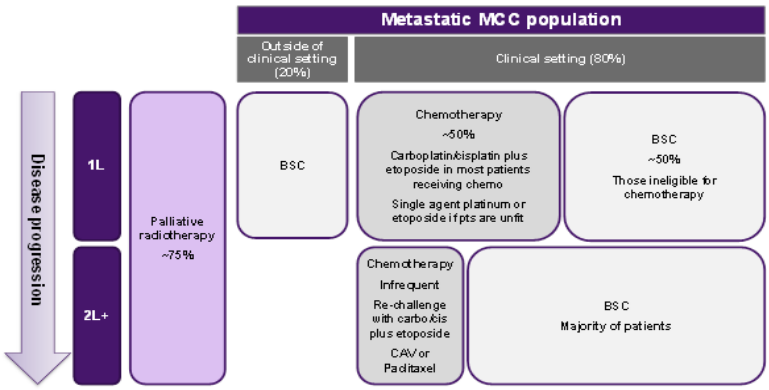
Avelumab, Merck

Marketing authorisation	Indicated for monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma
Administration & dose	10 mg/kg every 2 weeks by intravenous infusion over 60 minutes. (antihistamine and acetaminophen prior first 4 infusions) • continued until disease progression or unacceptable toxicity.
Mechanism of action	• Human IgG1 lambda monoclonal antibody • Dual mechanism of action: aim to bind and block the inhibitory signalling through PD-1/PD-L1 resulting in the activation of T-cells and cell-mediated immune responses against tumour cells or pathogens.
Innovation	• Ultra-orphan condition • EMA: Orphan Drug and Fast Track designation • MHRA: Promising Innovative Medicine (PIM) designation • FDA: Breakthrough Therapy

4

Treatment pathway for metastatic MCC

- **1st line (1L):** 50% of metastatic MCC patients will receive chemotherapy and 50% will receive palliative care/best supportive care (BSC)
- **2nd line (2L):** most patients will receive BSC



- There are no related NICE technology appraisals and no NICE clinical guidelines

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ACD clinical evidence: 2L+ cohort

Efficacy parameter	JAVELIN Merkel 200 Avelumab (Part A; March 2017: 18-month FU; N=88)	Study 100070-Obs001 Chemotherapy (Part A - US) (N=20)	Study 100070-Obs001 Chemotherapy (Part B - EU) (N=34)
BOR per RECIST 1.1 n (%)			
CR	[redacted]	0	0
PR	[redacted]	4 (20.0)	3 (8.8)
ORR (%)			
Response rate (CR+PR)	[redacted]	20.0	8.8
DoR (%)			
6–month DRR	[redacted]	0	0
PFS rate (%)			
6-month PFS	[redacted]	0	2.9
12-months PFS	[redacted]	0	0
OS rate (%)			
6-month OS	[redacted]	30.2	26.4
12-month OS	[redacted]	0	0

Key: BOR, best overall response; CR, complete response; DoR, Duration of response; DRR, durable response rate; FU, follow-up; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PR, partial response.

6

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ACD clinical evidence:1L cohort

Efficacy parameter	JAVELIN Merkel 200 Avelumab (Part B EU)		Study 100070-Obs001 Chemotherapy
	3-month FU (N=[redacted])	6-month FU (N=[redacted])	(Part A - US) (N=67)
BOR per RECIST 1.1 n (%)			
CR	[redacted]	[redacted]	10 (14.9)
PR	[redacted]	[redacted]	11 (16.4)
ORR (%)			
Response rate (CR+PR)	[redacted]	[redacted]	31.3
DoR (%)			
6–month DRR	-	[redacted]	14.9
PFS OS *FULL ANALYSIS (%; N=39)*			
6-months PFS rate	[redacted]		44.8
12-months PFS rate	-		21.8
OS *FULL ANALYSIS (%; N=39)*			
6-month OS rate	[redacted]		70.1
12-month OS rate	-		44.0

Key: BOR, best overall response; CR, complete response; DoR, Duration of response; DRR, durable response rate; FU, follow-up; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PR, partial response.

