NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avelumab for treating metastatic merkel cell carcinoma [ID1102]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Avelumab for treating metastatic merkel cell carcinoma [ID1102]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Avelumab for treating metastatic Merkel cell carcinoma

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Acronym	Definition
AE	Adverse event
AUC	Area under the curve
BOR	Best overall response
BSC	Best supportive care
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
DoR	Duration of response
DRR	Durable response rate
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EQ-5D	EuroQoL - 5 dimensions
ERG	Evidence Review Group
FACT-M	Functional Assessment of Cancer Therapy - Melanoma
FDA	Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat

Acronym	Definition
IV	Intravenous
KM	Kaplan-Meier
LY	Life year
MAIC	Matching Adjusted Indirect Comparison
NE	Non-estimable
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PIM	Promising Innovative Medicine
PP	Post-progression
PR	Partial response
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SCLC	Small cell lung cancer
SD	Stable disease
TEAE	Treatment-emergent adverse event
TOT	Time on treatment
TRAE	Treatment-related adverse events

Clinical effectiveness

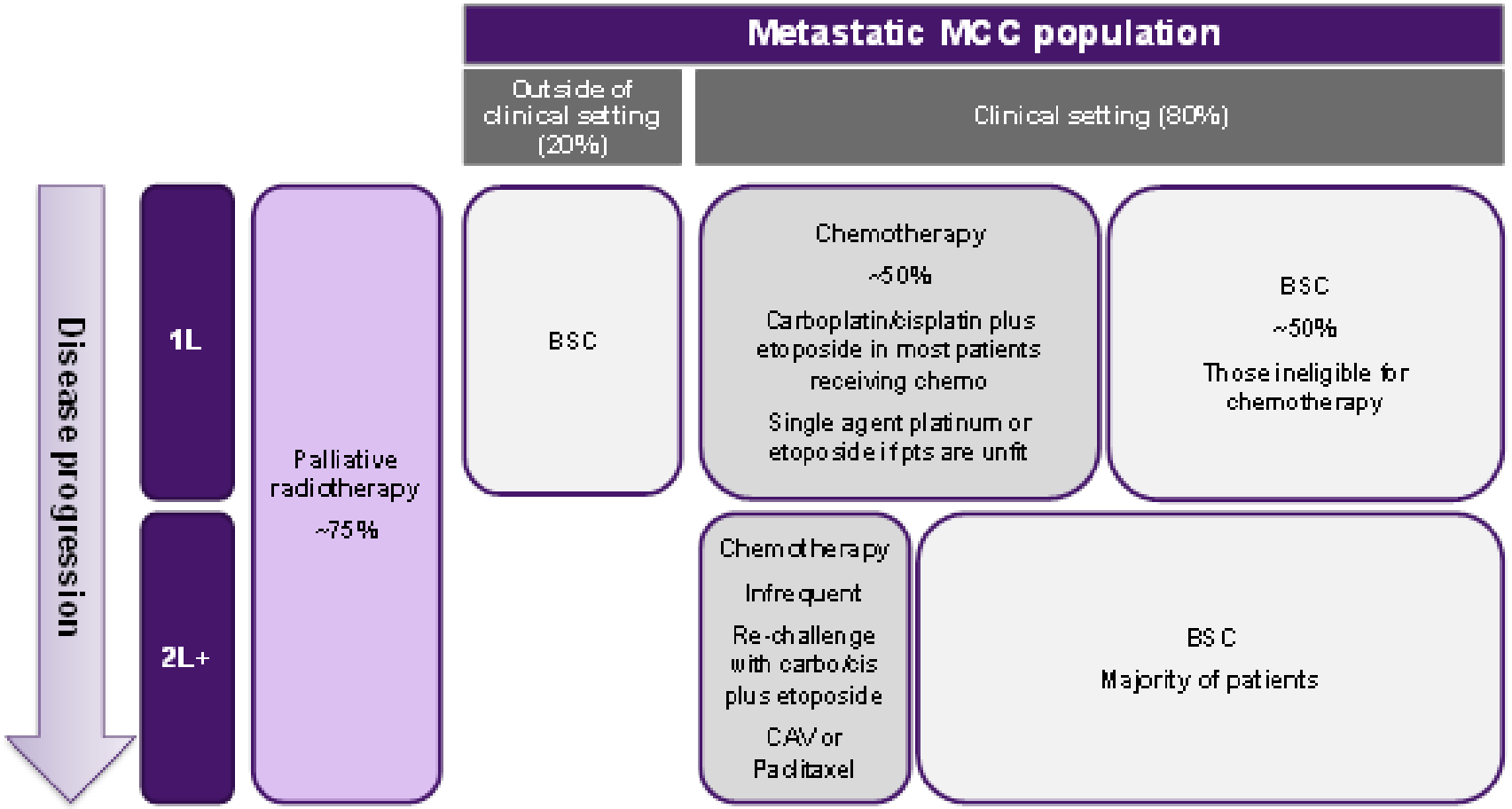
Key clinical issues for consideration

- The key clinical effectiveness evidence for avelumab was obtained from a single-arm study:
  - Is the trial generalizable to the UK population?
  - What is the committee's view on the OS and PFS estimates for treatment-experienced and treatment-naïve population?
- The population of patients with metastatic MCC was very small for treatment-naïve. What is the committee's view on the results in this population?
- Does the committee consider that the naïve comparison with observational data is appropriate?

Background

- Merkel cell carcinoma (MCC) is a rare skin cancer
- Merkel cells are present in the top layer of the skin that help us respond to touch
- Carcinoma occurs when the Merkel cells start to grow out of control. It usually presents as a lump of unbroken skin, similar to a boil or an infectious lump, often in areas of the body that receives direct sun exposure
- MCC is symptomless in the initial stages making it difficult to diagnose
- Common in older people and in people with fairer skin
- In 2010, 53 to 106 people were diagnosed in England
- Poor prognosis with a 5 year survival rate of 64%, dependent upon stage (stage I: 81%; stage II: 67%; stage III: 52%; stage IV: 11%)

Treatment pathway for MCC



- **1L:** 50% of mMCC patients will receive chemotherapy and 50% will receive palliative care/best supportive care (BSC)
- **2L:** most patients will receive BSC

Treatment guidelines for MCC

- No related NICE technology appraisals
- No clinical guidelines specific
- No approved therapies, no standard of care
- Related guidelines include:
  - NICE Quality Standard No. 130 “Skin Cancer” (September 2016): https://www.nice.org.uk/guidance/qs130
  - Skin cancer (updated February 2015) NICE pathway: http://pathways.nice.org.uk/pathways/skin-cancer
  - London Cancer: Skin Cancer Radiotherapy Guidelines (August 2014): http://www.londoncancer.org/media/76382/london-cancer-skin-radiotherapy-guidelines-2013-v1.0.pdf

Decision problem
Comparators for 1L and 2L+ is 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 (Bavencio) Pfizer/Merck

- 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 20 September 2017)
- Administered by IV infusion, 10 mg/kg over 60 minutes every 2 weeks (requires premedication with an antihistamine and acetaminophen before the first 4 infusions)
- 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

CHMP: Committee for Medicinal Products for Human Use; EC: European Commission; EMA: European Medicines Agency; MHRA: Medicines and Healthcare products Regulatory Agency; FDA: US Food and Drug Administration

Clinical expert opinion

- Proven efficacy in metastatic Merkel cell carcinoma
- Excellent option for second-line (after chemotherapy failure), with rapid kinetics of benefit, a solid response rate in about a third of patients, durable responses 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
- Variable duration of clinical benefit between individuals, depends on the degree of initial response.
- Natural history of MCC, described in retrospective case reviews, is line with clinical experience
- MCC is rare hence importance of patients being managed in specialist centres (seen as a potential equality issue for poorer people because travel can be expensive)
- Better tolerated than chemotherapy, although safety should continue to be monitored.
- No major implementations barriers anticipated

Impact on patients and carers

- Emotional burden of living with an aggressive and largely untreatable cancer
- Avelumab provides disease control, tolerability and sustained response
- Avelumab offers a real innovative step change, in treatment, for those with residual or inoperable disease
- First immunotherapy treatment for MCC
- Could be difficult in accessing if only available in specialist centre as it would necessitate extra travel
- Worry avelumab might be restricted to the age (as it is know as a “a disease of the older person”)

Company's clinical evidence

JAVELIN Merkel 200 trial study

Intervention: avelumab; no comparator (ITT analysis)		
	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	39 (still enrolling patients; target n=112)
Data cut-off	24 March 2017 Next analysis planned at 24 months [redacted]	24 March 2017 Next analysis planned at [redacted] with 3-month follow-up [redacted]
Outcomes	1º Best overall response (BOR) 2º DoR, PFS, OS, safety	1º Durable response rate (DRR)* 2º DoR, PFS, OS
Follow-up	Ongoing (18 months so far)	Varying lengths of follow-up: 29/39 have ≥ 3 months follow-up; 14 have 6 months follow-up
Completion date	June 2025 (primary completion date: Sept. 2019)	June 2025 (primary completion date: Sept. 2019); last patient recruitment [redacted]
Stopping rule	Treatment should continue until disease progression or unacceptable toxicity	
Add. Info.	Immunosuppressed patients were excluded; no UK patients were included	

*Durable response was defined as objective response (complete response [CR] or partial response [PR]) according to RECIST 1.1 lasting at least 6 months

CT: chemotherapy; DoR: duration of response; ITT: intention-to-treat; mMCC: metastatic Merkel cell carcinoma; OS: overall survival; PFS: progression-free survival

ERG's critique on JAVELIN Merkel 200

Theme	Critique
Evidence search	Evidence from ongoing or unpublished studies may have been missed (no trial registry search, suppl. search not described in detail)
Patient number	• The small sample size for the 1L and 2L+ cohorts may lead to uncertain and imprecise estimates of safety and efficacy
Baseline characteristics and trial generalisability	• Median age for 2L+ cohort slightly younger than clinical practice • Efficacy for 2L+ cohort might be underestimated as 35.2% were treated for third line and beyond although this might be due to more aggressive treatment in the non-UK countries • Concern around the generalisability of the trial result to the population in England most likely to be eligible for treatment with avelumab as there were no study sites in England and high proportion of patients with ECOG PS better than clinical practice
OS confounded	OS estimates likely to be confounded by the use of subsequent treatment although no data on subsequent treatments were recorded
Design	PFS and OS estimates should be interpreted with caution because of the nature of single-arm studies

ECOG PS: Eastern Cooperative Oncology Group performance status; OS: overall survival; PFS: progression-free survival

Clinical results for JAVELIN Merkel 200 2L+ cohort (PART A)

Efficacy parameter	Part A - 2L+ cohort (N=88)		
	6-month follow-up	*12-month follow-up*	*18-month follow-up*
BOR by RECIST 1.1			
CR, n (%)	8 (9.1)	10 (11.4)	10 (11.4)
PR, n (%)	20 (22.7)	19 (21.6)	19 (21.6)
SD, n (%)	9 (10.2)	9 (10.2)	9 (10.2)
PD, n (%)	32 (36.4)	32 (36.4)	32 (36.4)
Non-CR/Non-PD, n %	1 (1.1)*	0	0
Not evaluable, n %	18 (20.5)	18 (20.5)	18 (20.5)
ORR, % (95% CI)			
Response rate (CR+PR)	31.8 (21.9-43.1)	33.0 (23.3-43.8)	33.0 (23.3-43.8)

BOR: Best overall response; CR: Complete response; DoR: Duration of response; DRR: Durable response rate; PD: Progressive disease; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: Stable disease

Clinical results for JAVELIN Merkel 200 2L+ cohort (PART A)

Efficacy parameter	Part A - 2L+ cohort (N=88)		
	6-month follow-up	*12-month follow-up*	*18-month follow-up*
DoR (95% CI)			
Median (months)	NR (2.8 – 17.5)	NR (2.8 – 23.3)	NR (2.8 – 24.9)
6–month DRR (%)	29.1	30.7	30.7
PFS (95% CI)			
Median (months)	2.7 (0.03 –18.8)	2.7 (0.03 – 24.5)	2.7 (0.03 – 28.9)
6-month PFS rate,%	40 (29 – 50)	40 (29 – 50)	40 (29 – 50)
12-month PFS rate%	30 (19 – 41)	30 (21 – 41)	[redacted]
18-month PFS rate %	-	-	[redacted]
OS (95% CI)			
Median (months)	11.3 (7.5 – 14.0)	12.9 (7.5 – NE)	[redacted]
6-month OS rate %	69 (58 – 78)	70 (59 – 78)	[redacted]
12-month OS rate %	48 (35 – 60)	52 (41 – 62)	[redacted]
18-month OS rate %	-	-	[redacted]

DoR: Duration of response; NR: not reached; OS: overall survival; PFS: progression-free survival

Kaplan-Meier estimate in PFS in the 2L+ cohort (PART A) – ITT population

Kaplan-Meier estimate in OS in the 2L+ cohort (PART A)

Clinical results for JAVELIN Merkel 200 1L cohort (PART B)

Efficacy parameter	Part B – 1L cohort (N=39)	
	3-month follow-up (N=29)	*18-month follow-up (N=14)*
BOR by RECIST 1.1		
CR, n (%)	4 (13.8)	[redacted]
PR, n (%)	14 (48.3)	[redacted]
SD, n (%)	3 (10.3)	[redacted]
PD, n (%)	7 (24.1)	[redacted]
Non-CR/Non-PD, n %	0	[redacted]
Not evaluable, n %	1 (3.4)	[redacted]
ORR, % (95% CI)		
Response rate (CR+PR)	62.1 (42.3-79.3)	[redacted]

BOR: Best overall response; CR: Complete response; DoR: Duration of response; DRR: Durable response rate; PD: Progressive disease; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: Stable disease

Clinical results for JAVELIN Merkel 200 1L cohort (PART B)

Efficacy parameter	Part B – 1L cohort (N=39)	
	3-month follow-up (N=29)	*6-month follow-up (N=14)*
DoR (95% CI)		
Median (months)	NR (1.2 – 8.3)	[redacted]
6–month DRR (%)	-	[redacted]
PFS (95% CI)		
Median (months)	[redacted]	[redacted]
3-month PFS rate,%	[redacted]	[redacted]
OS (95% CI)		
Median (months)	[redacted]	[redacted]
3-month OS rate %	[redacted]	[redacted]

*ORR multiplied by Kaplan-Meier estimate for 6-month proportion of DoR
DoR: Duration of response; NR: not reached; OS: overall survival; PFS: progression-free survival

Kaplan-Meier estimate in PFS in the 1L cohort (PART B) – ITT population

Kaplan-Meier estimate in OS in the 1L cohort (PART B)

Durable response

- Defined as an objective response (CR or PR) according to RECIST 1.1 lasting at least 6 months.
- One of the key benefits 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: effect also observed in OS

*such as small cell lung cancer and advanced melanoma

Company's clinical evidence

Observational studies

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 based on BOR, DoR, PFS, OS, TTD, and DRR to the index (2L+) chemotherapy treatment*; the same outcomes were assessed for 1L for PART A only		Response rates, DoR of 1L and 2L
Inclusion criteria	Diagnosed with either metastatic MCC or distant metastatic MCC, including immunosuppressed patients**	Diagnosed with distant metastatic MCC, including immunosuppressed patients**	Diagnosed with distant metastatic MCC, including immunosuppressed patients
Study period	2004 - 2015		2002 - 2014

*BOR used RECIST 1.1 for PART A, BOR and DoR used clinical judgement for PART B **
**the company explained that immunosuppressed patients were not anticipated to achieve different survival outcomes from immunocompetent patients in 1L and 2L+ cohort (see clarification response) ;BOR: Best overall response; CR: Complete response; DoR: Duration of response; DRR: Durable response rate; OS: overall survival; PFS: progression-free survival

Note: chemotherapy regimens efficacy was assumed to be equal to the efficacy of BSC

ERG's critique on observational studies

- The inclusion of immunocompromised patients may be a confounder in any unadjusted analyses.
- The ERG is concerned that the differences in baseline characteristics (e.g., inclusion of immunocompromised patients and patients with better ECOG PS) 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 (it reports data on both 1L and 2L).

Clinical results for 2L+ cohort

Naïve comparison between trial and observational studies

- Favourable results for avelumab in the JAVELIN Merkel 200 trial in a treatment-experienced (=2L+) metastatic MCC population relative to chemotherapy in the observational studies (Study 100070-Obs001 and Iyer et al. 2016)

Efficacy parameter	JAVELIN Merkel 200 (Part A - 2L+ cohort) (N=88) *18-months 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				
CR, n (%)	10 (11.4)	0	0	1 (3.3)
PR, n (%)	19 (21.6)	4 (20.0)	3 (8.8)	6 (20.0)
SD, n (%)	9 (10.2)	2 (10.0)	3 (8.8)	1 (3.3)
PD, n (%)	32 (36.4)	8 (40.0)	28 (82.4)	22 (73.3)
Non-CR/Non-PD, n %	0	0	0	0
Not evaluable, n %	18 (20.5)	6 (30.0)	0	0

BOR: Best overall response; CR: Complete response; DoR: Duration of response; DRR: Durable response rate; PD: Progressive disease; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: Stable disease

Clinical results for 2L+ cohort (contd.)

Naïve comparison between trial and observational studies

- Response rates in US observational studies (Study 100070-Obs001 – Part A and Iyer et al. 2016) are surprisingly higher than EU study (Study 100070-Obs001 – Part B), probably due to more aggressive treatments administered in the US.

Efficacy parameter	JAVELIN Merkel 200 (Part A - 2L+ cohort) (N=88) *18 months FU*	Study 100070-Obs001 Overall		Iyer et al. 2016 (N=30)
		(Part A - US) (N=20)	(Part B - EU) (N=34)	
ORR (95% CI)				
Response rate (CR+PR)	33.0 (23.3-43.8)	20.0 (5.7-3.7)	8.8 (1.9-23.7)	23.3 (9.9-42.3)
DoR (95% CI)				
Median (months)	NE (18.0-NE)	1.7 (0.5-3.0)	1.9 (1.3-2.1)	3.3
6–month DRR (%)	30.7 (20.9-40.3)	0.0 (0.0-16.8)	0.0 (0.0-10.3)	6.7 (0.8-22.1)
PFS (95% CI)				
Median (months)	2.7 (1.4-6.9)	2.1 (1.0-3.2)	3.0 (2.6-3.1)	2.0 (1.3-2.7)
6-mo PFS rate,%	40.0 (29.0-50.0)	0.0	2.9 (0.2-13.0)	13
12-mo PFS rate%	29.0 (19.0-39.0)	0.0	0.0	NR
OS (95% CI)				
Median (months)	[redacted]	4.4 (2.2-6.2)	5.3 (4.3-5.8)	5.7 (NR)
6-month OS rate %	70.0 (59.0-78.0)	30.2(11.6-51.4)	26.4 (13.1-41.8)	NR
12-month OS rate %	51.0 (40.0-61.0)	0.0	0.0	NR

PFS Kaplan-Meier estimates for avelumab versus chemotherapy* the 2L+ cohort

*Data from the Study 100070-Obs001

OS Kaplan-Meier estimates for avelumab versus chemotherapy* the 2L+ cohort

*Data from the Study 100070-Obs001

Clinical results for 1L cohort

Naïve comparison between trial and observational studies

- Overall favourable results for avelumab in the JAVELIN Merkel 200 trial in a treatment-naïve (=1L) metastatic MCC population relative to chemotherapy in the observational studies (Study 100070-Obs001 and Iyer et al. 2016)

Efficacy parameter	JAVELIN Merkel 200 (Part A - 2L+ cohort) (N=88)		Study 100070-Obs001 Overall	Iyer 2016) (N=62)
	3-month FU (N=29)	*6-month FU (N=14)*	*(Part A - US) (N=67)*	
BOR per RECIST 1.1				
CR, n (%)	4 (13.8)	4 (28.6)	10 (14.9)	8 (12.9)
PR, n (%)	14 (48.3)	6 (42.9)	11 (16.4)	26 (41.9)
SD, n (%)	3 (10.3)	1 (7.1)	1 (1.5)	4 (6.5)
PD, n (%)	7 (24.1)	2 (14.3)	31 (46.3)	24 (38.7)
Non-CR/Non-PD, n %	0	0	-	-
Not evaluable, n %	1 (3.4)	1 (7.1)	-	-

BOR: Best overall response; CR: Complete response; DoR: Duration of response; DRR: Durable response rate; FU: follow-up; PD: Progressive disease; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: Stable disease

Clinical results for 1L cohort (contd.)

Naïve comparison between trial and observational studies

Efficacy parameter	JAVELIN Merkel 200 (Part A - 2L+ cohort) (N=88)		Study 100070-Obs001 Overall	Iyer et al. 2016 (N=30)
	3-month FU (N=29)	*6-month FU (N=14)*	(Part A - US) (N=20)	
ORR (95% CI)				
Response rate (CR+PR)	62.1 (42.3-79.3)	71.4 (41.9-91.6)	31.3 (20.6-43.8)	55
DoR (95% CI)				
Median (months)	NR (4.0-NR)	NR (4.0-NR)	5.7 (2.6-8.7)	3.0
6–month DRR (%)	-	64.5*	14.9 (7.4-25.7)	2.8
PFS (95% CI)				
Median (months)	9.1 (1.9-NR)			3.4
6-mo PFS rate,%	52.0 (31.0-69.0)		4.6 (3.0-7.0)	-
12-mo PFS rate%	-		21.8 (12.7-32.4)	-
OS (95% CI)	*FULL ANALYSIS (N=39)*			
Median (months)	NR (9.1-NR)		10.2 (7.4-15.2)	9.5
6-month OS rate %	83.0 (64.0-93.0)		70.1 (57.5-79.5)	-
12-month OS rate %	-		44.0 (31.5-55.8)	-

*ORR multiplied by Kaplan-Meier estimate for 6-month proportion of DoR

CI: Confidence interval; DoR: Duration of response; DRR: Durable response rate; FU: follow-up; NR: Not reached; ORR: Overall response rate;

ERG's critique on the clinical results

- ERG agree with chemotherapy used as a surrogate to provide the comparison of avelumab versus BSC in the economic modelling, as "efficacy outcomes with BSC and chemotherapy are likely to be very similar due to very poor patient performance with both"
- Limited quantity and quality evidence on the clinical efficacy of avelumab for the treatment of 2L+ and 1L mMCC due to the single-arm non-randomised
- OS data are immature for JAVELIN Merkel 200 and particularly for the 1L cohort (Part B) with median OS not yet being reached and data restricted to 3 months' follow-up. Comparative results should be interpreted with caution
- ERG considers it important to highlight that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as OS and so the data presented here should be interpreted with caution.

Indirect comparison

- In the CS, the company claimed there were no patient characteristics that were prognostic of outcomes in mMCC and for this reason they did not consider that statistical adjustments were necessary to match the observational data to the relevant cohorts within JAVELIN Merkel 200. The company presented data from each of the two single-arm studies side-by-side in the CS as a naïve comparison.
- At the clarification stage, the ERG requested a matched adjusted indirect comparison (MAIC) analysis of the JAVELIN Merkel 200 trial and the Study 100070-Obs001, as well as with Iyer. 2016 for PFS and OS (part A and part B) for 1L and 2L+
  - The company questioned the appropriateness of a MAIC because of
    - availability of individual level data for both studies (MAIC is recommended when only aggregated level data are available to avoid an "over-adjustment")
    - small number of patients did not show no patient characteristics were associated with differences in the efficacy of avelumab, whereas MAIC requires matching variables to be prognostic
  - The ERG considers the small number of patients means that there is a large amount of uncertainty around the results and therefore the possibility of prognostic indicators still remains.

Additional analysis

The company did not present MAIC analysis, they presented the following alternative

adjustment	Population	Alternative analysis	ERG critique
JAVELIN Merkel 200 trial and Study 100070 - Obs001	**2L+ cohort** • JAVELIN Merkel 200: n=88 with [redacted] • Observational: n=54 with PFS events n=54, OS events n=52	**Propensity score matching**	• only matched on age and gender and fail to balance the population for all characteristics. Analysis potentially unreliable • ERG would have preferred an analysis with further potential prognostic factors adjusted for
		Weibull regression	• included for immunosuppression status adjusted to JAVELIN Merkel 200 trial • lack of adjustment for other important variables such as ECOG status and stage of disease at diagnosis. • more robust analysis compared to the naïve comparison and propensity score matching because it adjusts for a greater range of likely covariates

Propensity score matched Kaplan-Meier curves for the 2L+ cohort

Note: The lighter shaded areas denoting the associated 95% confidence interval. The 95% confidence intervals for each curve demonstrate that with the reduced sample size, additional uncertainty is present for each curve

Additional analysis (contd.)

adjustment	Population	Alternative analysis	ERG critique
JAVELIN Merkel 200 trial and Study 100070-Obs001	**1L cohort** JAVELIN Merkel 200: n=39 with [redacted] • Observational: n=67 with PFS events n=58, OS events n=49	**No analysis**	[redacted]

For the adjustment of JAVELIN Merkel 200 trial and Iyer. 2016 study: MAIC was considered appropriate but problematic due to absence of requested characteristics and small number of patients (n=39).

*For propensity scoring, the literature recommends a minimum of 10 events for every characteristic to be included (Austin, 2011).

Adverse events

Avelumab has a similar safety profile as other immuno-therapies

- **JAVELIN Solid Tumor study** (n=1,540): Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, PK, biological, and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumours (include MCC and other tumour types)
  - No result was reported; ERG is unclear on its relevance
- **JAVELIN Merkel 200** (n=127) data cut-off for safety analyses was 18-months follow-up for 2L+ cohort (Part A) and 3-months follow-up for 1L cohort (Part B). [safety data fed into the model*]:
  - treatment with avelumab associated with a tolerable and manageable safety profile (most AEs were low grade)
  - safety profile for avelumab in line with reported AEs for other immuno-therapies in analogue diseases
- For the chemotherapy arm, data from SCLC and melanoma were extracted from the literature. Considered as a reasonable approach by ERG
- The ERG notes the absence of long-term safety data

*In the model, AE rates for 1L cohort were assumed the same as for 2L+ cohort because data from first few months of treatment in 1L cohort would be misrepresentative of AE rates as a whole

Adverse events (contd.)

Avelumab patients experienced a high proportion of TRAE

Adverse events	2L+ cohort (Part A) 18-month follow-up (N=88)	1L cohort (Part B) 3-month follow-up (N=39)
	median duration of therapy: [redacted]	median duration of therapy: [redacted]
TRAE	[redacted]	[redacted]
All Grade ≥3, n (%)	[redacted]	[redacted]
Serious TEAEs, n (%)	[redacted]	[redacted]
Serious TEAEs related to avelumab, n (%)	[redacted]	[redacted]
AE leading to discontinuation, n (%)	[redacted]	[redacted]
irAEs	[redacted]	[redacted]
Infusion-related AE	[redacted]	[redacted]
Leading to permanent discontinuation	[redacted]	[redacted]
Deaths, n (%)		
Related to TEAEs	[redacted]	[redacted]
Related to avelumab	[redacted]	[redacted]

irAEs: Treatment-emergent immune-related adverse events; TEAEs; Treatment-emergent adverse events; TRAE: treatment related adverse events

Health-related quality of life
Avelumab is associated with stability in HRQoL

- The JAVELIN Merkel 200 trial assessed the HRQoL of enrolled patients, using EQ-5D-5L and FACT-M* questionnaires
  - EQ-5D-5L mapped to EQ-5D-3L (van Hout et al. 2012**): baseline score = [redacted], higher than general population utility. CS reported it might be due to euphoria of patients after seeing skin lesion disappear or patients expecting long-term survival from treatment
  - Overall, results showed stability in patients' HRQoL over time
- NICE technical team looked for utilities used in previous appraisals for melanoma:

	Utility value	Reference
PFS	0.7954	NICE TA400 (nivolumab w/ipilumab)
	0.7795 - 0.8018	NICE TA384 (nivolumab)
	0.50	NICE TA268 (ipilimumab)
Progressed	0.7625	NICE TA400 (nivolumab w/ipilimumab)
	0.7054 - 0.7277	NICE TA384 (nivolumab)
	0.76	NICE TA268 (ipilimumab)

*Due to the similarities between MCC and melanoma, FACT-M was deemed to be a suitable tool
**In line with NICE position statement on EQ-5D-5L

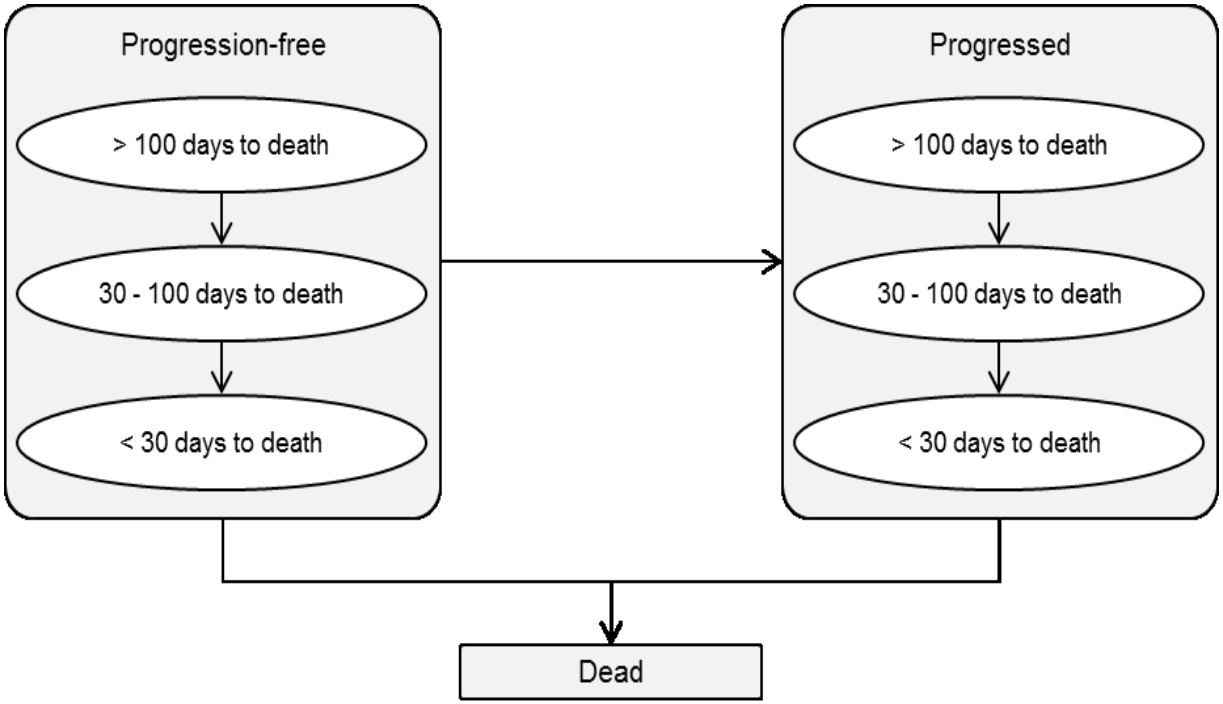
Cost-effectiveness

Key cost-effectiveness issues for consideration

- What clinical assumptions are the most plausible for the estimation of treatment effectiveness for treatment-experienced and treatment-naïve population?
- What clinical assumptions are the most plausible for the estimation of time on treatment for treatment-experienced and treatment-naïve population?
- Is the baseline utility value used in the model appropriate to use in the cost-effectiveness modelling?
- Does avelumab meet end-of life criteria for treatment-naïve patients? For treatment-experienced patients?

Model structure

- Partitioned-survival model (or ‘area under the curve’)
- 3 mutually exclusive health states: progression-free disease, progressed disease, death
- 3 sub-states: >100 days to death; 30-100 days until death; <than 30 days until death
- 2 populations considered separately: treatment-experienced (2L+), treatment-naïve (1L)
- Time horizon: 40 years
- Cycle length: 7 days



Comparative effectiveness data

Populations	Source	ERG critique
Avelumab versus BSC in 2L+ patients *(BSC is a proxy for chemotherapy)*	• Base case: pooled data from Study 100070-Obs001 Part A and Part B • Sensitivity analysis: meta-analysis of Study 100070-Obs001, Iyer 2016 and Samlowski 2010	Result should be interpreted with caution: Samlowski 2010 presents clinical heterogeneity because of it include a mix 1L (n=9) and 2L+ (n=12) patients
Avelumab versus chemotherapy in 1L patients	Pooled data from Study 100070-Obs001 and 6 studies (Iyer 2016; Voog 1999; Satpute 2014; Santamaria-Barria 2013; Fields 2011; Allen 2005)	Results are likely to have heterogeneities although it is not possible to predict the likely direction of the resulting bias

Base case clinical parameters
Extrapolation beyond trial period

- Avelumab was associated with similar long-term patterns in survival than other immuno-oncology therapies*
- For treatment-naïve patients (=1L), data were too immature** to be extrapolated, therefore the relative improvement with avelumab seen in 1L patients versus those in the 2L group was assessed by clinicians (see next slide)

Outcomes	Avelumab (JAVELIN Merkel 200 trial)		Comparators (pooled data from observational studies)	
	2L+ cohort	1L cohort	2L+ cohort	1L cohort
PFS	Spline "3-knot Odds"	HR=1 (assumed no difference between 1L and 2L+)	Weibull (chemotherapy and BSC)	Log-logistic (chemotherapy and BSC)
OS	Spline "1-knot Odds"	HR=0.80 (clinical validation)	Gompertz (chemotherapy and BSC)	Log-logistic (chemotherapy and BSC)
ToT	Log-logistic (assumed 1/3 patients remain on treatment beyond 2 years for 5 years – curve truncated at 2 years)	HR=1 (assumed no difference between 1L and 2L+)	6 cycles, 2/3 doses (chemotherapy) N/A (BSC)	6 cycles, 2/3 doses (chemotherapy) N/A (BSC)

*See NICE TA268, TA319, TA357, TA384, TA400, TA417, TA428

**Within the submitted cost-effectiveness model, the outcomes of OS, PFS and ToT were not based on data for treatment-naïve patients (1L), as these data were considered too immature for long-term extrapolation

K-M curves for JAVELIN Merkel 200 trial (Part A and B)

At the clarification, the ERG asked for the company to fit all parametric survival curves and splines to the KM curves for 1L data cohort for OS, PFS and ToT. After conducting the exercise, the company concluded that data from this trial are immature and are therefore not considered an accurate basis from which long-term extrapolation may be considered to inform the cost-effectiveness analysis.

ERG critique on treatment effectiveness (OS and PFS)

- Treatment effectiveness is likely to be one of the most influential factors on the economic model results. However the small sample size of both trial and observational studies makes it a a serious limitations
- Naïve comparison is unreliable because of imbalances in patient characteristics

2L+ cohort		1L cohort	
avelumab	**comparator**	**avelumab**	**comparator**
Concern on having different distributions between comparator and avelumab but might be suitable since avelumab causes an immune response	• **Weibull regression** is more reliable than log-logistic • Concern on the lack of adjustment for many characteristics	Concern on HR assumption (HR=0.8 relative to 2L+ cohort) based on clinical validation, causing result as unreliable as the effectiveness estimates of 2L+	• ERG's preferred approach is the **best parametric curve fitting** to the pooled data although the study 100070-Obs001 is the most appropriate data • Remain the issue of the lack of data

ERG critique on treatment discontinuation (ToT)

2L+ cohort	1L cohort
avelumab	**avelumab**

• Company's approach is flawed, very strong assumption on the discontinuation rate and time ("2/3 of patients discontinue treatment at 2 years")
  • unethical to discontinue treatment for patients who may still receiving benefit until there is evidence to suggest that no further benefit would be gained beyond this time
  • not clinically plausible
• ERG's preferred approach is **Weibull without any truncation to the curve**
	• Assumption that ToT is equivalent for both 1L and 2L+ is implausible
	• Assumption underestimates the treatment cost
	• ERG's preferred approach is **Weibull regression**

Health-related quality of life
Time to approach model

- 24 studies on utilities identified through a SLR but no relevant utilities for metastatic MCC could be extracted, therefore utilities and disutilities from literature for other disease area were used (small cell lung cancer [SCLC] and melanoma)
  - Potential limitations due to differences in demographics/ characteristics and disease features between MCC and SCLC/melanoma
- Because of limited data in post-progression heath state (EQ-5D-5L collected only in patients receiving avelumab - stopping rule apply to patients that have progressed), a time to death approach was favoured as a base-case
- Time to death approach modelled 3 time periods before death (<30 days to death, 30-100 days to death, <100 days to death)
- A linear mixed regression model was used to predict utility values according to disease progression status. Results were adjusted for AE disutilities

State	Utility value: mean (SE)	Justification
Progression-free	[redacted]	JAVELIN Merkel 200 patient-level data analysis
Post-progression	[redacted]	

ERG critique on HRQoL

- The linear mixed regression model is a reasonable approach that can capture the changes in quality of life that patients experience over their lifetime, in addition to the changes experienced after progression of the disease.
- The utilities may be high but the same values are applied regardless of treatment group, so the difference in utilities between health states is the key issue rather than the baseline magnitude, and this difference is plausible.
- A comparison with utilities from the literature should have been performed.

Resource and cost

- Company model includes costs associated with drug acquisition, drug administration and medical resource use, and managing of adverse events (are the same for 2L+ and 1L cohorts)
- Avelumab
  - Dose is weight-based so method of moments accounts for wastage were used (as opposed to use of mean weight or BSA)
  - Weight data for European patients (JAVELIN Merkel 200 – Part B) used in the base-case drug dosing calculations, as these patients are most representative of those treated in UK clinical practice.
  - ERG notes that the cost of premedication with an antihistamine and with paracetamol have been omitted (added as part of ERG's scenario analysis)
- Comparators
  - BSC is associated with no cost
  - Chemotherapy regimen cost weighted by market share of chemotherapy regimen (50/50 split of carboplatin and etoposide/cisplatin and etoposide regimens)
  - Safety data from 2 RCTs in patients with SLCL were used (carboplatin + etoposide from Socinski. 2009 and cisplatin + etoposide from Sun. 2016)
- End-of-life cost was taken from the literature

SCLC: small cell lung cancer

Company's base case results for 2L+ cohort after model correction

Deterministic

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Avelumab	£78,752	3.53	2.22	-	-	-	-
BSC	£7,465	0.41	0.31	£71,287	3.11	1.91	£37,350

Probabilistic

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Avelumab	£78,686	3.53	2.22	-	-	-	-
BSC	£7,448	0.41	0.31	£71,238	3.24	1.98	£36,310

Company's scenario analysis for 2L+ cohort

Requested by ERG at clarification

- Using propensity score: the ICER reduced from £37,409 (company's original base-case without the ERG correction) to £33,796

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Avelumab	£78,051	3.87	2.44	-	-	-	-
BSC	£7,319	0.41	0.31				£33,796

- Using Weibull regression analysis: the results demonstrate an increase in the ICER of approximately £235 versus the company's original base-case (without the ERG correction) .

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Avelumab	£78,218	3.53	2.22	-	-	-	-
BSC	£7,279	0.43	0.32				£37,645

Company's base case results for 1L cohort after model correction

Deterministic

Treatment	Total			Incremental			ICER incremental	ICER pairwise *(avelumab vs.)*
	Costs	LYs	QALYs	Costs	LYs	QALYs		
BSC*	£7,217	2.02	1.38	-	-	-	-	£46,148
Chemotherapy*	£10,608	2.02	1.37	£3,392	0.00	-0.01	Dominated	£43,553
Avelumab	£78,588	4.78	2.93	£71,371	2.76	1.55	£46,148	-

Probabilistic

Treatment	Total			Incremental			ICER incremental	ICER pairwise *(avelumab vs.)*
	Costs	LYs	QALYs	Costs	LYs	QALYs		
BSC*	£7,210	2.04	1.39	-	-	-	-	£44,148
Chemotherapy*	£10,611	2.04	1.38	£3,401	0.00	-0.01	Dominated	£42,337
Avelumab	£79,172	4.95	3.02	£71,962	2.91	1.64	£44,186	-

*to enable comparisons to inform the NICE decision problem, chemotherapy regimens efficacy was assumed to be equal to the efficacy of BSC

Company's scenario analysis for 1L cohort

Requested by ERG at clarification

Results from fitting different models to the KM curves (see slide 42)

Description of scenario	ICER
Company's originalbase case (without ERG correction) (HR applied to data from JAVELIN Merkel 200 – Part A)	**£43,633**
Same parametric model for each outcome (log-normal for OS, PFS and ToT)	£51,312
Splines for OS and PFS (spline 1-knot hazard for OS, PFS, log-normal for ToT)	£46,978
Most plausible parametric estimates (log-normal for OS, PFS, Weibull for ToT)	£42,935
Most plausible overall estimates (spline 1-knot hazard for OS, PFS, Weibull for ToT)	£39,409

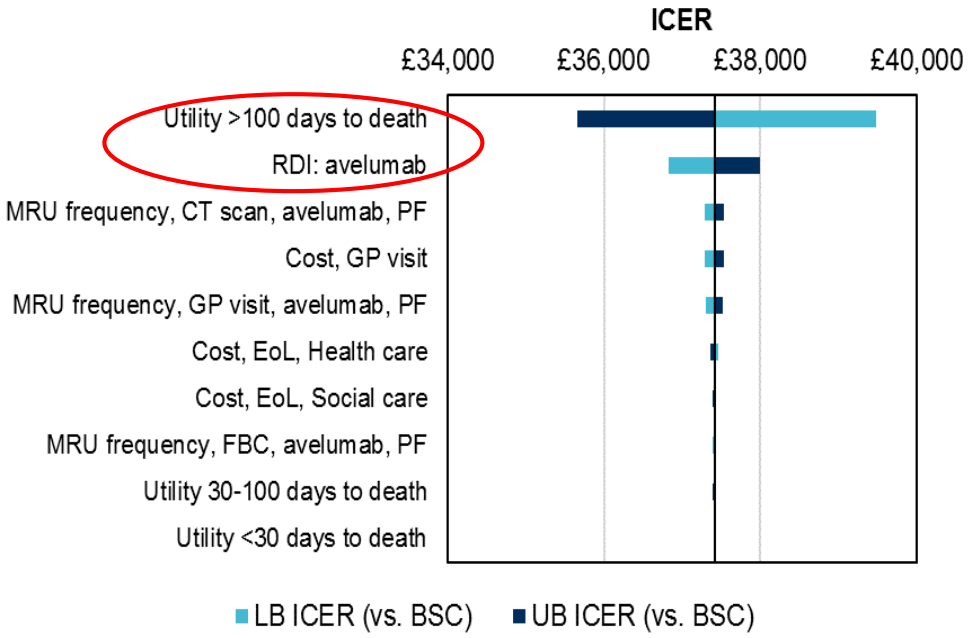
HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

Note: Plausibility of estimates were established based on long-term outcomes and comparison to clinical expectation (e.g. low number of patients on treatment at 5 years, immune-response tail in OS etc.)

