Slides for public

Lead team presentation Avelumab for metastatic Merkel cell carcinoma – STA

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee A

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Key clinical issues for consideration

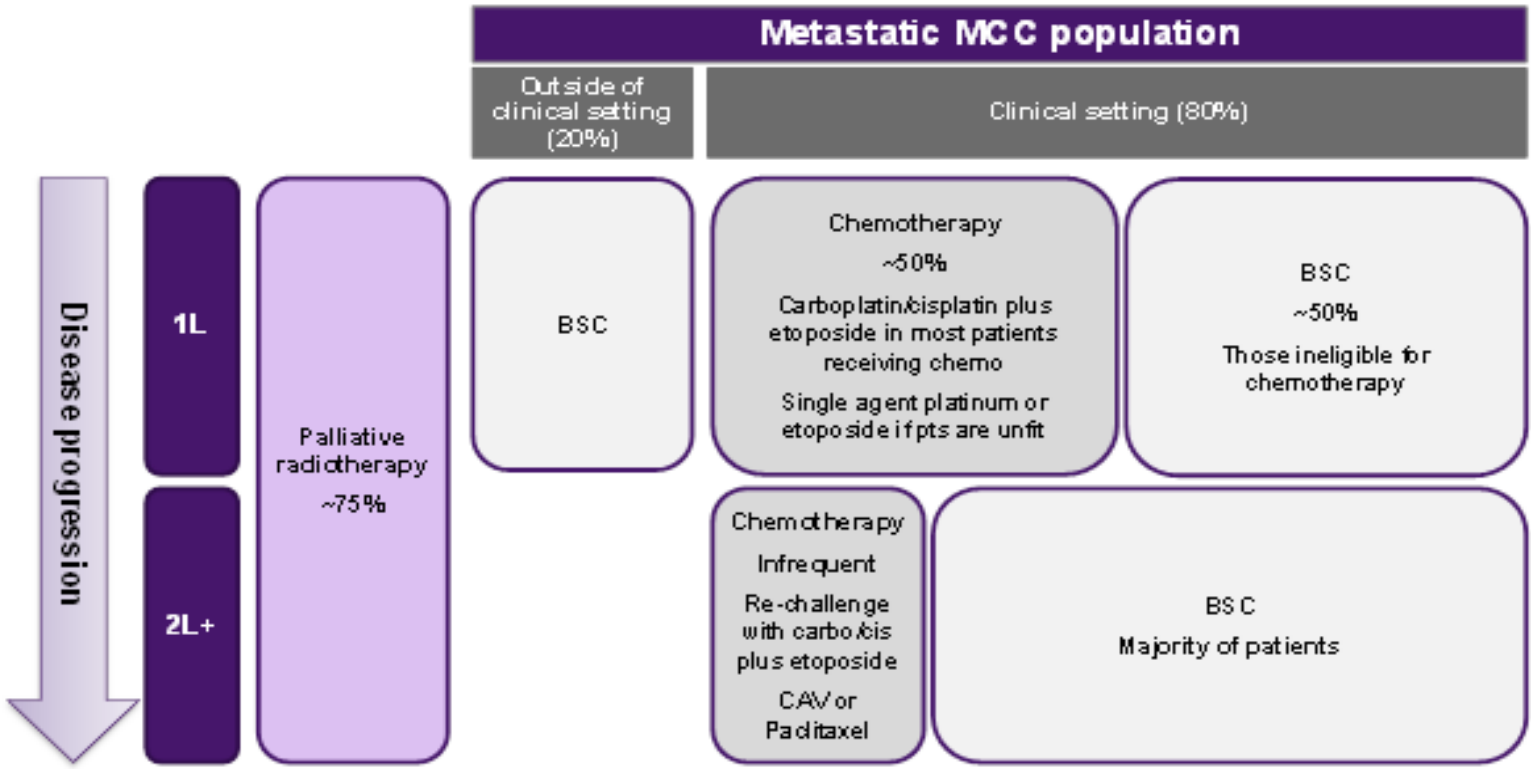
- Which patients would be considered for treatment with avelumab e.g. patients with immunosuppression were excluded from the trial?
- Given the response rates and the duration of response observed in the JAVELIN trial, how would this be expected to translate into PFS and OS benefit?
- Is the indirect comparison with the chemotherapy trials appropriate in comparing avelumab with standard practice?
- Are the observational studies used to compare with the trial data appropriate?
- What is the committee's view on the relative benefit of avelumab in 1st and 2nd line?