7

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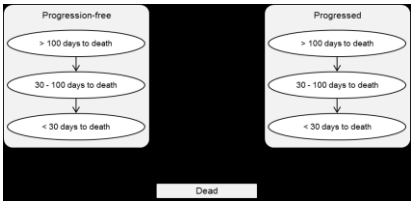
JAVELIN Merkel 200: Parts A and B (Kaplan-Meier data)

Key: 1L, treatment-naïve patients; 2L, treatment-experienced patients; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

8

ACD company's partitioned-survival model



- **2 separate populations**:
  - 2L+ treatment-experienced
  - 1L treatment-naïve
- **Avelumab 2L+**
  - **OS and PFS**: JAVELIN data (censored at 18 months for PFS) extrapolated using spline-based models
  - Comparator: *BSC* (assumed equivalent to chemotherapy) extrapolated pooled data from US part A & EU part B company conducted observational study 100070-Obs00
- **Avelumab 1L**
  - **OS**: hazard ratios from 2L+ multiplied by hazard ratio (0.8) elicited from clinical opinion.
  - **PFS**: assumed same as 2L+
  - Comparators: *chemotherapy* and *BSC* (assumed equivalent to chemotherapy) extrapolated data from US part A study 100070-Obs00

9

ACD Company's and ERG's results – 2L+

	Avelumab	BSC	Avelumab vs BSC
Company base case (no premedication; log-logistic for ToT & truncation; BSC: Weibull PFS & Gompertz OS)			
Costs	78,752	7,465	71,287
QALYs	2.22	0.31	1.91
LYs	3.53	0.41	3.11
ICER			**37,350**
ERG base case (premedication costs; Weibull ToT [no truncation]; BSC: Weibull regression model PFS & OS)			
Costs	92,644	7,413	85,232
QALYs	2.22	0.32	1.90
LYs	3.53	0.43	3.10
ICER			**44,914**
Post committee base case (premedication costs; BSC: Weibull regression model PFS & OS)			
Costs	£78,822	£7,413	71,409
QALYs	2.22	0.32	1.90
LYs	3.53	0.43	3.10
ICER			**£37,629**

10

Key: BSC, best supportive care; ToT, time on treatment;

ACD Company's and ERG's results – 1L

	Avelumab	Chemo	BSC	Ave vs chemo	Ave vs BSC
Company base case (no premedication cost; ToT = 2L+ ToT; HRs of 1 & 0.8 for PFS & OS vs. 2L+)					
Costs	78,588	10,608	7,217	67,979	71,371
QALYs	2.93	1.37	1.38	1.56	1.55
LYs	4.78	2.02	2.02	2.76	2.76
ICER				**43,553**	**46,148**
ERG base case (premedication costs; Weibull for ToT (no truncation); parametric curves for PFS & OS)					
Costs	159,570	10,608	7,217	148,962	152,353
QALYs	2.65	1.37	1.38	1.28	1.27
LYs	4.16	2.02	2.02	2.14	2.14
ICER				**116,388**	**120,383**
Post committee base case (premedication cost; parametric curves for PFS & OS)					
Costs	102,812	10,608	7,217	92,204	95,595
QALYs	2.65	1.37	1.38	1.28	1.27
LYs	4.16	2.02	2.02	2.14	2.14
ICER				**£72,033**	**£75,526**

11

ACD: committee's considerations for 2L+

- The committee's preferred assumptions for the modelling for 2L+ were:
  - using Weibull regressions to model PFS and OS
  - adding the cost of premedications
  - correct avelumab administration costs increases ICERs by around £1,000
  - produced an ICER 37,629 (revised ERG post committee base case) per QALY vs BSC:
- The committee accepted that avelumab meets the end-of-life criteria for second-line treatment of metastatic Merkel cell carcinoma.
- The committee acknowledged that the estimated ICERs for second-line use are not particularly high. However the estimates are highly uncertain, being based on 1 single-arm trial, a small number of patents and a naive indirect comparison and therefore could not be recommended in routine commissioning.