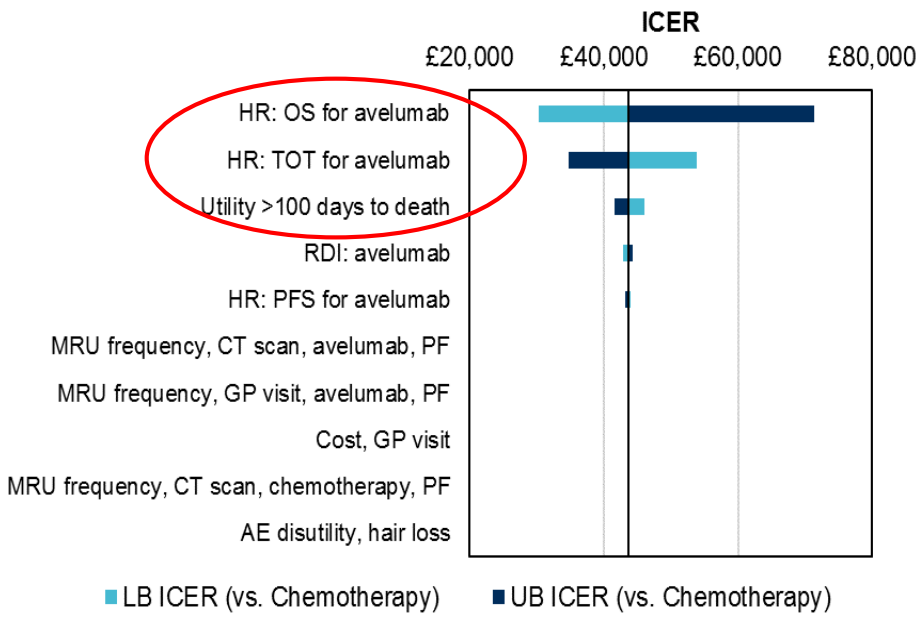
One-way sensitivity analysis

- Each parameter was set to its lower and upper bound and model results were recorded.

2L+ cohort



1L cohort



RDI: relative dose intensity

ERG's preferred base case – 1L

	Avelumab	BSC	Incremental value
Company's base case			
Total costs (£)	**£78,588**	**£7,217**	**£71,371**
QALYs	**2.93**	**1.38**	**1.55**
ICER			**£46,148**
Weibull time on treatment curve (without truncation)			
Total costs (£)	£92,392	£7,217	£85,176
QALYs	2.93	1.38	1.55
ICER			**£55,075**
Parametric curves for PFS and OS			
Total costs (£)	£159,375	£7,217	£152,158
QALYs	2.65	1.38	1.27
ICER (compared with base case)			**£75,430**
Addition of pre-medication costs			
Total costs (£)	£159,570	£7,217	£152,353
QALYs	2.65	1.38	1.27
ICER (compared with base case)			**£46,206**
ERG's alternative base case ICER			
ICER with all changes incorporated			**£120,383**

The ERG explored the impact of substituting GP visits for outpatient oncology visits for patients prior to progression: ICER decreased by less than £1,000

ERG's preferred base case – 2L+

	Avelumab (1)	Chemotherapy (2)	BSC (3)	Incremental (1-2)	Incremental (1-3)
Company's base case					
Total costs (£)	**£78,752**	**£9,838**	**£7,465**	**£68,914**	**£71,287**
QALYs	**2.22**	**0.30**	**0.31**	**1.92**	**1.91**
ICER				**£35,873**	**£37,350**
Weibull time on treatment curve (without truncation)					
Total costs (£)	£92,557	£9,838	£7,465	£82,718	£85,091
QALYs	2.22	0.30	0.31	1.92	1.91
ICER				£43,060	**£44,584**
Weibull regression models for PFS and OS					
Total costs (£)	£92,537	£9,630	£7,413	£82,906	£85,124
QALYs	2.22	0.31	0.32	1.91	1.90
ICER (compared with base case)				£36,199	**£37,582**
Addition of pre-medication costs					
Total costs (£)	£92,644	£9,630	£7,413	£83,014	£85,232
QALYs	2.22	0.31	0.32	1.91	1.90
ICER (compared with base case)				£35,920	**£37,397**
ERG's alternative base case ICER					
ICER with all changes incorporated				£43,488	**£44,914**

The ERG explored the impact of substituting GP visits for outpatient oncology visits for patients prior to progression: ICER decreased by approx. £500

End-of-life

Criterion	Comparator is chemotherapy	Overall survival estimates (months)
Treatment is indicated for patients with a short life expectancy, normally < 24 months		**Median**
	1L	10.2; 9.5 months (from Study 100070-Obs001 PART A, and Iyer. 2016)
	2L+	4.4; 5.3; 5.7 months (from Study 100070-Obs001 PART A, PART B and Iyer. 2016)
Treatment has the prospect of offering an extension to life, **normally** of a mean value of ≥ 3 months, compared with current NHS treatment		**Mean (based on the modelling)**
	1L	Company: 18.6 months ERG: 25.7* months
	2L+	Company: 37.3 months ERG: 37.2* months

* Incremental LYG from the scenario leading to the highest ICER

Equality issues

- No equality issues

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- with input from the Lead Team (John Watkins and Stephen Sharp)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avelumab for Merkel cell carcinoma [ID1102]

Company evidence submission

Submitted by Merck

August 2017

Version history

File name	*Version*	*Contains confidential information*	*Date*
Full draft	V1.1	Yes	August 2017

Contents

Figures and Tables

Abbreviations

Acronym	Definition
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BIM	Budget impact model
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
CAV	Cyclophosphamide + doxorubicin + vincristine
CE	Conformité Européene
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane© Center Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CT	Computed tomography
CTLA	Cytotoxic T-lymphocyte-associated protein
DARE	Database of Abstracts of Reviews of Effects
DH	Department of Health

DoR	Duration of response
DRR	Durable response rate
DSU	Decision Support Unit
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EOT	End-of-Treatment
EPAR	European Public Assessment Report
EQ-5D	EuroQoL - 5 dimensions
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
EU	Europe
FACT-M	Functional Assessment of Cancer Therapy - Melanoma
FBC	Full blood count
FDA	Food and Drug Administration
FRCP	Fellow of the Royal College of Physicians
GEE	Generalized estimating equation
GFR	Glomerular filtration rate
GP	General Practitioner
GPME	General population mortality extrapolation
HCHS	Hospital and Community Health Services
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare resource group
HRQL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio

IERC	Independent Endpoint Review Committee
IHC	Immunohistochemistry
IO	Immuno-oncologic
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
LB	Lower bound
LFT	Liver function test
LY	Life year
MAA	Marketing authorisation application
MAIC	Matching Adjusted Indirect Comparison
MCC	Merkel cell carcinoma
MCM	Mixed Cure Model
MDT	Multidisciplinary team
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHC	Major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MRU	Medical resource use
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
NCDR	National Cancer Data Repository
NCI-CTAE	National Cancer Institute - Common Technology Criteria for Adverse Events
NCPE	National Centre for Pharmacoeconomics
NE	Non-estimable
NHS	National Health Service

NHSE	National Health Service England
NHS-EED	National Health Service – Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NK	Natural killer
NR	Not reported
OLS	Ordinary Least Squares
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PF	Progression-free
PFS	Progression-free survival
PIM	Promising Innovative Medicine
PK	Pharmacokinetics
PO	Per os (by mouth)
PP	Post-progression
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal and Social Services
PSSRU	Personal and Social Services Research Unit
QALY	Quality-adjusted life year
QC	Quality control
RCT	Randomised controlled trial

RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RFT	Renal function test
RPFS	Radiographic progression-free survival
RU	Resource use
SAS	Statistical Analysis System
SCLC	Small cell lung cancer
SD	Stable disease
SE	Standard error
SGA	Subgroup analysis
SLD	Sum of the longest diameter
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
STC	Simulated Treatment Comparison
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TFT	Thyroid function test
TOT	Time on treatment
TRAE	Treatment-related adverse events
TSD	Technical Support Document
TTP	Time to progression
UB	Upper bound
UK	United Kingdom
US	United States
UV	Ultraviolet

VAT	Value-added tax

1 Executive summary

Merkel cell carcinoma (MCC) is an ultra-rare, aggressive and rapidly progressive neuroendocrine skin cancer, with limited systemic treatment options. It largely affects the elderly and has a poor prognosis, particularly in the case of metastatic disease. Less than 50% of patients with metastatic MCC are alive within one year of their diagnosis (median survival from the time of initial metastasis is approximately 9.6 months) and 5-year relative survival is estimated between 0% (for patients with regional nodal disease who have received at least one line of treatment in a single institution) and 18% (in 277 patients identified in the United States National Cancer Database [NCDB], whose treatment status was not detailed). The incidence of metastatic MCC in England is very low; we estimate that approximately 9 to 20 patients are diagnosed per year, increasing to a total of 70 to 81 patients when accounting for the additional MCC patients who may progress to metastatic disease. Metastatic MCC patients who experience disease progression after initial treatment have a worse prognosis at any stage of the disease, with a 0% survival rate at one year (Becker 2016).

Currently there are no licensed treatments in the UK for metastatic MCC. In England, first line patients are usually treated with chemotherapy combinations off-label, and despite an initial response in some patients, the durability of this response is limited. The median overall survival is poor (less than 10 months), and treatment-related toxicity is high (Schadendorf 2017). Many patients who are not eligible for chemotherapy due to poor health, will receive best supportive care (BSC). This is the treatment of choice at second-line and has no impact on survival outcomes. Radiotherapy is used throughout all lines of treatment to alleviate symptoms. The absence of licensed therapies in metastatic MCC, combined with the limited clinical effectiveness of chemotherapy agents, in particular the low durability of response, have resulted in a poorly defined and greatly limited treatment landscape for metastatic MCC in England.

Metastatic MCC negatively impacts health-related quality of life (HRQL) due to the physical and psychological impact of both the symptomatic disease and treatment-related experiences (Kaufman 2016a). Reasonable survival with a good HRQL remains elusive for most patients, highlighting the need for innovative new therapies.

Avelumab (BAVENCIO®) is a human IgG1 lambda monoclonal antibody that targets cancer cells through the inhibition of the immune checkpoint protein programmed death-ligand 1 (PD-L1) (BAVENCIO PI 2017). Additionally, due to its unmodified Fc-region, avelumab may illicit an innate immune system response through the induction of antibody-dependent cell-mediated cytotoxicity (ADCC), as seen in preclinical trials (Boyerinas 2015). It will be the only licensed treatment for metastatic MCC in the UK (positive CHMP opinion received on 21st July 2017; approval expected September 2017). It has an Orphan Drug Designation from the European Medicines Agency (EMA), and Orphan Drug, Fast Track, and Breakthrough Therapy designations from the US Food and Drug Administration (FDA) (European Medicines Agency 2016; Food and Drug Administration 2017). Avelumab has also recently been granted Promising Innovative Medicine (PIM) designation by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA). On 23rd March 2017, it received accelerated approval from the FDA for the treatment of adults and paediatric patients (over 12 years) with metastatic MCC.

Immune check point inhibitors are among the most significant innovative advances in oncology in recent years, and have transformed treatment expectations in difficult to treat cancers such as metastatic melanoma (NICE 2015; NICE 2016a). The use of an anti-PD-L1 antibody for the treatment of metastatic MCC is supported by the particular biology of this viral-induced tumour. Viral antigens are foreign and thus potentially strong immune stimulants, and many virus-associated tumours are characterised by robust immune infiltrates and PD-L1 expression (Nghiem 2016). Therefore, by targeting PD-L1 and engaging the immune system, treatment with avelumab has been shown to be effective against MCC.

The efficacy and safety of avelumab was assessed in the largest registrational trial in metastatic MCC; JAVELIN Merkel 200. This trial, in which avelumab was evaluated in patients who had failed at least one line of prior chemotherapy (Part A second line plus (2L+) cohort; n=88) and treatment-naïve patients (Part B first line (1L) cohort; current enrollment: n=39; target enrollment: n=112) is summarised in Section 1.3 below and detailed in Section 4. These analyses show that avelumab results in rapid and durable responses in first and second line (3 months duration of response (DoR) of 93% and 18 months DoR of 69%, respectively), improves survival (OS and PFS) and improves quality of life by delaying disease progression. Comparator data for this single arm trial are from observational studies, conducted by Merck in the EU and US, where recruitment criteria matched closely with those in the pivotal trial (Becker 2016;Cowey 2017). A robust analysis of these studies and other literature suggest that patient characteristics are not prognostic of outcomes and therefore naïve comparisons of avelumab data with these comparators are considered appropriate.

The treatment is well-tolerated and only a small number of patients experience Grade ≥3 adverse events (AEs); to date no treatment-related deaths have been observed in either the JAVELIN Merkel 200 or the JAVELIN Solid Tumor trials (a Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics (PK), biological, and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumours).

A robust cost-effectiveness analysis, summarised in Section 1.4, and detailed in Section 5, concludes that avelumab is a cost-effective treatment alternative to BSC (£37,409/quality adjusted life years [QALY]) for treatment-experienced patients and in treatment-naïve patients versus both chemotherapy and BSC (£43,633 and £46,219/QALY, respectively). The main drivers of cost-effectiveness are durability of response and OS benefits of avelumab in comparison to the poor outcomes of chemotherapy and BSC.

Avelumab for metastatic MCC is estimated to have a minimal budget impact with a projected total net budget impact of £4.3 million at year 5, under assumptions that every eligible patient will receive it. This is well below NHS England's new £20 million Budget Impact Test.

Metastatic MCC is associated with a short life expectancy (irrespective of line of therapy); median survival is estimated at 4 months for UK patients (Jackson 2015), meeting the first of National Institute for Health and Clinical Excellence's (NICE) end of life criteria. The economic model confirms that it is reasonable to expect avelumab to provide an extension to life of at least 3 months over standard of care (Section 4.12.4). Based on data from the JAVELIN Merkel 200 trial, observed and projected, avelumab meets the end-of-life criteria.

Avelumab has been available in England through a company sponsored early access programme since June 2016. [redacted] patients have so far received avelumab for metastatic MCC, with a further [redacted] approved applications (as of 28 July 2017). [redacted] has had over 10 months of avelumab treatment. Of the [redacted] patients known to have withdrawn, [redacted] patients discontinued for unknown reasons and [redacted] withdrew due to death; however, these both occurred within one month of treatment initiation and are unlikely to be related to treatment. Globally, [redacted] countries are currently participating in an early access programme for avelumab in metastatic MCC, and over [redacted] patients have been treated.

Avelumab provides a significant step-change in the treatment landscape of this ultra-rare and highly aggressive disease, addressing a large unmet need and providing substantial clinical benefit over current standard of care for a very small and vulnerable patient population.

1.1 Statement of decision problem

The decision problem addressed in this submission covers both the first-line [1L] and second-line [2L+] population in line with July 2017 CHMP decision and the expected full marketing authorisation for

avelumab in metastatic MCC and matches the final appraisal scope issued by NICE, summarised in Table 1 below.

Table 1: The decision problem

	Final scope issued by NICE	***Decision problem addressed in the company submission***	***Rationale if different from the final NICE scope***
Population	People with metastatic MCC	As per scope	-
Intervention	Avelumab	As per scope	-
Comparator(s)	Untreated metastatic MCC • Chemotherapy (such as cisplatin or carboplatin with or without etoposide) • BSC Previously treated metastatic MCC • BSC	Untreated metastatic MCC • Chemotherapy (cisplatin or carboplatin plus etoposide- option to select a chemotherapy "basket" is also available) • BSC Previously-treated metastatic MCC • BSC • Chemotherapy (cisplatin or carboplatin plus etoposide- option to select a chemotherapy "basket" is also available)	UK clinical expert opinion is that a 50:50 split of carboplatin plus etoposide and cisplatin plus etoposide is used for treatment-naïve patients with no expected differences in efficacy between regimens In the 2L the majority of patients will receive BSC with a minority of patients who are fit enough receiving chemotherapy. The choice of cytotoxic agent in 2L is dependent on the choice of chemotherapy a patient received at 1L. In some instances patients may be re-challenged with cisplatin or carboplatin with or without etoposide- The option of selecting a chemotherapy "basket" has also been included.
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	As per scope	-
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY.	As per scope	-

	Final scope issued by NICE	*Decision problem addressed in the company submission*	*Rationale if different from the final NICE scope*
	The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	No subgroups were identified	As per scope	-
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per scope	-

Abbreviation: BSC: Best Supportive Care; MCC: Merkel cell carcinoma; NHS: National Health Service; NICE: National Institute for Health and Care Excellence

1.2 Description of the technology being appraised

Avelumab (BAVENCIO®), a human IgG1 lambda monoclonal antibody that inhibits the immune checkpoint protein PD-L1 will be the first licensed treatment for metastatic MCC. Through blocking the interaction between PD-L1 on tumour cells and PD-1 on immune cells avelumab is thought to enable the reactivation of exhausted T-cells, that have been suppressed through this interaction and thus engage the adaptive immune system (BAVENCIO PI 2017). It will be the only approved checkpoint inhibitor with a proposed dual mechanism of action; engaging the innate immune system through ADCC, as well as leveraging the adaptive immune system, as seen in preclinical trials (Boyerinas 2015). Table 2 presents the key details for avelumab in relation to this submission.

Table 2: Technology being appraised

UK approved name and brand name	Avelumab (BAVENCIO®)
Marketing authorisation/CE mark status	The European MAA for avelumab was submitted to the EMA in October 2016 Positive CHMP opinion was received on 21st July 2017. The anticipated date of EMA marketing authorisation is September 2017
Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC) (Appendix 1; Merck KGaA 2016i)	The anticipated indication for avelumab is for the treatment of adults with metastatic MCC
Method of administration and dosage	10 mg/kg IV infusion over 60 minutes every 2 weeks

Abbreviation: CE: Conformité Européene; CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; IV: Intravenous; MCC: Merkel cell carcinoma; UK: United Kingdom

1.3 Summary of the clinical effectiveness

The Phase II, multicentre, international, single-arm, open-label JAVELIN Merkel 200 trial was initiated to evaluate the efficacy and safety of avelumab in subjects with metastatic MCC. It is the largest registrational trial in metastatic MCC to date. While there is an absence of direct comparative data this is common among trials for ultra-orphan conditions (with no approved treatments), due to the challenges in designing and recruiting patients to large randomised controlled trials (RCTs). Analyses conducted for this submission allow for a robust comparison with observational, natural history data in similar patients.

The JAVELIN Merkel 200 trial is currently being conducted in two parts across 72 study locations in North America, Europe, Australia and Asia (Merck KGaA 2016h); Part A included patients who have failed at least one line of prior chemotherapy (2L+ cohort; n=88) with follow-up ongoing, and Part B in patients with no prior systemic therapy for metastatic disease (1L cohort; target enrollment: n=112)(Merck KGaA 2016h). Part B was a later addition to the JAVELIN Merkel 200 trial, and therefore is currently still enrolling patients. The data available from Part B (1L cohort) are limited to a small number of enrolled patients with varying lengths of follow up (n=39), 29 of whom have ≥3months follow-up) and are immature compared to those obtained for Part A (2L+cohort). Further details of the trial design and planned analyses are available in Section 4.

This submission will present the most up-to-date evidence for avelumab using the latest 24th March 2017 data cut with a minimum of 18-month follow-up of Part A (2L+ cohort, n=88) and 39 (Part B) first-line patients, 29 of whom had ≥3 months follow-up with a response status recorded (Merck KGaA 2017c; Merck KGaA 2017b). Safety outcomes include the full patient cohort (Part A n= 88 and Part B n=39) who received at least one dose of avelumab (Merck KGaA 2017c; Merck KGaA 2017b). A small proportion of patients within Part B (1L cohort) had 6 months or more follow-up (n=14) and this limited more mature data set is presented where available (Merck KGaA 2017c). Additional data cuts are expected at the [redacted] with further data cuts in 2018. The study is planned to complete in June 2025, with the estimated primary completion date (final data collection date for primary outcome measure) scheduled for September 2019.

Data from both populations show promising clinical outcomes and confirm that avelumab is a well-tolerated treatment option in the metastatic setting with increased response rates and durable responses contributing to improved OS as observed by the maturing clinical trial data. Avelumab also

provides a treatment option for patients who may not be eligible for chemotherapy in the first-line setting, whilst maintaining patient HRQL which is so often compromised.

A systematic literature review (SLR) identified no RCTs for avelumab for the treatment of metastatic MCC. Several other studies were identified in the literature search including observational studies, case series and case reports; a small number of which were relevant to the NICE decision problem and are discussed in more detail in Section 5.3.3.

Due to the single arm design of JAVELIN Merkel 200 and the paucity of clinical data in metastatic MCC, observational studies were conducted by Merck KGaA and Pfizer Inc in Europe and the US to investigate the clinical efficacy of standard of care chemotherapy in metastatic MCC (Becker 2016) and (Cowey 2017). The aim of these studies was to establish the efficacy of current treatments, and to provide a context to facilitate interpretation of the trial results in the absence of head-to-head comparative trial data.

Our analysis (summarised in Section 5.3.3 and detailed in Appendix 10) found that regardless of treatment received in the second-line plus setting, outcomes were uniformly poor. Furthermore, the analysis found that patient characteristics were not prognostic of outcomes in metastatic MCC and for this reason, no statistical adjustments (such as Matching Adjusted Indirect Comparison [MAIC], or Simulated Treatment Comparison [STC]) were conducted to match the observational data to the relevant cohorts within JAVELIN Merkel 200.

Given the lack of data available on BSC, chemotherapy was used as a proxy of BSC in both the first-line and second-line plus setting. This approach is conservative for first-line as it assumes the benefits of chemotherapy without the associated costs.

Avelumab has shown an objective response rate of 33% in treatment-experienced patients and 62% in treatment-naïve patients.

Results from the 2L+ cohort (minimum 18-months follow-up) found that metastatic MCC patients who had progressed after at least one line of prior therapy showed an objective response rate (ORR) with avelumab of 33% (29/88; 95% Confidence Interval [CI]: 23.3-43.8). The overall, clinical benefit of avelumab is 43% which consists of 11% (10/88) of patients having a complete response (CR), 22% (19/88) having partial responses (PRs) and 10% (9/88) with stable disease (SD) (Merck KGaA 2017b). In a subgroup analysis of the 2L+ cohort, a trend towards improved responses was observed with fewer lines of prior therapy. Tumour response is strongly associated with the risk of disease progression; of the 29 treatment-experienced patients with a CR or PR, only [redacted] experienced disease progression by the March 2017 data cut (minimum of 18-months follow-up).

In comparison, outcomes from two observational studies and published historical data found that patients receiving chemotherapy in the 2L+ setting have an ORR between 23% and 29%, with a CR rate between 0.0% and 3%, a PR rate between 29% and 10% and a further 3% to 14% have SD (Cowey 2017; Becker 2016; Iyer 2016). A more detailed comparison is provided in Section 4.9.

Although data collected from the 1L cohort (Part B) is less mature than in the 2L+ cohort (Part A) (n=39 patients vs. n=88, respectively), initial results (≥3 months follow-up, n=29) demonstrate an ORR of 62% (18/29; 95% CI: 42.3-79.3); nearly double that observed in the 2L+ cohort, with 14% (4/29) having CR and 48% (14/29) PRs, as well as 10% (3/29) with SD. An ORR of [redacted] was reported in the proportion of patients who had ≥6 months follow-up (n=14) (Merck KGaA 2017c).

Chemotherapy in the first-line setting is associated with lower ORRs, 29% to 55%; 13% to 14% of

which are CRs, 16% to 42% are PRs and 2% to 7% are SDs (Cowey 2017; Iyer 2016).

Despite the responses observed with chemotherapy, these are short lived in both the 1L and 2L+ setting (0 to 7% of patients responding by 6 months). A more detailed comparison is provided in Section 4.9.

Avelumab demonstrates rapid and durable tumour responses

Treatment-experienced patients (Part A 2L+ cohort) had rapid tumour responses; 76% (22/29) of the observed CR or PR responses had occurred by week 7. Responses were sustained, with 66% (19/29) of patients who responded continuing to respond at a minimum of 18-months follow-up (Merck KGaA 2017b).

Patients in the 1L cohort (Part B) with a ≥3 months follow-up (n=29) also showed rapid tumour responses with 89% (16/18) of ORR responses (CR or PR) observed by week 7. At 3 months, 93% of responding patients were still responding (Merck KGaA 2017c).

Outcomes from two observational studies and published historical data show that the initial response observed with chemotherapy is usually of a short duration in both the first-line and second-line plus setting; median duration of response (DoR) is between 3.0 months and 6.7 months and 1.7 months and 3.3. months, respectively (Cowey 2017; Becker 2016; Iyer 2016). Median DoR with avelumab treatment has not yet been reached in either the 2L+ cohort or the 1L cohort (Merck KGaA 2017c; Merck KGaA 2017b).

Six-month durable response rates are greater with avelumab treatment compared with chemotherapy

Chemotherapy response rates in the metastatic setting are short lived. In treatment-experienced patients the 6-month durable response rate (DRR) is very poor with only 0 to 7% of responding patients continuing to respond to treatment (Cowey 2017; Becker 2016; Iyer 2016). A naïve comparison with JAVELIN Merkel 200 shows that avelumab has a more favourable 6-months DRR in treatment-experienced patients of 31% (Merck KGaA 2017b).

The 6-month DRR outcome for the 1L cohort is still immature (DRR of [redacted]) however, if we are to consider that the second-line plus cohort showed that at 6 months, 93% of responders were durable, we can anticipate that most of the 62% of objective responders in first-line will also be durable.

The durable responses observed with avelumab treatment are supportive of the OS outcomes observed. In the treatment-experienced patient population, all responders are still alive at the time of follow-up (minimum of 18 months follow-up) where historical data shows that patients would have otherwise died by 12 months (Merck KGaA 2017b).

In treatment-experienced metastatic MCC patients, avelumab has demonstrated durable survival benefits with OS rate of [redacted] at 18 months. In treatment-naïve patients, avelumab has a 3-month OS rate of [redacted], with median OS not reached and recruitment still ongoing.

Avelumab in treatment-experienced patients (part A 2L+ cohort) resulted in an 18-month overall survival (OS) rate of [redacted] and a median OS of 12.6 months (95% CI: 7.5-19.0), with follow-up still ongoing (Merck KGaA 2017b). This is greater than the 12-month overall survival rate of 0% from the start of second-line chemotherapy and more than double chemotherapy's expected median survival time of between 4.3 months and 5.7 months (range: 35 days to 2.4 years) (Cowey 2017; Becker

2016; Iyer 2016). Even at 6-months the OS rate for avelumab is more than double that of chemotherapy (70% vs. 27%-28%).

In treatment-naïve patients (Part B 1L cohort), avelumab resulted in a 3-month OS rate of [redacted], with the median OS not yet reached and recruitment still ongoing (Merck KGaA 2017c). Limited 6-month follow-up data from 14 patients shows avelumab to have a more be more favourable OS than chemotherapy (6-month OS rate: [redacted] vs. 66.7%) (Merck KGaA 2017c; Cowey 2017).

PFS rate in treatment-experienced patients at a minimum of 18-months follow-up is 29%, with a median PFS of 2.7 months.

PFS rate in treatment-naïve patients at 3 months and 6 months is 67% and [redacted], respectively with an immature median PFS of 9.1 months

Treatment-experienced patients showed an 18-month PFS rate of [redacted], and a sustained median PFS of 2.7 months (95% CI: 1.4-6.9) (Merck KGaA 2017b). In comparison, chemotherapy is associated with a 12-month PFS rate of 0% and a median PFS of between 2.0 (95% CI: 1.3-2.7) and 3.0 (95% CI: 2.5-3.2) (Cowey 2017; Becker 2016; Iyer 2016).

Similarly, the March 24th data-cut of the 1L patient cohort (n=39) has also shown more promising results for avelumab in a naïve comparison against chemotherapy. At 3 months, avelumab has a PFS rate of 67% (95% CI: 48-80). Avelumab has an immature 6-month PFS rate of [redacted] and an immature median PFS of 9.1 months 95% CI: 1.9-not reached) whereas, chemotherapy has a 6-month PFS of 47.1% (95% CI: 33.0-59.9) and a median PFS of 4.6 months (95% CI: 2.8-7.7) Merck KGaA 2017c; Cowey 2017).

In severe diseases, median PFS may be low even with immuno-oncology treatment like avelumab, because response rates in some groups are less than 50%. One of the key benefits of avelumab is the durability of response in those who do respond. This is driven by the mechanism of action that triggers a sustained activation of the immune system to attack the tumour. Instead, efficacy endpoints such as DRR or landmark analysis (highlighted above) are better indicators of efficacy for the proportion of patients who have responded to treatment.

Clinically meaningful tumour reduction in avelumab responders was associated with clinically meaningful improvements in HRQL as assessed by FACT-M

Current treatments in MCC have limited impact on symptoms of disease and in addition, treatment-related adverse events can negatively impact on health-related quality of life (HRQL). Unlike cytotoxic chemotherapy, avelumab had no major impact on patients' health status overall with the EQ-5D or FACT-M scores, suggesting a stability in patients HRQL over time. Prevention of disease progression with avelumab treatment, as assessed on the EQ-5D Index scale, also contributed to improved HRQL.

In treatment-experienced patients, avelumab is well tolerated with less than 10% of patients experiencing Grade ≥3 treatment-emergent adverse events (TEAEs). Among treatment-naïve patients, [redacted] experienced Grade ≥3 TEAEs events. No treatment-related death was reported in either cohort.

Avelumab is well-tolerated in treatment-experienced patients with fewer than 10% (8/88) of patients experiencing Grade ≥3 TEAE. No treatment-related deaths were reported with avelumab and treatment discontinuation was low 7% (6/88) of patients) Merck KGaA 2017b).

Among treatment-naïve patients (n=39), only [redacted] experienced Grade ≥3 TEAEs. Consistent with the treatment-experienced patients, no treatment-related deaths were reported (Merck KGaA 2017c).

1.4 Summary of the cost-effectiveness analysis

A *de novo* partitioned-survival model, constructed in Microsoft Excel® assessed the cost-effectiveness of avelumab in treatment-experienced patients (2L+ cohort) with metastatic MCC versus BSC and in treatment-naïve patients (1L cohort) versus chemotherapy and BSC. The model considers each of these populations separately due to distinct differences in the expected outcomes at each line of therapy.

The Markovian structure considers three mutually exclusive health states related to survival including progression-free disease, progressed disease and death. Transitions between model health states are informed by the area under PFS and OS curves derived from JAVELIN Merkel 200 data. Utility values were applied based on time (in days) until death estimated from within the model. The model considers utility values in three health states: >100 days until death, 30-100 days until death and <30 days until death. Further details and justification of this approach are provided in Section 5.4.

The choice of model structure was based on a review of recent models constructed to inform cost-effectiveness analyses of oncology medicines, particularly immune-oncology therapies, several of which have been considered by NICE via the technology appraisal process (NICE 2016a; NICE 2016e; NICE 2017b; NICE 2014a). Underpinning the model was the assessment of clinical outcomes (survival, progression, AEs and HRQL) from the JAVELIN Merkel 200 trial. Costs, medical resource use frequencies and comparator data were sourced from published literature. Observed Time on Treatment (ToT) data were used as the basis for modelling of avelumab treatment costs.

The latest safety, efficacy and ToT data for both cohorts are from a data-cut at 24th March 2017; a minimum of 18-month follow up for the 2L+ cohort (n=88) and from the 39 patients recruited to date to the 1L cohort. The application of utilities for both cohorts in the model is based on empirical data for treatment-experienced patients (i.e. both treatment-experienced and treatment-naïve patients share the same time-to-death utility values), from the latest utility data that were available (the previous data-cut; 03 September 2016, a minimum of 12-months follow-up).

The selection of the most appropriate methods for extrapolation of PFS, OS and ToT outcomes followed a comprehensive application of methods to the observed data. Flexible modelling approaches such as spline modelling, Mixture Cure Model (MCM) and others, were applied alongside standard parametric extrapolation. By inspecting fit to Kaplan-Meier (KM)-curves, comparisons of Akaike Information Criterion (AIC) statistics, and obtaining expert opinion, it was determined that spline models provided the most realistic long-term estimates of PFS and OS. The spline models were strong statistical fits to the data and did not impose the assumption of a monotonic hazard function which consensus and emerging data suggests is less applicable to immune-oncology (IO) therapies because of their mode of action (Schadendorf 2015). A standard parametric model was deemed as an appropriate fit for the ToT data. ToT extrapolations beyond two years were informed by the expert consensus that only a proportion of patients would receive treatment beyond this time point and that no patient was likely to be on treatment for longer than five years.

Constraints were applied to survival projections where necessary, including capping PFS with the OS curve and adjusting raw OS extrapolation estimates to account for the hazard of death seen in the general population. In addition, we placed heavy emphasis on the face validity of the model results and the assumptions were informed by the expert opinion of physicians who have had extensive experience treating either metastatic MCC patients or more broadly using IO therapies such as

nivolumab (Opdivo®, Bristol Myers Squibb Pharmaceuticals Ltd.), ipilimumab (Yervoy®, Bristol Myers Squibb Pharmaceuticals Ltd.), and pembrolizumab (Keytruda®, Merck Sharp & Dohme). The expectation of an immune-response tail in the survival trajectories of patients treated with avelumab was confirmed by the clinical experts, with supportive evidence noted via observed high response rates and emergent immune-response tail in the observed progression-free survival data in JAVELIN Merkel 200.

Key model assumptions validated and informed by technical and clinical expert opinion as well as key differences between the modelling of treatment-naïve (1L) and treatment-experienced (2L+) cohorts are outlined below.

Assumptions applied to both 2L+ and 1L model

Assumption	Rationale
Model cycle length of 1 week	A weekly cycle length is assumed to be sufficiently short enough to represent the frequency of clinical events and interventions (Siebert 2012) .
Outcomes with BSC are comparable to those with chemotherapy	No data are available to inform the efficacy of BSC for the treatment of metastatic MCC for treatment-naïve or treatment-experienced patients, and as such chemotherapy was chosen as a proxy for use within the economic model. This assumption was validated by clinical experts (Merck KGaA 2017d).
Chemotherapy regimens are equally efficacious	Due to small patient numbers receiving each type of chemotherapy, it was assumed within the model that all chemotherapy regimens are associated with broadly similar outcomes. This assumption was validated by clinical experts (Merck KGaA 2017d).
Only a proportion of patients on avelumab will continue treatment beyond 2 years	Based on clinical expert feedback, it is reasonable to assume that only one third (33.33%) of patients projected to be on treatment at 2 years will continue treatment beyond this time point. 2 years has strong support from clinical community, and precedence in other cancer types where IO treatments are given.
There is a maximum treatment duration for all patients	Based on clinical expert feedback, it is reasonable to expect that no patient will remain on treatment beyond 5 years; therefore, treatment is capped in the model at this time point.
Chemotherapy regimens reflect UK practice	The most commonly administered chemotherapy regimens in clinical practice in England were suggested as carboplatin/etoposide and cisplatin/etoposide at the advisory board meeting. A 50:50 split of these regimens were assumed to apply within the model, validated at a further clinical validation meeting (Merck KGaA 2017d).
Patient weight assumption is based on the EU patients in the JAVELIN Merkel 200 trial	These patients are the most comparable patients to those likely to be treated in UK settings.
Data from other cancers such as SCLC inform dosing regimens and AE rates for chemotherapy treatments, and medical resource use frequencies	SCLC was considered the best proxy by clinicians to MCC disease and SCLC data were utilised where there was a lack of data specifically for metastatic MCC patients.

Abbreviations: AE: Adverse event; BSC: Best supportive care; EU: European Union; HR: Hazard ratio; IO: immune-oncology; MCC: Merkel cell carcinoma; SCLC: Small cell lung cancer; UK: United Kingdom

Assumptions applied to the 1L model only

There are limited survival data for treatment-naïve metastatic MCC patients receiving avelumab – at present, data are available for 39 patients, with a maximum follow-up of 11 months. As such, these data were deemed too immature for direct consideration within the model and an alternative method, where a hazard ratio (HR) was applied to data from the 2L+ cohort to estimate outcomes for

treatment-naïve patients, was utilised. This makes use of the more mature evidence supporting the efficacy and safety of avelumab in treatment-experienced patients (summarised above), using it as a basis for assumptions about the efficacy of avelumab in treatment-naïve patients. Clinicians considered it reasonable to assume that the shape of the 1L OS curves will be the same as those seen in the 2L+ cohort, but they anticipated an uplift in the curve by a factor of at least 20%. The model has therefore applied a HR of 0.80 to the 2L+ OS data to derive OS for treatment-naïve patients treated with avelumab. For PFS and ToT, clinicians did not feel able to provide an estimated HR for use within the model. In the absence of clear opinion, a conservative approach of assuming a HR of 1 (i.e. no difference in these outcomes between treatment naïve and treatment-experienced patients) was applied for PFS and ToT. Comparator data within the model for this cohort is based on pooled data from treatment-naïve patients in a Merck-conducted observational study and from other studies reporting outcomes for this specific patient cohort.

The approach to modelling avelumab efficacy in 1L patients (i.e. the assumption of a 20% OS benefit over that seen in 2L+ patients) can be considered conservative. Early data from the treatment-naïve cohort suggest a doubling in ORR compared to 2L+ (62% vs. 33%). Experience in the 2L+ cohort and in previous IO therapies suggests that these responses will be durable and that durable responses are associated with survival improvements. It is therefore reasonable to anticipate significantly better survival outcomes in treatment-naïve patients (on the basis of their relatively improved response rates) than in treatment-experienced, likely of a greater magnitude than that assumed in this model.

Cost-effectiveness results

As summarised in Table 3, for treatment-experienced metastatic MCC patients, compared with BSC, avelumab is associated with 3.11 life years gained, 1.91 incremental QALYs, and incremental costs of £71,399 per patient. The incremental cost-effectiveness ratio (ICER) is £37,409 per additional QALY gained. Table 4 shows that for treatment-naïve metastatic MCC patients, compared with chemotherapy, avelumab is associated with 2.76 life years gained, 1.56 incremental QALYs, and incremental costs of £68,104 per patient. The incremental cost-effectiveness ratio (ICER) is £43,633 per additional QALY gained. Compared with BSC, avelumab is associated with 1.55 incremental QALYs, incremental costs of £71,481; an ICER of £46,219 per QALY gained.

Table 3: Results of the base case analysis – treatment-experienced, discounted incremental results (avelumab vs. BSC)

Treatment	*Total*			*Incremental*			*ICER*
	Costs	*LYs*	*QALYs*	*Costs*	*LYs*	*QALYs*	
Avelumab	£78,718	3.53	2.22				
BSC	£7,319	0.41	0.31	£71,399	3.11	1.91	£37,409
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; BSC, best supportive care.							

Table 4: Results of the base case analysis – treatment naive, discounted, fully incremental

Treatment	*Total*			*Incremental*			*ICER*
	Costs	*LYs*	*QALYs*	*Costs*	*LYs*	*QALYs*	
Avelumab	£78,584	4.78	2.93				
Chemotherapy	£10,480	2.02	1.37	£68,104	2.76	1.56	£43,633
BSC	£7,103	6.07	1.38	£71,481	2.76	1.55	£46,219
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; BSC, best supportive care.							

Sensitivity analyses were undertaken to explore key areas of uncertainty associated with the cost-effectiveness analysis. Parameter uncertainty was explored through probabilistic and deterministic OWSA, with structural uncertainty and key assumptions explored through scenario analyses (fully presented in Section 5.8.3).