Background

- Merkel cell carcinoma (MCC) is a rare skin cancer
- Merkel cells are present in the top layer of the skin, carcinoma occurs when they grow out of control
- May be associated with immunosuppression
- Usually presents as a lump of unbroken skin, often in areas of the body that receive direct sun exposure
- MCC is symptomless in the initial stages and may be difficult to diagnose
- Common in older people and in those with fairer skin
- In 2010, 53 to 106 people were diagnosed in England
- Poor prognosis with a 5 year survival rate dependent upon stage
- Early stage disease treated with local surgery and radiotherapy
- Stage IV metastatic disease, subject of this appraisal, 5 year survival 11%

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

Decision problem
Comparators for 1L and 2L+ are different

	NICE scope	DP addressed in the CS
Population	People with metastatic MCC	In line with scope although ERG considers there is a lack of definition of the 1L and 2L+ populations
Comparator	Untreated metastatic MCC (=1L) • Chemotherapy (such as cisplatin or carboplatin with or without etoposide) • BSC Previously treated metastatic MCC (=2L+) • BSC	Untreated metastatic MCC (=1L) • Chemotherapy (defined as 50/50 of the combinations cisplatin + etoposide and carboplatin + etoposide) • BSC Previously treated metastatic MCC (=2L+) • Chemotherapy (received by 5% of patients) • BSC
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	In line with scope, although no data were reported for HRQoL in the 1L cohort

BSC, best supportive care; HRQoL: health-related quality of life; MCC, Merkel Cell Carcinoma

Avelumab

- 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.
- Indicated for "**treatment of adults with metastatic Merkel cell carcinoma (MCC)**" (MA granted on 18 September 2017)
- IV infusion, 10 mg/kg over 60 minutes every 2 weeks*
- Ultra-orphan condition; EMA: Orphan Drug and Fast Track designation; MHRA: Promising Innovative Medicine (PIM) designation; FDA: Breakthrough Therapy
- List price: £768 per 200 mg; average cost of treatment course: £65,086

*requires premedication with an antihistamine and acetaminophen before the first 4 infusions

Clinical expert opinion

- Proven efficacy in metastatic Merkel cell carcinoma.
- Variable duration of clinical benefit between individuals, depends on the degree of initial response.
- Excellent option for second-line (after chemotherapy failure), a higher (30%) and more durable response rate than chemotherapy and overall 40% patients alive and free of progression at 6 months.
- Data not yet in the public domain for first-line treatment but expecting many suitable patients because of advanced age and/or co-morbidities
- Better tolerated than chemotherapy, although safety should continue to be monitored.
- Natural history of MCC described in retrospective case reviews (used for comparison with avelumab), in line with clinical experience.
- No major implementations barriers anticipated but MCC is rare & should be managed in specialist centres.

Clinical expert opinion (contd.)

- Avelumab should be used as early in the pathway as possible for potential maximisation of beneficial outcomes.
- With avelumab available, more patients will be able to receive treatment in first-line setting.
- In first-line, avelumab would be expected to achieve a slightly better response rate than in the second-line but the increase would be modest.
- Immunotherapy is generally easier to deliver than cytotoxic.