12

ACD: committee's considerations for 1L

- The committee's preferred assumptions for 1L were:
  - using parametric curves to model PFS, OS
  - adding the cost of premedications
  - produced an ICER of £75,526 (revised ERG post committee base case) per QALY vs BSC.
- The committee concluded that avelumab meets the criteria to be considered a life-extending end-of-life treatment for first-line treatment of metastatic Merkel cell carcinoma.
- The committee had concerns about underlying issues with clinical data, particularly very small number of patients and uncertainties around methods generating survival estimates.
- The committee's preference is that avelumab should be made available through the Cancer Drugs Fund, for both first-line and second-line treatment. This will allow further clinical data to be collected to establish whether, and for which patients, avelumab is clinically and cost effective.

13

ACD consultation responses

Consultee comments from:

- Company
- NET Patient Foundation

Commentator comment from:

- Department of Health 'no comments'.

Web comments

- 2 received

14

ACD consultation comments (1)

NET Patient Foundation

- *Having Avelumab available through the CDF would be of great benefit to patients, our concern is that this has been given a 3 year review date, at which point even though NICE consider this a life extending end of life treatment with costs that are beneath the ICER there is a chance it could be removed.*

- *We are concerned the uncertainties raised by NICE regarding further data to reduce uncertainties will not be met whilst the drug is on the CDF. The study performed is already the largest clinical trial in MCC and the data for avelumab as a second line treatment is already fairly mature. The concerns about uncertainties of patient numbers and comparators for second line treatments wont be resolved whilst it is on the CDF. As stated throughout, MCC is a rare cancer and within the patient group those suitable for Avelumab are going to be an even smaller number*.

15

ACD consultation comments (2)

Web comments

- *The response rates appear to be higher first line which makes the likelihood of this drug being more clinically and cost effective first line the most likely outcome.*

- *…The data* [Javelin]* *support the use of Avelumab in the second line setting. It is thought that earlier use of Avelumab in the first line setting may demonstrate slightly better response rates compared with chemotherapy. We have noted that earlier use of checkpoint inhibition in other tumour types may be more beneficial and it is hoped that this may also hold true for MCC. Approval of Avelumab in the first line therapy will allow us to prospectively evaluate the data in this rare group of patients with significant unmet need*

16

Key: *, added.

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Company's ACD response: 2L+

Avelumab should be funded through routine commissioning:

- Revised company base case:
  - added administration cost (same as committee preferred)
  - ToT based on clinical experts: 5% at 2 years (small difference vs. company original value of 5.4%)
  - **ICER of £37,846 per QALY vs. BSC (similar to original base case and post committee ICERs)**
- CDF will not resolve the clinical uncertainties as no further data collection:
  - JAVELIN part A is mature: primary endpoint, median PFS & OS reached; 83% of patients discontinued; 19 subjects remains [15 on treatment]
  - September 2017: 24-month OS rate= [redacted]; sustained response in [redacted] with ORR; [redacted] since March; DoR not reached
  - collection of comparator data in CDF would not be possible
- Naïve indirect comparison uncertainty: BSC OS estimates are uncertain, but the modelled mean OS would need to be 12.6 months (vs. 5.1 months) to produce an ICER of £50,000 per QALY. This is clinically implausible.
- The committee's, ERG's & company's ICER <50,000 per QALY.

17

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ERG critique: 2L+

- The new ICER of £37,846 per QALY vs. BSC is similar to the ERG's post-committee ICER of £37,629
- Notes that committee estimated cost of administration was £100, while the increased cost in the new base is only £54 (from £199 to £253)
- Agrees that CDF will not provide further data and that JAVELIN part A 2L+ data mature
- Validity of threshold analysis: company's analyses only focus on changing the effectiveness of BSC. However, if the difference in mean survival is considered, a change from a mean difference of 37 months to 30 months results in ICER increasing to £50,000.
- September 2017 data: [redacted]
- ERG considers 2L+ ICERS uncertain but suitable for decision making

18

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Company ACD response 1L: September data