Probabilistic sensitivity analysis results demonstrated that cost-effectiveness results were most sensitive to assumptions regarding the HRQL of patients and predicted long-term survival outcomes based on the shape of the cost-effectiveness scatterplots. OWSA showed the key parameters of influence on cost-effectiveness results were utility values and the HR applied to demonstrate OS and ToT for treatment-naïve patients. Scenario analyses highlighted key areas of uncertainty around the extrapolation of survival and anticipated duration of avelumab treatment.

1.5 Key considerations

Emerging evidence from the ongoing JAVELIN trial suggests that avelumab can change the disease trajectory for patients with metastatic MCC. This potential has been acknowledged through its Orphan Drug and Fast Track designation by the European Medicines Agency (EMA) and Breakthrough Therapy approval by the US Food and Drug Administration (FDA), PIM designation from the MHRA, positive FDA approval and positive CHMP opinion. Clinicians are eager to have access to a treatment which improves upon the outcomes currently seen across the available treatments for this condition.

Response rates are higher than with current treatment options and most importantly, for those who do respond, their responses are durable and are associated with improved survival. Data in the 1L are less mature, but early results and the consistency of experience with IOs in other disease areas gives confidence that treatment-naïve patients too will experience durable responses and improved survival. To date, results from the JAVELIN trial indicate that outcomes in 1L patients will improve further upon those observed in the treatment-experienced cohort. This positions avelumab in the most appropriate part of the MCC pathway according to clinical experts.

While the JAVELIN Merkel 200 trial is the largest clinical trial in this indication, the associated small patient numbers and single-arm design present some limitations in the context of an HTA.[*] These challenges are no different to those faced in the majority of assessments of ultra-rare conditions and literature comments on the cost-utility analysis as a necessary, but insufficient, basis for their evaluation (Drummond 2007). To address the inherent uncertainty in this appraisal, Merck KGaA/Pfizer have sought advice from a range of clinical and health economics experts[†], generated and undertaken robust analysis of comparator data and made a comprehensive and critical assessment of the methods available to extrapolate the observed data.

In conclusion, our analyses support avelumab as a promising and innovative treatment for a small, under-served patient population, with limited unlicensed treatment options that deliver a poor benefit to risk ratio. Avelumab, therefore represents a step change in therapy to these patients, one that is also a cost-effective use of NHS resources with limited budget impact.

[*] Merck KGaA/Pfizer met with NICE, NHSE and clinical experts (through the Office for Market Access) in October 2016, to discuss the HTA for avelumab. As a cancer treatment, NICE's STA process (as opposed to the HST route) was deemed appropriate.

[†] Validation is discussed in detail in Section 5.10; in summary: [redacted]

2 The technology

- Avelumab (BAVENCIO®) is a human IgG1 lambda monoclonal antibody that targets cancer cells through the inhibition of the immune checkpoint protein, programmed death-ligand 1 (PD-L1). Through a proposed dual mechanism of action, avelumab enables the reactivation of exhausted T-cells and the engagement of the innate immune system
- Avelumab has been granted Orphan Drug and Fast Track designation by the European Medicines Agency (EMA) and Breakthrough Therapy approval by the US Food and Drug Administration (FDA). As of March 23rd 2017, avelumab received FDA accelerated approval for the treatment of adults and paediatric patients (over 12 years) with metastatic MCC
- Avelumab has also been granted Promising Innovative Medicine (PIM) designation by the UK Medicines and Healthcare products Regulatory Agency (MHRA). The designations and US approval reflects the demonstrable efficacy of avelumab in a very small patient population affected by a very rare and aggressive disease with a large unmet need due to poor outcomes and limited treatment options
- The EMA application was submitted in October 2016. Positive CHMP opinion was received on 21st July 2017 for the treatment of adult patients with metastatic MCC and approval is expected on 23rd September 2017
- Avelumab will be the only approved treatment for metastatic MCC in Europe
- The evidence base supporting this submission includes the largest clinical trial in metastatic MCC alongside two observational studies conducted by Merck/Pfizer to determine the safety, efficacy and tolerability of avelumab in metastatic MCC and what constitutes standard of care in patients with metastatic MCC.
- Avelumab offers a true step-change in the treatment paradigm for patients with metastatic MCC in England, addressing a high unmet need, alleviating a huge disease burden and providing substantial clinical benefit beyond standard of care in what is a very small patient population (estimated 70 to 81 patients per year)

2.1 Description of the technology

Brand name: BAVENCIO®

UK approved name: Avelumab

Therapeutic class: Anti-neoplastic agent; programmed death-ligand 1 (PD-L1) immune-checkpoint inhibitor

Brief overview of the mechanism of action:

Avelumab (BAVENCIO®) is a human IgG1 lambda monoclonal antibody that specifically targets cancer cells through the inhibition of the immune checkpoint protein, PD-L1.

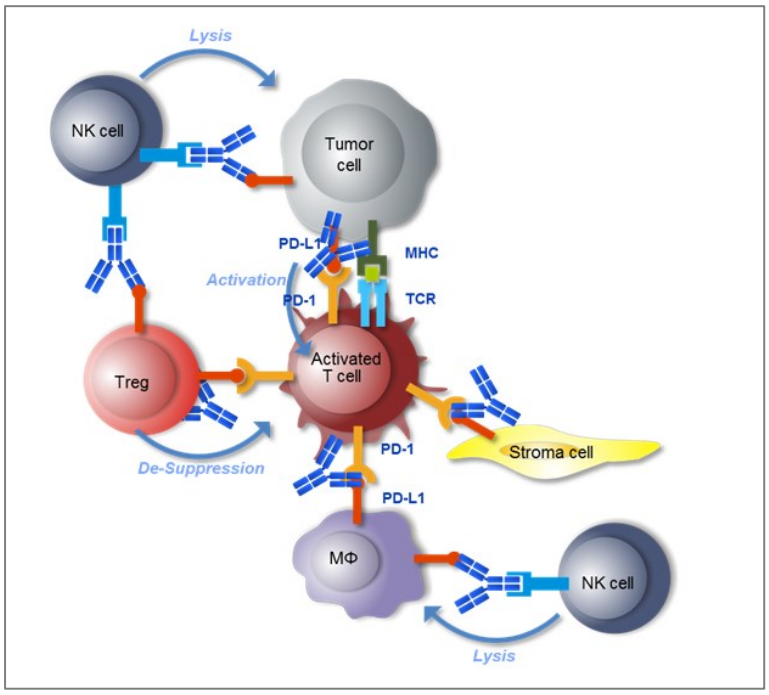
PD-L1 may be expressed on tumour cells and tumour-infiltrating immune cells and can contribute to the inhibition of the anti-tumour response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors (found on T-cell and antigen presenting cells) supresses cytotoxic T-cell activity, T-cell proliferation and cytokine production. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This interaction interrupts the inhibitory effects of PD-L1 on the immune response resulting in the restoration of anti-tumour activity (Figure 1). In syngeneic mouse tumour models, this blocking of PD-L1 activity resulted in decreased tumour growth (BAVENCIO PI 2017).

In addition to leveraging the adaptive immune system through preventing the interaction between PD-L1 and PD-1/B7.1, avelumab has also been shown *in vitro* to engage the innate immune system through the induction of antibody-dependent cell-mediated cytotoxicity (ADCC) (Boyerinas 2015). ADCC is a well-established immune effector mechanism in which therapeutic antibodies direct immune effector cells of the innate immune system to kill antigen-expressing cancer cells (Iannello 2005; Boyerinas 2015). Other PD-1/PD-L1 inhibitors, including pembrolizumab, nivolumab, durvalumab, and atezolizumab, do not exhibit these ADCC properties either because they are of an immunoglobulin phenotype not associated with ADCC (IgG4) or because they have had their Fc portion modified.

The dual mechanism of action of avelumab (reactivation of exhausted T-cells and the engagement of the innate immune system) enables the immune system to target the cancer as opposed to the more generic cell death caused by cytotoxic chemotherapy. The use of an anti-PD-L1 antibody for the treatment of metastatic MCC is supported by the particular biology of this viral-induced tumour. Viral antigens are foreign and thus potentially strong immune stimulants, and many virus-associated tumours are characterised by robust immune infiltrates and PD-L1 expression (Nghiem 2016). Therefore, by targeting PD-L1 and engaging the immune system, treatment with avelumab should be beneficial in treating MCC.

MCC is traditionally treated with non-targeted chemotherapy agents which function through a non-specific cytotoxicity resulting in apoptosis of rapidly dividing cancer cells. These treatments are not specific to cancer cells and can attack all rapidly dividing cell types, such as cells lining the gut epithelium, hair follicles, and haemopoietic cells in the bone marrow. As such, traditional anti-cancer therapies give rise to undesirable toxic side effects including mucositis, diarrhoea, hair loss, and low blood counts; which can be further exacerbated in combination chemotherapy due to the toxic mix of chemicals being administered. Furthermore, chemoresistance can emerge rapidly in cancer types such as MCC, so whilst initial responses to chemotherapy are seen in patients with metastatic MCC, chemoresistance emerges, which further limits treatment options (Iyer 2016).

Figure 1: Proposed action of avelumab through adaptive and innate immune process in the tumour microenvironment



Abbreviations: ADCC: Antibody-dependent cell-mediated cytotoxicity; ADCP: Antibody-dependent cellular phagocytosis; MHC: Major histocompatibility complex; NK: Natural killer; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1; TCR: T-cell receptor

2.2 Marketing authorisation and health technology assessment

Avelumab was granted Orphan Drug designation for the treatment of metastatic MCC by the Food and Drug Administration (FDA) (25th September 2015) and the European Medicines Agency (EMA) (6th June 2016; EU Orphan designation number: EU/3/15/1590), as well as Fast Track and Breakthrough Therapy Designations in October 2015 and November 2015, respectively (European Medicines Agency 2016; Food and Drug Administration 2017). These designations reflect the demonstrable efficacy of avelumab in patients living with metastatic MCC, a rare and aggressive disease with a large unmet need due to poor outcomes and limited treatment options.

Avelumab (BAVENCIO®) will be the first licensed treatment for metastatic MCC in Europe. The European marketing authorisation application (MAA) for avelumab to treat metastatic MCC in adults was submitted to the EMA in October 2016. A positive CHMP opinion was received on 21st July 2017 for avelumab as a monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC). Final approval is anticipated on 23rd September 2017. The expected market launch date for avelumab in England is 9th October 2017. The draft Summary of Product Characteristics (SmPC) is included in Appendix 1. A European Public Assessment Report (EPAR) was not available at the time of submission. A risk management plan has been developed for the use of avelumab (refer to the full draft avelumab risk management plan in Appendix 2 for full details).

Avelumab will be submitted to the Scottish Medicines Consortium (SMC) (anticipated date [redacted]) and the National Centre for Pharmacoeconomics (NCPE) (anticipated date [redacted]) for adult patients with metastatic MCC. Form A will be submitted to the All Wales Medicines Strategy Group (AWMSG) in [redacted].

Avelumab has received accelerated approval by the FDA (23rd March 2017) for the treatment of adults and paediatric patients (over 12 years) with metastatic MCC. Approval is based on data from the Phase II single arm JAVELIN Merkel 200 trial (2L+ cohort: n=88; 1L cohort: n=39).‡

‡ The submission reports the latest data available (24th March 2017 data cut) from the two parts of the JAVELIN Merkel 200 trial;

- Part A: at a minimum of 18 months follow up in treatment-experienced patients (2L+ cohort)
- Part B: total treatment-naïve patients recruited by the time of the data cut (n=39); 29 of whom had a minimum of 3-months follow up, with recruitment ongoing.

2.3 Administration and costs of the technology

Administration and costs associated with avelumab are summarised in Table 5 below.

Table 5: Costs of the technology being appraised

	Description	***Cost***	***Source***
Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate); one vial of 10 mL contains 200 mg of avelumab		SmPC (Merck KGaA 2016i)
Acquisition cost (excluding VAT) *		£768 per 200 mg (list price; confirmed by DH as subject to MAA)	Merck KGaA/Pfizer
Method of administration	Intravenous infusion	£199 (simple parenteral chemotherapy) every two weeks - outpatient; SB12Z - NHS reference costs 2015-2016	SmPC (Merck KGaA 2016i)
Doses	10 mg/kg over 60 minutes	£3,261.04 (per dose)	SmPC (Merck KGaA 2016i); Table 50 below
Dosing frequency	Every 2 weeks	-	SmPC (Merck KGaA 2016i)
Average length of a course of treatment	The recommended dose of avelumab is to be administered intravenously over 60 minutes every 2 weeks. Average duration of treatment calculated via the area under the curve within the model yields a mean ToT of 9.4 months (for both treatment-experienced and treatment-naïve patients).	-	SmPC (Merck KGaA 2016i) JAVELIN Merkel 200 CSR (Merck KGaA 2016h)
Average cost of a course of treatment	The average dose per treatment is estimated to be 849mg; an average cost per course of £65,086	£65,086	Section 5

Anticipated average interval between courses of treatments	There is a 2 week interval between treatments		SmPC (Merck KGaA 2016i)
Anticipated number of repeat courses of treatments	Administration of avelumab should continue until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms, no change in performance status for greater than two weeks, and no need for salvage therapy, could continue treatment. Median PFS in the JAVELIN Merkel 200 2L+ cohort was 2.7 months and 9.1 months in the 1L cohort.	-	Advised by clinical experts
Dose adjustments	Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability, as detailed in the SmPC. The median dose intensity in the 2L+ cohort from JAVELIN Merkel 200 was 9.92 mg/kg/cycle The median dose intensity in the 1L cohort was 10mg/kg/cycle.		SmPC (Merck KGaA 2016i) JAVELIN Merkel 200 CSR (Merck KGaA 2016h)
Anticipated care setting	Secondary care: dispensed by hospital pharmacy		Merck KGaA/Pfizer

*Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

Abbreviations: DH: Department of Health; SmPC: Summary of Product Characteristics; VAT: Value-added tax

2.4 Changes in service provision and management

Treatment with avelumab must be initiated and supervised by physicians experienced in the treatment of cancer. Hospital oncology units already have the staffing and infrastructure needed for the administration of cancer treatments. It is anticipated that the administration of avelumab would utilise this existing National Health Service (NHS) infrastructure.

Avelumab is delivered intravenously every 2 weeks and resource use associated with administration will be additional to what is required for patients receiving best supportive care (BSC). However, this is not expected to be greater than the resource already in place to administer chemotherapy. Administration is fully accounted for in the economic modelling presented in Section 5.

Managing adverse events

As with other immuno-therapies, patients should also be regularly monitored for signs or symptoms of adverse events (AEs) with a potential immunological cause during treatment. Clinicians treating MCC patients are likely to be experienced with the use of immuno-oncology therapies for other skin cancers and will be familiar with monitoring patients for such AEs.

No concomitant therapies are specified in the marketing authorisation for avelumab, other than those used to manage AEs. Common AEs (as detailed in Section 4.11) are well characterised and can be quickly resolved with temporary discontinuation, administration of corticosteroids and/or supportive care, as recommended in the safety management guidelines outlined in the SmPC (Appendix 1).

To mitigate potential infusion-related reactions associated with the intravenous (IV) administration of avelumab, premedication with an antihistamine and acetaminophen is required prior to the first four infusions, and based on clinical judgement for subsequent infusions.

Avelumab is well tolerated by patients with metastatic MCC, with most treatment-related adverse events (TRAEs) reported to be low-grade (Grade 1 or 2). Only 9.1% (8/88) of treatment-experienced patients, and [redacted] of treatment-naïve patients experienced a Grade ≥3 adverse event (AE) related to avelumab in the JAVELIN Merkel 200 trial (Merck KGaA 2017c; Merck KGaA 2017b) This tolerability profile is in line with other immuno-therapies in analogue diseases (Ribas 2015; Weber 2015) and more favourable than standard of care cytotoxic chemotherapy regimens (Voog 1999). AEs observed with immuno-therapies may differ from those observed with traditional chemotherapy. Early identification and management of AEs is an important part of the safe administration of avelumab. The SmPC states that patients receiving avelumab should be monitored continuously as an AE may occur at any time during or after discontinuation of therapy. This monitoring is expected to occur as part of routine clinical practice.

The immune-based mechanism of action of avelumab means that many of its drug-related AEs are immune-related in nature (irAEs); which results in a safety profile that is in line with other immuno-therapies. As described in the draft SmPC, for suspected irAEs, adequate evaluation should be performed to confirm aetiology and exclude other causes.

All irAEs that have occurred with avelumab, including severe irAEs, are well characterised and most were reversible when managed with temporary discontinuation of avelumab, administration of corticosteroids and/or supportive care, depending on the severity of the AE. The draft SmPC has pre-defined treatment algorithms for irAEs, which may include use of corticosteroids and non-corticosteroid immunosuppressants. A guideline is due to be published by ESMO later this year focusing specifically on management of side effects associated with immunotherapies

A full description of all AEs, along with their severity, is given in Section 4.11. A full list of irAEs and guidelines for discontinuation or withholding of doses in response to irAEs will be provided in the draft SmPC in Appendix 1.

2.5 Innovation

Addressing high unmet need

Metastatic MCC is an ultra-rare neuroendocrine skin cancer predominantly affecting the elderly and associated with rapid disease progression and a poor prognosis; 79% of patients diagnosed with MCC (any stage) are dead within 2 years of diagnosis (Lemos 2010; Kaae 2010; Public Health England 2010).

Treatment options are limited. Off-label, first-line doublet chemotherapy has become the standard of care for treatment-naïve patients fit enough to tolerate it (See Section 3.3, Figure 3 for the current clinical pathway of care in England). However, cytotoxic chemotherapy regimens are inappropriate for approximately 50% of patients, due to advanced age, poor performance status and multiple co-morbidities typical of the elderly population with the disease (Bhatia 2011; Voog 1999; Kaufman 2016a). The National Comprehensive Cancer Network (NCCN) MCC guidelines (Version 1.2017) acknowledge that there is insufficient data to assess whether chemotherapeutic regimens improve either relapse-free survival or overall survival in MCC patients with distant metastatic disease (NCCN MCC Guidelines® with Evidence Blocks™ 2017).

Initial responses are observed in up to 55% of patients with first-line chemotherapy (Cowey 2017; Iyer 2016). However, MCC becomes resistant and responses are seldom durable (median DoR: 3.0 months-6.7 months), resulting in relapses and aggressive disease progression (Cowey 2017; Iyer 2016). The survival benefit is also limited, with median OS of up to 10.5 months, for patients receiving first-line therapy (Cowey 2017; Iyer 2016). Clinicians are reluctant to treat some patients with chemotherapy due to the limited efficacy and severe toxicity, which means, for many patients, BSC is the only treatment option.

BSC is the mainstay 2L+ treatment (chemotherapy used infrequently) and outcomes are substantially worse; response rates as low as 10.3% have been observed in a European retrospective observational study, with a median DoR of 1.9 months, median OS of 5.3 months, and a 12-months OS rate of 0% (Becker 2016).

The absence of licensed therapies in metastatic MCC and the limited clinical effectiveness of chemotherapy agents, in particular the low durability of response, have resulted in a poorly defined and greatly limited treatment landscape for metastatic MCC in England. The introduction of an immuno-oncology therapy provides a therapeutic option associated with improved tolerability and improved response duration.

A tolerable and efficacious treatment

Avelumab has demonstrated clear clinical benefit in both treatment-naïve and treatment-experienced patients with metastatic MCC in the ongoing JAVELIN Merkel 200 study (Section 4). In comparison to chemotherapy, avelumab has also demonstrated a tolerable safety profile, providing a substantial and important improvement on the high toxicity profile of chemotherapeutic agents (detailed in Section 2.1) currently used for metastatic MCC.

In addition to the improved safety profile of avelumab, health-related quality of life (HRQL) is unaffected during the course of treatment; with both EQ-5D and FACT-M scores remaining stable relative to baseline when assessed in the JAVELIN Merkel 200 trial.

A unique mechanism of action

Avelumab is unique in that it will be the only approved checkpoint inhibitor with a proposed dual mechanism of action; that enables the immune system to target the cancer as opposed to the more generic cell death caused by cytotoxic chemotherapy (See Section 2.1 for more details on the mechanism of action of avelumab). This may be of particular importance in MCC because of the disease's viral-induced biology resulting in robust immune infiltrates and PD-L1 expression (Nghiem 2016).

These features highlight avelumab as a "step-change" in the treatment landscape for MCC, addressing an unmet need and providing substantial clinical benefit over current standard of care. This has been recognised by the Medicines and Healthcare products Regulatory Agency (MHRA) and in June 2017, avelumab was granted Promising Innovative Medicine (PIM), an early indication that the product is a promising candidate in the treatment, diagnosis or prevention of a life-threatening or seriously debilitating condition with unmet need.

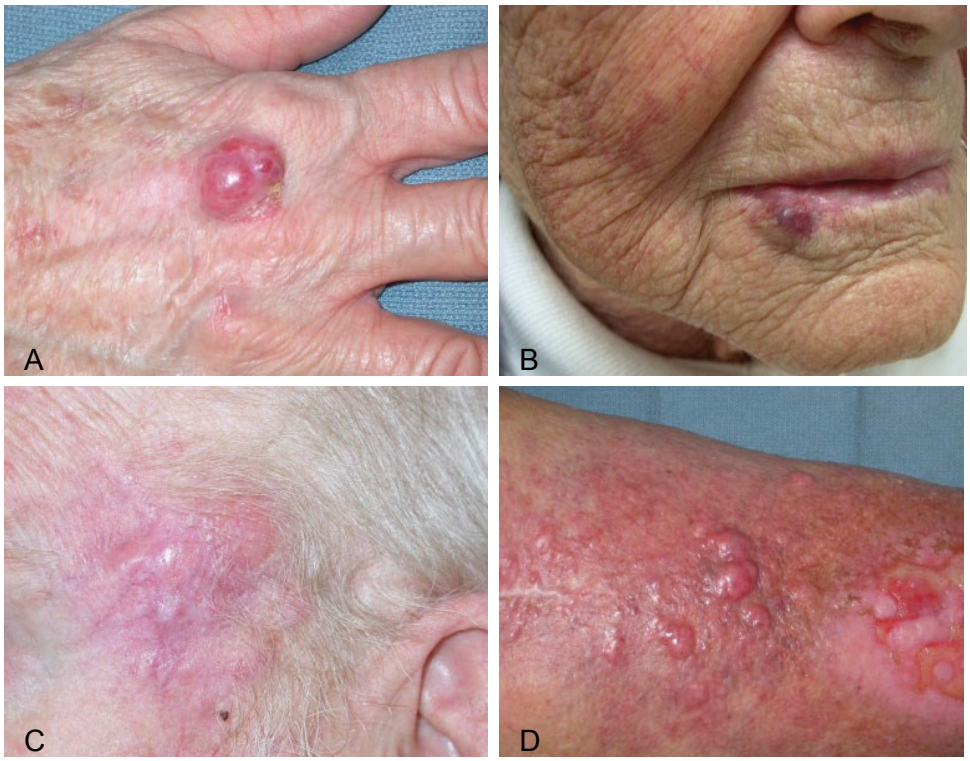
3 Health condition and position of the technology in the treatment pathway

- Merkel cell carcinoma (MCC) is an ultra-rare, neuroendocrine skin cancer (estimated to affect approximately 75 patients per year), that is aggressive and rapidly progressive, with tumour cell doubling times of 5 to 12 days. It predominantly affects the elderly who have limited treatment options and a poor prognosis, particularly in the case of metastatic disease
- Current options for treatment-naïve patients with metastatic MCC consist of palliative off-label use of chemotherapy or best supportive care (BSC). Estimated median survival from diagnosis is between 4 months and 13 months, with one year survival under 50%
- Following the failure of first-line therapy, treatment options are very limited, with most patients receiving BSC and only a small proportion fit enough to receive further rounds of chemotherapy. Treatment-experienced patients have a worse prognosis at any stage of the disease, with a 0% survival rate at one year.
- Treatment outcomes with chemotherapy in the metastatic setting are poor and short-lived, with survival duration typically less than 10 months. Long-term survival without a decrease in HRQL remains elusive for most patients, highlighting the need for innovative new therapies for the treatment of metastatic MCC
- As the only licensed treatment, avelumab will offer an effective treatment option with meaningful clinical benefit over traditional chemotherapy or BSC for both treatment-naïve and treatment-experienced patients with metastatic MCC

3.1 Disease background

MCC is aggressive and rapidly progressing, including frequent lymph node involvement and early metastasis (National Cancer Registration and Analysis Service 2010; Grabowski 2008; Chen 2015; Saini 2015; Smith 2012). Primarily MCC is a disease of the elderly, the highest incidence of MCC is observed in patients greater than 65 years of age (Kaae 2010; Kukko 2012; Lemos 2010; Reichgelt 2011). Patients with MCC typically present with firm, red-violet cutaneous tumour nodules located in sun-exposed areas of the head and neck or upper extremities (Smith 2012; Bichakjian 2007; Saini 2015; Agelli 2003) making it a very symptomatic condition that is highly visible (Figure 2).

Figure 2: Clinical examples of MCC



SOURCE: (Bichakjian 2007)

(A): primary MCC on the hand; (B): primary MCC on the lower lip; (C): locally recurrent MCC on the left temple; (D): multiple in transit MCC metastases are observed adjacent to primary radiation field.

Abbreviations: MCC: Merkel cell carcinoma

Based on clinical characteristics, MCC is classified in four stages; from primary tumours ≤2 cm (Stage I) through to metastatic (Stage IV) (Edge 2010). MCC is defined as metastatic when the primary tumour has metastasised beyond the regional lymph nodes. Metastatic MCC has a poor prognosis, less than 50% of patients with the disease can expect to be alive within one year of diagnosis (Lemos 2010; Kaae 2010).

The aetiology of MCC is multifactorial, with viral factors (Merkel cell polyomavirus [MCPyV]) and ultraviolet (UV)-induced skin damage contributing to disease development (Saini 2015). It is believed that in approximately 75% of cases, MCC is caused by MCPyV (Feng 2008; Spurgeon 2013).

Although there are no specific risk factors for metastatic MCC identified in the literature, previous MCPyV infection, advancing age, fair skin, previous malignancies, and UV light exposure are all associated with an increased risk (Faust 2014; Hodgson 2005; Agelli 2003; Koljonen 2009). MCC has also been associated with autoimmune conditions and immunosuppression from organ transplantation and Human Immunodeficiency Virus (HIV) infection, suggesting that impaired immunity may be a predisposing factor for tumour development (Kempf 2013; Lanoy 2010a; Lanoy 2010b; Engels 2002; Lanoy 2009), though is not thought to be prognostic of outcome.

3.2 Burden of metastatic MCC

Effects of metastatic MCC on patients and quality of life

MCC is an aggressive disease with a significant clinical burden, developing at an exponential rate with tumour cell doubling times of 5 to 12 days, and high rates of nodal and distant metastatic spread (Allen 2005; Swann 2007; Tothill 2015). Clinical advisors confirmed that in over 50% of cases, metastases are

predominantly located in the lymph nodes or on the skin, making it a very symptomatic condition that is visible to the patient. The visibility of the cancer causes psychological distress because patients are acutely aware of the rapid tumour progression which can cause considerable anxiety and concern. The disfiguring nature of the tumours, which commonly develop fungating lesions that weep, alongside the increased risk of skin infections, was confirmed by clinical advisors to cause further distress. As with most advanced cancers, clinical experts in MCC confirmed that metastatic MCC is associated with pain and discomfort; especially in the presence of bone metastases.

There is a lack of HRQL data available regarding the impact of MCC and its management. To address this evidence gap, the Phase II study assessing the safety and efficacy profile of avelumab in metastatic MCC (JAVELIN Merkel 200; EMR 100070-003 – see Section 4), was designed to include a qualitative study of patient experiences using exploratory interviews. The results showed that diagnosis of metastatic MCC is associated with a substantial negative psychological impact which may have physical manifestations, such as hindered sleep (Kaufman 2016a).

There is also a considerable clinical and psychological burden associated with current treatments for metastatic MCC. In the absence of approved treatments in metastatic MCC, current therapy in treatment-experienced patients consists of chemotherapy or BSC, (alongside palliative radiotherapy), with most patients at second-line and further receiving BSC (and palliative radiotherapy). Chemotherapy is associated with a heavy physical and psychological burden due to debilitating treatment-related experiences (Kaufman 2016a). AEs associated with chemotherapy, such as fatigue, nausea and vomiting can greatly impair daily functioning (Sommariva 2016) while serious adverse events (SAEs) such as high grade septic shock and febrile neutropenia can lead to death (Voog 1999). This high risk of severe toxicity and toxic death observed in patients with MCC treated with chemotherapy is particularly pronounced in patients above 65 years, which is probably due to the poor physical condition of many of these patients (Voog 1999). In addition to the physically debilitating and potentially lethal side effects of chemotherapy, AEs such as hair loss can be very distressing for patients (Lemieux 2008).

Overall, the toxicity profile of chemotherapeutic agents may negatively impact HRQL, especially in this predominantly elderly population with frequent co-morbidities (Nathan 2016; Nghiem 2017). The effect on HRQL may be different depending on the chemotherapy regimen used; for example, treatment with cisplatin plus etoposide causes greater emotional issues associated with hair loss than treatment with carboplatin plus gemcitabine (Lee 2009).

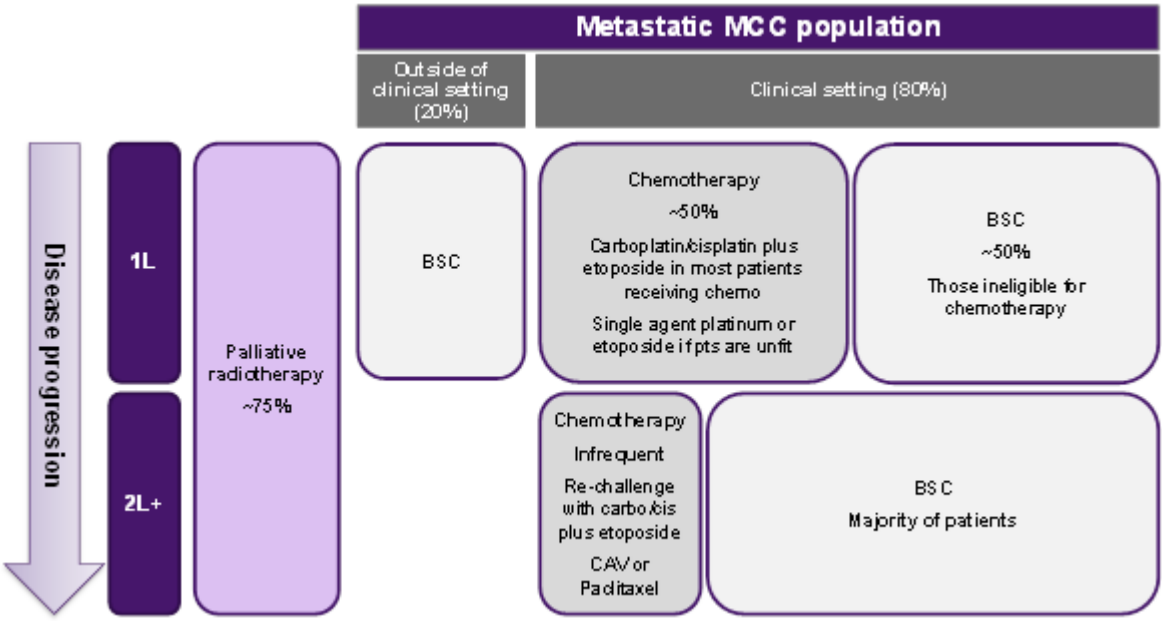
3.3 Clinical pathway of care

There are no treatment guidelines specific for metastatic MCC in England and the clinical pathway of care is poorly defined due to a lack of licensed treatments, uncertainty surrounding potential treatment outcomes, and a lack of recommendations for second-line and further treatment of metastatic MCC. The available NICE skin cancer pathway and London Cancer guidelines are not specific for MCC (NICE 2014c; Anand 2014).

For patients with metastatic MCC, regardless of line of therapy, treatment is palliative and aims to prolong survival through the induction of durable responses, whilst maintaining HRQL (Lebbe 2015). There are no effective treatments for patients who progress after initial treatment. Clinical experts have confirmed that prognosis with chemotherapy is similar to BSC for patients who require second-line or further treatment for metastatic MCC.

Figure 3 provides an overview of the treatments used at first-line and second-line (and further) settings in current clinical practice in England for the treatment of metastatic MCC according to MCC experts. In addition to the current clinical pathway, the recommendations of European MCC guidelines and London Cancer guidelines are also detailed below.

Figure 3: Schematic of the current clinical pathway for the treatment of metastatic MCC in England according to MCC experts



SOURCE: As confirmed by clinical experts in MCC.

*Defined as patients who do not receive treatment at a specialised clinic or skin MDT.

Abbreviations: 1L: First-line; 2L+: Second-line plus; BSC: Best supportive care; CAV: Cyclophosphamide + doxorubicin + vincristine; MCC: Merkel cell carcinoma; MDT: Multidisciplinary team

European guidelines for MCC (Lebbe 2015)

First-line:

- Mono- or poly-chemotherapy regimens are recommended in first-line treatment; however, there is no standard of care regimen
- Combinations recommended include carboplatin, cisplatin and etoposide, cyclophosphamide with vincristine, doxorubicin, prednisone, bleomycin or 5-fluorouracil
- BSC or palliative radiotherapy can be discussed in patients ineligible for chemotherapy

Second-line:

- There are no recommendations for second-line treatment

***London Cancer guidelines for MCC* (Anand 2014)**

First-line:

- Palliative therapy with radiotherapy or adjuvant chemotherapy is recommended

Second-line:

- There are no recommendations for second-line treatment

Limitations of current treatment options

In the current clinical setting in England, outcomes for patients with metastatic MCC are poor. For treatment-naïve patients, off-label use of chemotherapy is associated with initial responses; however,

these are often of limited duration, with median DoR ranging from 3.0 months to 6.7 months (Cowey 2017; Iyer 2016; Nghiem 2017). As confirmed by several clinicians In England (and the UK), most patients are treated with a combination of carboplatin plus etoposide or cisplatin plus etoposide. These chemotherapy combinations can have detrimental effects, especially in an elderly patient cohort. Such adverse effects include acute and delayed emesis in 30-90% of patients, which requires the proactive prescription of anti-emetics. In addition, they may cause gastrointestinal disorders, alopecia, renal and liver abnormalities, as well as myelosuppression, thrombocytopenia and leukopenia all of which may require clinical intervention (Rutledge 2013)

Data are lacking on outcomes for patients treated at first-line with BSC however based on the initial responses observed with chemotherapy in this patient population, it is anticipated that BSC alone will be associated with worse outcomes.

Outcomes for treatment-experienced patients with metastatic MCC are worse than those newly diagnosed (treatment-naïve); with the median DoR ranging from 1.7 months to 3.3 months (Cowey 2017; Becker 2016; Nghiem 2017). The poor outcomes reported with chemotherapy regimens in second-line treatment of metastatic MCC, alongside the toxic side-effects associated with chemotherapy and the poor performance status of patients', helps to explain why most patients in England receive BSC for second-line or further treatment. As such it is expected that outcomes seen in practice are worse than those seen in the literature as active treatments are unlikely to be given.

While traditional therapies such as chemotherapy and radiotherapy do offer benefits to some patients in the short-term, long-term survival with a good HRQL remains elusive for most patients with metastatic MCC, highlighting the need for new therapies.

Due to the rarity and severity of metastatic MCC, and the lack of available treatment options which offer durable, life-extending responses there is a high unmet need in this very small patient population which would be addressed with the introduction of avelumab.

3.4 Life expectancy, prevalence and incidence of the disease

Life expectancy

Data specific for England are limited; mortality data from the National Cancer Data Repository (NCDR) reports that 79% of patients with MCC (at any stage at diagnosis) do not survive past 2 years of diagnosis (Public Health England 2010).

Estimates from other countries show a median survival in patients with metastatic MCC between 4 months and 13 months from the time of initial metastases (Allen 2005; Jackson 2015; Iyer 2016; Santamaria-Barria 2013). In this decision problem, avelumab is clearly being considered for a condition that meets NICE's first criterion for an end-of-life medicine; namely it is indicated for patients with a short life expectancy, normally less than 24 months. Although chemotherapy is frequently associated with initial tumour regression, survival duration (regardless of line of therapy) is generally less than 10 months (Schadendorf 2017). For patients with metastatic MCC treated with first-line chemotherapy, the median OS is estimated to be between 5.7 months and 10.2 months (Iyer 2016; Voog 1999; Cowey 2017). Survival estimates decrease further with increased lines of therapy. In the second-line setting, estimates for patients (n=34) in the EU suggest the OS at 6 months was 26.4% (95% CI: 13.1-41.8), while at 12 months the OS was 0.0% (Becker 2016).

Prevalence and incidence

Epidemiology data specifically for England are limited, however in Europe MCC is reported to occur with a low incidence of between 0.2 per 100,000 and 0.4 per 100,000 per year (average of 0.3 per

100,000) (Kaufman 2016c). Table 6 provides an estimate of the number of patients with metastatic MCC per year in England.

The calculated estimates of incidence are reflective of clinical practice, as confirmed by clinical experts in MCC. However, this may be an under estimation as approximately 20% of patients may not be treated by MCC physicians (patients ineligible for chemotherapy are not seen at specialist centres) and therefore are not accounted for within these calculations.

Table 6: Estimated number of patients with metastatic MCC in England per year

		Reference
Incidence of MCC in Europe	0.3 per 100,000	(Kaufman 2016c)
Population of England	55,268,100	(ONS 2016)
Number of MCC patients in England per year	55,268,100/100,000 x 0.3 = **165 cases**	
Proportion of MCC patients metastatic at diagnosis	5% - 12%	(Stokes 2009; Fitzgerald 2015; Jackson 2015)
Number of patients with metastatic MCC in England per year	(165 x 0.05) = **8 cases** (165 x 0.12) = **20 cases**	
Additional proportion of MCC patients relapsing with metastatic disease	37%	(Allen 2005; Stokes 2009; Santamaria-Barria 2013)
Number of patients relapsing with metastatic disease in England per year	(165 x 0.37) = **61 cases**	
Total number of metastatic MCC patients in England per year	**70 - 81 cases**	

References: See appropriate row of table

Abbreviations: MCC: Merkel cell carcinoma

Based on a population of 3,099,100 in Wales, and using the same incidence rates for MCC (0.3 per 100,000) and proportion estimates for metastatic MCC cases both at diagnosis (5% to 12%) and those relapsing from local disease (37%), it can be estimated that approximately four patients have metastatic MCC per year in Wales (ONS 2016; Stokes 2009; Fitzgerald 2015; Jackson 2015; Public Health England 2010; Allen 2005; Santamaria-Barria 2013). As with the estimates calculated for England, clinical advisors suggested that this figure may be a small underestimation of the actual numbers of patients in Wales, due to the estimated 20% of patients who do not reach the clinic.

For more details regarding the calculation of the population eligible to receive avelumab, please refer to Section 6.

3.5 Clinical guidance and guidelines

Related guidelines and pathways

There are no guidelines specific for MCC. Related guidelines include:

- NICE Quality Standard No. 130 “Skin Cancer” (September 2016): https://www.nice.org.uk/guidance/qs130
- Skin cancer (updated February 2015) NICE pathway:

http://pathways.nice.org.uk/pathways/skin-cancer

- London Cancer: Skin Cancer Radiotherapy Guidelines (August 2014):

  http://www.londoncancer.org/media/76382/london-cancer-skin-radiotherapy-guidelines-2013-v1.0.pdf

Related NICE technology appraisals

There are currently no NICE technology appraisals related to the treatment of metastatic MCC.

Related Public Health Guidelines

There are currently no Public Health Guidelines related to the treatment of metastatic MCC.

3.6 Issues relating to current clinical practice

There are currently no approved therapies for the treatment of metastatic MCC in England, and as such, there is no standard of care. In the first-line setting, all patients with metastatic MCC are treated with chemotherapy or BSC, alongside palliative radiotherapy (see Section 3.3, Figure 3). As confirmed by clinical advisors, second-line and further treatment of metastatic MCC is predominantly BSC, with palliative radiotherapy. Chemotherapy is rarely used in the second-line and further settings in England as it is deemed by clinical experts to provide no additional benefit to patients over BSC.

MCC is primarily a disease of the elderly, with the highest incidence observed in patients greater than 65 years of age (median age in England confirmed by clinical experts: >80 years) (Kaae 2010; Kukko 2012; Lemos 2010; Reichgelt 2011). The advanced age of the population means that systemic therapy is poorly tolerated due to the high toxicity profile of the cytotoxic regimens commonly used. Consequently, the survival rate is usually very low and there is a considerable unmet need for efficacious treatments that are better tolerated in an elderly population. Prolonged survival accompanied by good HRQL is not achievable with currently available treatment options (Becker 2016; Iyer 2016).

3.7 Impact on current treatment pathways

Avelumab would fit into the existing skin cancer NICE pathway as a treatment option for people with metastatic MCC.

3.8 Assessment of equality issues

No equality issues are foreseen.