Patients' issues

- Burden of living with a rare, aggressive and largely untreatable cancer
- Lack of clarity and certainty affects quality of life & wellbeing
- Patients want disease control, tolerability, sustained response and hope
- Patients views of the benefits of avelumab
- Patients' concerns re availability of and access to avelumab

Source: NET Patient Foundation

JAVELIN Merkel 200 trial study (avelumab; no comparator)

	PART A	PART B
Design	Phase II, single-arm, open-label	
Population	patients with mMCC who have failed at least 1 line of prior CT **(=2L+)**	patients with mMCC with no prior systemic therapy for metastatic disease **(=1L)**
N	88	[redacted](still enrolling patients; target n=112)
Data cut-off	24 March 2017 Next analysis [redacted]	24 March 2017 Next analysis [redacted]
Outcomes	1º Best overall response (BOR) 2º Duration of response (DoR), PFS, OS, safety	1º Durable response rate (DRR) defined as objective response [CR or PR] lasting at least 6 months 2º DoR, PFS, OS
Follow-up	Ongoing (18 months so far)	Varying lengths of follow-up: [redacted] have ≥ 3 months follow-up; [redacted] have 6 months follow-up
Completion date	June 2025 (primary completion date: Sept. 2019)	June 2025 (primary completion date: Sept. 2019)
Stop. rule	Treatment should continue until disease progression or unacceptable toxicity	
Add. Info.	Exclusion of immunosuppressed patients; no UK patients were included	

CR: complete response; CT: chemotherapy; ITT: intention-to-treat; mMCC: metastatic Merkel cell carcinoma; PR: partial response; OS: overall survival; PFS: progression-free survival

ERG's critique on JAVELIN Merkel 200

Theme	Critique
Evidence search	Evidence may have been missed
Patient number	[redacted]
Baseline characteristics and trial generalisability	• Younger patients than clinical practice in 2L+ cohort • Possible underestimation of efficacy for 2L+ cohort • Concern around generalisability of trial result (no English patients; patients have ECOG PS better than clinical practice)
OS confounded	Due to use of subsequent treatments
Design	PFS and OS should be interpreted with caution because of the nature of single-arm studies

ECOG PS: Eastern Cooperative Oncology Group performance status

Company carried out naïve comparison of JAVELIN with two other observational studies of chemotherapy in metastatic MCC

- Study 100070-Obs001 & Iyer 2016
- Immunocompromised patients were included in the observational studies (excluded in JAVELIN)
- Company's view: immunosuppressed patients not anticipated to achieve different survival outcomes from immunocompetent patients in JAVELIN
- Chemotherapy regimens efficacy in observational studies was assumed to be equal to the efficacy of BSC
- Company's view: chemotherapy not proven effective in second or later line

Observational studies used for comparison

Study 100070-Obs001 (intervention: chemotherapy)			Iyers et al. 2016 (intervention: chemotherapy)
	PART A - US	**PART B - EU**	
Design	Retrospective observational studies		
Population	patients who received systemic chemotherapy for ○ at least 1 line (2L) ○ 1 line (1L)	patients who received any 2 lines or later systemic chemotherapy (2L+)	patients who received 1 or 2 lines systemic chemotherapy (1L and 2L)
N	20 (2L); 67 (1L)	34	30 (1L); 62 (2L)
Outcomes	ORR, DoR, PFS, OS, TTD, DRR		Response rates, DoR
Inclusion criteria	Include immunosuppressed patients		Include immunosuppressed patients
Study period	2004 - 2015		2002 - 2014

DoR: duration of response; DRR: durable response rate; ORR: overall response rare; OS: overall survival; PFS: progression-free survival; TTD: time to death

ERG's critique of observational studies

- The inclusion of immunocompromised patients may be a confounder in any unadjusted analyses.
- ERG is concerned that the differences in baseline characteristics are not accounted for in the naïve comparisons presented in the CS.
- ERG is unclear why the Iyer. 2016 paper was selected from the other papers identified by the SLR.