JAVELIN Merkel 200 March 2017 (Part B)	March 2017		September 2017 ([redacted])	
	3-month FU (N=[redacted])	6-month FU (N=[redacted])	3-month FU (N=[redacted])	6-month FU (N=[redacted])
BOR: CR (%)	[redacted]	[redacted]	-	
BOR: PR (%)	[redacted]	[redacted]	-	
ORR (CR+PR; %)	[redacted]	[redacted]	[redacted] *	[redacted] **
6–month DRR (%)	-	[redacted]	[redacted] ***	
6-month PFS rate (%)	[redacted]		-	
6-month OS rate (%)	[redacted]		[redacted]	

- Grade 3/4 TRAE profile in line with March data; [redacted] March data), but at [redacted] consistent with PD-1/L1 class; not unexpected in 1L

ERG critique:

- planned sample size is 112 patients, but September data have [redacted]
- [redacted] safety profile [redacted]
- ORR and DOR [redacted]

Key: BOR, best overall response; CR, complete response; DRR, durable response rate; FU, follow-up; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PR, partial response.
Notes: *, 13 weeks follow-up; **, [redacted] ***, [redacted]

19

Company's ACD response: 1L base case (1)

The company is in discussion with NHSE about a commercial arrangement for use of avelumab for 1L in CDF.

- ERG's post committee base case ICER was £75,526 per QALY vs. BSC and £72,033 per QALY vs. chemotherapy
- Revised company base case:
  - added administration cost (committee preferred)
  - identified an error in calculation of background mortality
  - based on clinical experts: 5% at 2 years (vs. company original of 8.5%; decreases ICER by approximately £5,000)
  - adjusted ERG's implausible extrapolations: OS/PFS hazards capped at 2nd line (decreases ICER further by approximately £10,000)
  - chemotherapy (not BSC) is the appropriate comparator
  - **ICER of £58,315 per QALY vs. chemotherapy**

20

Company's ACD response: 1L base case (2)

Two main changes contribute to lowering the ERG's post committee base case ICER of £75,526 vs. BSC and £72,033 vs. chemotherapy:

- **Time on treatment**: 5% treatment at 2 years (previously 8.5%) reduced ICER vs. chemotherapy from £72,033 to **£67,293**
- **OS & PFS modelling**: company indicates that ERG's modelling gives worse overall survival benefit OS & PFS for 1st line vs 2nd line and this is implausible. To address this issue, event hazards were capped at 1.74 years (when they becomes implausible) by the corresponding OS/PFS hazards from 2L+ . This is a conservative assumption, as the hazard is at most the same as 2L+, and it is expected to be lower.
- Incorporation of all company's changes results in new company base-case ICER of **£58,315** per QALY vs. chemotherapy
- ICER (at the current avelumab price) for treatment-naïve patients lies between **£48,148** (company's original base case) and **£58,315** per QALY gained (company's revised ERG base case) vs. chemotherapy

21

ERG critique: 1L

- Agrees that chemotherapy is the appropriate comparator
- Concerned about assumption that only 5% remain on treatment at 2 years as evidence suggests greater proportion of patients (8.5% more reasonable)
- Company's comment that 1L hazards should not be > 2L+ is reasonable. However, model adjustments do not decrease uncertainty.
- Agrees that the uncertain tail of time on treatment KM plot may have unrealistic influence on fitted curves.
- The ICER of £48,148 is based on flawed assumption of PH and cannot be considered a lower bound for the ICER.
- The ICER of 58,315 cannot be considered an upper bound, even the committee requested ICER of £72,033 could be low. Uncertainty is too great to provide reliable ICER or range in which it is likely to fall.
- All 1L ICERS needs to be considered with caution as they are based on extremely limited evidence. The uncertainty may be reduced when further JAVELIN data become available.

22

Equality issues

- No equality issues
- Company: putting 2L+ cost-effective indication into the CDF will prevent access of the drug to patients in Wales and Northern Ireland who cannot benefit from the fund.

23

Key issues for consideration

- Does the committee consider that the clinical effectiveness of avelumab in first line (1L) is likely to be equivalent to that in second line (2L+)?
- The company and the ERG both present ICERs for avelumab vs. BSC for 2L+ under £50K. The company argues that no further data collections are planned for Javelin part A (2L+ line) so the CDF option will not resolve uncertainty. Is the committee minded to reconsider avelumab for routine commissioning for 2L+, despite the uncertainty?
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24