4 Clinical effectiveness

- The key clinical and safety evidence for avelumab is derived from the JAVELIN Merkel 200 trial. Recruitment to the 2L+ cohort (Part A) has closed (n=88) while recruitment to the 1L cohort (Part B) is still ongoing (n=39, target n=112)
- Treatment with avelumab (10 mg/kg every two weeks) demonstrated rapid and sustained responses leading to prolonged survival in both the 2L+ and 1L cohorts
- Avelumab is a manageable and well tolerated treatment; reported adverse reactions are mainly low grade (Grade 1-2) and there were no treatment-related deaths

Best overall response rate

- 2L+ cohort: The objective response rate (ORR) with avelumab was 33% (95% CI: 23.3-43.8) at minimum 18-months follow-up with 11% (10/88) of patients having a complete response (CR).
- 1L cohort: Avelumab treatment resulted in an ORR of 62% (95% CI: 42.3-79.3) in patients who had had ≥ 3-months of follow-up, with 14% (4/29) having CR. An ORR of 71% (95% CI: 41.9-91.6) was reported in the proportion of patients who had ≥6-months follow-up data (n=14).

Duration of response

- 2L+ cohort: Avelumab treatment resulted in rapid tumour responses; 76% (22/29) of the observed CR or partial (PR) responses had occurred by week 7. Responses were sustained, with 66% (19/29; 95% CI: 44-81) of patients who responded continuing to respond at 18-months follow-up
- 1L cohort: Avelumab treatment resulted in a rapid tumour response; [redacted] of responses (CR or PR) were observed by week 7 (≥3-month follow-up)
- Median duration of response with avelumab treatment was not estimable in either the 2L+ cohort or the 1L cohort of patients

Durable response rate

- 2L+ cohort: Responses were durable with a 6-month durable response rate [DRR] of 31%, which is clinically meaningful in patients with metastatic MCC (chemotherapy 6 month DRR between 0-7%).
- The durable responses observed with avelumab treatment are supported by the survival outcomes observed in this patient population, with all responders (29/29; 100%) still alive at the time of follow-up (minimum of 18 months).
- 1L cohort: The 6-month DRR reported in patients with at least 6-months follow-up (n=[redacted]) was [redacted]%

Overall survival

- 2L+ cohort: Avelumab treatment resulted in an 18-month overall survival (OS) rate of [redacted] with a median OS of [redacted]
- 1L cohort: Avelumab treatment resulted in a 3-month OS rate of [redacted] with the median OS not reached

Progression-free survival

- 2L+ cohort: Avelumab treatment resulted in an 18-month progression-free survival (PFS) rate of [redacted] and a sustained median PFS of 2.7 months (95% CI: 1.4-6.9)
- 1L cohort: Avelumab treatment resulted in a 3-month PFS rate of 67% (95% CI: 48-80), an immature 6-month PFS rate of 52% (95% CI: 31.0-69.0), and a median PFS of 9.1 months (95% CI: 1.9-not reached)
-

Versus current standard of care[§]

- 2L+ cohort: In a naïve comparison versus current standard of care, avelumab was associated with an improved 6-month DRR (31% vs. 0%-7%), 12-month PFS (29.0% vs. 0.0%), 12-month OS (50.0% vs. 0.0%), and a higher CR rate (11.4% vs. 0.0%-3.3%). At 18-months follow-up, avelumab has a PFS rate of [redacted] and an 18-months OS rate of [redacted]
- 1L cohort: In a naïve indirect comparison versus current standard of care, avelumab was associated with an improved ORR (62%-71% vs. 29%-55%), 6-month OS ([redacted] vs. 67%), and a higher CR rate (14%-29% vs. 13%-14%)

Health-Related Quality of Life (HRQL)

- No major changes from baseline in patients' self-reported health status or quality of life were found with FACT-M scores, suggesting a stability in patients' health-related quality of life (HRQL) over the course of treatment
- Response to avelumab, as assessed by a 30% decrease in tumour size, corresponds to a predicted mean improvement of 5.5 points on the FACT-M Total score at week 7

Safety

- Avelumab is well-tolerated with an adverse event (AE) profile superior to chemotherapy. The safety profile for avelumab is in line with reported AEs for other immuno-oncology therapies in analogue diseases
- 2L+ cohort: Avelumab is well-tolerated with less than 10% (8/88) of patients experiencing Grade ≥3 AEs related to avelumab administration. No deaths were reported to be associated with avelumab treatment and treatment discontinuation was low (7%; 6/88)
- 1L cohort: Only [redacted] of patients experienced Grade ≥3 AEs related to avelumab administration. No deaths were reported to be associated with avelumab treatment

Summary

- In treatment-experienced and treatment-naïve patients avelumab increases response rates and duration of response contributing to improved OS when compared with current standard of care. Avelumab also provides a treatment option for patients who may not be eligible for chemotherapy, whilst providing a tolerable safety profile and

[§] Analyses undertaken for the purposes of economic modelling suggest that patient characteristics are not predictive of outcomes in metastatic MCC and on this basis no statistical adjustments (e.g. Matching Adjusted Indirect Comparison [MAIC], or Simulated Treatment Comparison [STC]) were undertaken; see Section XXX.

maintaining patient HRQL

4.1 Identification and selection of relevant studies

Search strategy

A systematic literature review (SLR) was conducted to identify clinical studies on efficacy and safety relevant to the NICE decision problem. Table 7 outlines the databases searched. In addition to the database searches, conference proceedings were searched for the last 5 years (2013-2017) to ensure all relevant data was included for review. Full details of the conference proceedings searched are included in Appendix 3.

Searches of the electronic databases and relevant conference proceedings were conducted on 27th January 2016 (Nghiem 2017). Searches were conducted again on 27th March 2017 to include the most recent findings in the literature. Full details of the database searches are included in Appendix 3. The complete quality assessment of included studies can be found inside Appendix 4.

Table 7: Summary of data sources for the systematic review

Search strategy component	***Sources***	***Date limits***
Electronic database searches Key biomedical electronic literature databases recommended by HTA agencies	MEDLINE® MEDLINE® In-process Excerpta Medical Database (Embase®) Cochrane® Central Register of Controlled Trials (CENTRAL)	From database start

Abbreviations: Embase®: Excerpta Medica Database; HTA: Health Technology Assessment; MEDLINE®: Medical Literature Analysis and Retrieval System Online

4.1.1 Study selection

To be included in the SLR, studies had to meet the predefined key eligibility criteria presented in Table 8. The primary inclusion criteria were adult patients aged 18 years or older, with no restriction on gender or ethnicity. Studies were included regardless of line of therapy. It should be noted that studies that enrolled a mixed population of Stage I, II, IIIa, and Stage IIIB/IV MCC and those that did not provide subgroup analysis for metastatic population were excluded.

The first screening of the literature included or excluded citations on the basis of the abstract using predefined inclusion/exclusion criteria. The second stage of screening was based on review of the full texts. All citations meeting the inclusion criteria after the second stage of screening were extracted. The screening and extractions were screened by two independent reviews; any discrepancies were resolved by a third independent reviewer.

Table 8: Key eligibility criteria used in the search strategy

	Criteria	***Rationale***
Inclusion criteria	Population • Age: Adults (≥18 years) • Gender: Any • Ethnicity: Any	Consistent with evidence base for avelumab and the anticipated marketing authorisation.

	Criteria	***Rationale***

	• Disease: Metastatic MCC
	  ○ Distant metastatic MCC
	  ○ Regional or lymph node metastatic MCC	

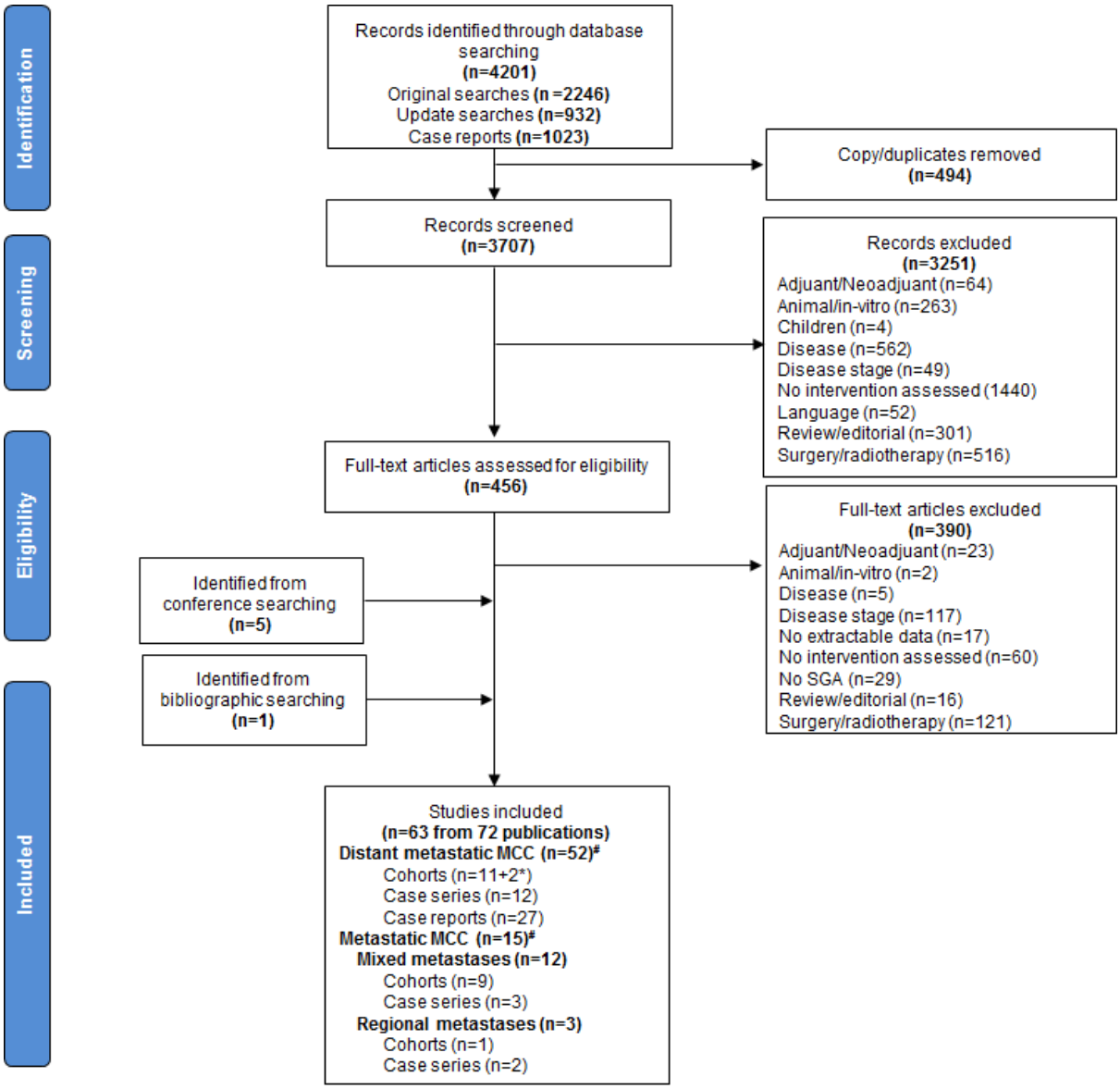
	Intervention • Avelumab	Intervention defined by the NICE decision problem for treatment of patients with metastatic MCC
	Comparator • Any pharmacological intervention	Since the primary objective of the clinical review was to assess the clinical efficacy, QoL, safety, and tolerability associated with pharmacological interventions for the treatment of patients with metastatic MCC, no restriction on pharmaceutical interventions was applied
	Study design • All RCTs irrespective of blinding status • Non-RCTs • Single-arm trials • Observational studies (retrospective analysis, prospective studies, cohort studies, case control studies, case series, case reports)	RCTs are considered as the gold standard of clinical evidence, minimising the risk of confounding factors and allowing the comparison of the relative efficacy of the interventions Other studies will supplement evidence provided by RCTs Observational studies include wider patient population and present real-life effectiveness data
	Language restrictions • Both English and non-English language studies for all study designs except case reports • Inclusion of case reports was restricted to studies published in English language	Considering the paucity of data in the population, articles in both English and non-English language were included
Exclusion criteria	Population • Studies including a mixed population of Stage I, II, IIIa, and Stage IIIB/IV MCC, with no specific subgroup analysis for metastatic MCC	Only studies focusing on metastatic MCC were considered to align to the decision problem
	Comparator • Studies exclusively focusing on the role of radiotherapy, chemo-radiotherapy, hormonal therapy, or surgery were excluded	In line with the anticipated NICE scope, studies were restricted to those evaluating the efficacy of comparators. Comparators were restricted to chemotherapies and BSC.

	Criteria	*Rationale*
	• Studies investigating the role of maintenance/consolidation therapy after surgery were excluded • Adjuvant or neo-adjuvant therapy were excluded	

Abbreviation: MCC: Merkel cell carcinoma; QoL: Quality of life; RCT: Randomised controlled trial

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the number of studies included and excluded at each stage of the systematic review is presented in Figure 4.

Figure 4: PRISMA flow diagram of the systematic review process



*Two additional studies (Bhatia 2015; Bhatia 2016) with distant metastases was included in the SLR but has been discussed separately since it evaluated intra-tumoural response (i.e. localised response) of Interleukin-12 and G100 respectively, instead of systemic response; #There is an overlap of studies across two categories (distant metastatic MCC and metastatic MCC). Three studies (Voog 1999; Feun 1988; Pectasides 2006) reported data for both distant metastases as well as for regional metastatic MCC

*Includes an indicative list of exclusion reasons; final trial flow might not reflect all exclusion reasons presented in sample flow diagram | SGA: Sub-group analysis

As shown in the PRISMA flow diagram a total of 63 studies (reported in 72 publications) were included in the review (52 studies included patients with distant metastases, 15 studies included patients with metastatic MCC and three studies included patients with regional metastases). Appendix 5 presents the full list of studies identified in the SLR, with a complete list of avelumab and comparator publications and studies excluded after full text review provided in Appendix 6. Large variability in parameters were reported across each of the studies identified, therefore not making them relevant for inclusion in the analysis of the economic model. A full list of studies relevant to the decision problem is given in Section 5.3.3. Only one study (Kaufman 2016c) was identified for avelumab and included in the SLR.

Section 5.3.3 and Appendix 10 detail the analyses performed to prepare for the comparative effectiveness studies of avelumab versus standard of care.

4.2 List of relevant randomised controlled trials

No randomised controlled trials (RCTs) were identified in the SLR for avelumab for the treatment of metastatic MCC.

4.3 List of non-randomised and non-controlled evidence

The SLR identified one record (Kaufman 2016c) reporting on one Phase II, non-RCT that evaluated avelumab in a treatment-experienced metastatic MCC patient population; JAVELIN Merkel 200 (EMR100070-003). This is the only clinical evidence directly relevant to the decision problem described in Section 1.1. JAVELIN Merkel 200 is being conducted across 72 study locations in North America, Europe, Australia and Asia. It is a Phase II, open-label, single-arm study aiming to evaluate the efficacy and safety of avelumab in adult patients with metastatic MCC and has two parts (Table 9).

Part A of the study was initiated in patients with metastatic MCC who had failed at least one prior line of chemotherapy (referred to throughout this submission as the second-line plus [2L+] cohort) 2L+ cohort (Part A) was initiated on 25th July 2014 (first dose in first patient), and is currently ongoing (n=88). Data presented in this submission are based on the most recent data at (minimum for all patients) 18 months follow-up (24th March 2017), as well as 6-month (conducted 6 month after the accrual of the last patient) and 12-month (conducted 12-month after the accrual of the last patient) follow-ups (Merck KGaA 2016e; Merck KGaA 2017b; Kaufman 2016c).

Part B was a later modification to the study, designed to investigate avelumab in treatment-naïve patients (referred to as the first-line [1L] cohort throughout this submission). The modification was based on the clinical grounds that treating metastatic MCC earlier in the disease would yield better response rates, treatment outcomes and prognosis. 1L cohort (Part B) was initiated on 15th April 2016 (first dose in first patient), with recruitment currently ongoing (target n=112). As the 1L cohort was a later modification to the trial, the majority of the data presented in this submission are based on the latest data available, from the 24th March 2017 data cut, after the recruitment of the 25th patient. This included 39 patients, 29 of which had at least 3-motnhs follow-up. A small proportion of the 39 patients (n=14) had longer follow-up (≥6 months) and this more mature data has been included where available. The longer term data are supportive of the long-term benefits of avelumab treatment in a treatment-naïve metastatic MCC patient population(Merck KGaA 2017c).

The data presented in this submission (Sections 4.3 to 4.11) are from Part A and Part B of JAVELIN Merkel 200 study (Table 9), and are from both published and unpublished sources (Kaufman 2017;

Kaufman 2016c; D'Angelo 2017; Merck KGaA 2016h; Merck KGaA 2016e; Merck KGaA 2017b; Kaufman 2016a; Merck KGaA 2016c; Merck KGaA 2017c).

Table 9: List of relevant non-randomised clinical trials

Trial no. (acronym)	***JAVELIN Merkel 200 – 2L+ cohort (Part A) (EMR100070-003)***	***JAVELIN Merkel 200 – 1L cohort (Part B)* (EMR100070-003)***
Phase	Phase II	Phase II
Objective	The primary objective is to assess the clinical activity of avelumab as determined by the ORR according to RECIST 1.1 by an IERC in patients with metastatic MCC after failing 1L chemotherapy	The primary objective is to evaluate the clinical activity of avelumab as 1L treatment for metastatic or distally recurrent MCC as determined by the DRR according to RECIST 1.1 by an IERC
Population	Patients must have histologically proven metastatic MCC and must have received at least one line of chemotherapy in the metastatic setting.	Patients must have histologically proven metastatic MCC and must be treatment-naïve to systemic therapy in the metastatic setting.
Intervention	Avelumab 1h IV infusion, 10 mg/kg, once every 2 weeks, until therapeutic failure, unacceptable toxicity, or any criterion for withdrawal from the trial or the trial drug is fulfilled. Premedication with an antihistamine and with paracetamol is required 30-60 minutes prior to each dose of avelumab for the first four infusions and subsequently as needed.	Avelumab 1h IV infusion, 10 mg/kg, once every 2 weeks, until therapeutic failure, unacceptable toxicity, or any criterion for withdrawal from the trial or the trial drug is fulfilled. Premedication with an antihistamine and with paracetamol is required 30-60 minutes prior to each dose of avelumab for the first four infusions and subsequently as needed.
Comparator	None (single arm study)	None (single arm study)
References	Primary reference: (Kaufman 2016c) Secondary references: (Merck KGaA 2016h; Merck KGaA 2016e; Merck KGaA 2017b; Kaufman 2017; Kaufman 2016a)	Primary reference: (D'Angelo 2017) Secondary references: (Merck KGaA 2017c; Merck KGaA 2016c)

*Recruitment is currently ongoing

Abbreviation: 1L: First-line; 2L+: Second-line and further; DRR: Durable response rate; IERC: Independent Endpoint Review Committee; IV: Intravenous; MCC: Merkel cell carcinoma; N/A: Non-applicable; ORR: Objective response rate; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1

4.3.1 Summary of methodology of the relevant clinical evidence

As detailed in Section 2.2, a single-arm trial was deemed by CHMP to be an acceptable approach to assess the efficacy and safety of avelumab in metastatic MCC. CHMP recommended that good quality comparative control data should be generated given the lack of a comparator arm in JAVELIN Merkel 200. Recognising that literature on outcomes for patients with metastatic MCC remains sparse and may be subject to reporting bias, a retrospective observational study was designed to address this data gap. The observational study, conducted in two parts was initiated to obtain real-world evidence in the US and the EU for patients with metastatic MCC who had received one or more lines of prior chemotherapy treatment. The observational studies had similar inclusion/exclusion criteria JAVELIN

Merkel 200, and as they were commissioned by the manufacturer, and patient-level data were available for analysis. Statistical analyses undertaken for the purposes of economic modelling suggests that patient characteristics are not predictive of outcomes in metastatic MCC and for this reason, no statistical adjustments (such as Matching Adjusted Indirect Comparison [MAIC], or Simulated Treatment Comparison [STC]) were conducted to match the observational data to the relevant cohorts within JAVELIN Merkel 200. Results are therefore presented side-by-side below. Further details on the observational study methodology and results are provided in Section 4.9.

4.3.2 JAVELIN Merkel 200 – 2L+ cohort (Part A)

A summary of the methodology of JAVELIN Merkel 200 –2L+ cohort (Part A) is presented in Table 10.

Clinical trials assessing cancer therapies traditionally use survival-based primary outcomes, such as overall survival (OS) or progression-free survival (PFS). However, the ultra-rare disease status, combined with poor prognosis and no approved treatments available, means that there is a high unmet need for patients with metastatic MCC. Clinical trials which enable the most rapid demonstration of clinical efficacy with a clinically feasible study design, could help accelerate the regulatory process. Furthermore, efficacy end-points such as median PFS may underestimate the benefits of immune-oncology drugs. One of the key benefits of such therapies is the durability of response, driven by the mode of action that triggers the immune system to attack the tumour leading to a sustained response. Instead, efficacy endpoints such as durable response rate or landmark analysis are better indicators of efficacy for the proportion of patients who have responded to treatment. As a result, a response-based outcome was deemed to be acceptable.

The primary endpoint of JAVELIN Merkel 200 –2L+ cohort was confirmed best overall response (BOR; defined as CR or PR according to RECIST Version 1.1 as determined by Independent Endpoint Review Committee (IERC), obtained from start of study drug until documented disease progression, assessed every 6 weeks). In clinical practice, response is not assessed against as strict criteria based on radiological data as it is in clinical trials; rather it is based on a more general assessment of clinical benefit. The assessment of immuno-oncology therapies against Response Evaluation Criteria in Solid Tumors (RECIST) criteria for response is therefore a conservative estimate of response compared to clinical practice assessment of immuno-oncology treatment effect. The traditional survival outcomes, overall survival (OS) and progression-free survival (PFS), were included as secondary outcomes.

Qualitative, semi-structured patient interviews were also conducted with patients enrolled in JAVELIN Merkel 200 to acquire a comprehensive picture of the impact of metastatic MCC and its management on health-related quality of life (HRQL) (see qualitative patient interviews section under Section 4.7).

A data cut with a minimum of 24-month follow-up is planned for [redacted].

Table 10: Summary of methodology of JAVELIN Merkel 200 – 2L+ cohort (Part A)

Trial name (trial number)	JAVELIN Merkel 200 – 2L+ cohort (Part A) (EMR100070-003)
Location	The study was conducted in 35[5] cancer treatment centres and academic hospitals in North America, Europe (not UK), Australia, and Asia
Trial design	Multicentre, international, prospective, single-group, open-label, Phase II study to evaluate the efficacy and safety of avelumab in patients (n=88) with metastatic MCC

[5] Number of centres has since expanded to include 72 study locations since the addition of Part B to the JAVELIN Merkel 200 trial

Key eligibility criteria for participants	Enrolled patients must have received at least one line of chemotherapy for the treatment of metastatic MCC. Eligible patients were enrolled before treatment start, after verification of fulfilling all inclusion criteria and without matching any exclusion criteria. The key eligibility criteria for the study were: • Adults aged ≥18 years • Estimated life expectancy of more than 12 weeks • At least one unidimensional measurable lesion by RECIST 1.1 • Histologically proven Stage IV MCC • At least one prior line of chemotherapy and progression after the most recent line of chemotherapy • Prior adjuvant therapy allowed • Patients with HIV, immunosuppression, or haematologic malignancies, and previous solid organ transplant recipients were excluded • Naïve to therapies targeting T-cell co-regulatory proteins (i.e. immune checkpoint inhibitors), concurrent anticancer treatment, or systemic treatment with corticosteroids or other immunosuppressive drugs • No previous vaccinations for prevention of infectious disease within 4 weeks of trial drug administration or while on trial (with the exception of inactivated vaccines) • Unselected for PD-L1 expression or MCPyV status • ECOG PS 0-1 and adequate haematological, hepatic, and renal function

Trial drugs	Eligible patients received avelumab at a dose of 10 mg/kg as a 60 minute IV infusion once every 2 weeks (one treatment cycle). The dose of avelumab was calculated based on the weight of the patient determined on the day of each drug administration. Any medications (other than those excluded by the clinical study protocol) that were considered necessary for the patients' welfare and would not interfere with avelumab could be given at the Investigator's discretion. Patients received treatment with avelumab until significant clinical deterioration, including: • Therapeutic failure (patients may stay on treatment beyond observation of progressive disease provided there is no significant clinical deterioration) • Unacceptable toxicity • Withdrawal of consent • Other protocol-specified criterion for withdrawal from the study or study drug was fulfilled Patients who experienced a confirmed CR according to RECIST 1.1 could be treated for a maximum of 12 months and a minimum of 6 months after confirmation, at the discretion of the Investigator. If the Investigator believed that a patient could benefit from treatment beyond 12 months, it was permissible after discussion with the Sponsor. If a patient with a confirmed CR relapsed after stopping treatment, but prior to the end of the study, one re-initiation of treatment was allowed at the discretion of the Investigator and agreement of the Medical Monitor
Primary outcomes	The primary endpoint of the trial was confirmed BOR, defined as CR or PR according to RECIST 1.1, as determined by an IERC. The confirmed BOR was defined as the best response obtained among all tumour assessment visits after the start of the study treatment until documented disease progression, excluding assessments after start of subsequent anticancer therapy, taking the following requirements for confirmation into account: • CR or PR needed to be confirmed at a subsequent tumour assessment, preferably 6 weeks after the initial observation of response and according to the normal 6-week assessment schedule but no sooner than 5 weeks after the initial documentation of CR or PR • PR could be confirmed at an assessment later than the next assessment after the initial documentation of PR • The minimum duration for a BOR of SD was defined as at least 6 weeks after start of study treatment.

Secondary/ tertiary outcomes	• DoR according to RECIST 1.1 (defined as the time from first documented CR or PR until documented PD or death, whichever occurred first) as determined from IERC tumour assessments • PFS time (defined as the time from the first administration of avelumab until documented PD or death, whichever occurred first), according to RECIST 1.1, as determined by an IERC • Occurrence and severity of TRAEs according to NCI-CTCAE v4.0 • OS time (from first administration of avelumab until the date of death) • Response status according to RECIST 1.1 at 6 months and 12 months after start of study treatment • Serum titers of anti-avelumab antibodies • Population PK profile (sparse sampling)
Exploratory outcomes	• BOR, duration of response, and PFS per Investigator assessment • irBOR and irPFS according to modified irRC, respectively, per Investigator assessment • TTP under last prior anticancer therapy • Tumour shrinkage in target lesions per time point from baseline • Expression of PD-L1 in tumour tissue • Expression of CD8 in tumour tissue • Expression of MCPyV in tumour tissue • Changes in soluble factors (e.g. cytokine profiles) • Changes in MCPyV-specific humoral responses • Changes in EQ-5D and FACT-M scores over the treatment period • Description of effects of avelumab treatment as perceived and reported in interviews by patients with metastatic MCC

Duration of follow-up	• Consent date for first enrolled patient: 03 July 2014 • First patient, first dose: 25th July 2014 • Primary analysis was conducted at 6 months (03 March 2016) • Exploratory analysis was conducted at 12 months (03 September 2016) and 18 months (24th March 2017) • Next analysis planned at 24 months ([redacted]) • Estimated study completion date 30th June 2025 • Estimated primary completion date (final data collection date for primary outcome measure) scheduled for 27th September 2019.
Pre-planned subgroups*	Objective response by: • Age (Group 1: <65 years, ≥65 years; Group 2: ≤Median, >Median) • Gender (male, female) • Pooled region (North America, Europe, Rest of World) • Time from initial diagnosis to study entry (≤1 year, >1 year and ≤2 years, >2 years) • Site of primary tumour (skin, non-skin) • Visceral metastases at baseline (present, absent) • Disease burden at baseline (Baseline SLD ≤median, Baseline SLD >median) • Baseline ECOG PS (ECOG PS 0, ECOG PS 1) • Number of previous systemic treatments for metastatic disease (n=1, n≥2) • Number of previous systemic therapies for metastatic disease or locally advanced therapies (n=1, n≥2) • Tumour PD-L1 cell expression at cut-off of 1% (PD-L1 expression <1%, PD-L1 expression ≥1%) • Tumour PD-L1 cell expression at cut-off of 5% (PD-L1 expression <5%, PD-L1 expression ≥5%) • Tumour MCPyV status by IHC and by PCR (positive, negative) • Combination of PD-L1 expression (cut-off of 1%) and IHC MCPyV status (PD-L1+/MCPyV+, PD-L1+/MCPyV-, PD-L1-/MCPyV+, PD-L1-/MCPyV-)

SOURCE: (Merck KGaA 2016c; Merck KGaA 2016g)

*JAVELIN Merkel 200 was not powered for any subgroup analysis and as such all analyses were exploratory in nature

Abbreviations: AE: Adverse event; BOR: Best overall response; CR: Complete response; DoR: Duration of response; ECOG PS: Eastern Cooperative Oncology Group performance score; EQ-5D: EuroQol-5 dimensions; FACT-M: Functional Assessment of Canter Therapy – Melanoma; HIV: Human immunodeficiency virus; IERC: Independent Endpoint Review Committee; IHC: Immunohistochemistry; irBOR: Immune-related best overall response; irPFS: Immune-related progression-free survival; irRC: Immune-related response criteria; ITT: Intent-to-treat; IV: Intravenous; MCC: Merkel cell carcinoma; MCPyV: Merkel cell polyomavirus; N/A: Non-applicable; NCI-CTCAE: National Cancer Institute-Common Technology Criteria for Adverse Events; ORR: Objective response rate; OS: Overall survival; PCR: Polymerase chain reaction; PD: Progressive disease; PD-L1: Programmed death ligand-1; PFS: Progression-free survival; PK: Pharmacokinetics; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SD: Stable disease; SLD: Sum of the longest diameter; TRAE: Treatment-related adverse event; TTP: Time to progression

4.3.3 JAVELIN Merkel 200 – 1L cohort (Part B)

The study design and analysis of JAVELIN Merkel 200 – 1L cohort (Part B) is similar to that of 2L+ cohort (Part A) (see Table 10) and is summarised in Table 11.

JAVELIN Merkel 200 – 1L cohort (Part B) was initiated on 15th April 2016 (first dose in first patient), and is currently ongoing. At the time of submission, a data-cut from a pre-planned interim analysis was available. The analysis was planned at 3 months after the accrual of the 25th patient (3 months; 24th March 2017). This data-cut was segmented into three analyses; response based efficacy for patients with ≥3-month follow-up (N=29) and patients with 6-month follow-up (N=14) and both efficacy and safety endpoints for the full 39 patients. A data cut for a minimum of 50 patients with ≥3-months follow-up is planned for [redacted] with additional data cuts expected in 2018.

The primary analysis for Part B will be conducted 15 months after the accrual of the last patient (Merck KGaA 2016c).

Table 11: Summary of methodology specific for JAVELIN Merkel 200 – 1L cohort (Part B)

Trial name (trial number)	JAVELIN Merkel 200 – 1L cohort (Part B) (EMR100070-003)
Location	US and Europe (Not UK)
Key eligibility criteria for participants	Enrolled patients must treatment-naïve to systemic therapy for metastatic MCC. The key eligibility criteria for the study were: • Adults aged ≥18 years • No prior therapy with any antibody/drug targeting T-cell coregulatory proteins such as anti-PD-1, anti-PD-L1, or anti-Cytotoxic T-lymphocyte-associated (CTLA) protein-4 antibody • No concurrent anticancer treatment
Trial drugs	Patients who experienced a confirmed CR could be treated for a minimum of 12 months after confirmation, at the discretion of the Investigator. If the Investigator believed that a patient could benefit from treatment beyond 12 months, it was permissible after discussion with the Sponsor.
Primary outcomes	The primary endpoint is durable response, defined as an objective response (CR or PR) according to RECIST 1.1, determined by an IERC, with a duration of at least 6 months
Exploratory outcomes	• Correlate immunogenicity of avelumab with clinical results (ORR and AEs) • Tumour shrinkage in target lesions at each time point from baseline • Changes in biomarkers in relation to disease responses to avelumab • Association between tumour PD-L1 expression and BOR • Benefits of avelumab treatment as perceived by patients with metastatic MCC
Duration of follow-up	• Consent date for first enrolled patient: 31st March 2016 • First patient, first dose: 15th April 2016 • Interim exploratory analysis was conducted at 3 months after the accrual of the 25th patient (24th March 2017) • Next analysis planned at [redacted] with 3-month follow-up in Part B ([redacted]) • Additional data cuts are highly likely. Dates for future analyses can be provided during the appraisal process

	• Estimated study completion date 30th June 2025 • Estimated primary completion date (final data collection date for primary outcome measure) scheduled for 27th September 2019
Pre-planned subgroups*	Objective response by: • Age (Group 1: <65 years, ≥65 years; Group 2: ≤Median, >Median) • Gender (male, female) • Race (Caucasian/White, Asian, Black/African American, Other) • Pooled region (North America, Europe, Asia, Rest of World) • Time from initial diagnosis to study entry (≤1 year, >1 year and ≤2 years, >2 years) • Site of primary tumour (skin, non-skin) • Visceral metastases at baseline (present, absent) • Lymph node disease only at baseline (yes, no) • Baseline CD8 T-cell density (<median, ≥median) • Number of previous systemic chemotherapies (n=0, n≥1) • Tumour PD-L1 cell expression at cut-off of 1% (PD-L1 expression <1%, PD-L1 expression ≥1%) • Tumour PD-L1 cell expression at cut-off of 5% (PD-L1 expression <5%, PD-L1 expression ≥5%) • Tumour MCPyV status by IHC and by PCR (positive, negative) • Combination of PD-L1 expression (cut-off of 1%) and IHC MCPyV status (PD-L1+/MCPyV+, PD-L1+/MCPyV-, PD-L1-/MCPyV+, PD-L1-/MCPyV-)

SOURCE: (Merck KGaA 2016c; Merck KGaA 2016d)

*JAVELIN Merkel 200 was not powered for any subgroup analysis and as such all analyses were exploratory in natureAbbreviations: AE: Adverse event; BOR: Best overall response; CR: Complete response; IERC: Independent Endpoint Review Committee; IHC: Immunohistochemistry; ITT: Intent-to-treat; MCC: Merkel cell carcinoma; MCPyV: Merkel cell polyomavirus; N/A: Not applicable; ORR: Objective response rate; PCR: Polymerase chain reaction; PD-1: Programmed death protein-1; PD-L1: Programmed death ligand-1; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1

4.4 Statistical analysis of the relevant clinical evidence

4.4.1 JAVELIN Merkel 200 – 2L+ cohort (Part A)

Table 12 provides a summary of the statistical analyses in 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial. All data was evaluated as observed and no imputation methods for missing values were used, unless otherwise specified.

Table 12: Summary of statistical analyses in JAVELIN Merkel 200 – 2L+ cohort (Part A)

Trial	*Hypothesis objective*	*Statistical analysis*	*Sample size, power calculation*	*Data management, patient withdrawals*
JAVELIN Merkel 200 – 2L+ cohort (Part A)	The primary endpoint of the trial is the confirmed BOR according to RECIST 1.1, based on independent review of tumour assessments. The ORR will be determined as the proportion of subjects with a confirmed BOR of PR or CR. The trial aims at demonstrating an ORR >20% by means of an exact binomial test	The analysis of efficacy was performed on the ITT population (i.e. all patients who received ≥1 dose of study treatment). There was 1 interim analysis for futility after 20 patients had been enrolled and observed for ≥3 months, and 1 interim analysis for efficacy 6 months after 56 patients had been enrolled. The primary analysis was conducted 6 months after the accrual of the last subject. An exploratory analysis of secondary and exploratory endpoints was conducted 12 months after the accrual of the last subject. **Futility:** Enrolment was stopped for futility if there was no response (confirmed or unconfirmed) observed in the first 20 patients after 3 months of follow-up. **Efficacy:** The 2-stage group sequential testing approach was applied for efficacy. The null hypothesis could be rejected if 20 patients in the interim analysis after 56 patients, or 25 patients in the primary analysis after 84 patients, showed a confirmed PR or CR according to RECIST 1.1. The corresponding nominal p-values of the exact binomial test were 0.0045 and 0.0214, respectively. The resulting overall probability of reaching a positive result in the interim or primary analysis under the null hypothesis assumption of an ORR ≤20% was ≤0.0225, as derived from the binomial distribution; therefore, the overall type I error rate is controlled at a level of 2.5% (1-sided). Under the given assumptions, the power to reject the null hypothesis at the interim or the primary analysis was approximately 87% **Primary endpoint analysis** The Clopper-Pearson method was used to calculate the 2-sided CI for the ORR at both the interim and the primary analyses. **Secondary endpoint analyses** DoR, PFS and OS were analysed with K-M methods to estimate parameters; median values were calculated with corresponding 2-sided CIs using the Brookmeyer-Crowley method. Safety analyses were performed on the safety analysis set and based on a review of the incidence of TEAEs, and changes in vital signs, ECGs, body weight, and laboratory values	The planned total sample size was 84 patients. The following assumptions were made for the sample size calculation: • An ORR of 35% • An overall alpha = 0.025 (1-sided) for the test of the null hypothesis of an ORR ≤20%	Statistical analysis system (SAS) version 9.2 (or higher) was used for the statistical analysis, and R software package version 2.15.2 was used for the sample size calculations All data was evaluated as observed and no imputation method for missing values were used, unless otherwise specified. **Tumour response** was based on the IERC assessment of overall response at each time point. **DoR** was censored at the date of the last adequate tumour assessment **OS time** was censored at the last recorded date that the patient was known to be alive **PFS time** was censored on the date of the last adequate tumour assessment in patients with no PD or death. Patients who had no trial tumour assessments and did not die were censored on the date of first study treatment

SOURCE: (Merck KGaA 2016g)

Abbreviations: 2L+: Second-line and further; BOR: Best overall response; CI: Confidence interval; CR: Complete response; DoR: Duration of response; ECG: Electrocardiogram; K-M: Kaplan-Meier; MCC: Merkel cell carcinoma; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; TEAE: Treatment-emergent adverse event

4.4.2 JAVELIN Merkel 200 – 1L cohort (Part B)

Table 13 provides a summary of the statistical analyses in JAVELIN Merkel 200 – 1L cohort (Part B). The full statistical analysis plan has been included in the reference pack.