Clinical results for 2L+ cohort

Efficacy parameter	JAVELIN Merkel 200 (Part A - 2L+ cohort, N=88) *18-mo follow-up*	Study 100070-Obs001 Overall		Iyer 2016 (N=30)
		(Part A - US) (N=20)	(Part B - EU) (N=34)	
BOR per RECIST 1.1 n (%)				
CR	[redacted]	0	0	1 (3.3)
PR	[redacted]	4 (20.0)	3 (8.8)	6 (20.0)
ORR (%)				
Response rate (CR+PR)	[redacted]	20.0	8.8	23.3
DoR (%)				
6–mo DRR	[redacted]	0	0	6.7
PFS rate (%)				
6-mo PFS	[redacted]	0	2.9	13
12-mo PFS	[redacted]	0	0	NR
OS rate (%)				
6-month OS	[redacted]	30.2	26.4	NR
12-month OS	[redacted]	0	0	NR

RECIST 1.1: response evaluation criteria in solid tumours (version 1.1)

KM curve for PFS* - 2L+ cohort

Avelumab is associated with a longer PFS compared to chemotherapy

*Data from the JAVELIN Merkel 200 trial and Study 100070-Obs001

KM curve for OS* - 2L+ cohort

Avelumab is associated with a longer OS compared to chemotherapy

*Data from the JAVELIN Merkel 200 trial and Study 100070-Obs001

Clinical results for 1L cohort

Efficacy parameter	JAVELIN Merkel 200 (Part A – 1Lcohort)		Study 100070-Obs001 Overall	Iyer et al. 2016 (N=62)
	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)	8 (12.9)
PR	[redacted]	[redacted]	11 (16.4)	26 (41.9)
ORR (%)				
Response rate (CR+PR)	[redacted]	[redacted]	31.3	55
DoR (%)				
6–month DRR	-	[redacted]	14.9	2.8
PFS (%)				
6-mo PFS rate	[redacted]		44.8	-
12-mo PFS rate	-		21.8	-
OS *FULL ANALYSIS* [redacted]				
6-month OS rate	[redacted]		70.1	-
12-month OS rate	-		44.0	-

Adverse events

Avelumab has a tolerable safety profile

Adverse events, n (%)	2L+ cohort 18-mo follow-up (N=88) median duration of therapy: [redacted]	1L cohort 3-mo follow-up (N=[redacted]) median duration of therapy: [redacted]
Treatment related AE (TEAE)	[redacted]	[redacted]
All Grade ≥3	[redacted]	[redacted]
Serious treatment-emergent AEs	[redacted]	[redacted]
Serious treatment-emergent AEs related to avelumab	[redacted]	[redacted]
AE leading to discontinut.	[redacted]	[redacted]
Immune-related AE	[redacted]	[redacted]
Infusion-related AE	[redacted]	[redacted]
Leading to permanent discontinuation	[redacted]	[redacted]
Deaths		
Related to TEAEs	[redacted]	[redacted]
Related to avelumab	[redacted]	[redacted]

- The data came for JAVELIN Merkel 200 trial
- The ERG notes the absence of long-term safety data

ERG's critique of the clinical results

- ERG agree with the use of chemotherapy as a surrogate for BSC in the model
- Limited evidence on the clinical efficacy for 2L+ and 1L cohort due to the single-arm non-randomised
- Immature OS data particularly for the 1L cohort

Key clinical issues for consideration

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Back-up slides

Durable response

- Defined as an objective response (CR or PR) lasting at least 6 months.
- Durability of response a key potential benefit of avelumab
- Driven by the mechanism of action that triggers a sustained activation of the immune system
- Immuno-oncology therapies have shifted the focus of new treatments from survival curves (median PFS) to the tail of the curve (2-year or 5-year PFS rates)
- For 2L+ cohort data, avelumab's effect is in line with other immuno-oncology therapies in analogue disease areas* (median PFS avelumab: [redacted]; median PFS analogues: 1.4 - 4.7 months)
- Correlation between PFS and OS: benefit is also observed in OS

*such as small cell lung cancer and advanced melanoma