Table 13: Summary of statistical analyses in JAVELIN Merkel 200 – 1L cohort (Part B)

Trial	*Hypothesis objective*	*Statistical analysis*	*Sample size, power calculation*	*Data management, patient withdrawals*
JAVELIN Merkel 200 – 1L cohort (Part B)	The primary endpoint of the trial is durable response, defined as objective response (CR or PR) according to RECIST 1.1 and as determined by an IERC, with a duration of at least 6 months	The analysis of efficacy was based on the ITT analysis set (i.e. all patients who received ≥1 dose of study treatment). There was 1 exploratory interim analysis and one primary analysis planned for this study. For the interim analysis, the clinical cut-off date was 3 months after the 25th patient received the first dose of avelumab; for the primary analysis, the clinical cut-off date will be 15 months after the last subject enrolled received the first dose of avelumab. **Primary endpoint analysis** The Clopper-Pearson method was used to calculate the 2-sided CI for the DRR. **Secondary endpoint analyses** OS, DoR and PFS were analysed with K-M methods; the Clopper-Pearson method was used to calculate the 2-sided CI for confirmed ORR. Safety analyses were performed on the safety analysis set and based on a review of the incidence of TEAEs, and changes in vital signs, ECGs, body weight, and laboratory values	The planned total sample size was 112 patients to address the primary objective, relevant subgroup analyses, consistency, and further safety assessments. The following assumptions were made for the sample size calculation: • A DRR of 45% (the probability to observe lower bound of 95% CI above 20% would be >99% and above 30% would be 90%).	SAS version 9.2 was used for the statistical analysis, and R software package version 2.15.0 was used for the sample size calculations All data was evaluated as observed and no imputation method for missing values were used, unless otherwise specified. For patients with a CR but neither documented disease progression nor death within 12 weeks after the last tumour assessment as of the cut-off date for the analysis, the **DoR** was censored at the date of the last tumour assessment For patients still alive at the time of data analysis or who were lost to follow-up, **OS time** was censored at the last recorded date that the patient was known to be alive. If a patient has not had an event (PD or death), **PFS** was censored at the date of last adequate tumour assessment

SOURCE:(Merck KGaA 2016d)

Abbreviations: 2L+: Second-line and further; BOR: Best overall response; CI: Confidence interval; CR: Complete response; DoR: Duration of response; ECG: Electrocardiogram; K-M: Kaplan-Meier; MCC: Merkel cell carcinoma; ORR: Overall response rate; OR: Overall survival; PFS: Progression-free survival; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; TEAE: Treatment-emergent adverse event

4.5 Participant flow in the studies

4.5.1 JAVELIN Merkel 200 – 2L+ cohort (Part A)

A total of 125 patients were enrolled and screened for participation in 2L+ cohort (Part A) of the study, with 88 patients receiving at least one dose of avelumab and included in the intent-to-treat (ITT) and Safety analysis sets (Figure 5). At ≥18 months follow-up, [redacted] were continuing in active treatment. It was verified with clinical experts that this is considered a large sample size based on the ultra-rare disease status and poor prognosis. Discontinuation of treatment had also occurred in [redacted] at the time of follow-up (see Table 14 for reasons for discontinuation). In line with other immune-oncology therapies, patients who discontinued for reasons other than disease progression, showed a continued response (Section 4.7.2)

Figure 5: Subject disposition in JAVELIN Merkel 200 – 2L+ cohort (Part A)

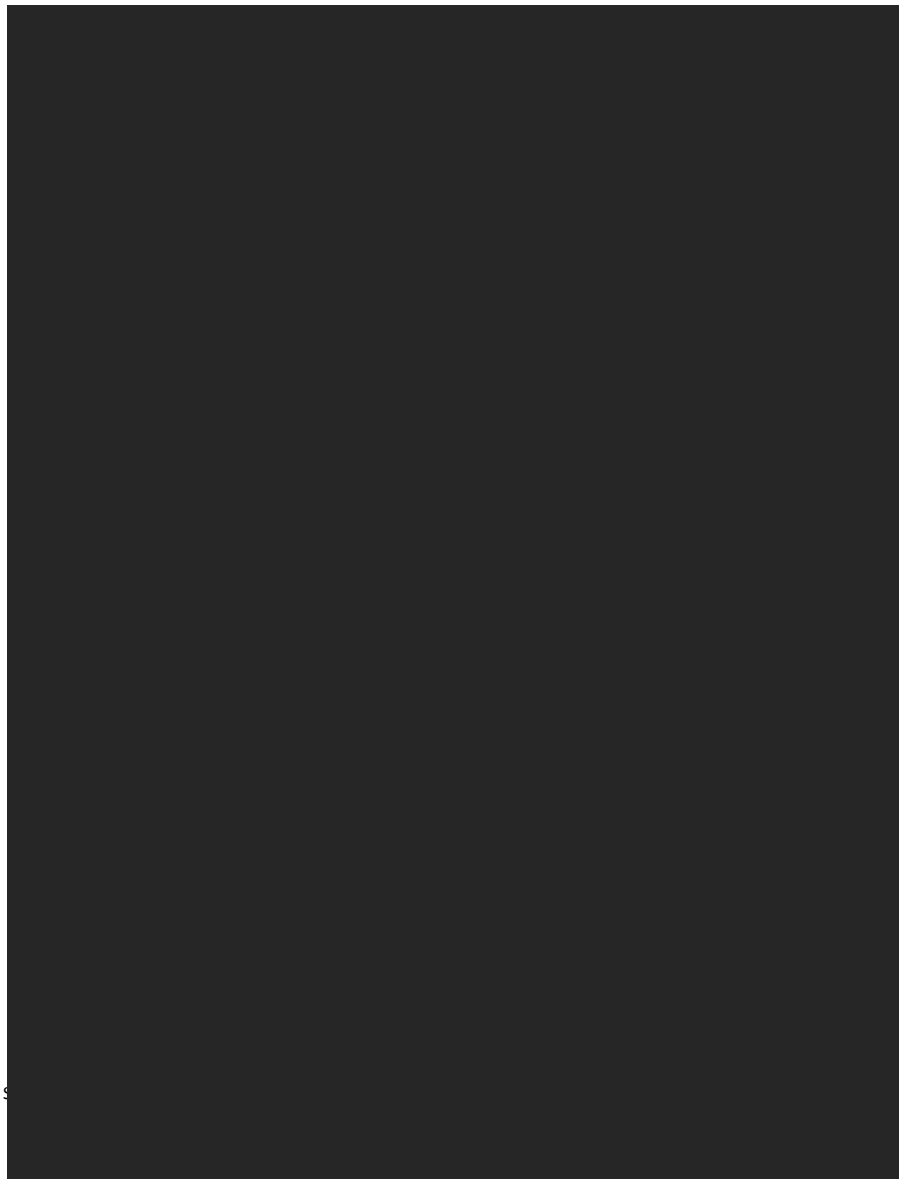


Table 14: Patient disposition in JAVELIN Merkel 200 - 2L+ cohort (Part A) – 18-month follow-up

Disposition	***Avelumab N=88***
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

SOURCE: (Merck KGaA 2017b)

*One patient discontinued treatment due to treatment-related Grade 1 creatinine elevation, which occurred after the treatment-emergent period and followed an event of Grade 2 treatment-related acute intestinal nephritis

Baseline characteristics of the patient population are shown in Table 15. The mix of Eastern Cooperative Oncology Group performance status (ECOG PS) 0 and 1 scores, visceral disease at study entry, sum of target lesion diameters, and lymph node disease of patients enrolled in the trial are in line with clinical practice in England, as confirmed by clinical experts in MCC. Clinical experts have suggested that although the median age of patients (72.5 years) enrolled in JAVELIN Merkel 200 is likely to reflect the lower end of the age range seen in clinical practice in England (median age approximately 80 years), it is a reasonable representation of the population in England with metastatic MCC.

Table 15: Characteristics of participants in JAVELIN Merkel 200 – 2L+ cohort (Part A)

Baseline characteristic	***JAVELIN Merkel 200 – 2L+ cohort (Part A)***
	Avelumab (N=88)
Age	
<65 years, n (%)	22 (25.0)
≥65 year, n (%)	66 (75.0)
Median, years (range)	72.5 (33-88)
Gender, n (%)	
Male	65 (73.9)
Female	23 (26.1)
ECOG PS, n (%)	
0	49 (55.7)
1	39 (44.3)
Weight (kg)	
Median (range)	82.85 (47-153)

Baseline characteristic	***JAVELIN Merkel 200 – 2L+ cohort (Part A)***
	Avelumab (N=88)
Region, n (%)	
North America	51 (58.0)
Europe	29 (33.0)
Rest of world	8 (9.1)
Site of primary tumour, n (%)	
Skin	67 (76.1)
Lymph node	12 (13.6)
Other	2 (2.3)
Missing	7 (8.0)
Metastatic involvement at study entry, n (%)	
Yes	88 (100.0)
No	0 (0.0)
Number of prior systemic cancer therapies received, n (%)	
1	52 (59.1)
2	26 (29.5)
≥3	10 (11.4)
Number of prior systemic cancer therapies received for metastatic disease, n (%)	
1	57 (64.8)
2	27 (30.7)
≥3	4 (4.5)
Prior anticancer therapy, n (%)	
Chemotherapy for metastatic disease	88 (100.0)
Chemotherapy for non-metastatic disease	3 (3.4)
Antibody therapy	1 (1.1)
Experimental T cell co-regulator therapy	1 (1.1)
Kinase inhibitors	3 (3.4)
Other	4 (4.5)
Prior chemotherapy for metastatic disease, n (%)	
Etoposide	61 (69.3)
Carboplatin	45 (51.1)
Cisplatin	25 (28.4)
Doxorubicin	9 (10.2)
Visceral disease at study entry, n (%)	
Present	47 (53.4)
Absent	41 (46.6)
Lymph node disease only at study entry, n (%)	
Yes	19 (21.6)
No	69 (78.4)

Baseline characteristic	*JAVELIN Merkel 200 – 2L+ cohort (Part A)*
	Avelumab (N=88)
Sum of target lesion diameters (SLD) at baseline	
Median SLD, mm (range)	79 (16-404)
Tumour PD-L1 expression, n (%)[+]	
PD-L1+	58 (65.9)
PD-L1-	16 (18.2)
Not evaluable	14 (15.9)
Tumour MCPyV status, n (%)	
MCPyV+	46 (52.3)
MCPyV-	31 (35.2)
Not evaluable	11 (12.5)

*Not-evaluable included those data that were missing, of poor quality, or otherwise not available to provide results

[+]Determined in post-hoc analysis

SOURCE: (Merck KGaA 2016h)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; MCPyV: Merkel cell polyomavirus; PD-L1: Programmed death ligand-1

4.5.2 JAVELIN Merkel 200 – 1L cohort (Part B)

JAVELIN Merkel 200 – Part B is an ongoing study and data is evolving. The study aims to recruit a total of 112 patients. A total of 52 patients were screened for participation in the 1L cohort (Part B) of the study. Of these 13 patients did not receive study medication (pre-defined eligibility criteria not met [n=11], adverse event [AE; n=1], other [n=1]); 39 patients receiving at least one dose of avelumab and included in the intent-to-treat (ITT) and safety analysis sets. At the time of this submission three data cut-off were available; a ≥3 month follow-up data set comprising of 29 patients with response-based outcomes, a further 6-month cut-off data set comprising of 14 patients and a data set comprising of other efficacy and safety outcomes for the full 39 patients set. At ≥3 months follow-up, [redacted] patients [redacted] were continuing in active treatment. Study treatment had been discontinued in [redacted] patients [redacted] at the time of data cut-off (see Table 16 for reasons for discontinuation).

Table 16: Patient disposition in JAVELIN Merkel 200 - 1L cohort (Part B) – minimum follow up of 13 weeks

Disposition	*Avelumab N=39*
Patients continuing in treatment period, n (%)	[redacted]
Reason for discontinuation of treatment, n (%)	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

SOURCE: (Merck KGaA 2017c)

Baseline characteristics of the patient population are presented in Table 17. The median age of patients ([redacted] years) enrolled in JAVELIN Merkel 200 – 1L cohort (Part B) is reflective of the age range for metastatic MCC in clinical practice in England, as confirmed by clinical experts (median age of 80 years).

Table 17: Characteristics of participants in JAVELIN Merkel 200 – 1L cohort (Part B)

Baseline characteristic	*JAVELIN Merkel 200 – 1L cohort (Part B)*
	Avelumab (N=39)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

SOURCE: (Merck KGaA 2017c)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status

4.6 Quality assessment of the relevant clinical evidence

The quality assessment of the JAVELIN Merkel 200 trial can be found in Appendix 8.

4.7 Clinical effectiveness results of the relevant clinical evidence

4.7.1 Best overall response (BOR) by RECIST 1.1

- 2L+ cohort (Part A): The objective response rate (ORR) with avelumab was 33% (95% CI: 23.3-43.8) at minimum 18-months follow-up with 11% (10/88) of patients having a complete response (CR).
- Part B (1L+ cohort): Avelumab treatment resulted in an ORR of 62% (95% CI: 42.3-79.3) in 29 patients who had a minimum of 3-months follow-up, with 14% (4/29) having CR.

An ORR of [redacted] was reported in the proportion of patients who had ≥6 months of follow-up data (n=14).

The results for the analysis of BOR in JAVELIN Merkel 200 are presented in Table 18.

In 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial the efficacy criterion for the primary endpoint (confirmed BOR) was met, as the null hypothesis of ORR ≤20% could be rejected. The data reported here highlights that initial responses observed with avelumab treatment at minimum of 6-months (ORR: 31.8%) have improved at 12-months follow-up (33%; Table 18) due to a late responder (ORR at 6 months n=28; ORR at 12 months n= 29). Additionally, 10% of patients had a stable disease (SD).

In the 1L cohort (Part B) of the JAVELIN Merkel 200 trial at 3-months follow-up, an increased ORR was reported with IERC assessment compared with investigator assessment (62.1% vs. 55.2%). IERC assessment also reported increased PR (48.3% vs. 44.8%), while SD was increased with investigator assessment (17.2% vs. 10.3%). In a small proportion of patients (n=14) with longer follow-up (6-month follow-up), a similar trend was observed with an increased ORR reported with IERC assessment ([redacted]). IERC assessment also reported increased CR ([redacted]), whereas SD was increased with investigator assessment ([redacted]). As the data for 1L cohort (Part B) is currently evolving, the interim analysis reported here has been conducted in only small numbers of patients (minimum 3-months follow-up n=29; minimum of 6-months follow-up n=14). As such, with such small cohorts it is expected that you would see a discrepancy between IERC and investigator assessment. However, whilst the overall IERC reported increased efficacy, the data are largely in line with the investigator assessment and what was observed in the second-line and further cohort.

Initial responses with avelumab treatment in treatment-naïve patients (Part B – 1L cohort) are promising and at a minimum follow-up of 3-months are almost double the responses observed in treatment-experienced patients (Part A – 2L+ cohort) (ORR: 62.1% vs. 31.8%), with data still evolving.

Table 18: Summary of the best overall response in JAVELIN Merkel 200

BOR by RECIST 1.1 n (%)	***2L+ cohort (Part A)***			***1L cohort (Part B)***	
	6-month follow-up (N=88)	***12-month follow-up (N=88)***	***18-month follow-up (N=88)***	***3-month follow-up (N=29)***	***6-month follow-up (N=14)***
CR	8 (9.1)	10 (11.4)	10 (11.4)	4 (13.8)	[redacted]
PR	20 (22.7)	19 (21.6)	19 (21.6)	14 (48.3)	[redacted]
SD	9 (10.2)	9 (10.2)	9 (10.2)	3 (10.3)	[redacted]
PD	32 (36.4)	32 (36.4)	32 (36.4)	7 (24.1)	[redacted]
Non-CR/non-PD	1 (1.1)*	0	0	0	[redacted]
Non-evaluable¥	18 (20.5)	18 (20.5)	18 (20.5)	1 (3.4)	[redacted]
ORR, % (95% CI)	31.8 (21.9-43.1)	33.0 (23.3-43.8)	33.0 (23.3-43.8)	62.1 (42.3-79.3)	[redacted]

SOURCE: (Merck KGaA 2016h; Merck KGaA 2017c; Merck KGaA 2016e; Merck KGaA 2017b)

*Patient 4070003 was assessed with a CR according to IERC assessment at last visit prior to the data cut-off on Study Day 253 (22 February 2016). The data cut-off for this report was prior to the next tumour assessment for this patient, thus the CR could not be confirmed and a confirmed BOR of non-CR / non-PD was recorded.

¥Patients not assessable for a confirmed BOR had no baseline lesions identified by the independent review committee (n=4), baseline but no post-baseline assessments (n=10; four patients died within 6 weeks after the start of treatment and six additional patients discontinued study treatment in the first 6 weeks), all non-assessable post-baseline assessments (n=2), no post-baseline tumour assessment before the start of new anticancer therapy (n=1), or SD of insufficient duration (<6 weeks after start date without further tumour assessment; n=1)

Abbreviations: BOR: Best overall response; CI: Confidence interval; CR: Complete response; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; RECIST: Response evaluation criteria in solid tumours; SD: Stable disease

The ORR results were robust and consistent across sensitivity analyses in 2L+ cohort (Part A) of JAVELIN Merkel 200; 33.0% according to both IERC assessment and investigator assessment at minimum 12-month follow-up (Table 19). Investigator assessment reported increased partial response (PR; 22.7% vs. 21.6%), SD (14.8% vs. 10.2%), progressive disease (PD; 39.8% vs. 36.4%) values compared with IERC assessment. IERC assessment at 18-months follow-up was consistent with this assessment at 12-months follow-up.

According to immune-related response criteria (irRC), there was one more patient with a CR than using RECIST 1.1 (according to IERC) at 12-months follow-up. There were also more patients assessed with immune-related SD (irSD; 15 patients, 17.0%) and fewer with immune-related PD (irPD; 24 patients, 27.3%) compared with RECIST 1.1 assessments (SD = 9 patients, 10.2% and PD = 32 patients, 36.4%).

Table 19: Sensitivity analyses for confirmed best overall response in JAVELIN Merkel 200

	2L+ cohort (Part A): 18-month follow-up	***2L+ cohort (Part A): 12-month follow-up***		***1L cohort (Part B): 3-month follow-up***	
	IERC assessment N=88 (100%)	***Investigator assessment N=88 (100%)***	***IERC assessment N=88 (100%)***	***Investigator assessment N=29 (100%)***	***IERC assessment N=29 (100%)***
BOR (n (%))					
CR	10 (11.4)	9 (10.2)	10 (11.4)	3 (10.3)	4 (13.8)
PR	19 (21.6)	20 (22.7)	19 (21.6)	13 (44.8)	14 (48.3)
SD	9 (10.2)	13 (14.8)	9 (10.2)	5 (17.2)	3 (10.3)
PD	32 (36.4)	35 (39.8)	32 (36.4)	7 (24.1)	7 (24.1)
Non-CR/Non-PD	0	-	0	-	0
Not evaluable	18 (20.5)	11 (12.5)	18 (20.5)	1 (3.4)	1 (3.4)
ORR					
CR + PR (Response rate)	29 (33.0)	29 (33.0)	29 (33.0)	16 (55.2)	18 (62.1)
95% CI	23.3-43.8	23.3-43.8	23.3-43.8	35.7-73.6	42.3-79.3

SOURCE: (Merck KGaA 2017c; Merck KGaA 2016e; Merck KGaA 2017b)

Abbreviations: BOR: Best overall response; CI: Confidence interval; CR: Complete response; IERC: Independent Endpoint Review Committee; ITT: Intent-to-treat; ORR: Overall response rate; PD: Progressive disease; PP: Per protocol; PR: Partial response; SD: Stable disease

4.7.2 Duration of response (DoR) as determined from IERC tumour assessments

- 2L+ cohort (Part A): Avelumab treatment resulted in rapid tumour responses; 76% (22/29) of the observed CR or partial (PR) responses had occurred by week 7. Responses were sustained, with 66% (95% CI: 44-81) of patients who responded continuing to respond at a minimum of 18-months follow-up

- 1L cohort (Part B): Avelumab treatment resulted in a rapid tumour response; 89% (16/18) of responses (CR or PR) were observed by week 7 (≥3-month follow-up)
- Median duration of response with avelumab treatment was not estimable in either the 2L+ cohort or the 1L cohort of patients
- 2L+ cohort (Part A): Responses were durable (6-month durable response rate [DRR] of 31%) at minimum of 18-months follow-up; 18-month DoR rate of 66%, which is clinically meaningful in patients with metastatic MCC
- The durable responses observed with avelumab treatment are supported by the survival outcomes observed in this patient population, with all responders (29/29; 100%) still alive at the time of follow-up (minimum 18-months)
- 1L cohort (Part B): The 6-month DRR reported in patients with at least 6-months follow-up (n=14) was [redacted] %

In 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial (≥18-month follow-up), avelumab treatment resulted in rapid tumour responses, with the majority of responders (22/29; 76%) responding by week 7 (at the first post baseline tumour assessment) with either a CR or PR (Figure 6). The median time to response was 6.1 weeks (range: 6-36). Responses were also sustained, with 66% (95% CI: 44-81) of responders at the time of analysis (≥18-month follow-up based on Kaplan-Meier estimates), and many patients experiencing continued responses after treatment discontinuation (Figure 6). The durable responses observed with avelumab treatment are supported by the survival outcomes observed in this patient population, with all responders (29/29; 100%) still alive at the time of follow-up (minimum of 18-months).

Figure 6: Time to and duration of response to avelumab in 29 patients with a confirmed response (CR or PR) in the ITT population of JAVELIN Merkel 200 – 2L+ cohort (Part A) with 18 months follow-up

SOURCE: (Merck KGaA 2017b)

Some patients who experienced a response stopped discontinued treatment before disease progression or the 6 month minimum recommended treatment time due to adverse events, organisational issues such as protocol non-compliance, or suspected disease progression.

Abbreviations: CR: Complete response; PR: Partial response

Durable response was defined as an objective response (CR or PR) according to RECIST 1.1 lasting at least 6 months. To adjust for the bias due to the administrative censoring at data cut-off caused by the limited follow-up time, the durable response rate (DRR) was estimated in a post-hoc analysis, as the product of the ORR and the KM estimate of 6-month durability of response. By KM estimates (censored at cut-off), the proportion of responses with a duration of ≥6 months in the 2L+ cohort (Part A) was 93% (95% CI: 75-98), 71% (95% CI: 51-85) with ≥12 months duration, and [redacted] with a duration of 18-months (Table 20). The 6-month DRR increased from 29.1% at 6-months follow-up to 30.7% at 12-months due to one none evaluable patient turned into a CR (Table 20).

At the 18-month data cut-off, the median DoR was not estimable ([redacted]), with the maximum duration of response of [redacted] (Table 20). Other immuno-oncology therapies in analogue diseases have also reported median DoR that have not been reached at primary analysis (Ribas 2015; Weber 2015).

In the 1L cohort (Part B) of the JAVELIN Merkel 200 trial, avelumab treatment also resulted in rapid tumour responses. At ≥3 months follow-up, [redacted] responding patients had experienced a confirmed response (CR or PR) by week 7. Amongst the responding patients [redacted] experienced a CR within 20 weeks of treatment initiation. Ongoing responses were reported in [redacted] of responding patients at ≥3-month follow-up (Figure 8). The median DoR was not reached ([redacted]) at ≥3-month follow-up, or in those patients with longer follow-up [redacted]) (Table 20). In those patients with ≥6 months follow-up (n=14), the proportion of responses with a duration of ≥6 months was [redacted], resulting in a 6-month DRR of [redacted] (Table 20).

Figure 7: Time to and duration of response to avelumab in 18 patients with a response (CR or PR) in the full analysis set of JAVELIN Merkel 200 (Part B – 1L cohort) with ≥3 months follow-up

Table 20: Duration of response according to IERC assessment in the JAVELIN Merkel 200 trial

	2L+ cohort (Part A)			***1L cohort (Part B)***	
	6-month follow-up (N=28)	***12-month follow-up (N=29)***	***18-month follow-up (N=29)***	***3-month follow-up (N=29)***	***6-month follow-up (N=14)***
Number of patients without event (censored), n (%)	23 (82.1)	21 (72.4)	20 (69.0)	15 (83.3)	[redacted]
Number of patients with an event, n (%)	5 (17.9)	8 (27.6)	9 (31.0)	3 (16.7)	[redacted]
Progressive disease, n (%)	5 (17.9)	8 (27.6)	9 (31.0)	2 (11.1)	[redacted]
Death, n (%)	0	0	0	1 (5.6)	
Duration of response					
Median, months	NR	NR	NR	NR	[redacted]
Range	2.8-17.5	2.8-23.3	2.8-24.9	1.2-8.3	[redacted]
95% CI	8.3-NR	18.0-NR	18.0-NR	(4.0-NR)	[redacted]
Proportion of DoR, % (95% CI)					
3 months	96 (77-99)	97 (78-100)	97 (78-100)	93 (61-99)	[redacted]
6 months	92 (70-98)	93 (74-98)	93 (75-98)	[redacted] -	[redacted]
12 months	74 (47-89)	74 (53-87)	71 (51-85)	-	
15 months	-	-	[redacted]	-	
18 months	-	-	[redacted]		
6-month DRR*, %	29.1	30.7	30.7	-	[redacted]

SOURCE: (Merck KGaA 2016h; Merck KGaA 2017c; Merck KGaA 2016e; Merck KGaA 2017b)

*ORR multiplied by Kaplan-Meier estimate for 6-month proportion of DoR

⁺Calculated from a small patient population (n=14) as data is currently evolving

Abbreviations: CI: Confidence interval; DoR: Duration of response; DRR: Durable response rate; IERC: Independent Endpoint Review Committee; NR: Not reached; ORR: Objective response rate

4.7.3 Overall survival (OS)

- 2L+ cohort (Part A): Avelumab treatment resulted in an 18-month overall survival (OS) rate of [redacted] with a median OS of [redacted]
- 1L cohort (Part B): Avelumab treatment resulted in a 3-month OS rate of [redacted] with the median OS not reached

In the 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial (minimum 18-month follow-up), [redacted] had died. Whilst the OS data are not fully mature, results suggest that treatment with avelumab provides durable responses, with all responders (29/29; 100%) alive at the time of follow-up (Table 20). These durable responses are represented by the suggestion of a plateau observed in the Kaplan-Meier curve for OS (Figure 8). Based on Kaplan-Meier estimates, the OS rate at 18 months was [redacted], and the median OS was [redacted] (Table 21). As patients (n=88) have

progressed through 2L+ cohort (Part A) of JAVELIN Merkel 200 and data has matured, the median OS has increased from 11.3 months at 6-months follow-up to [redacted] at 18-months follow-up.

In the 1L cohort (Part B) of the JAVELIN Merkel 200 trial (≥3-month follow-up), [redacted] had died. Based on Kaplan-Meier estimates (Figure 9), a 3-month OS rate of [redacted] was reported. The median OS had not been reached (Table 21).

Table 21: OS according to IERC assessment in JAVELIN Merkel 200

	2L+ cohort (Part A)			***1L cohort (Part B)***
Outcome	***6-month follow-up (N=88)***	***12-month follow-up (N=88)***	***18-month follow-up (N=88)***	***3-month follow-up (N=39)***
OS rate, % (95% CI)			[redacted]	[redacted]
3 months	87 (78-93)	87 (78-93)	[redacted]	[redacted]
6 months	69 (58-78)	70 (59-78)		
12 months	48 (35-60)	52 (41-62)		
15 months	-	44 (32-54)		
18 months	-	-		
OS				
median, months (95% CI)	11.3 (7.5-14.0)	12.9 (7.5-NE)	[redacted]	[redacted]
Range, months	0.4-18.8	0.4-24.7	[redacted]	[redacted]

SOURCE: (Merck KGaA 2016h; Merck KGaA 2016e; Merck KGaA 2017b)

Abbreviations: CI: Confidence interval; IERC: Independent Endpoint Review Committee; ITT: Intent-to-treat; OS: Overall survival; NE- non-evaluable

Figure 8: Kaplan-Meier estimate of OS in the ITT population in the 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial (n=88)

[redacted]

Figure 9: Kaplan-Meier estimate of OS in the full analysis set with ≥3 months follow-up in the 1L cohort (Part B) of the JAVELIN Merkel 200 trial (n=39)

4.7.4 Progression-free survival (PFS)

- 2L+ cohort (Part A): Avelumab treatment resulted in an 18-month progression-free survival (PFS) rate of 29% (95% CI: 19-39), and a sustained median PFS of 2.7 months (95% CI: 1.4-6.9)
- 1L cohort (Part B): Avelumab treatment resulted in a 3-month PFS rate of 67% (95% CI: 48-80), and a median PFS of 9.1 months (95% CI: 1.9-not reached)

In the 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial, 56 of 88 patients (63.6%) had been reported with a progression or death event (Table 22). As with the OS data, the results from the analysis of PFS suggest that treatment with avelumab is associated with durable responses. Median PFS, from 6-month to 18-month follow-up, has been sustained at 2.7 months (95% CI: 1.4-6.9). The proportion of patients who responded to avelumab and were progression-free at 18 months was 29% (95% CI: 19-39), driven largely by those patients who had durable responses (Figure 10) and who remained progression free at 18 months. In concordance with this, a plateau was observed in the Kaplan-Meier plot for PFS. At ≥18-month data follow-up, there were 19 patients (22%) at risk and 64% (56/88) of patients had a PFS event (PD in 55% of patients and death in 9% of patients) (Table 22).

In the 1L cohort (Part B) of the JAVELIN Merkel 200 trial (≥3-month follow-up), [redacted] had a progression or death event (Table 22). PFS time ranged from [redacted]; with a median PFS of 9.1 months (95% CI: 1.9-not reached). Based on Kaplan-Meier estimates (Figure 11), the proportion of patients who responded to avelumab and were progression-free at 3 months was 67% (95% CI: 48-80) (Table 22).

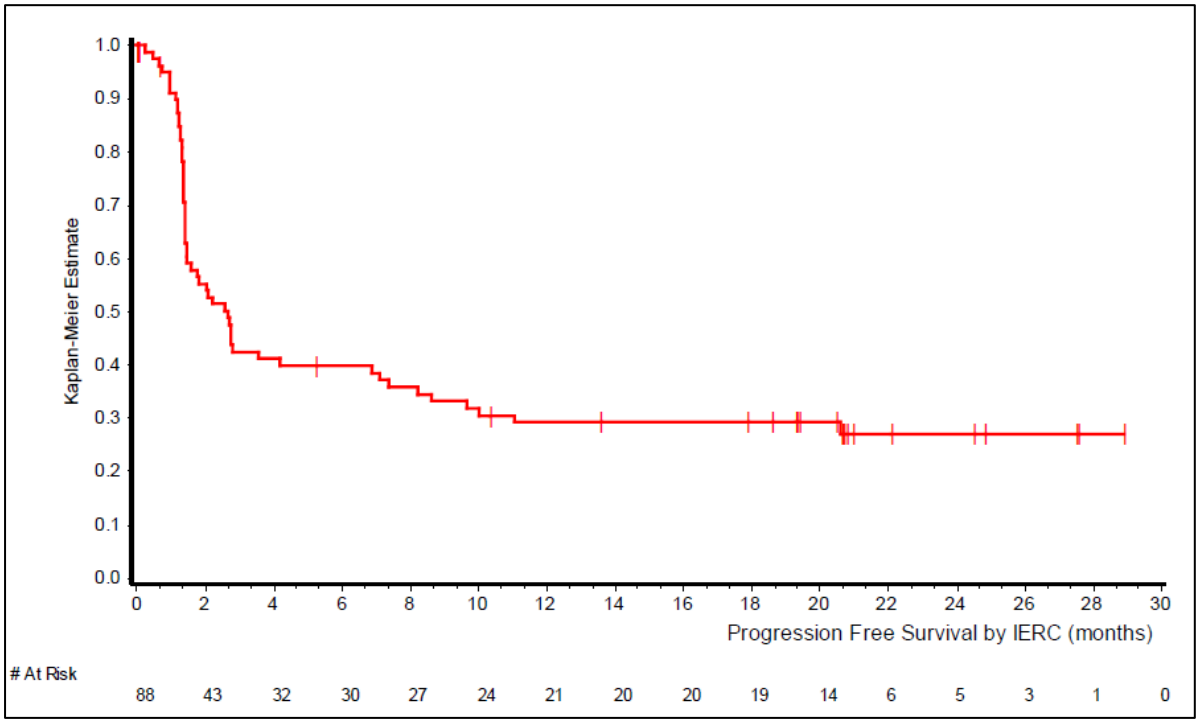
Table 22: PFS according to IERC assessment in the JAVELIN Merkel 200 trial

	2L+ cohort (Part A) N=88 (100%)			***1L cohort (Part B) N=39 (100%)***
n (%)	***6-month follow-up***	***12-month follow-up***	***18-month follow-up***	***3-month follow-up***
Number of patients without event (censored)	36 (40.9)	33 (37.5)	32 (36.4)	[redacted]
Number of patients with an event	52 (59.1)	55 (62.5)	56 (63.6)	[redacted]
Progressive disease	44 (50.0)	47 (53.4)	48 (54.5)	[redacted]
Death	8 (9.1)	8 (9.1)	8 (9.1)	[redacted]
PFS time				
Median (months)	2.7	2.7	2.7	9.1
Range	0.03-18.8	0.03-24.5	0.03-28.9	0.03-11.0
95% CI	1.4-6.9	1.4-6.9	1.4-6.9	1.9-NR
PFS rates (95% CI)				
3 months	42 (31-53)	42 (31-53)	42 (31-53)	67 (48-80)
6 months	40 (29-50)	40 (29-50)	40 (29-50)	-
12 months	30 (19-41)	30 (21-41)	29 (19-39)	-
15 months	-	30 (21-41)	[redacted]	-
18 months	-	-	[redacted]	-

SOURCE: (Merck KGaA 2016h; Merck KGaA 2017c; Merck KGaA 2016e; Merck KGaA 2017b)

Abbreviations: CI: Confidence interval; IERC: Independent Endpoint Review Committee; ITT: Intent-to-treat; NE: Not-estimable; PFS: Progression-free survival

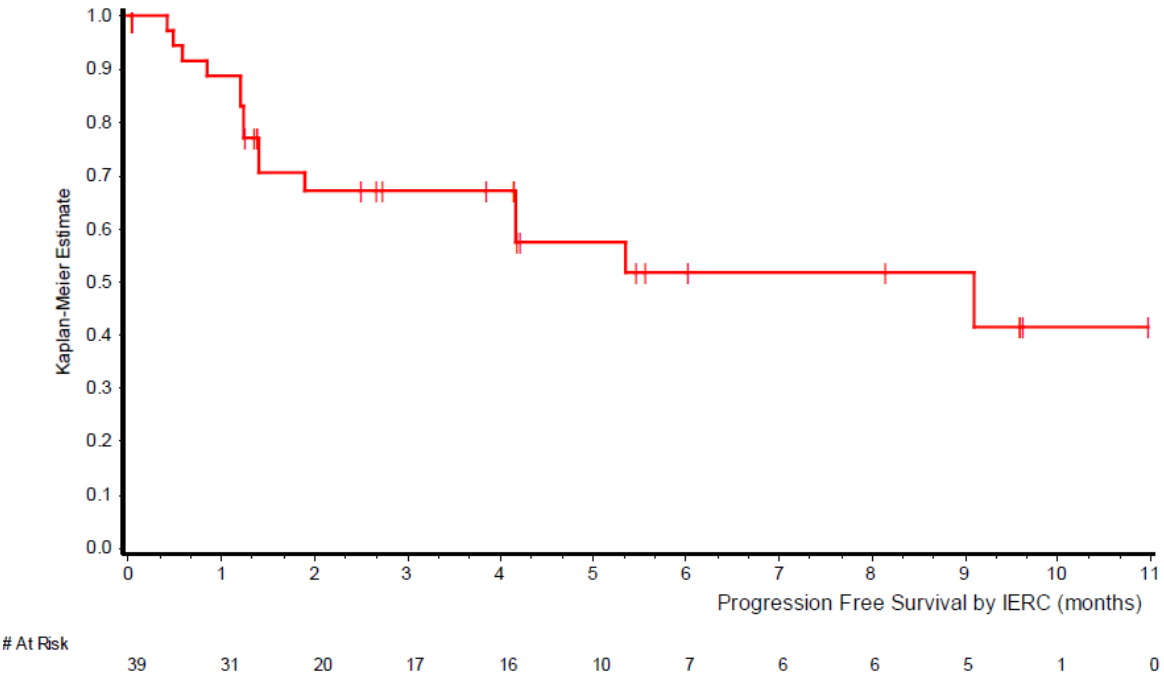
Figure 10: Kaplan-Meier estimate of PFS in the ITT population of 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial (n=88)



SOURCE: (Merck KGaA 2017b)

Vertical lines show censored events. Abbreviations: IERC: Independent endpoint review committee

Figure 11: Kaplan-Meier estimate of PFS in full analysis set with ≥3 months follow-up in the 1L cohort (Part B) of the JAVELIN Merkel 200 trial (n=39)



SOURCE: (Merck KGaA 2017c)

Vertical lines show censored events. Abbreviations: IERC: Independent endpoint review committee

By providing durable responses, partly due to memory immune responses, immuno-oncology therapies have shifted the focus of new treatments from the slope of the survival curve (median PFS) to landmark analysis focusing on the tail of the curve (2-year or 5-year PFS rates) (Harris 2016). The durable progression-free effect observed in JAVELIN Merkel 200 – 2L+ cohort (Part A) is in line with other immuno-oncology therapies with 2L+ data in analogue disease areas. Outcomes with immuno-therapies in these analogue diseases report median PFS results ranging from 1.4 months to 4.7 months, which is not too dissimilar to the median PFS of 2.7 months observed with avelumab (Antonia 2016; Weber 2015; Ott 2016; Ribas 2015). In addition, the 6-month PFS rate of 40% observed with avelumab falls in the higher end of the range observed with other immunotherapies (30% - 48%) (Ott 2016; Weber 2015; Ribas 2015). The 12-month PFS rate of 29% with avelumab, appears to be superior to the literature presenting outcomes with other immunotherapies in SCLC (11% - 23%), whilst the 6-month PFS rate of 40% is similar to other immunotherapies in advanced melanoma (34%-48%) (Antonia 2016; Weber 2015; Ribas 2015). As presented above, and due to the aggressive nature of metastatic MCC (disease progression results in poor survival outcomes), this progression-free durable effect is also observed in OS and, as verified by clinical experts, presents a correlation between PFS and OS. The 12-month PFS rate of 29% was sustained at 18-months follow-up i.e. no patients progressed within the 6 month period.

In severe diseases, median PFS may be low even with immuno-oncology treatment like avelumab, because response rates in some groups are less than 50%. One of the key benefits of avelumab is the durability of response in those that do respond. This is driven by the mechanism of action that triggers a sustained activation of the immune system to attack the tumour. Instead, efficacy endpoints such as DRR (discussed above in section 4.7.2) or landmark analysis are better indicators of efficacy for the proportion of patients who have responded to treatment.

4.7.5 Tumour shrinkage in target lesions at each time point from baseline

- Part A (2L + cohort) and 1L cohort (Part B): The majority of responses with avelumab (≥30% decrease from baseline in target lesions) were persistent and durable

In the 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial (≥18-month follow-up), most decreases in target lesions appeared to begin within the first 6 weeks of treatment, with few patients experiencing a 20% or greater increase from baseline in target lesions followed by a decrease (Figure 12). The majority of responses with ≥30% decrease from baseline in target lesions (n=29) were persistent and durable (≥6 months).

Figure 13 shows the change in the sum of target lesion diameter between baseline and best post-baseline assessment in the 2L+ cohort (Part A) of JAVELIN Merkel 200.

Figure 12: Percent change from baseline in target lesions in the ITT population of JAVELIN Merkel 200 – 2L+ cohort (Part A) (n=65)[††]

[††] Subjects with baseline and at least one post-baseline target lesion assessment

[redacted]

Figure 13: Change in sum of target lesion diameter between baseline and best post-baseline assessment according to IERC assessment of the ITT population of JAVELIN Merkel 200 – 2L+ cohort (Part A) (n=65)‡‡

[redacted]

SOURCE: (Merck KGaA 2017b)

In the 1L cohort (Part B) of the JAVELIN Merkel 200 trial, as with 2L+ cohort (Part A), most patients experienced a decrease in target lesions, appearing within the first 6 weeks of treatment (Figure 14).

[redacted]

Figure 14: Percent change from baseline in target lesions in the full analysis set (≥3 months follow-up) of JAVELIN Merkel 200 – 1L cohort (Part B) (n=30)§§

§§ Subjects with baseline and at least one post-baseline target lesion assessment

4.7.6 Health-related quality of life outcomes

- No major changes from baseline in patients' self-reported health status or quality of life were found with the FACT-M scores, suggesting a stability in patients' HRQL over time
- Response to avelumab, as assessed by a 30% decrease in tumour size, corresponds to a predicted mean improvement of 5.5 points on the FACT-M Total score at week 7

The JAVELIN Merkel 200 trial assessed the HRQL of enrolled patients, using EQ-5D and FACT-M questionnaires. FACT-M is a disease specific instrument developed for melanoma and was selected in the absence of a MCC-specific tool. Due to the similarities between MCC and melanoma (aggressive skin malignancies of neuroendocrine origin associated with immunosuppression and UV exposure (Grabowski 2008)), the melanoma specific module of FACT-M was deemed to be a suitable tool. Further analysis was conducted to assess the psychometric properties of FACT-M in the MCC population which confirmed the relevance of these results in this patient population (summarised with the FACT-M results).

In the 2L+ cohort (Part A) across the study duration, at least 60% of the available patients completed each questionnaire but this fell to 21 of 61 patients (34.4%) for each questionnaire at End-of-Treatment (EOT) visit. The limited proportion of patients (21-72 patients) with available patient reported outcome (PRO) data represent a potential source of bias, especially post week 25. Study follow up for all patients was up to week 25 only and evaluation of data beyond this point is not complete. However, given the lack of data available in metastatic MCC these results are a valuable resource in determining the impact of avelumab on HRQL in this patient population.

EQ-5D

Details of the EQ-5D analysis are detailed in Section 5.4.1.

FACT-M

Investigations were conducted to confirm the adequacy of FACT-M in the MCC population in terms of content validity, construct validity, internal consistency reliability, and ability to detect change over time (from baseline to week 7). The analysis reported good item convergent validity (≥75%), good discriminant validity with some evidence of insufficient item discriminant validity in the melanoma subscale, very good internal consistency reliability, and encouraging ability to detect change given the small sample size (n=37). The MCIDs were in line with previously reported values in the literature for FACT-M domains. Overall, the psychometric properties of FACT-M in the MCC population were found to be acceptable, thus making it a potential candidate for assessing HRQL in MCC trials.

In treatment-experienced patients, the change in mean FACT-M Total scores indicated positive but low score changes seen in patients contributing to study visits beyond week 13 (Figure 15). A slight decrease in HRQL at the EOT was observed and may be expected since the EOT visit is normally following disease progression.

Figure 15: FACT-M Total scores from baseline to EOT in the ITT analysis set of 2L+ cohort (Part A) of JAVELIN Merkel 200

Association of tumour response with HRQL

In treatment-experienced patients a positive association between clinical response (percentage reduction in tumour size) and patients' self-reported health status/HRQL (change from baseline) was generally observed at the first post-baseline assessment, at week 7. While sample size at subsequent time points was reduced (from 70 patients at baseline, to 20 patients at EOT), similar results were observed throughout the treatment period (week 13, week 19, and week 25). This suggests that reduction in tumour size was associated with improvements in HRQL. Figure 16 describes the association of percent reduction in tumour size and FACT-M Total score at week 7. The results support the value proposition for avelumab and are consistent with the expectation that the mechanism of action of avelumab would result in a clinical benefit.

[redacted]

Figure 16: Tumour size change versus FACT-M total score at week 7 (n=39)

Qualitative patient interviews

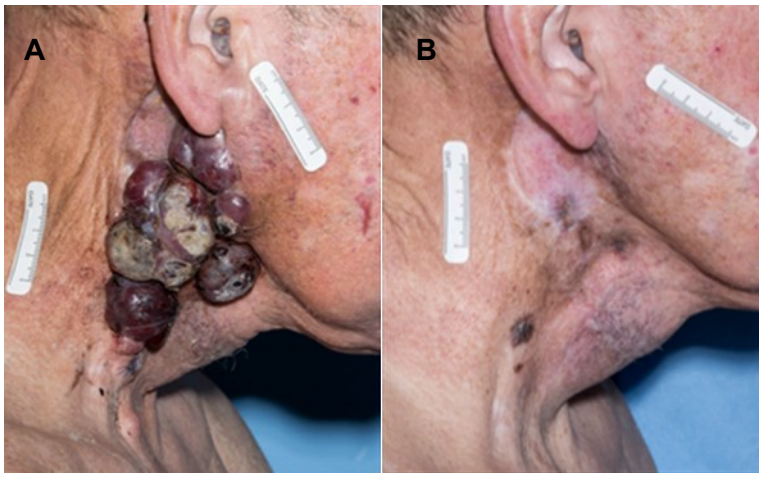
There is a lack of data available regarding the impact of metastatic MCC and its management on patients' HRQL. To address this data gap, qualitative, semi-structured patient interviews were conducted with patients from 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial to acquire a comprehensive picture of the impact of metastatic MCC and its management on patients' lives. In addition, the interviews were designed to explore patients' previous experience with chemotherapy, and of avelumab treatment since baseline (Kaufman 2016a).

All patients (n=88) with metastatic MCC enrolled in JAVELIN Merkel 200 (except those patients in Japan, n=3) were invited to participate in the optional qualitative patient interviews. Each of the patients who agreed to participate in the qualitative study (n=33) was to be interviewed three times: one baseline interview conducted during the screening period and two follow-up interviews at week 13 (n=21) and week 25 (n=17). Interviews were conducted by a trained psychologist/researcher, and analysed using a qualitative software package (ATLAS.ti Version 7) (Kaufman 2016a).

The results of the interviews (n=19) indicated that metastatic MCC had negative psychological impacts on patients, due to challenging diagnosis, painful presentation of the disease and rapid disease progression (Kaufman 2016a). Diagnosis of metastatic MCC also had a negative psychological impact on patient's relatives and friends in providing help and support (Kaufman 2016a).

Patients (13/21; 62%) reported a clear benefit with avelumab treatment, as reflected by substantial and visible improved tumour status (Figure 17), which was associated with better physical and psychological status compared with their previous experience of treatment with chemotherapy. Patients were optimistic about the future (Kaufman 2016a). Patient satisfaction with avelumab was high relative to their previous negative experiences with chemotherapy and radiotherapy, which were described as highly debilitating, both physically and mentally (Kaufman 2016a).

Figure 17: Change in tumour status from baseline (A) to 5.3 months of treatment with avelumab (B)



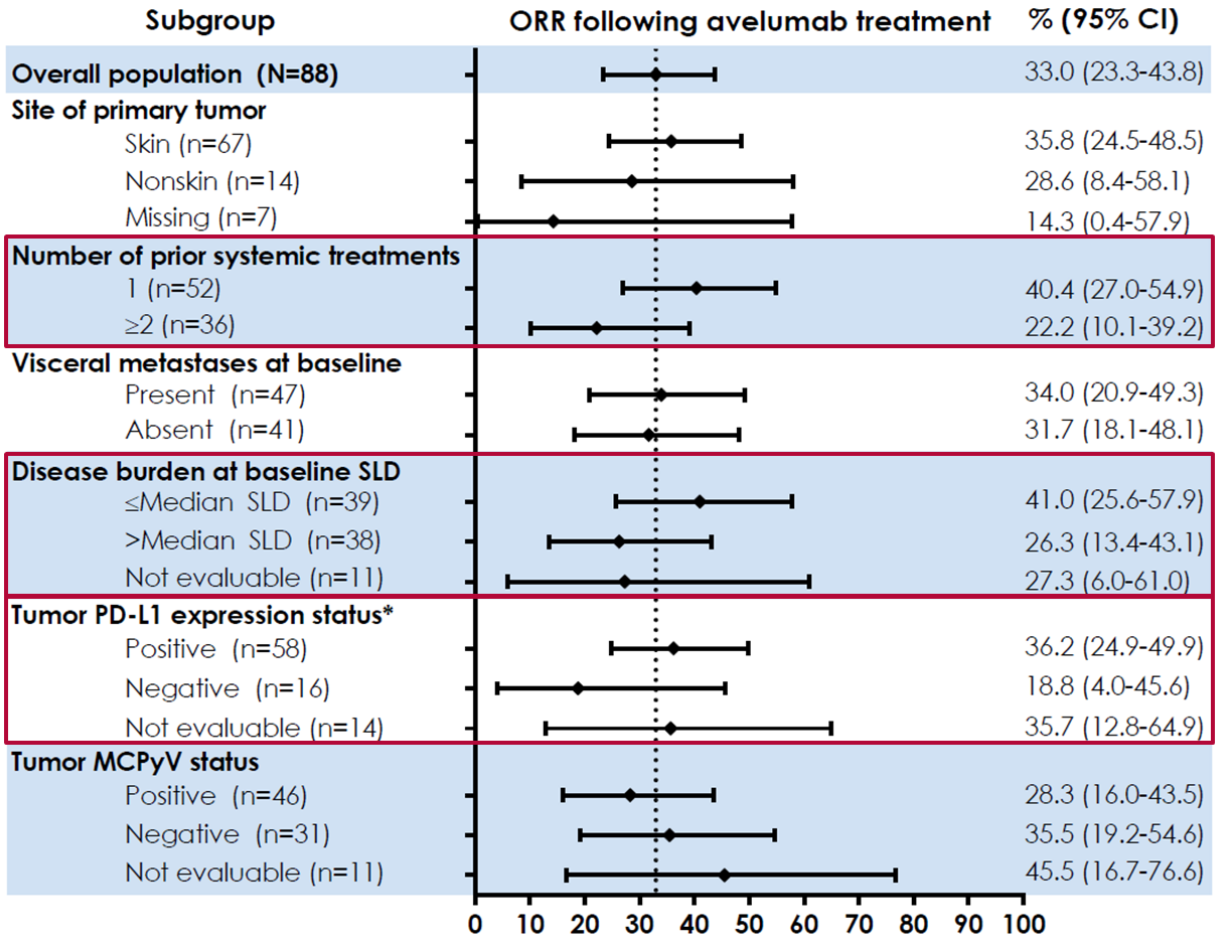
SOURCE: (Kaufman 2016b)

4.8 Subgroup analysis

- No significant differences in response were observed across subgroups

Post-hoc subgroup analyses of patients in the ITT population of 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial (n=88) are shown in Figure 18. Responses to avelumab were observed across all subgroups defined by demographic and baseline characteristics. Avelumab was observed to be effective in both positive and negative PD-L1 and MCPyV expression subgroups, and so neither PD-L1 or MCPyV expression was considered predictive of outcome.

Figure 18: Objective response by subgroup for select patient characteristics in the 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial



SOURCE: (Kaufman 2017)

Non assessable specimens included those that were missing, of poor quality, or otherwise not available to provide results

Abbreviation; CI: Confidence interval; MCPyV: Merkel cell polyomavirus; PD-L1: Programmed death ligand-1; SLD: sum of longest diameters

4.9 Observational studies of outcomes with chemotherapy

As introduced previously, high quality comparative data were generated to supplement the avelumab data package. A retrospective, observational study (Study 100070-Obs001) was conducted in the US (Part A) and the EU (Part B) to investigate clinical outcomes with chemotherapy treatment and to provide a reference for the avelumab data (Cowey 2017; Becker 2016). The methodology for the observational study (Study 100070-Obs001) is provided in Appendix 9. Recognising that literature on outcomes for patients with metastatic MCC remains sparse (as concluded in the systematic review in Section 4.1) and the lack of a comparator arm in the JAVELIN Merkel 200 trial, this study was designed to address this data gap.

The observational Study 100070-Obs001 Part A (the US sub-study, conducted as 2 cohorts: one for 2L+ and one for 1L) and Part B (the EU sub-study conducted as one cohort in the 2L+) were designed to mimic the entry criteria of the ongoing Part A (2L+ avelumab) and Part B (1L avelumab) of the JAVELIN Merkel 200 trial, including adult patients with distant metastatic MCC (Cowey 2017; Becker 2016). Similarly, exclusion criteria from the JAVELIN Merkel 200 trial were followed such as exclusion of patients with evidence of treatment with any antibody/drug targeting T-cell co-regulatory proteins,

patients enrolled in any clinical trials, and patients observed with any solid tumour in the prior several years, with the exception of basal or squamous cell carcinoma of the skin, bladder carcinoma *in situ*, or cervical carcinoma *in situ.*

In addition, as an output from the SLR (Section 4.1), only one published study (Iyer 2016) was identified that summarised the observations of responses to both 1L and 2L chemotherapy treatment in a purely distant metastatic MCC population. This study investigated the response rates and durability of 2L chemotherapy among 30 patients with distant metastatic MCC, and among 62 patients in the 1L setting (Iyer 2016).

4.9.1 Clinical effectiveness results of the observational studies

The options for formally comparing these observational data with JAVELIN Merkel 200 were investigated by the economic modellers and naïve comparisons were deemed to be appropriate as reported in Section 5.10 and Appendix 10. The observational studies had similar inclusion/exclusion criteria JAVELIN Merkel 200, and as they were commissioned by Merck, patient-level data were available for analysis. Robust statistical analyses undertaken for the purposes of economic modelling confirms that based on available data, patient characteristics do not appear to be predictive of outcomes in metastatic MCC but that outcomes do differ based on whether a patient has previously received chemotherapy for metastatic MCC. For this reason, no statistical adjustments (such as Matching Adjusted Indirect Comparison [MAIC], or Simulated Treatment Comparison [STC]) are required to match the observational data to JAVELIN Merkel 200. Results are therefore presented side-by-side below.

The data from the only published study (Iyer 2016) summarising observations of responses to both first-line and second-line chemotherapy treatment is also presented alongside the observational study data to provide further context.

Second-line and further setting

Currently there are substantial gaps in the literature and clinical practice to allow for BSC outcomes to be quantified and compared to avelumab's as part of the scope of this submission. This is not surprising due to the ultra-rare status of MCC which means low patient numbers which further decrease in metastatic disease. To enable comparisons to inform the NICE decision problem, efficacy data from chemotherapy regimens were assumed to be equal to those of BSC. This assumption was verified by clinical experts as reasonable. Specifically, as confirmed by clinical experts, efficacy outcomes with BSC and chemotherapy are likely to be very similar due to very poor patient performance with both. As such, although data from observational studies are related to chemotherapy regimens, the majority of which are relevant to current clinical practice in England, the outcomes reported are so poor that they compare to those of BSC.

In the second-line and further setting, the results of this observational study, as well as the study conducted by Iyer et al. are shown in Table 23 alongside the efficacy results from 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial. Overall, the results for avelumab in the JAVELIN Merkel 200 trial in a treatment-experienced metastatic MCC population are favourable relative to Study 100070-Obs001 and Iyer et al., demonstrating improved 6-month DRR (30.6% vs. 0.0%-6.7%), 12-month PFS (29.0% vs. 0.0%), 12-month OS (50.0% vs. 0.0%), and a higher CR rate (11.4% vs. 0.0%-3.3%).

The response rates observed with the US real world evidence studies (Study 100070-Obs001 – Part A ORR: 28.6% and Iyer et al. ORR: 23.3%) are higher than those reported in the EU study (ORR: 10.3%). The results from this latter study are expected to be similar to those observed in clinical practice in England, as verified by clinical experts. This could be due to the more aggressive treatments administered in the US, resulting in improved outcomes over those observed with chemotherapy

regimens or BSC in England. However, the lack of complete responses and durable responses is as expected and in line with experience in England, as confirmed by clinical experts.

Table 23: Efficacy results from JAVELIN Merkel 200 – 2L+ cohort (Part A), Observational study 100070-Obs001 (Part A and B) and Iyer et al. 2016 in the 2L+ setting

Efficacy parameter	***JAVELIN Merkel 200 (Part A - 2L+ cohort) (N=88)***	***Study 100070-Obs001 Overall***		***Study 100070-Obs001 Immunocompetent[a]***		***Retrospective study[b] (Iyer 2016) (N=30)***
		(Part A - US) (N=20)	***(Part B - EU) (N=34)***	***(Part A - US) (N=14)***	***(Part B - EU) (N=29)***	
BOR per RECIST 1.1						
CR, n (%)	10 (11.4)	0	0	0	0	1 (3.3)
PR, n (%)	19 (21.6)	4 (20.0)	3 (8.8)	4 (28.6)	3 (10.3)	6 (20.0)
SD, n (%)	9 (10.2)	2 (10.0)	3 (8.8)	2 (14.3)	3 (10.3)	1 (3.3)
PD, n (%)	32 (36.4)	8 (40.0)	28 (82.4)	5 (35.7)	23 (79.3)	22 (73.3)
Non-CR/Non-PD*, n (%)	0	0	0	0	0	0
Not evaluable, n (%)	18 (20.5)	6 (30.0)	0	3 (21.4)	0	0
ORR						
Response rate (CR+PR) (95% CI)	33.0 (23.3-43.8)	20.0 (5.7-43.7)	8.8 (1.9-23.7)	28.6 (8.4-58.1)	10.3 (2.2-27.4)	23.3 (9.9-42.3)
DoR						
Median, months (95% CI)	NE (18.0-NE)	1.7 (0.5-3.0)	1.9 (1.3-2.1)	1.7 (0.5-3.0)	1.9 (1.3-2.1)	3.3
6–month DRR, % (95% CI)	30.7 (20.9-40.3)[d]	0.0 (0.0-16.8)	0.0 (0.0-10.3)	0.0 (0.0-23.2)	0.0 (0.0-11.9)	6.7 (0.8-22.1)
PFS						
Median, months (95% CI)	2.7 (1.4-6.9)	2.1 (1.0-3.2)	3.0 (2.6-3.1)	2.2 (1.2-3.5)	3.0 (2.5-3.2)	2.0 (1.3-2.7)
6-month PFS rate by KM, % (95% CI)	40.0 (29.0-50.0)	0.0	2.9 (0.2-13.0)	0.0	3.4 (0.3-14.9)	13
12-month PFS rate by KM, % (95% CI)	29.0 (19.0-39.0)	0.0	0.0	0.0	0.0	NR

Efficacy parameter	*JAVELIN Merkel 200 (Part A - 2L+ cohort) (N=88)*	*Study 100070-Obs001 Overall*		*Study 100070-Obs001 Immunocompetent[a]*		*Retrospective study[b] (Iyer 2016) (N=30)*
		(Part A - US) (N=20)	*(Part B - EU) (N=34)*	*(Part A - US) (N=14)*	*(Part B - EU) (N=29)*	
OS						
Median, months (95% CI)	[redacted]	4.4 (2.2-6.2)	5.3 (4.3-5.8)	4.3 (2.1–6.2)	5.3 (4.3–6.0)	5.7 (NR)
6-month OS rate by KM, % (95% CI)	70.0 (59.0-78.0)	30.2 (11.6-51.4)	26.4 (13.1-41.8)	26.8 (7.3-51.5)	27.5 (13.0-44.2)	NR
12-month OS rate by KM, % (95% CI)	51.0 (40.0-61.0)	0.0	0.0	0.0	0.0	NR

*One patient did not have measurable disease at baseline and thus a BOR of PR or SD could not be distinguished

[a]Analysis conducted on the immunocompetent patients did not show any meaningful impact on OS. As such the overall population has been used in the economic model

[b]Data from Iyer 2016 was reported after 2L chemotherapy and not-specific for immunocompetent patients (13.3% had systemic immune suppression)

[c]Based on number of patients with confirmed response (CR+PR)

[d]Based on the ORR and the KM estimate for 6-month durability

SOURCE: (Merck KGaA 2017b; Cowey 2017; Becker 2016; Iyer 2016; Merck KGaA 2016b)

Abbreviations: BOR: Best overall response; CI: Confidence interval; CR: Complete response; DoR: Duration of response; DRR: Durable response rate; KM: Kaplan-Meier; NR: Not reported; ORR: Overall response rate; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: Stable disease

First-line setting

Table 24 presents the results of the JAVELIN Merkel 200 trial 1L cohort (Part B) alongside the outcomes of the first-line cohort included in the US Observational study and the study conducted by Iyer et al. in treatment-naïve patients.

First-line treatment of metastatic MCC in England consists of radiotherapy alongside either BSC or chemotherapy, as confirmed by clinical experts (See Section 3.3, Figure 3). For patients receiving chemotherapy, almost all receive a regimen of carboplatin plus etoposide. Outcomes with this regimen are investigated in both Study 100070-Obs001 and Iyer et al., and despite more aggressive administration likely in the US, these studies provide evidence which is clinically relevant to treatment practices in England.

Overall, the results for avelumab in the JAVELIN Merkel 200 trial in a treatment-naïve metastatic MCC population are favourable relative to Study 100070-Obs001 and Iyer et al., demonstrating improved ORR (62%-71% vs. 29%-55%), 6-month OS ([redacted] vs. 67%), and a higher CR rate (14%-29% vs. 13%-14%).

Table 24: Efficacy results from JAVELIN Merkel 200 – 1L cohort (Part B), Observational study 100070-Obs001 (Part A) and Iyer et al. 2016 in treatment-naïve patients

Efficacy parameter	*JAVELIN Merkel 200 (Part B - 1L cohort)*		*Study 100070-Obs001 (Part A - US) Overall (N=67)*	*Study 100070-Obs001 (Part A - US) Immunocompetent[a] (N=51)*	*Retrospective study[b] (Iyer 2016) (N=62)*
	3-month follow-up (N=29)	*6-month follow-up (N=14)*			
CR, n (%)	4 (13.8)	4 (28.6)	10 (14.9)	7 (13.7)	8 (12.9)
PR, n (%)	14 (48.3)	6 (42.9)	11 (16.4)	8 (15.7)	26 (41.9)
SD, n (%)	3 (10.3)	1 (7.1)	1 (1.5)	1 (2.0)	4 (6.5)
PD, n (%)	7 (24.1)	2 (14.3)	31 (46.3)	21 (41.2)	24 (38.7)
Non-CR/Non-PD*, n (%)	0	0	-	-	-
Not evaluable, n (%)	1 (3.4)	1 (7.1)	-	-	-
ORR, % (95% CI)	62.1 (42.3-79.3)	71.4 (41.9-91.6)	31.3 (20.6-43.8)	29.4 (17.5-43.8)	55
Median DoR, months (95% CI)	NR (4.0-NR)	NR (4.0-NR)	5.7 (2.6-8.7)	6.7 (1.2-10.5)	3.0
DRR, % (95% CI)[c]	-	64.5[+]	14.9 (7.4-25.7)	15.7 (7.0-28.6)	2.8
	Full analysis set (N=39)				
Median PFS, months (95% CI)	9.1 (1.9-NR)		4.6 (3.0-7.0)	4.6 (2.8-7.7)	3.4
6-month PFS rate, % (95% CI)	52.0 (31.0-69.0)		44.8 (32.7-56.2)	47.1 (33.0-59.9)	-
12-month PFS rate, % (95% CI)	-		21.8 (12.7-32.4)	24.8 (13.8-37.4)	-
Median OS, months (95% CI)	[redacted]		10.2 (7.4-15.2)	10.5 (7.2-15.2)	9.5
6-month OS rate, % (95% CI)	[redacted]		70.1 (57.5-79.5)	66.7 (52.0-77.8)	-
12-month OS rate, % (95% CI)	-		44.0 (31.5-55.8)	45.3 (31.0-58.6)	-

[a]Analysis conducted on the immunocompetent patients did not show any meaningful impact on OS. As such the overall population has been used in the economic model

[b]Study included all patients regardless of immunocompetent status

[c]Based on the ORR and the KM estimate for 6-month durability

[+]Calculated from a small patient population (n=14) as data is currently evolving

SOURCE: (Merck KGaA 2017c; Cowey 2017; Iyer 2016)

Abbreviations: BOR: Best overall response; CI: Confidence interval; CR: Complete response; DoR: Duration of response; DRR: Durable response rate; KM: Kaplan-Meier; NR: Not reached; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: Stable disease

4.10 Indirect and mixed treatment comparisons

As avelumab was studied in an uncontrolled clinical trial, mixed treatment comparisons and NMAs could not be performed. For the purposes of economic modelling, comparator data were taken from a series of historical controls (including observational studies), and analysed as appropriate for the underlying datasets.

A summary of the approach taken is given in Section 5.3.3 with a full report provided in Appendix 10. The analysis demonstrates that no characteristics available in the patient data are prognostic of outcomes (including factors such as ECOG PS and stage at diagnosis). As such there is no advantage to balancing groups through techniques such as matching adjusted indirect comparison or simulated treatment comparison – to match on characteristics that do not predict outcomes will likely introduce bias.

4.11 Adverse reactions

Overall safety summary

The safety of avelumab was initially investigated in the JAVELIN Solid Tumor study. This was a Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, PK, biological, and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumours. The methodology for the JAVELIN Solid Tumor trial is provided in Appendix 11. A total of 53 subjects were enrolled in the dose escalation phase of the trial, receiving avelumab in doses ranging from 1 mg/kg to 20 mg/kg. The proceeding expansion phase of the study enrolled 1,452 subjects with multiple tumour types, across 16 expansion cohorts, all of whom received at least one dose of avelumab (10 mg/kg). Although the expansion cohorts did not include any patients with MCC, it is expected that the safety profile of a monoclonal antibody would not differ to any major extent relative to different types of solid tumours, therefore including this study allows for a more comprehensive evaluation of the avelumab safety profile. Consequently the safety data base consisting of a total of 1,540 patients treated with the proposed dose and treatment schedule of 10 mg/kg every 2 weeks is considered of an acceptable magnitude for identifying the safety profile of avelumab in the short-term perspective (European Medicines Agency 2016).

In JAVELIN Merkel 200, treatment with avelumab, in both treatment-experienced and treatment-naïve patients, was associated with a tolerable and manageable safety profile, where most AEs were low grade.

All safety analyses were conducted using the safety analysis set, which included all patients in the 2L+ cohort (Part A) and 1L cohort (Part B) of the study who received at least one dose of study treatment. Data cut-off for safety analyses was 18-months follow-up for 2L+ cohort (Part A) and 3-months follow-up for 1L cohort (Part B).

In the 2L+ cohort (Part A) the median duration of therapy was 17 weeks (range: 2.0-132.0 weeks) with a median number of infusions of [redacted]. In the 1L cohort (Part B) the median duration of therapy was [redacted] with a median number of infusions of [redacted]. The majority of patients (both treatment-naïve

and treatment-experience) received between [redacted] of the planned dose per cycle. No patients received greater than [redacted] of the planned dose.

Adverse events Table 25 presents the most common TEAEs reported in the JAVELIN Merkel 200 trial, in both 2L+ cohort (Part A) and 1L cohort (Part B). Only [redacted] of patients in the 2L+ cohort and [redacted] (8/39) of patients in the 1L cohort experienced Grade ≥3 TEAEs related to avelumab, with no deaths related to avelumab reported. The safety profile for avelumab presented here is in line with reported AEs for other immuno-therapies in analogue diseases (Ribas 2015; Weber 2015).

Table 25: Most common TEAEs in ≥10% of patients with avelumab treatment in JAVELIN Merkel 200

Adverse events	***2L+ cohort (Part A) 18-month follow-up (N=88)***		***1L cohort (Part B) 3-month follow-up (N=39)***	
	Any grade, n (%)	***Grade ≥3, n (%)***	***Any grade, n (%)***	***Grade ≥3, n (%)***
Fatigue*	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral oedema[+]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain[¥]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Rash[¤]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus**	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Decreased weight	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea[Φ]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]	[redacted]	[redacted]

*Fatigue is a composite term that includes fatigue and asthenia

[+]Peripheral oedema is a composite term that includes peripheral oedema and peripheral swelling

[¥]Abdominal pain is a composite term that includes abdominal pain and abdominal pain upper

[¤]Rash is a composite term that includes rash, maculopapular rash, erythema, and dermatitis bullous

**Pruritus is a composite term that includes pruritus and pruritus generalised

[Φ]Dyspnoea is a composite term that includes dyspnoea and dyspnoea exertional

SOURCE: (Merck KGaA 2017c; Merck KGaA 2017b)

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; NR: Not reported; TEAE: Treatment-emergent adverse event

Serious adverse events and deaths

In the 2L+ cohort (Part A), serious TEAEs were reported [redacted], including [redacted] related to treatment with avelumab at a minimum of 18-months follow-up. Serious TEAEs were reported in [redacted]) of patients enrolled in the 1L cohort (Part B) of the JAVELIN Merkel 200 trial at 3 months, of which [redacted] were deemed related to administration of avelumab.

Deaths due to any TEAE were reported in [redacted] in the 2L+ cohort (Part A) and [redacted] patients in the 1L cohort (Part B); [redacted].

Adverse events leading to discontinuation

In the 2L+ cohort (Part A), avelumab was permanently discontinued for TEAEs in [redacted] patients at 18 months and in [redacted] patients at 3 months in the 1L cohort (Part B).

At 12-months follow-up of 2L+ cohort (Part A), AEs resulting in permanent discontinuation were ileus, Grade 3 transaminitis, Grade 3 creatine kinase elevation, tubulointerstitial nephritis, and Grade 3 pericardial effusion. Avelumab was temporarily discontinued in [redacted] patients for adverse events, excluding temporary dose interruption for infusion-related reactions where infusion was restarted the same day. The most common AE requiring dose interruption was anaemia.

Selected adverse events of special interest

In the 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial, treatment-emergent immune-related AEs (irAEs) were observed in [redacted] patients (Table 26) at 18-months follow-up. Most irAEs were low grade (Grade 1-2), although Grade ≥3 irAEs were experienced in [redacted] The most common immune-mediated reactions were [redacted].

Table 26: Summary of immune-mediated adverse events experienced with avelumab treatment in JAVELIN Merkel 200 – 2L+ cohort (Part A)

	2L+ cohort (Part A) (N=88)	
Immune-related adverse events	***Any grade, n (%)***	***Grade ≥3, n (%)***
Patients with ≥1 treatment-emergent irAE	[redacted]	[redacted]
Immune-mediated endocrinopathies: Thyroid disorders Hypothyroidism	[redacted]	[redacted]
Immune-mediated rash Erythema Pruritus Rash Rash maculo-papular	[redacted]	[redacted]
Immune-mediated colitis Diarrhoea	[redacted]	[redacted]
Immune-mediated hepatitis Transaminases increased Alanine aminotransferase increased Aspartate aminotransferase increased	[redacted]	[redacted]
Immune-mediated nephritis and renal dysfunction Tubulointertitial nephritis	[redacted]	[redacted]
Immune-mediated endocrinopathies: Adrenal insufficiency	[redacted]	[redacted]
Immune-mediated endocrinopathies: Pituitary dysfunction	[redacted]	[redacted]
Immune-mediated endocrinopathies: Type 1 diabetes mellitus	[redacted]	[redacted]
Immune-mediated pneumonitis	[redacted]	[redacted]
Other immune-mediated adverse events Autoimmune disorder	[redacted]	[redacted]

*An infusion-related reaction in this analysis was based on a composite definition with five different MedDRA terms

SOURCE: (Merck KGaA 2017b)

Abbreviation: MedDRA: Medical Dictionary for Regulatory Activities

Treatment-emergent irAEs were reported in [redacted] in the 1L cohort (Part B) of the JAVELIN Merkel 200 trial, of which [redacted].

Infusion-related adverse events

Infusion-related reactions were reported in [redacted] in the 2L+ cohort (Part A) and [redacted] in the 1L cohort (Part B) and were mild or moderate in severity, and manageable (Table 27). In Part B, [redacted] experienced an infusion-related AE which lead to permanent

discontinuation of avelumab. In Part A, [redacted]

Table 27: Summary of infusion-related adverse events experienced with avelumab treatment in JAVELIN Merkel 200 – 2L+ cohort (Part A)

	2L+ cohort (Part A) (N=88)	*1L cohort (Part B) (N=39)*
	18-month follow-up, n (%)	*3-month follow-up, n (%)*
Patients with ≥1 infusion-related reaction	[redacted]	[redacted]
Grade 1		
Grade 2		
Grade ≥3		
Number of patients with infusion-related reactions leading to permanent discontinuation of study treatment	[redacted]	[redacted]
Time relative to first onset	[redacted]	[redacted]
Infusion 1		
Infusion 2		
Infusion ≥3		

SOURCE: (Merck KGaA 2017c; Merck KGaA 2017b)

4.12 Interpretation of clinical effectiveness and safety evidence

4.12.1 Principal findings of the clinical evidence base

In both treatment-experienced and treatment-naïve patients avelumab increases response rates and duration of response contributing to improved OS. Avelumab also provides a treatment option for patients who may not be eligible for chemotherapy, whilst providing a tolerable safety profile and maintaining patient HRQL. Despite data presented for treatment-naïve patients being immature (≥3 months follow-up), it is still evolving with initial results looking very promising outcomes. As concluded from the JAVELIN Merkel 200 trial:

Avelumab has shown an objective response rate of 33% in treatment-experienced patients and 62% in treatment-naïve patients

Results from the 2L+ cohort (minimum 18-months follow-up) found that metastatic MCC patients who had progressed after at least one line of prior therapy showed an objective response rate (ORR) with avelumab of 33% (29/88; 95% Confidence Interval [CI]: 23.3-43.8). The overall, clinical benefit of avelumab is 43% which consists of 11% (10/88) of patients having a complete response (CR), 22% (19/88) having partial responses (PRs) and 10% (9/88) with stable disease (SD) (Merck KGaA 2017b). In a subgroup analysis of the 2L+ cohort, a trend towards improved responses was observed with fewer lines of prior therapy. Tumour response is strongly associated with the risk of disease progression; of the 29 treatment-experienced patients with a CR or PR, only nine experienced disease progression by the March 2017 data cut (minimum of 18-months follow-up).

In comparison, outcomes from two observational studies and published historical data found

that patients receiving chemotherapy in the 2L+ setting have an ORR between 23% and 29%, with a CR rate between 0.0% and 3%, a PR rate between 29% and 10% and a further 3% to 14% have SD (Cowey 2017; Becker 2016; Iyer 2016). A more detailed comparison is provided in Section 4.9.

Although data collected from the 1L cohort (Part B) is less mature than in the 2L+ cohort (Part A) (n=39 patients vs. n=88, respectively), initial results (≥3 months follow-up, n=29) demonstrate an ORR of 62% (18/29; 95% CI: 42.3-79.3); nearly double that observed in the 2L+ cohort, with 14% (4/29) having CR and 48% (14/29) PRs, as well as 10% (3/29) with SD. An ORR of [redacted] was reported in the proportion of patients who had ≥6 months follow-up (n=[redacted]) (Merck KGaA 2017c).

Chemotherapy in the first-line setting is associated with lower ORRs, 29% to 55%; 13% to 14% of which are CRs, 16% to 42% are PRs and 2% to 7% are SDs (Cowey 2017; Iyer 2016).

Despite the responses observed with chemotherapy, these are short lived in both the 1L and 2L+ setting (0 to 7% of patients responding by 6 months).

Avelumab demonstrates rapid and durable tumour responses

Treatment-experienced patients (Part A 2L+ cohort) had rapid tumour responses; 76% (22/29) of the observed CR or PR responses had occurred by week 7. Responses were sustained, with 66% (19/29) of patients who responded continuing to respond at a minimum of 18-months follow-up (Merck KGaA 2017b).

Patients in the 1L cohort (Part B) with a ≥3 months follow-up (n=29) also showed rapid tumour responses with 89% (16/18) of ORR responses (CR or PR) observed by week 7. At 3 months, 93% of responding patients were still responding (Merck KGaA 2017c).

Outcomes from two observational studies and published historical data show that the initial response observed with chemotherapy is usually of a short duration in both the first-line and second-line plus setting; median duration of response (DoR) is between 3.0 months and 6.7 months and 1.7 months and 3.3. months, respectively (Cowey 2017; Becker 2016; Iyer 2016). Median DoR with avelumab treatment has not yet been reached in either the 2L+ cohort or the 1L cohort (Merck KGaA 2017c; Merck KGaA 2017b).

Six-month durable response rates are greater with avelumab treatment compared with chemotherapy

Chemotherapy response rates in the metastatic setting are short lived. In treatment-experienced patients the 6-month durable response rate (DRR) is very poor with only 0 to 7% of responding patients continuing to respond to treatment (Cowey 2017; Becker 2016; Iyer 2016). A naïve comparison with JAVELIN Merkel 200 shows that avelumab has a more favourable 6-months DRR in treatment-experienced patients of 31% (Merck KGaA 2017b).

The 6-month DRR outcome for the 1L cohort is still immature (DRR of [redacted]%) however, if we are to consider that the second-line plus cohort results showed 93% of responders were durable, we can anticipate that most of the [redacted] of objective responders in first-line will also be durable.

The durable responses observed with avelumab treatment are supportive of the OS outcomes observed. In the treatment-experienced patient population, all responders are still alive at the time of follow-up (minimum of 18 months follow-up) where historical data shows that patients would have otherwise died by 12 months (Merck KGaA 2017b).

In treatment-experienced metastatic MCC patients, avelumab has demonstrated durable survival benefits with OS rate of [redacted]% at 18 months. In treatment-naïve patients, avelumab has a 3-month OS rate of [redacted]%, with median OS not reached and recruitment still ongoing

Avelumab in treatment-experienced patients (part A 2L+ cohort) resulted in an 18-month overall survival (OS) rate of [redacted] and a median OS of [redacted], with follow-up still ongoing (Merck KGaA 2017b). This is greater than the 12-month overall survival rate of 0% from the start of second-line chemotherapy and more than [redacted] chemotherapy's expected median survival time of between 4.3 months and 5.7 months (range: 35 days to 2.4 years) (Cowey 2017; Becker 2016; Iyer 2016). Even at 6-months the OS rate for avelumab is more than double that of chemotherapy (70% vs. 27%-28%).

In treatment-naïve patients (Part B 1L cohort), avelumab resulted in a 3-month OS rate of [redacted], with the median OS not yet reached and recruitment still ongoing (Merck KGaA 2017c). Limited 6-month follow-up data from 14 patients shows avelumab to have a more be more favourable OS than chemotherapy (6-month OS rate: [redacted] vs. 66.7%) (Merck KGaA 2017c; Cowey 2017).

PFS rate in treatment-experienced patients at a minimum of 18-months follow-up is 29%, with a median PFS of 2.7 months

PFS rate in treatment-naïve patients at 3 months and 6 months is 67% and 52%, respectively with an immature median PFS of 9.1 months

Treatment-experienced patients showed an 18-month PFS rate of 29%, and a sustained median PFS of 2.7 months (95% CI: 1.4-6.9) (Merck KGaA 2017b). In comparison, chemotherapy is associated with a 12-month PFS rate of 0% and a median PFS of between 2.0 (95% CI: 1.3-2.7) and 3.0 (95% CI: 2.5-3.2) (Cowey 2017; Becker 2016; Iyer 2016).

Similarly, the March 24th data-cut of the 1L patient cohort (n=39) has also shown more promising results for avelumab in a naïve comparison against chemotherapy. At 3 months, avelumab has a PFS rate of 67% (95% CI: 48-80). Avelumab has an immature 6-month PFS rate of [redacted] and an immature median PFS of 9.1 months 95% CI: 1.9-not reached) whereas, chemotherapy has a 6-month PFS of 47.1% (95% CI: 33.0-59.9) and a median PFS of 4.6 months (95% CI: 2.8-7.7) Merck KGaA 2017c; Cowey 2017).

In severe diseases, median PFS may be low even with immuno-oncology treatment like avelumab, because response rates in some groups are less than 50%. One of the key benefits of avelumab is the durability of response in those that do respond. This is driven by the mechanism of action that triggers a sustained activation of the immune system to attack the tumour. Instead, efficacy endpoints such as DRR or landmark analysis (highlighted above) are better indicators of efficacy for the proportion of patients who have responded to treatment.

Clinically meaningful tumour reduction in avelumab responders was associated with clinically meaningful improvements in HRQL as assessed by FACT-M

Current treatments in MCC have limited impact on symptoms of disease and in addition, treatment-related adverse events can negatively impact on health-related quality of life (HRQL). Unlike cytotoxic chemotherapy, avelumab had no major impact on patients' health status overall with the EQ-5D or FACT-M scores, suggesting a stability in patients HRQL over time. Prevention of disease progression with avelumab treatment, as assessed on the EQ-5D Index scale, also contributed to improved HRQL.

In treatment-experienced patients, avelumab is well tolerated with less than [redacted] of patients experiencing Grade ≥3 treatment-emergent adverse events (TEAEs). Among treatment-naïve patients, [redacted] experienced Grade ≥3 TEAEs events. No treatment-related death was reported in either cohort

Avelumab is well-tolerated in treatment-experienced patients with fewer than [redacted] of patients experiencing Grade ≥3 TEAE. No treatment-related deaths were reported with avelumab and treatment discontinuation was low ([redacted]) of patients) Merck KGaA 2017b).

Among treatment-naïve patients (n=39), only [redacted] experienced Grade ≥3 TEAEs. Consistent with the treatment-experienced patients, no treatment-related deaths were reported (Merck KGaA 2017c).

4.12.2 Strengths of the current evidence base

- Avelumab has shown promising and durable results in the largest registrational clinical trial in metastatic MCC to date; JAVELIN Merkel 200
- Avelumab demonstrated efficacy in both treatment-experienced and treatment-naïve patients, thereby offering a valuable treatment option for those who have failed chemotherapy and for treatment-naïve patients
    - In treatment-naïve patients, avelumab fulfils a considerable unmet need in those who are ineligible for cytotoxic chemotherapy
- In a naïve comparison against standard of care chemotherapy regimens, avelumab is associated with improved and durable responses, improved survival and increased periods of non-progression
- Unlike cytotoxic chemotherapy, the current standard of care, treatment with avelumab is associated with stability in HRQL, with improvements seen in patients whose disease does not progress
- Avelumab is well-tolerated in treatment-experienced patients with metastatic MCC

4.12.3 Limitations of the current evidence base

- JAVELIN Merkel 200 is a single arm study and therefore there are no head-to-head data comparing avelumab with current standard of care therapies. Observational studies were conducted in the US and Europe investigating the clinical efficacy of chemotherapy regimens to provide a context for the findings of the JAVELIN Merkel 200 trial and a robust assessment of the appropriate methods for establishing comparative efficacy was conducted to ensure that these data are used appropriately in the economic modelling. The absence of direct evidence cannot be considered a strong limitation in the context of an ultra-rare condition; such study designs are not uncommon where logistical and ethical requirements dictate a certain approach to evidence generation.
- The generalisability of trial findings to a particular geography is often raised as a potential limitation of the evidence base. Whilst there were no UK patients enrolled in JAVELIN Merkel 200, experts in MCC provided a clinical overview of MCC in order to validate that the patient characteristics of those enrolled in the study are reflective of practice in England. Therefore, study results are generalisable to patients in England.

- At the time of data analysis, the median OS reported, for both 2L+ and 1L cohorts in the JAVELIN Merkel 200 trial, was immature. However, this trial is currently ongoing with a data cuts expected at the [redacted] and additional analyses in 2018.
- The study is planned to complete in June 2025, with the estimated primary completion date (final data collection date for primary outcome measure) scheduled for September 2019. completion in May 2019.

4.12.4 End of life considerations

Metastatic MCC is associated with a short life expectancy (irrespective of line of therapy); median survival estimated at 4 months in the UK (Jackson 2015), meeting the first of NICE's end of life criteria. The economic model confirms that it is reasonable to expect avelumab to provide an extension to life of at least 3 months over standard of care (Table 28). Based on data from the JAVELIN Merkel 200 trial, observed and projected, avelumab meets the end-of-life criteria.

Table 28: End-of-life criteria

Criterion	*Data available*	*Cross reference*
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**Treatment-experienced patients (2L+ setting)** • The median survival from diagnosis was estimated to be 4 months (mean 9.3 months, range 0.5 – 33 months) in a cohort of 16 English patients who were either initially diagnosed with metastatic MCC or subsequently developed metastatic disease (Jackson 2015) • Additional estimates of life expectancy from diagnosis of metastatic MCC are taken from studies conducted outside of the UK, and range between 6 months (Santamaria-Barria 2013) to 13 months (Iyer 2016) • Median OS from the EU and US chemotherapy observational studies were 5.3 months and 4.3 months, respectively (Cowey 2017; Becker 2016). Pooling the data give a median of 5.2 months, and a modelled mean of 5.0 months • A meta-analysis of all studies at 2L indicates a median survival of 4.6 - 5.1 months and a mean survival of 5.1 - 5.5 months **Treatment-naïve patients (1L setting)** • Median OS from the US chemotherapy observational study was 10.5 months (Cowey 2017) • Pooling the US observational data with a further 5 literature studies (Iyer 2016; Santamaria-Barria 2013; Voog 1999; Fields 2011; Allen 2005) (median survival in each: 10.1, 6, 7.9, 15.9 and 11.5 months). • Meta-analysed data used within the model led to estimated median survival of 11.8 months and mean survival of 24.3 months	Section 3.4
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	**Treatment-experienced patients (2L+ setting)** • Median OS from the JAVELIN Merkel 200 trial – 2L+ cohort (Part A) is [redacted] months (≥18-month follow-up), with a restricted mean of [redacted] months, and a modelled mean of 42.3 months • Survival outcomes with BSC are anticipated to be similar to those observed with chemotherapy according to clinical experts with a modelled mean of 5.0 months • The survival gain is therefore estimated to be 37.3 months **Treatment-naïve patients (1L setting)** • Median OS from the JAVELIN Merkel 200 trial – Part B (1L cohort) [redacted]. The modelled mean is 57.3 months • The modelled survival outcomes for chemotherapy (and BSC) is 24.2 months • The estimate survival gain is therefore estimated to be 33.1 months, albeit subject to uncertainty due to the short-term follow-up in the avelumab clinical data	

Abbreviation: EU: Europe; MCC: Merkel cell carcinoma; NHS: National Health Service; OS: Overall survival; US: United States

4.13 Ongoing studies

MerckKGaA/Pfizer are planning to conduct an observational study collecting retrospective SACT registry data from across the UK. The aim of the study is to better understand the survival outcomes of metastatic MCC patients and how they compare to the observational studies already conducted across Europe and the US. Data collection is planned for the end of the year with completion of the analysis and results by the beginning of 2018.

4.14 Summary

In treatment-experienced and treatment-naïve patients avelumab increases response rates and duration of response contributing to improved OS when compared with current standard of care. Avelumab also provides a treatment option for the approximately 50% of treatment-naïve patients, and the majority of treatment-experienced patients, who may not be eligible for chemotherapy, whilst providing a tolerable safety profile and maintaining patient HRQL.

5 Cost effectiveness

De novo cost-effectiveness model

- A de novo partitioned-survival model was constructed in Microsoft Excel®
- Clinical outcomes associated with avelumab including survival, progression, occurrence of adverse events (AEs) and health-related quality of life (HRQL) were sourced from patient-level data available as part of the JAVELIN Merkel 200 trial
- Costs, medical resource use frequencies and comparator efficacy data were sourced from published literature and observational trial data, with subsequent validation by practicing clinicians

Survival

- Spline-based models were used to model avelumab overall survival and progression-free survival, to appropriately reflect the change in hazard observed in the trial data, in addition to clinical expectation of long-term survival. Due to current data availability for treatment-naïve patients, clinical opinion was pivotal to incorporate expected outcomes in this patient group. Clinical consensus was that overall survival would likely be improved if avelumab were given upfront, as opposed to following chemotherapy.
- Clinical outcomes for patients treated with chemotherapy or best supportive care were taken from available published literature and subsequently validated by practicing clinicians. Clinicians were aligned in their expectation of poor outcomes, particularly in treatment-experienced patients, regardless of regimen used. Furthermore, clinicians explained that for patients treated with best supportive care outcomes are not expected to exceed those for patients treated with chemotherapy; hence an assumption of equal efficacy across comparator treatments was imposed in the model. This is a conservative assumption as best supportive care assumes the benefit of chemotherapy without the associated costs.

Utility analysis

- Utility data was taken from JAVELIN Merkel 200 – Part A. EQ-5D-5L values were mapped to EQ-5D-3L using the "crosswalk" algorithm. The data were then analysed using a time-to-death approach.
- Disutilities attributable to adverse events were incorporated based on available data from published literature

Base case results

- For treatment-experienced metastatic MCC patients, compared with best supportive care, avelumab is associated with 3.11 life years (LYs) gained, 1.91 incremental quality-adjusted life years (QALYs), and incremental costs of £71,399 per patient. The incremental cost-effectiveness ratio (ICER) is £37,409 per additional QALY gained
- For treatment-naïve metastatic MCC patients, compared with chemotherapy, avelumab is associated with 2.76 LYs gained, 1.56 incremental QALYs, and incremental costs of £68,104 per patient. The ICER is £43,633 per additional QALY gained
- For treatment-naïve metastatic MCC patients, compared with BSC, avelumab is associated with 2.76 LYs gained, 1.55 incremental QALYs, and incremental costs of

Sensitivity analyses

- Parameter uncertainty was explored through probabilistic and deterministic one-way sensitivity analyses, with structural uncertainty and key assumptions explored through scenario analyses
- The results of the economic analysis were most sensitive to assumptions regarding the HRQL of patients and predicted long-term survival outcomes.

5.1 Published cost-effectiveness studies

An SLR was conducted to establish the existence of previous cost-effectiveness studies undertaken in patients with metastatic MCC.

The search was originally performed 28th July 2016, and subsequently updated 16th May 2017, on Ovid (Medline, Medline in Process, EMBASE), Cochrane Library and the entre for Reviews and Dissemination (CRD) databases (namely DARE [Database of Abstracts of Reviews of Effects], HTA [Health Technology Assessment] and NHS-EED [NHS-Economic Evaluation Database]). The following annual conferences held from August 2016 to May 2017 were searched for abstracts reporting cost-effectiveness studies:

- American Society of Clinical Oncology (ASCO)
- European Society of Medical Oncology (ESMO)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

The search strategy for Cochrane Library and the CRD databases was adapted from the search in Medline and Embase. A detailed search strategy is provided in Appendix 7. The relevance of each reference for data extraction was assessed based on pre-specified eligibility criteria. The criteria used are summarised in Table 29.

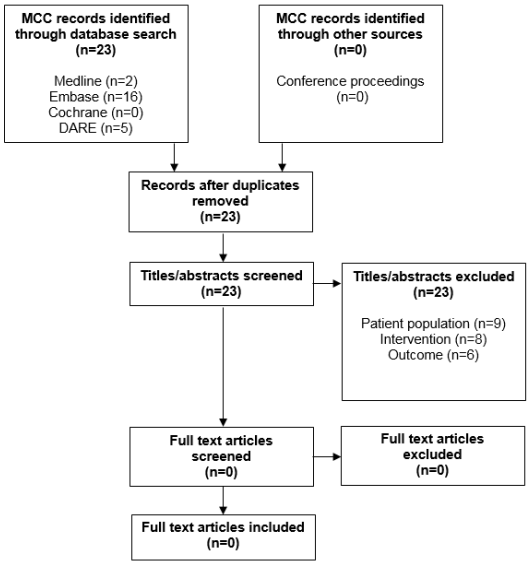
Table 29: Eligibility criteria for economic evaluations in metastatic MCC

Inclusion criteria		***Rationale***
Population	Age: adults aged ≥18 years Gender: any Ethnicity: any Disease: metastatic MCC	Consistent with evidence base and anticipated marketing authorisation.
Interventions/Comparators	Any pharmacological treatment	This allows all relevant evidence to be identified
Outcomes	Cost- effectiveness, direct/indirect costs, resource use, BSC costs, costs, life years, QALYs, ICERs	The aim of the review was to identify relevant economic evaluations, which reported costs.
Study design	Cost-effectiveness analyses, cost-minimisation analyses, cost-utility analyses, cost/burden of illness, costing studies	The aim of the review was to identify relevant economic evaluations
Limits	No language restrictions	With limited data in MCC, all languages were included to identify all published literature
Exclusion criteria		***Rationale***
Intervention/Comparators	Studies exclusively focusing on the role of radiotherapy, chemo-radiotherapy, hormonal therapy, diagnostics, screening or surgery Studies investigating the role of maintenance/consolidation therapy after surgery Adjuvant or neo-adjuvant therapy Does not include chemotherapy regimens that are listed as comparators	In line with the anticipated NICE scope, studies were restricted to those evaluating the efficacy of comparators. Comparators were restricted to chemotherapies and BSC.
Population	Studies that included children and adults and did not provide subgroup analysis for the adult populations	Consistent with the evidence base for avelumab
Outcomes	No relevant costs or resource use	Aim of the review was to identify relevant economic evaluations reporting costs or resource use
Study design	Systematic literature reviews and meta-analyses	Studies from systematic literature reviews and meta-analyses were cross checked to ensure all relevant publications were identified
Country	None	Review was kept broad considering the limited data

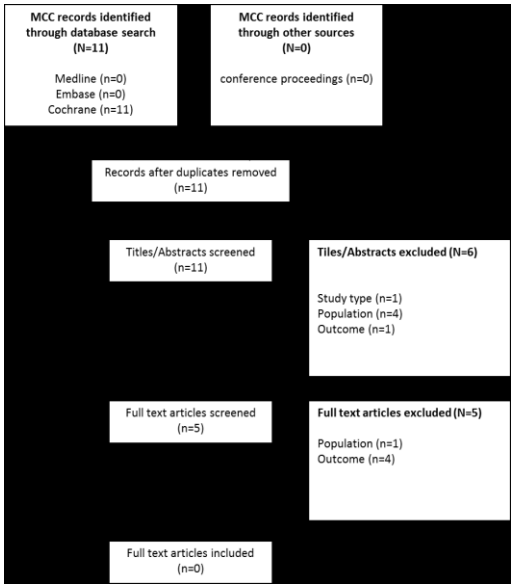
Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; MCC: Merkel cell carcinoma; QALY: Quality-adjusted life years

The PRISMA diagram in Figure 19 presents the flow of studies identified in the cost-effectiveness review. Database searches identified a total of 34 studies (including results from updated search), all of which were excluded upon title and abstract screening. Therefore, no eligible studies were identified at the time of this submission.

Figure 19: PRISMA diagrams for identified cost-effectiveness studies (original and update searches)



A: original search (28th July 2016)



B: updated search (16th May 2017)

Abbreviations: MCC: Merkel Cell Carcinoma

5.2 De novo analysis

5.2.1 Patient population

The population considered in the de novo cost-effectiveness analysis is adult patients with metastatic MCC, as per the population considered in JAVELIN Merkel 200 (Kaufman 2016c), the anticipated EMA licence for avelumab (expected in September 2017), and as specified in the decision problem for this appraisal.

This comprises two cohorts:

- Treatment-experienced (second-line and further [2L+]) metastatic patients, who have previously received at least one line of chemotherapy for metastatic MCC and must have progressed after the most recent line of chemotherapy (Part A of the JAVELIN Merkel 200 trial)
- Treatment-naïve (first-line [1L]) metastatic patients (Part B of the JAVELIN Merkel 200 trial).

The model considers each of these populations separately due to differences in the expected outcomes at each line of therapy and the immaturity of the data for treatment-naïve patients at the time of submission. An overview of the modelling differences between these cohorts is provided in In summary, the inputs for both models are noted below in Table 73.

Table 73. A summary of the JAVELIN Merkel 200 trial, including baseline patient characteristics as per each part of the trial (Part A and Part B), is provided in Section 4.5.

The JAVELIN Merkel 200 trial currently represents the largest clinical trial for this ultra-rare indication, yet small patient numbers were considered one of the biggest challenges of this cost-utility analysis, a commonly expected limitation within the evaluation of orphan drugs (Drummond 2007).

5.2.2 Model structure

An "area under the curve" (AUC, also known as a partitioned-survival) model was constructed in Microsoft Excel®. To provide an overview of the economic analysis undertaken the structure of the model is shown in Figure 20, with a supportive conceptual model diagram demonstrating key features shown in Figure 21.

Figure 20: De novo model schematic

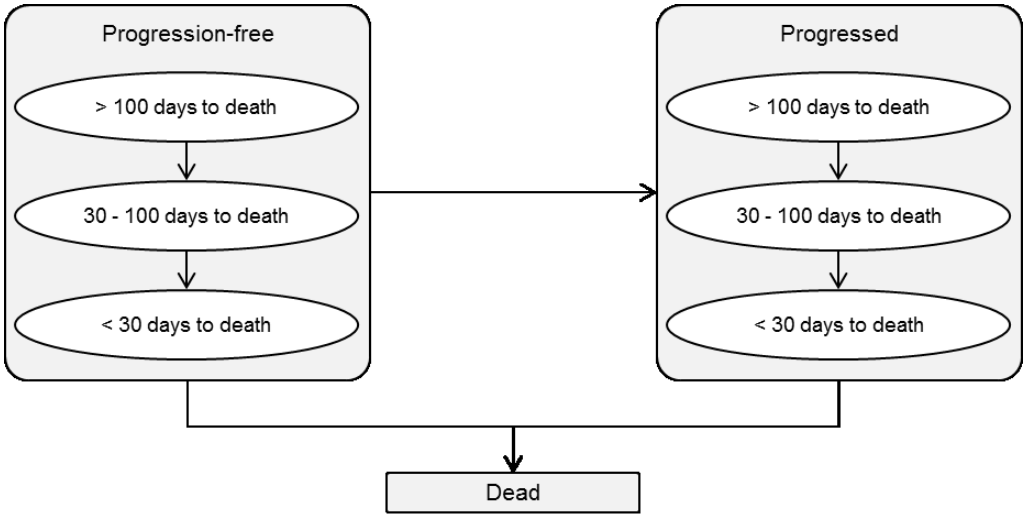
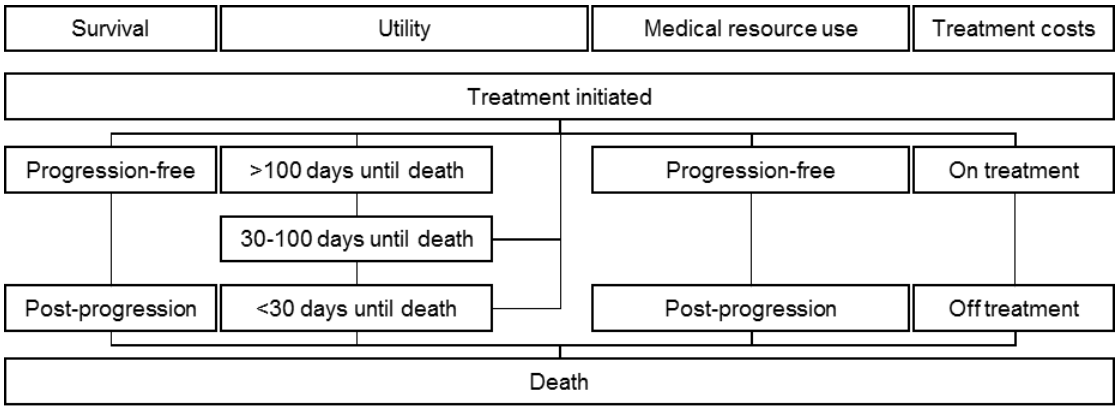


Figure 21: Conceptual model diagram



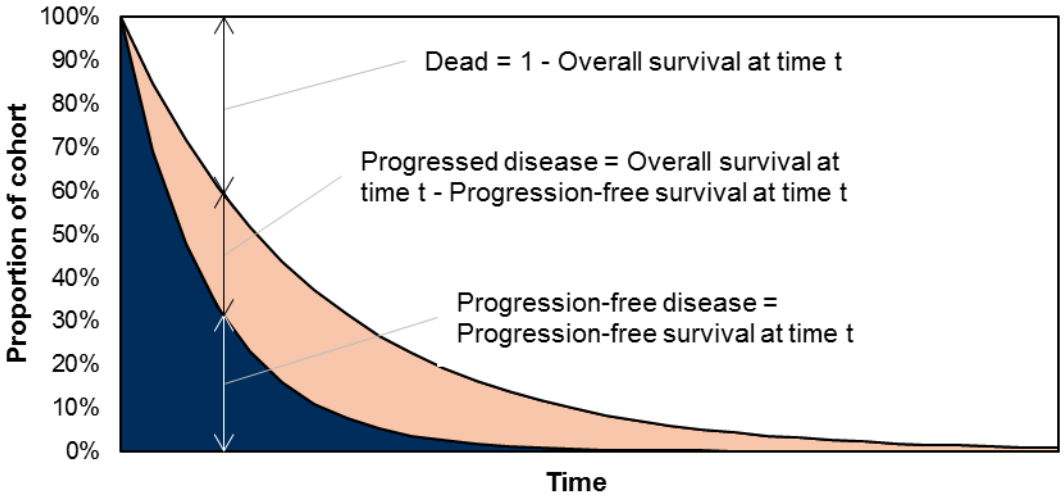
The Markovian structure considers three key mutually exclusive health states related to survival:

- Progression-free disease
- Progressed disease
- Death

All patients enter the model in the "Progression-free disease" health state. From here, patients may transition to the other health states, or remain in this health state at each model cycle. Following progression, patients are unable to transition back to the "Progression-free disease" health state, and "Death" is an absorbing health state.

Transitions between model health states are informed by the area under PFS and OS curves derived from JAVELIN Merkel 200 data. This is shown in Figure 22.

Figure 22: Area under the curve explanation



At any time point of the simulation, a patient can be alive with non-progressed disease (pink area), alive with progressed disease (navy area) or dead (white area). The proportion of patients who have died is estimated by 1-OS, the proportion of those with progressed disease is estimated by OS-PFS, and the proportion with progression-free disease is taken directly from trial PFS estimates. For example, at the time point shown by the arrow in Figure 22, 40% of patients are in the dead state, 30% of patients are alive and progression-free and 30% of patients are alive with progressed disease.

The choice of model structure was based on a review of recent models constructed to inform cost-effectiveness analyses of oncology medicines, particularly immuno-oncology therapies, several of which have been considered by NICE via the technology appraisal process (NICE 2016a; NICE 2016e; NICE 2017b; NICE 2014a). Outcomes modelled mirror those in the JAVELIN Merkel 200 trial and assumptions associated with selected model structure (patients cannot recover their progression-free status) are consistent with the definitions of PFS and OS. The approach is also representative of the clinical pathway for metastatic MCC in that a patient's treatment course and outcomes will depend largely on whether their disease has progressed or not.

The costs incurred and QALYs accrued by patients are dependent on the health state which they are currently occupying; either in terms of treatment status, progression status, or time to death. These are multiplied by state occupancy to calculate the weighted costs and QALYs per cycle of treatment. Medical resource use estimates differ according to progression status, and drug acquisition and drug administration costs are only accrued by patients while on treatment. Further details of how costs and resource use are applied are provided in Section 5.5. Utility values are applied based on time (in days) until death estimated from within the model. The model considers utility values in three health states: >100 days until death, 30 days to 100 days until death and <30 days until death. Further details and justification of this approach are provided in Section 5.4.

A summary of the key features of the analysis is presented in Table 30.

Table 30: Features of the de novo analysis

Factor	*Chosen values*	*Justification*
Time horizon	40 years	Sufficient to ensure that 100% of modelled patients have died
Cycle length*	1 week (7 days)	Short enough to accurately model costs and outcomes
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case (NICE 2013)
Discount of 3.5% for utilities and costs	Yes	NICE reference case (NICE 2013)
Perspective (NHS/PSS)	Yes	NICE reference case (NICE 2013)

Notes: *Half-cycle correction was not applied in the model due to the short (weekly) cycle length.

Abbreviations: NHS: National Health Service; NICE: National Institute of Health and Care Excellence; PSS: Personal and Social Services; QALYs: Quality-adjusted life years

In order to ensure the scientific rigour of the economic modelling approach, MerckKGaA/Pfizer have partnered with a number of Health Economic advisers and clinical experts. Further details of the validation process undertaken are provided in Section 5.10.

5.2.3 Intervention technology and comparators

The intervention technology considered within the economic analysis is avelumab (BAVENCIO®, Merck Serono Europe Ltd. [an affiliate of Merck KGaA, Darmstadt, Germany]). Avelumab is an intravenously administered fully human anti-PD-L1 IgG1 monoclonal antibody indicated for the treatment of metastatic MCC (Kaufman 2016c).

Avelumab is administered at a dose of 10 mg/kg by a 1-hour intravenous infusion once every 2 weeks until confirmed disease progression, unacceptable toxicity, or occurrence of any other criterion for withdrawal. Treatment beyond confirmed disease progression was permitted within the JAVELIN Merkel 200 trial (discussed further in Section 5.3) (Kaufman 2016c).

The comparators considered within the economic analysis, as per the NICE final scope, are chemotherapy and BSC for treatment-naïve patients, and BSC for treatment-experienced patients. Currently, there are no NICE-recommended or EMA approved treatments for patients with metastatic MCC, and as such, the "chemotherapy" comparator considers a variety of off-label therapies that could be offered to metastatic MCC patients in England. These comparators were informed by observational studies conducted in the EU and US (Cowey 2017; Becker 2016). In England, clinical expert opinion is that a 50:50 split of carboplatin plus etoposide and cisplatin plus etoposide is used for treatment-naïve patients with no expected differences in efficacy between regimens.

Clinical advice was that patients rarely receive chemotherapy beyond first-line in England, and therefore BSC is considered as the primary comparator for treatment-experienced metastatic MCC patients as chemotherapy is not thought to extend life (given the lack of published evidence demonstrating an improvement in outcomes due to chemotherapy treatment) (NICE 2017a). UK clinicians confirmed that a small proportion (estimated at 5%) of patients receive chemotherapy in second-line, hence a sensitivity analysis has been conducted including the cost of chemotherapy with the same split of chemotherapy regimens as used in the treatment-naïve setting. The choice of chemotherapy is unlikely to be different in second line setting and regardless, there are no expected differences in efficacy between chemotherapy regimens.

In the main company submission document, the analysis versus BSC is presented as the sole relevant comparison for treatment-experienced patients as per the NICE final scope. A scenario where the

chemotherapy comparator is considered for treatment-experienced patients is provided in Section 5.8.3.

Further details of the implementation of the comparators within the economic analysis with respect to outcomes and costs are discussed in Sections 5.3 and 5.5, respectively.

5.3 Clinical parameters and variables

Clinical data regarding the safety and efficacy of avelumab for treatment-experienced and treatment-naïve cohorts were derived from the JAVELIN Merkel 200 trial. The latest data for both cohorts is from a data-cut at 24th March 2017 as described in Section 4.3.

Recruitment of treatment-naïve patients in Part B of the JAVELIN Merkel 200 trial is ongoing, thus more mature data are expected over time. As stated previously, the economic model considers treatment-experienced and treatment naïve cohorts separately, although many clinical parameters and variables are the same for both cohorts. A summary of the differences in modelling approaches for treatment-experienced and treatment-naïve patients is provided in In summary, the inputs for both models are noted below in Table 73.

Table 73.

In addition to PFS and OS from the JAVELIN Merkel 200 trial, the following additional clinical data were utilised within the economic model:

- Time to permanent treatment discontinuation (discussed in detail within Section 5.3.2),
- Patient baseline characteristics (such as age, gender, weight, etc.),
- Occurrence of TRAEs, and
- HRQL data (discussed in detail within Section 5.4).

Each of these outcomes/data sources are discussed in turn below, for treatment-experienced and treatment-naïve patients. It should be noted that the JAVELIN Merkel 200 trial was a single-arm open-label trial (i.e. all patients received avelumab). Therefore, to inform comparator outcomes for treatment-experienced and treatment-naïve patients, observational data sources were sought, (Merck KGaA 2016a; Iyer 2016; Voog 1999; Satpute 2014; Santamaria-Barria 2013; Fields 2011; Allen 2005). Given the differences in the approaches taken to model the comparators across the lines of therapy, these data are discussed separately in Section 5.3.3 and 5.3.4.

5.3.1 Avelumab: progression-free and overall survival

In this section we described observed and extrapolated PFS and OS data for avelumab-treated patients; first in the treatment-experienced cohort and then in the treatment-naïve cohort.

Treatment-experienced metastatic MCC patients - Observed data (PFS and OS)

As described in Section 4.7.4, median PFS for treatment-experienced patients in the JAVELIN Merkel 200 trial was 2.7 months and the proportion of patients who were progression-free at 18 months was 29%. Median OS for treatment-experienced patients was [redacted]. OS and PFS data are presented alongside one another in Kaplan–Meier form in Figure 23 for comparison.

Figure 23: Kaplan–Meier plots of OS and PFS for treatment-experienced patients in JAVELIN Merkel 200

The log-cumulative hazard plots of PFS and OS from the JAVELIN Merkel 200 trial are shown in Figure 24 and Figure 25, respectively.

Figure 24: Log-cumulative hazard plot of PFS for treatment-experienced patients in JAVELIN Merkel 200

Figure 25: Log-cumulative hazard plot of OS for treatment-experienced patients in JAVELIN Merkel 200

The observed PFS and OS data for treatment-experienced patients in the JAVELIN Merkel 200 trial demonstrate decreasing hazards over time, as well as the emergence of a plateau (particularly for PFS) which is characteristic of immuno-oncology therapies. For example, at 18 months, [redacted] patients are still at risk of a PFS event, and only one patient experienced an event beyond this time.

These key features of the observed survival data are discussed further in the extrapolation section below.

Treatment-experienced metastatic MCC patients – Extrapolation (PFS and OS)

Long-term effects (i.e. beyond the available 18-month data cut) are as yet unobserved in JAVELIN Merkel 200 2L+ cohort (Part A). However, other immuno-oncology therapies with the same or similar mechanisms of action have longer-term data available (Schadendorf 2015). These data demonstrate consistent patterns in the long-term survival outcomes associated with these novel therapies, achieved by a proportion of patients – that is, a decreasing probability of progression and death shown by the plateau in the survival curves. Based both on the results of JAVELIN Merkel 200 and clinical opinion, it is believed avelumab would be associated with similar long-term patterns in survival. For this reason the previous appraisals of immuno-oncology therapies by NICE (TA268, TA319, TA357, TA384, TA400, TA417, TA428) are relevant in considering the approaches undertaken and precedents set by NICE and Appraisal Committees (NICE 2012; NICE 2014b; NICE 2015; NICE 2016a; NICE 2016c; NICE 2016e; NICE 2017c)}. After investigating a number of different approaches (which are shown below), we found the most appropriate projections to be taken from:

- PFS: Spline "3-knot Odds", and
- OS: Spline "1-knot Odds".

The rationale for these choices is outlined in detail below and follows a comprehensive application of methods to the observed data. All considered methods are incorporated in the submitted economic model in order to enable comprehensive scenario testing.

NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 provides a useful guide detailing extrapolation methods for survival analysis to inform cost-effectiveness analysis. As well as standard parametric approaches (deemed appropriate for data demonstrating monotonic hazard functions), the document presents flexible modelling approaches that can be adopted for complex hazard functions, as is the case for immune-oncology treatments.

Based on TSD14, other techniques adopted in literature and those considered in previous NICE technology appraisals, the following four methods were applied to extrapolate the survival data observed in the JAVELIN Merkel 200 trial:

- Spline modelling,
- Parametric survival modelling,
- Mixture Cure Modelling, and
- General Population Mortality extrapolation.

These are covered in turn below and we ask the Evidence Review Group (ERG) and the NICE Committee to be pragmatic when considering the uncertainty associated with these findings, given the nature of the evidence base for this ultra-rare condition.

PFS: Overview

A range of candidate survival extrapolation techniques were considered to model PFS data from the JAVELIN Merkel 200 trial. Due to the non-monotonic hazard function of the PFS data (Figure 24), non-flexible methods such as standard parametric models were unsuitable for consideration to inform PFS. Consequently, spline models were identified as a more flexible approach to modelling PFS. Spline models were also considered in the previous NICE STA of nivolumab in treatment-experienced advanced renal cell carcinoma for modelling PFS.

PFS: Spline models

NICE TSD 14 indicates that spline-based models are one example of more flexible modelling approaches that are potentially useful when standard parametric models may be inappropriate (Latimer 2013). In addition, as spline models consider separate sections of the observed Kaplan-Meier data they have the potential to more accurately reflect the survival outcomes for different sub-populations that exist within the data (though the ability to unpick different sub-populations is not an explicit feature of the spline models themselves).

Spline models were fitted using the "flexsurv" package in the statistical package, R. Royston and Parmar (2002) provide a detailed explanation of the approach; however, a brief explanation is provided for context (Jackson 2017).

In a spline-based model, the survivor function S(t) is transformed and modelled as a natural cubic spline function of log time x = log(t). Three potential functional forms or model types were considered:

- "Hazard", where the "log cumulative hazard" is modelled as a spline function,
- "Odds", where the "log cumulative odds" is modelled as a spline function, and
- "Normal", where "-Φ-1(S(t))" is modelled as a spline function ("Φ-1()" is the inverse normal distribution function).

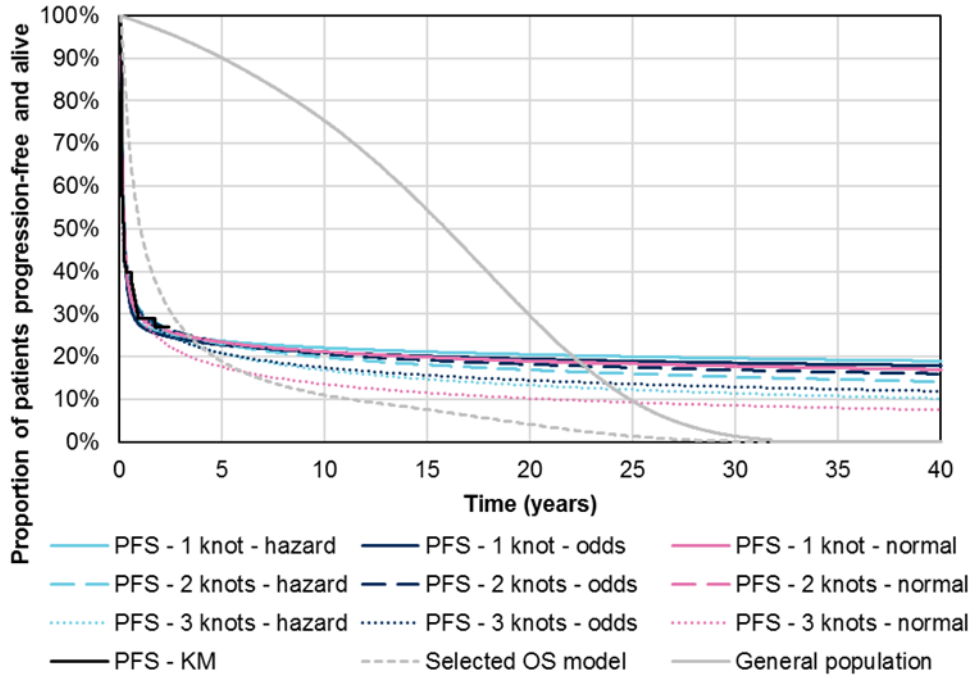
Knots are positioned at the first and last events that were observed. In the literature, these knots are termed the "minimum" and "maximum" knots. Intermediate knots are then positioned between the minimum and maximum knots. With no intermediate knots, the "hazard", "odds" and "normal" spline models are equivalent to Weibull, log-logistic and log-normal models, respectively (Jackson 2017).

With this model, the positions of the intermediate knots are by default set as equally-spaced quantiles of the log uncensored survival times. This accounts for data that are clustered together closely, where it may be desirable to identify and specifically model these clusters in. The knot locations can also be set manually, although usually only if there is clear rationale for why specific points in time are prognostic in terms of survival outcomes (Jackson 2017). There is no clear rationale to manually set knot locations for this analysis, hence they were set by default as equally-spaced quantiles of the log uncensored survival times.

One, two or three intermediate knots were explored in this analysis. Any more than three intermediate knots could lead to over-fitting of the spline models, as three intermediate knots suggests there are four specific subgroups of patients which is more than would be supported by the number of patients in the analysis. Over fitting the spline models may lead to poor performance as the model overreacts to minor data fluctuations.

In common with other models, additional constraints on PFS projections were necessary as the projections themselves lack face validity in the longer term: the projections shown in Figure 26 demonstrate implausible estimates of PFS greater than the OS of the general population. The modelling constraints used included capping PFS with the OS curve and adjusting raw extrapolation estimates to account for the hazard of death seen in general population mortality data. These methods are further described in the sections below.

Figure 26: Spline curve fits for PFS for treatment-experienced patients in JAVELIN Merkel 200

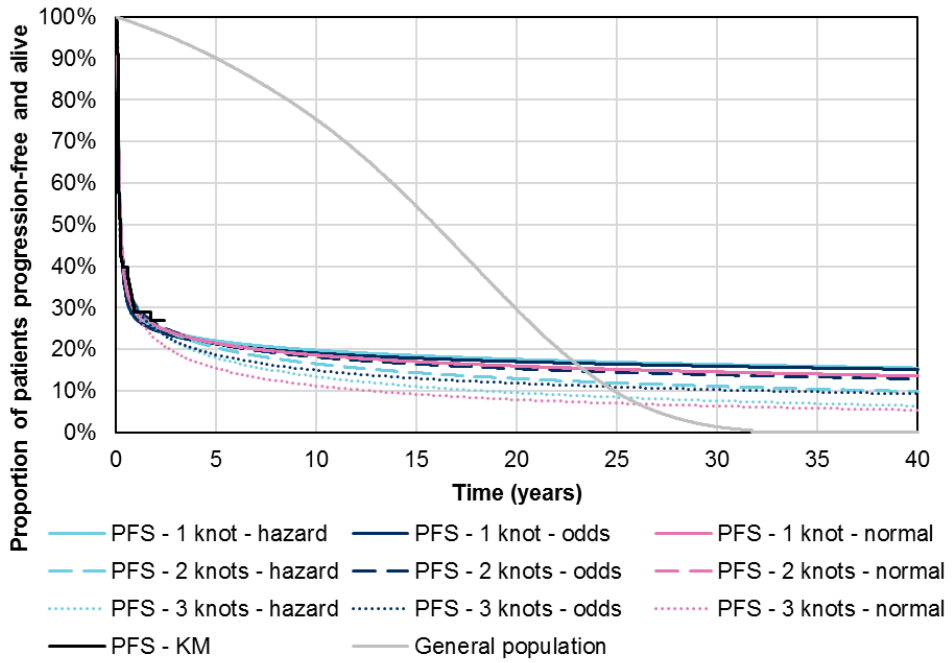


Note: The projections shown here are adjusted within the economic model to avoid over-estimation versus the predicted OS for avelumab patients.
Abbreviations: KM: Kaplan–Meier; OS: overall survival; PFS: Progression-free survival

These plots demonstrate high long-term PFS estimates (for example, 10-year PFS estimates of 10%-20%), likely driven by the plateau noted in the observed Kaplan–Meier data (Figure 23).

Expert advice from members of the UK modelling steering committee (see Section 5.10) suggested exploring scenarios wherein the final few observations may be omitted from consideration as a means of restricting the ability of the spline model to be overly influenced by the tail end of the Kaplan-Meier curve (as the final knot is placed at the last data point), when few patients are still in the study. Therefore, alternative time points were explored. For example, as the minimum follow-up time for all patients in Part A of the JAVELIN Merkel 200 trial is 18 months at the time of this submission, the scenario presented in Figure 27 considers all PFS times after 18 months to be censored at 18 months.

Figure 27: Spline curve fits for PFS for treatment-experienced patients in JAVELIN Merkel 200 (18-month maximum)



Note: The projections shown here are adjusted within the economic model to avoid over-estimation versus the predicted OS for avelumab patients.
Abbreviations: KM: Kaplan–Meier; PFS: Progression-free survival

By limiting the maximum observed event time to 18 months, the plateau shown in the PFS curve is still apparent but less pronounced. This approach was used in our base case however it has marginal impact on the outcome. The statistical goodness of fit was explored using Akaike and Bayesian information criteria (AIC and BIC, respectively), as shown in Table 31.

Table 31: Statistical goodness of fit – PFS for treatment-experienced patients in JAVELIN Merkel 200; spline curves

Model fitted	*All patients*		*18-month cut-off*	
	AIC (rank)	*BIC (rank)*	*AIC (rank)*	*BIC (rank)*
1-knot Odds	302.03 (6)	309.46 (5)	300.23 (6)	307.66 (5)
1-knot Normal	303.13 (7)	310.57 (7)	301.44 (7)	308.87 (7)
1-knot Hazard	306.59 (9)	314.02 (8)	304.56 (9)	311.99 (8)
2-knots Odds	300.12 (5)	310.02 (6)	298.38 (5)	308.29 (6)
2-knots Normal	305.20 (8)	315.11 (9)	303.51 (8)	313.42 (9)
2-knots Hazard	298.94 (4)	308.85 (4)	297.15 (4)	307.06 (4)
3-knots Odds	288.27 (1)	300.65 (1)	286.15 (1)	298.54 (1)
3-knots Normal	291.69 (3)	304.07 (3)	291.83 (3)	304.21 (3)
3-knots Hazard	289.68 (2)	302.06 (2)	287.55 (2)	299.93 (2)

Note: The AIC and BIC scores should not be compared across the "all patients" and "18 months" analyses, as these analyses consider different numbers of events (for the "all patients" analysis, one patient experienced an event beyond 18 months; whereas in the "18 months" analysis, no patients experienced an event beyond 18 months [i.e. the remaining [redacted] at risk beyond 18 months were censored at 18 months]).

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion

A final spline-based approach was also considered for the use of PFS in conjunction with OS, where the long-term projection of PFS was adjusted to be informed by the hazard of death seen in the OS projection. In the model, this is referred to as a "custom spline" model, and considers a period of one year between 18 and 30 months over which the hazard of an event in the PFS curve gradually follows the hazard of an event in the OS curve. The selection of these time points is arbitrary, but relates to the 18-month cut-off and the approximate end of available Kaplan-Meier data at 30 months. This is provided as a sensitivity analysis within Section 5.8.3.

As summarised previously, the PFS: Spline "3-knot Odds" was selected for the base case given its superior statistical fit.

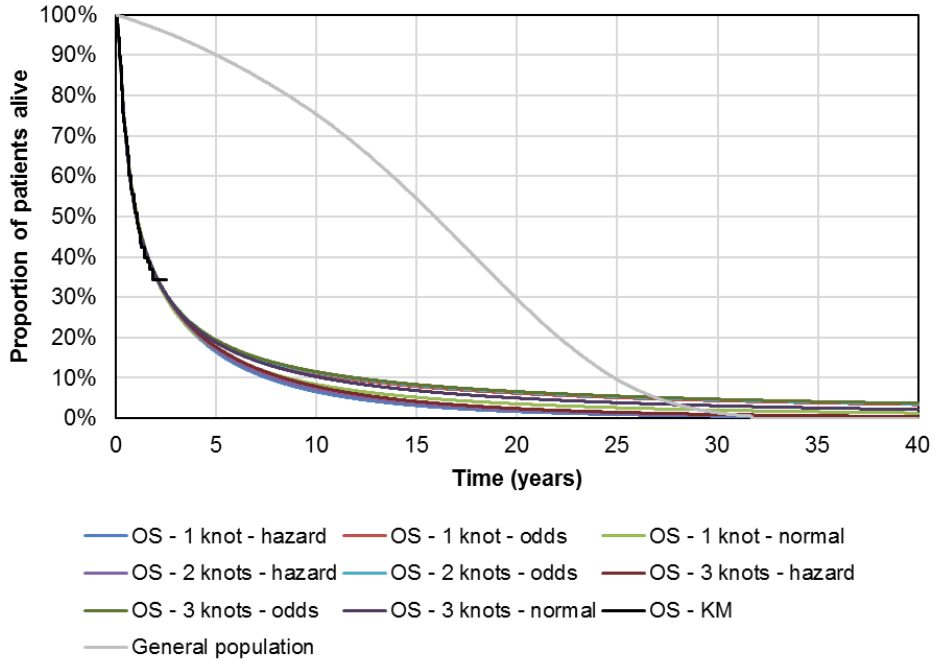
OS: Overview

A comprehensive range of survival modelling methods were explored to model OS data from the JAVELIN Merkel 200 trial. Spline models were considered as a flexible approach to modelling survival, which based on the log-cumulative hazard plot may be able to provide more realistic long-term estimates without imposing the assumption of a monotonic hazard function. Given that OS data are less mature than PFS, parametric models were also considered for completeness. Mixture-cure models were explored following advice from economic experts and their use in published literature, within the context of immuno-oncology therapies (Chen 2016; Othus 2017). In addition, a model averaging approach using the age-adjusted general population mortality to extrapolate outcomes for a given proportion of patients associated with long-term survival was considered (henceforth referred to as the "general population mortality extrapolation" method [GPME]). This approach was explored given its use in a prior NICE STA of the immuno-oncology therapy, nivolumab in treatment-experienced advanced renal cell carcinoma (NICE 2016e). The methods of each approach are described in turn below along with their strengths and limitations.

OS: Spline models

As per PFS, spline models were fit to the observed OS data using the "flexsurv" package in R. Spline curve fits are presented for each of the combinations of functional form and number of intermediate knots, along with the Kaplan–Meier plot for OS in Figure 28.

Figure 28: Spline curve fits for OS for treatment-experienced patients in JAVELIN Merkel 200



Abbreviations: KM: Kaplan–Meier; OS: Overall survival

The statistical goodness of fit was explored using AIC and BIC scores, as shown in Table 32.

Table 32: Statistical goodness of fit – OS for treatment-experienced patients in JAVELIN Merkel 200; spline curves

Model fitted	*AIC (rank)*	*BIC (rank)*
1-knot Odds	432.29 (1)	439.73 (1)
1-knot Normal	432.60 (3)	440.03 (3)
1-knot Hazard	432.52 (2)	439.95 (2)
2-knots Odds	434.28 (5)	444.19 (5)
2-knots Normal	434.23 (4)	444.14 (4)
2-knots Hazard	434.46 (6)	444.37 (6)
3-knots Odds	436.27 (8)	448.65 (8)
3-knots Normal	436.09 (7)	448.48 (7)
3-knots Hazard	436.44 (9)	448.83 (9)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion

The spline models are considered in the model base case, as we consider these models to be the most appropriate survival extrapolation technique for the JAVELIN Merkel 200 OS data in treatment-experienced patients. The 1-knot Odds model provided the superior statistical fit. For completeness, other modelling methods have been considered, but are associated with notable limitations.

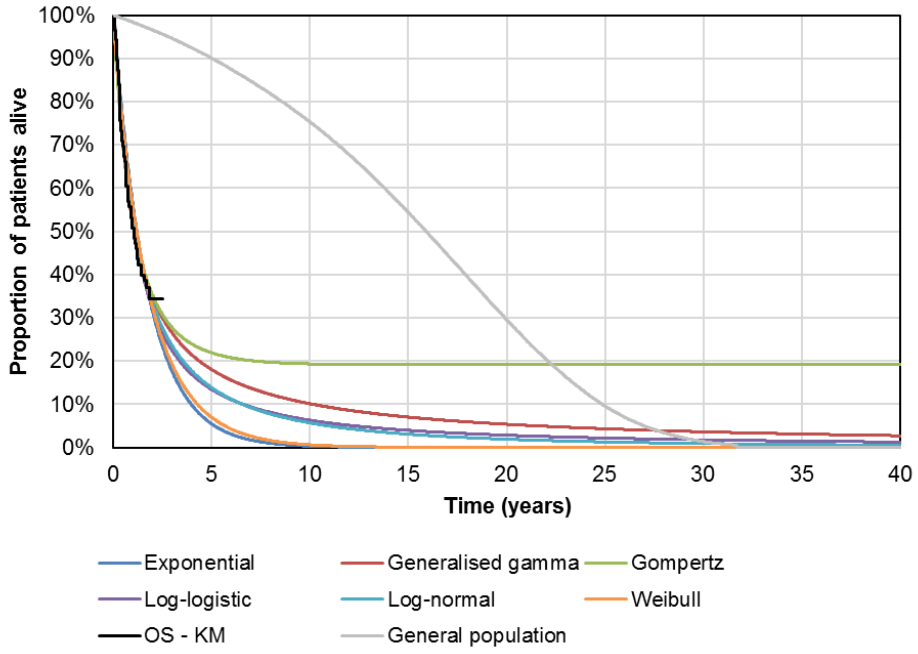
OS: Parametric survival models

The following standard parametric models were fit to OS data:

- Exponential,
- Generalised gamma,
- Gompertz,
- Log-logistic,
- Log-normal, and
- Weibull.

Parametric curve fits are presented for each of these distributions along with the Kaplan–Meier plot for OS in Figure 29.

Figure 29: Parametric curve fits for OS for treatment-experienced patients in JAVELIN Merkel 200



Abbreviations: KM: Kaplan–Meier; OS: Overall survival

The statistical goodness of fit was explored using AIC and BIC scores, as shown in Table 33.

Table 33: Statistical goodness of fit – OS for treatment-experienced patients in JAVELIN Merkel 200; parametric curves

Model fitted	*AIC (rank)*	*BIC (rank)*
Exponential	436.76 (5)	439.24 (3)
Generalised Gamma	432.54 (2)	439.97 (5)
Gompertz	434.88 (4)	439.83 (4)
Log-logistic	433.40 (3)	438.36 (2)
Log-normal	431.54 (1)	436.49 (1)
Weibull	438.41 (6)	443.36 (6)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion

The parametric curve fits shown in Figure 29 provide a good visual fit to the observed OS data from the JAVELIN Merkel 200 trial, with measures of statistical fit similar to the spline models according to the AIC and BIC.

The statistical goodness-of-fit scores for the parametric models, suggest the best fitting curves are the log-normal, log-logistic and generalised gamma distributions. These three curves each demonstrate long-term survival estimates that are distinctly dissimilar to those seen for the exponential and Weibull curves. The Gompertz curve produces clinically implausible long-term estimates.

It should be noted that the long-term estimates of OS when extrapolated using several of the standard parametric models fail to account for the "long tail" of the Kaplan–Meier plot of PFS (as shown in Figure 23). The PFS curve appears to plateau from a relatively early date. For example, from 12 months onward, [redacted] are still at risk with only [redacted] occurring until the end of follow up. Clinicians agreed that in this disease area, PFS and OS are closely correlated.

Alternative survival extrapolation methods were considered in line with the clinical expectation of a plateau in the OS curve for patients treated with avelumab, and the inability for standard parametric survival models to consider the observed plateau in the PFS data from JAVELIN Merkel 200.

OS: Mixture cure models

Mixture cure models (MCMs) have previously been used to describe the long-term survival trends observed in patients treated with immuno-oncology therapies in other cancer types and were also a suggested approach of health economic experts. Most recently, this approach was utilised by Othus et al. (2017) for modelling the survival of advanced melanoma patients treated with ipilimumab (Othus 2017).

MCMs were fitted using the "gfcure" package in R, and a survivor function for long-term survivors was implemented within the economic model separately to the derivation of survival based on the observed trial data.

MCMs consider a split-population where one group of patients may be considered to follow a trajectory typical of the natural course of the disease (denoted the "uncured" fraction) and another may be considered to follow a trajectory as per the unaffected age-adjusted general population (denoted the "cured" fraction). The proportion of patients in each category can be estimated using the model itself. The functional form of a MCM is presented in Equation 1 (Othus 2017; Lambert 2007).

Equation 1: Mixture cure model functional form

$$\boldsymbol{S_{Overall}(t) = S_{General\ population}(t)(\pi + (1-\pi)S_{Uncured}(t))}$$

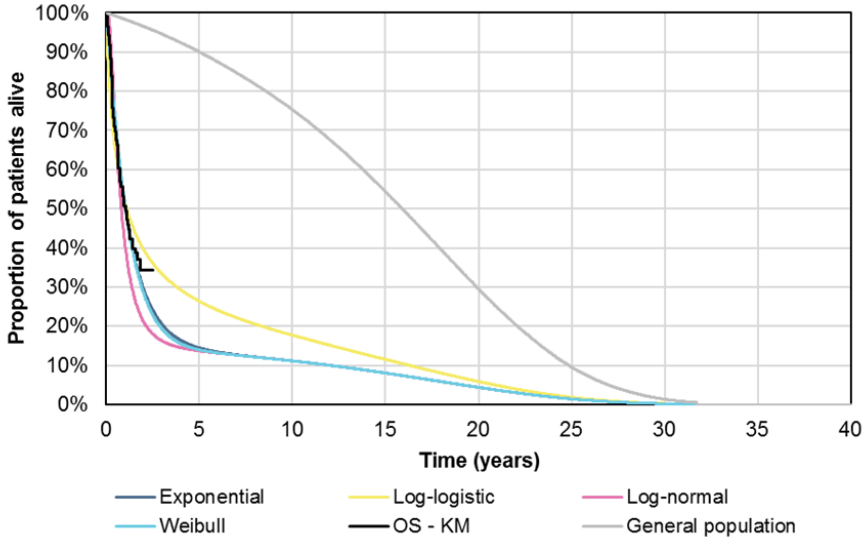
Abbreviations: t: Time; S: Survivor function; π: "Cured" fraction

MCMs were fitted using the following parametrisations of the "uncured" fraction:

- Exponential,
- Log-logistic,
- Log-normal, and
- Weibull.

The generalised gamma and Gompertz distributions were not possible to fit using the "gfcure" package. MCMs are presented for each of these parameterisations, along with the Kaplan–Meier plot for OS in Figure 30.

Figure 30: Mixture cure models for OS for treatment-experienced patients in JAVELIN Merkel 200



Abbreviations: KM: Kaplan–Meier; OS: Overall survival

The MCMs predicted 14.8% of patients to be representative of the statistical "cure" fraction, leaving 85.2% representative of the statistical "uncured" fraction. When presenting these models to clinical and statistical experts at an advisory board, some issues were raised with the models produced.

Firstly, the use of a log-logistic distribution to characterise the survival trajectory of "uncured" patients was considered methodologically flawed, due to the "heavy tail" noted for this distribution regardless of the existence of a statistical cure modelling approach. Secondly, the abrupt change in hazard was noted as a potential caveat of these survival curves given the lack of clinical rationale supporting a sudden change in hazard, noted in particular to apply to the exponential, log-normal and Weibull MCMs.

However, MCMs provide an alternative survival implementation for consideration within the economic analysis that attempts to quantify the expectation of a long-term surviving fraction of patients. Though these MCMs are not considered as informative of the model base-case settings, the option to use these models features within the analysis and the associated results are explored as sensitivity analysis.

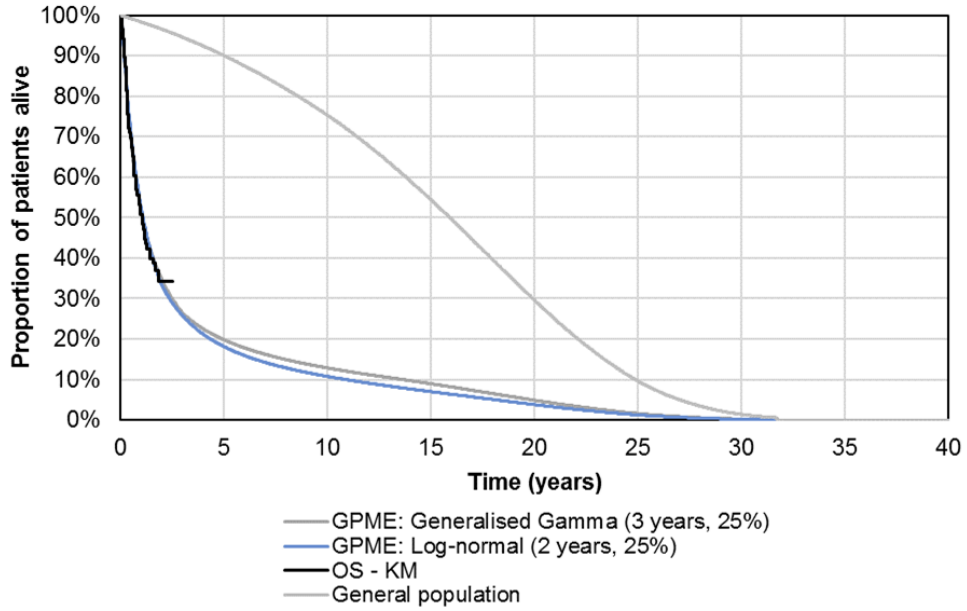
OS: General Population Mortality Extrapolation

As an alternative to the MCM, general population mortality extrapolation (GPME) was considered. This method accounts for a proportion of patients achieving durable long-term responses. This approach has previously been used within NICE TA417 (nivolumab for treatment-experienced advanced renal cell carcinoma) as a pragmatic method to quantify the expectation of an immune-response tail in the survival of PD-1/PD-L1 immune-checkpoint inhibitors (NICE 2016e).

This method considers extrapolations from standard approaches (such as parametric models) as well as potentially more complex approaches that do not sufficiently capture an immune-response tail (e.g. hazard-based spline models). At a given point in time (e.g. 2 years), a proportion of patients still alive (e.g. 50%) are assumed to follow the survival trajectory of the age-matched general population, with the remainder of patients continuing along the same trajectory as before.

This method of accounting for a fraction of patients that follow a trajectory of survival as per the general population has the advantage of being incredibly flexible to alternative assumptions – thus presenting a very useful tool for demonstrating the potential range of long-term survival trajectories that may occur. Example trajectories are shown in Figure 31 using an example "cure" fraction of 25% to 50%, an initiation time of between 2 years and 3 years and the log-normal/ generalised gamma parametric curves.

Figure 31: Example general population mortality extrapolations for OS



Abbreviations: GPME: General population mortality extrapolation; KM: Kaplan–Meier; OS: Overall survival

The GPME method relies on two key inputs: the proportion of patients in each group and the time point at which this separation of curves is expected to initiate. Limited data are available to inform such assumptions, demonstrating further why this method should be acknowledged to present a pragmatic quantification of the expected immune-response tail in the OS of patients treated with avelumab. As such, careful consideration should be taken when interpreting results based on extrapolation using this technique.

In summary: base-case OS and PFS model settings

Based on these candidate models for OS and PFS, the "1-knot Odds" spline model was selected to inform the model base-case for OS, and the "3-knot Odds" spline model was selected to inform the model base-case for PFS. Section 5.7.2 compares the clinical outcomes predicted by the economic model, in terms of medians and restricted means[***], to empirical trial data.

Splines were deemed the candidate models for PFS following assessment of the log-cumulative hazard plots which clearly show decreasing hazards over time and the emergence of a plateau.

*** Restricted means (mean survival up until a given time point) are used as true mean cannot be calculated when survival data are incomplete

For both the “all patients” (where all PFS data were considered) and “18-month” (where all times beyond 18 months were recorded as censor points at 18 months) PFS analyses, the 3-knot PFS splines produced the best statistical goodness of fit in terms of both AIC and BIC. The model, based on the maximum observed event time of 18 months, was selected to inform the model base-case for the following reasons:

- The “3-knots Odds” spline has superior statistical goodness of fit compared with other spline-based models,
- The “3-knots Odds” spline also demonstrates good visual fit within the first 18 months of observed data,
- The use of the 18-month data cut spline prevents over-fitting to the tail-end of the Kaplan-Meier function for the full follow-up period of the 18-month data cut,
- The “3-knot Odds” spline when combined with the “1-knot Odds” spline for OS produces a plateau that seamlessly joins with the expected trajectory for OS such that an abrupt change in hazard is not observed.

All spline models demonstrate similar estimates of PFS within the observed period, but long-term extrapolations vary. The “3-knot Odds” spline produces a 5-year PFS estimate of 20.9% (adjusted to 18.9% accounting for the capping by the OS curve), with all splines producing 5-year estimates between 17.6% and 23.7% (“3-knots Normal” and “1-knot Odds”). In the absence of long-term data to select the most appropriate extrapolation, the “3 knot Odds” spline was considered an acceptable choice to inform the base-case with alternative trajectories from other spline models providing similar results.

For OS, spline-based models were considered the most appropriate choice to inform the model base-case for the following reasons:

- The log cumulative hazard plot presented in Figure 25 is non-linear indicating that standard parametric models would be a less appropriate fit for OS data.
- Spline models have greater sensitivity to reflect the changing hazards in the observed survival data from the JAVELIN Merkel 200 trial. This “flexible” feature of spline models means the extrapolations are able to consider more appropriately a reduction in hazard at later points in time.
- It is expected that some patients will fail to respond to avelumab and die within the earlier part of the observed period of data. Others will achieve durable responses and long-term survival. Of course there will be patients in in between these points. Therefore, the use of a statistical model that is able to detect differences in hazard over the entire observed period is aligned with the clinical expectation of the type of patient towards the end of the observed period having differential hazards of death compared with those patients included towards the start of the observed period.
- As seen in previous studies in other indications, the mechanism of action of anti-PD-1/PD-L1 monoclonal antibodies suggest a proportion of patients achieve long-term survival outcomes. Early signs of the expectation of patients to achieve these long-term survival outcomes are response rates and remaining progression-free for a long period of time with a very low hazard towards the end of the data. Consulted clinicians felt that in this disease area PFS and OS were closely correlated, and hence the plateau observed in the PFS curve will be mirrored in the curve for OS.
- The “1-knot Odds” spline provides the best statistical goodness of fit compared with other spline models, and provides comparable measures of statistical goodness of fit when

compared with parametric models. Hence, the spline models provide viable extrapolation estimates for the OS of avelumab-treated patients, without compromising reasonable estimates of statistical goodness of fit.

- Clinical expert opinion described the survival trajectory of patients who survive until 5 years post initiation of treatment with avelumab would be similar to that of the age-adjusted general population. The hazard function of the "1-knot Odds" spline only produces a hazard of death below that of the general population at approximately 13 years post initiation of treatment with avelumab, at which point the model assumes the hazard of death as per the general population. In this regard, the "1-knot Odds" spline provides a conservative estimate of survival between 5 years and 13 years.

As with PFS, the clinical plausibility and face validity of the long-term OS projections has been considered: Modelling techniques have been utilised to ensure that outcomes demonstrate face validity (for example, by ensuring the hazard of death at any time does not exceed that of the age-adjusted general population, and by clinically validating all model extrapolations).

Treatment-naïve metastatic MCC patients

Data for the survival of patients with treatment-naïve metastatic MCC receiving avelumab are limited – at present, data are available for 39 patients, with a maximum follow-up of 11 months. As such, these data were deemed too immature for direct application within the model. OS and PFS data are presented alongside one another in Kaplan–Meier form in Figure 32 for comparison.

Figure 32: Kaplan–Meier plots of OS and PFS for treatment-naïve patients in JAVELIN Merkel 200

As an alternative to utilising these immature data, an alternative modelling approach were taken. Analyses were conducted to establish the relative improvement with avelumab that might be seen in treatment-naïve patients versus those in the treatment-experienced group.

A Cox proportional hazards regression model was fitted to OS and PFS data from the JAVELIN Merkel 200 trial (Part A and Part B) to provide an estimated HR for the difference in survival between treatment-experienced and treatment-naïve patients. The results of this analysis are presented graphically in Figure 33.

Figure 33: Cox proportional hazards regression models for OS and PFS

The resulting HRs, i.e. the relative effect of avelumab in treatment-naïve patients versus treatment-experienced patients are [redacted]. Given the immaturity of these data, these HRs were not considered substantive enough for use within the economic model. Clinical expert opinion was therefore sought to elicit a hypothetical HR which may be expected to apply for treatment-naïve patients.

Clinical experts were asked whether they thought a benefit would be observed in the survival for treatment-naïve patients compared with treatment-experienced patients. All clinicians were experienced in using immune-oncology products (such as ipilimumab, nivolumab and pembrolizumab) in tumours such as metastatic melanoma, renal cell carcinoma and NSCLC. Drawing on their experiences and emerging data in this space, clinicians provided an estimated HR of 0.80 for OS. This HR was therefore assumed to apply through the model for the derivation of OS for 1L avelumab-treated patients.

For PFS, clinicians did not feel able to provide an estimated HR for use within the model. Therefore, a HR of 1 (i.e. no difference in these outcomes between treatment naïve and treatment-experienced patients) was applied for PFS due to lack of validation to suggest otherwise. In reality, as PFS projections are capped by the OS curve in the economic model, incorporating a HR for OS will have some small effect on PFS projections (i.e. an improvement in OS indirectly implies an improvement in long-term PFS). Modifying the HR for PFS makes limited difference to the results as it only impacts the small monitoring costs accrued in the pre-progression state (utilities are addressed separately by a time to death analysis and treatment costs are modelled using ToT).

5.3.2 Avelumab: time on treatment

Treatment-experienced metastatic MCC patients

In order to model treatment costs, the duration over which patients receive treatment with avelumab is required. Observed time on treatment (ToT) data for avelumab were obtained from the JAVELIN Merkel 200 trial (Merck KGaA 2016f).

The use of ToT data to inform the proportion of patients receiving avelumab over time within the economic model is considered a more robust approach than relying on the assumption that patients are treated until disease progression or death. This is because within the JAVELIN Merkel 200 trial, patients were eligible to discontinue for reasons other than disease progression or death (such as withdrawal of consent and adverse events) and are allowed to continue treatment beyond progression if still receiving benefit.

The alternative approach, i.e. to use PFS as a proxy for ToT, was criticised by ERGs in previous appraisals, with the most relevant example for consideration in this appraisal being TA428: Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (NICE 2017c).

The Kaplan-Meier curve for ToT for treatment-experienced patients in JAVELIN Merkel 200 is presented in Figure 34. Median ToT is 113 days, whereas median PFS is 82 days demonstrating the importance of not using PFS as a proxy for ToT if these data are available.

Figure 34: Kaplan-Meier plot for avelumab time on treatment in JAVELIN Merkel 200 (treatment-experienced patients)

The log-cumulative hazard plot of ToT from the latest data cut (minimum 18-months follow-up, 24th March 2017) in the JAVELIN Merkel 200 trial is shown in Figure 35.

Figure 35: Log-cumulative hazard plot of time on treatment in JAVELIN Merkel 200 (treatment-experienced patients)

The expectation of how the ToT curve may continue beyond the available data from the JAVELIN Merkel 200 trial is less clear. Expert opinion was sought from three clinicians to establish how avelumab would be expected to be administered in practice, based on clinician experience of immuno-oncology therapies in other indications (such as ipilimumab, nivolumab and pembrolizumab).

The range of parametric curve estimates for ToT beyond the duration of follow up in the JAVELIN Merkel 200 trial provided a broad spectrum of candidate models from which assumptions regarding ToT could be made. Based on expert opinion (see below), most of the long-term projections lacked face validity in that they suggested an unreasonable proportion might remain on treatment in the longer term. The parametric models for ToT are presented in Figure 36 with goodness of fit statistics presented in Table 34.

[redacted] explained that if a patient had a controlled response, they would remain on treatment for a further 6 months. For patients with prolonged responses, it would be reasonable to consider continuing treatment for up to 2 years, and then consider monitoring thereafter for disease recurrence. If the disease then subsequently progressed, the patient would ideally be retreated. In his experience with melanoma, [redacted] explained that over time as clinicians have become more experienced with PD-L1s a larger proportion of patients discontinue treatment at 2 years compared with when immunotherapy treatment was first made available in this indication. He estimated that about a third of patients with metastatic MCC would continue treatment beyond 2 years. In terms of a maximum treatment duration expected, [redacted] stated it would be unlikely that patients continue treatment beyond 5 years, and that this would apply regardless of treatment history (i.e. whether patients are treatment-experienced or treatment-naïve).

[redacted] explained that in melanoma, patients experiencing a controlled response would discontinue treatment at 2 years, and a small proportion of patients with stable disease or prolonged responses may continue treatment for longer. A similar concept would be likely to apply for metastatic MCC with an estimate of less than 50% of patients remaining on avelumab treatment. The need for treatment would be assessed via CT or Positron emission tomography (PET) scans, and if patients had no active disease they would be taken off treatment. Patients could potentially receive treatment for up to 3 years to 4 years, but are unlikely to still be on treatment beyond 5 years.

[redacted] also estimated that the number of patients receiving avelumab would reduce by half each subsequent year. For instance, if 20 patients were on treatment in the first year, 10 would be on treatment in the second year, 5 would be on treatment in the third year and so on.

[redacted] explained that 2 years is a natural point at which physicians will discuss with patients stopping treatment, noting that at ASCO, analysis was presented regarding pembrolizumab for the treatment of advanced melanoma using this time point. The outcome of the analysis suggested that treatment-experienced advanced melanoma patients who discontinued pembrolizumab based on patient/physician decision in the absence of progressive disease or AEs were at low risk for short-term progression, irrespective of their best tumour response (Jansen 2017). [redacted] also suggested a maximum feasible treatment duration would be in the region of 5 years, re-iterating that most patients, i.e. two thirds would discontinue at 2 years.

Figure 36: Parametric curve fits for ToT for treatment-experienced metastatic MCC patients

Table 34: Statistical goodness of fit – ToT for treatment-experienced metastatic MCC patients; parametric curves

Model	*AIC (rank)*	*BIC (rank)*
Exponential	972.43 (6)	977.38 (6)
Generalised Gamma	943.41 (3)	950.84 (5)
Gompertz	940.92 (2)	945.87 (2)
Log-logistic	939.90 (1)	944.86 (1)
Log-normal	943.65 (5)	948.61 (4)
Weibull	943.59 (4)	948.55 (3)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; MCC: Merkel cell carcinoma: ToT: Time on treatment

Spline models were also considered for modelling ToT, given their use to model OS and PFS. As per PFS and OS, spline models were fit to the observed ToT data using the "flexsurv" package in R. The spline models for ToT are presented in Figure 37, with goodness of fit statistics presented in

Table 35.

Figure 37: Spline curve fits for ToT for treatment-experienced metastatic MCC patients

Table 35: Statistical goodness of fit – ToT for treatment-experienced metastatic MCC patients; spline curves

Model fitted	*AIC (rank)*	*BIC (rank)*
1-knot Odds	442.52 (5)	449.95 (1)
1-knot Normal	443.33 (8)	450.76 (2)

1-knot Hazard	445.02 (9)	452.45 (6)
2-knots Odds	441.66 (2)	451.57 (4)
2-knots Normal	441.3 (1)	451.21 (3)
2-knots Hazard	442.22 (3)	452.13 (5)
3-knots Odds	442.55 (6)	454.93 (8)
3-knots Normal	443.32 (7)	455.71 (9)
3-knots Hazard	442.47 (4)	454.86 (7)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; MCC: Merkel cell carcinoma; ToT: Time on treatment

The best fitting parametric curve, visually and according to AIC and BIC estimates, was the log-logistic; whereas the best fitting spline model was the "2-knot normal". Both models produced equivalent predictions, as shown in Figure 38.

Figure 38: Comparison of log-logistic and "2-knot normal" spline for ToT for treatment-experienced patients in JAVELIN Merkel 200

Given the log-logistic demonstrates superior statistical goodness of fit compared with the "2-knot normal" spline, it was selected to inform the model base-case. As described above, however, this curve lacks face validity, as it projects a considerable proportion of patients will remain on treatment for ≥10 years. Discussion regarding likely treatment duration with immuno-oncology therapies has featured in several other immunotherapy STAs (NICE 2016c; NICE 2016e). Clinical opinion (discussed above) confirms that it is reasonable to assume that a sizable proportion of metastatic MCC patients would no longer be receiving treatment beyond 2 years.

In our base-case, we therefore assume that a third (33.33%) of those patients projected by the best fitting parametric curve (log-logistic) remain on treatment at 2 years and continue to receive treatment beyond this time point. This approach addresses concerns with the face validity of the parametric curves, while also acknowledging the uncertainty associated with long-term treatment duration given the lack of long-term data available at present (at 2 years, 5/88 treatment-experienced patients are at risk within the ToT analysis). This approach allows for a proportion (as is expected clinically) of patients to continue treatment, rather than assuming definitively that 100% of patients would receive no more than 2 years of treatment, which all of the consulted clinicians agreed would be unlikely in clinical practice.

Furthermore, there is a point beyond which it is clinically implausible to believe that the average patient, most of whom are old in age, would still be receiving avelumab every 2 weeks. Clinical opinion sought for this appraisal confirms that it is reasonable to assume this to be at most 5 years – at which point we assume any remaining patients discontinue.

The base-case ToT projection, accounting for the opinion of clinical experts, is shown alongside the Kaplan-Meier plot in Figure 39.

Figure 39: Base-case ToT curve applied – treatment-experienced metastatic MCC

To quantify the uncertainty attributable to differential assumptions placed on the ToT for avelumab, scenario analyses were explored using alternative assumptions for the parameterisation of the ToT data, the proportion of patients predicted by the parametric curves assumed to remain on treatment beyond 2 years, as well as the maximum plausible ToT for all patients. These scenarios are provided in Section 5.8.3.

Treatment-naïve metastatic MCC patients

As per the survival data for patients with treatment-naïve metastatic MCC receiving avelumab, data regarding ToT are also limited. A Cox proportional hazards regression model was fitted to ToT data from the JAVELIN Merkel 200 trial (Part A and Part B) to provide an estimated HR for the difference in treatment duration between treatment-experienced and treatment-naïve patients. The results of this analysis are presented graphically in Figure 40.

Figure 40: Cox proportional hazards regression models for ToT

As discussed in Section 5.3.1, the clinicians consulted were unable to provide validation for the difference in expected duration of treatment for treatment-experienced and treatment-naïve patients. Furthermore, this HR is derived from a small patient sample ( ). It is therefore assumed that treatment duration remains the same as for both patient cohorts (i.e. a HR of 1.00 is applied), with the same assumptions made in relation to discontinuation at 2 years and 5 years. This assumption is aligned with expert opinion that the maximum treatment duration is expected to be approximately

5 years and that a third of patients are expected to discontinue at 2 years across both patient groups. Further to this, the application for ToT is aligned with the application for PFS, where it is assumed (within the context of the model) PFS is equal across both cohorts.

5.3.3 Chemotherapy: overall survival and progression-free survival

As efficacy outcomes differ depending on whether the patient is treatment-experienced or treatment-naïve (i.e. receiving second-line or further or first-line comparator treatment), different approaches were used to analyse data for each line, as discussed in a full report provided in Appendix 10. An overview of the results of the analysis is provided in the sections below.

Treatment-experienced metastatic MCC patients

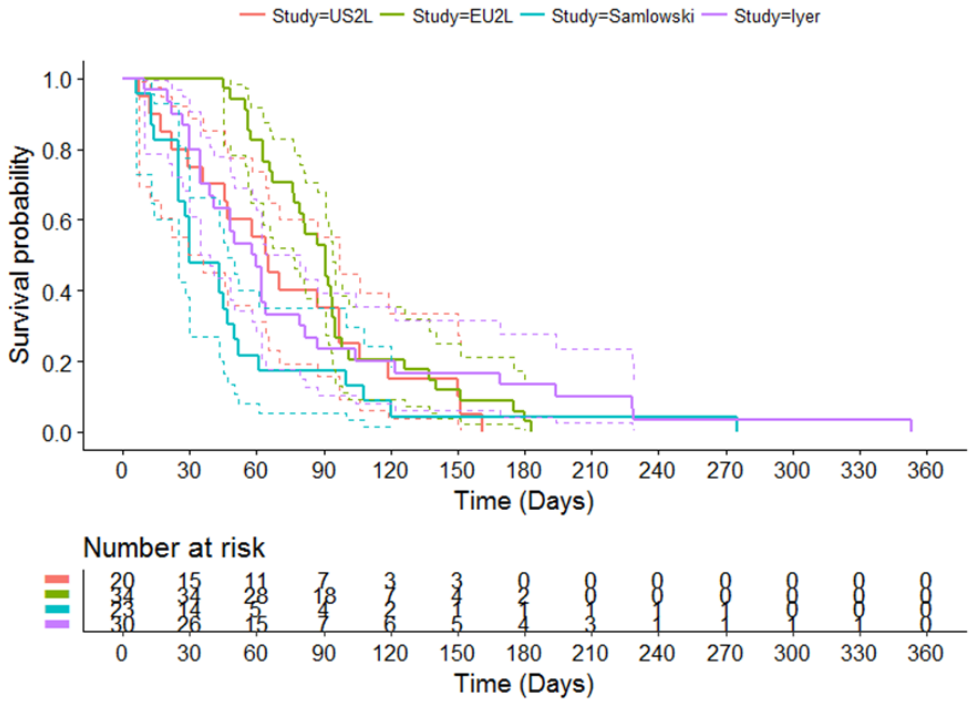
For treatment-experienced metastatic MCC patients, systematic reviews identified little data of relevance. As a result of this, Merck KGaA/Pfizer conducted an observational study in two parts; one in the EU (EU2L) (n=34) (Becker 2016), and one in the US (US2L) (n=20) (Cowey 2017), from which both PFS and OS data are available.

In addition to these studies, data are available from two studies in the literature: Iyer et al. provide data on PFS (and report a median OS of 5.7 months without reporting a Kaplan–Meier curve), and Samlowski et al. provide evidence on both PFS and OS for a mixed cohort of treatment-naïve (n=9) and treatment-experienced (n=14) patients (Iyer 2016; Samlowski 2010). Kaplan-Meier plots for PFS and OS for all identified studies in treatment-experienced metastatic MCC patients are provided in Figure 41 and Figure 42, respectively. Appendix 10 describes the identification of these studies and contains full details of the analyses performed.

Analysis using visual inspection of Kaplan–Meier plots and regression analysis of the individual patient data from the observational study conducted by Merck KGaA/Pfizer, suggested that no patient characteristics beyond line of therapy (age, gender, immunosuppression status, ECOG, or stage at diagnosis) are prognostic of outcomes, and thus there was no need to adjust for differences in patient characteristics between studies (as outcomes were uniformly poor).

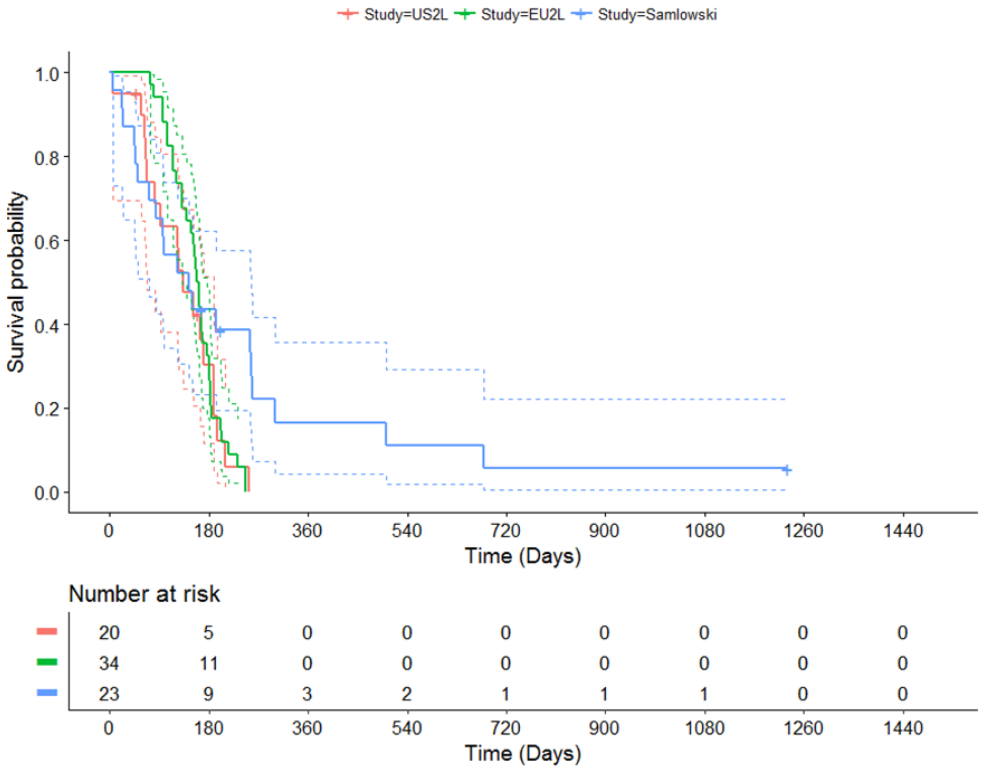
Figure 41 and Figure 42 show that whilst studies do have differences in survival which although unlikely to be related to patient characteristics based on analysis of patient level data (and similar populations being reported in literature studies), indicates between study variability particularly with regard to the literature studies, and as such, naïve pooling would be inappropriate for all studies.

Figure 41: PFS in comparator studies for treatment-experienced metastatic MCC patients



Abbreviations: MCC: Merkel cell carcinoma; PFS: Progression-free survival

Figure 42: OS in comparator studies for treatment-experienced metastatic MCC

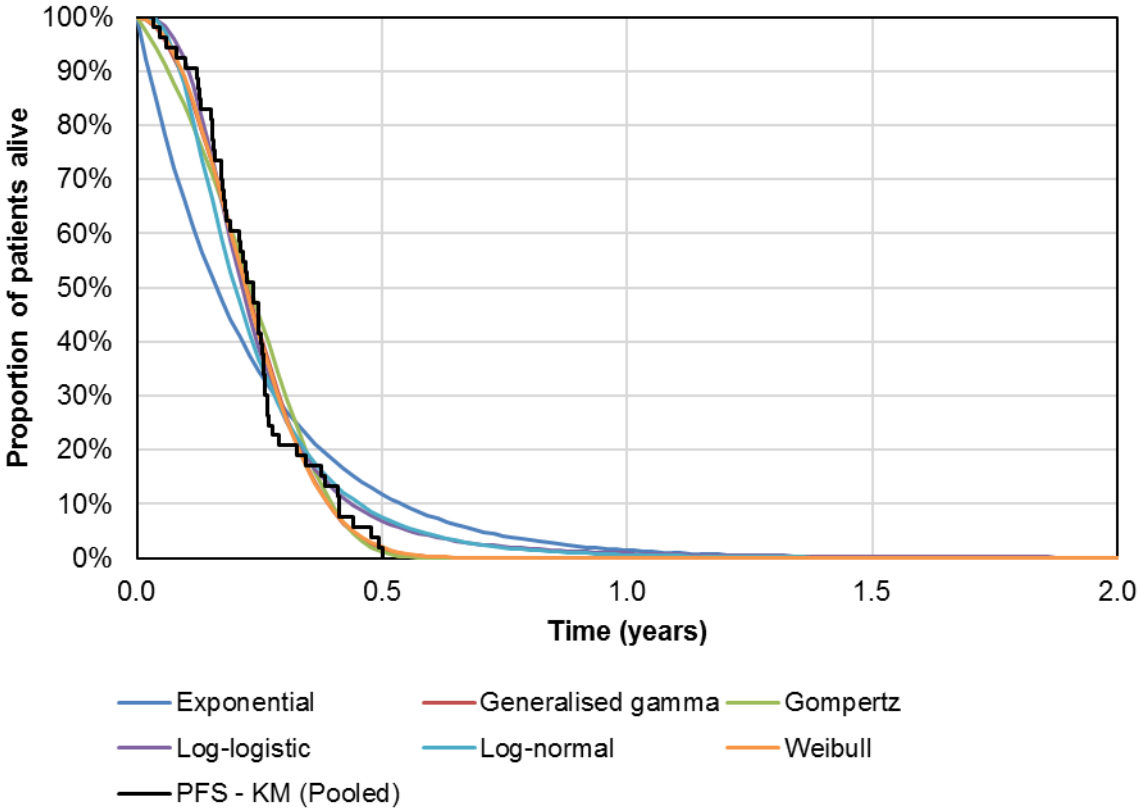


Note: The study by Samlowski et al. contains both treatment-naïve and treatment-experienced patients (Samlowski 2010). This may explain the long-term survival observed in this study.

Abbreviations: MCC: Merkel cell carcinoma; OS: Overall survival

Due to the differences in outcomes (and limited reporting) in the studies identified in the literature (and also the inclusion of first-line patients in the Samlowski study), the base-case in the economic model is the analysis of EU and US observational studies conducted by Merck KGaA/Pfizer (which were then pooled at the patient level after analysis suggested the studies were comparable).These studies have the further advantage that they were similar in study design to JAVELIN Merkel 200 by having similar inclusion/exclusion criteria, and thus likely to have enrolled similar patients (criteria which were unlikely to be met by the literature studies, which would have resulted in unobservable differences). Parametric curve fits for PFS and OS to these data are provided in Figure 43 and Figure 44, with fit statistics are provided in Table 36 and Table 37.

Figure 43: Pooled EU and US treatment-experienced parametric survival curves and Kaplan–Meier plots for PFS



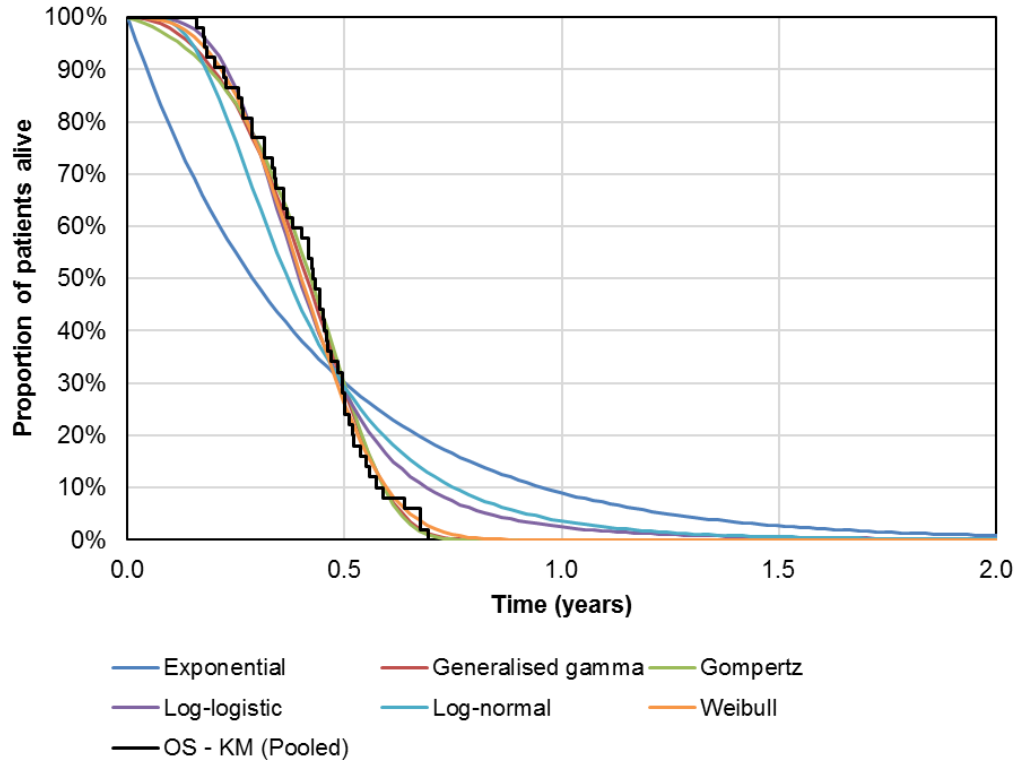
Abbreviations: EU: Europe; KM: Kaplan-Meier; PFS: Progression-free survival; US: United States

Table 36: Statistical goodness of fit for pooled EU and US parametric survival curves for PFS

Model	***AIC (rank)***	***BIC (rank)***
Exponential	590.65 (6)	592.64 (6)
Generalised Gamma	559.30 (2)	565.27 (3)
Gompertz	560.94 (3)	564.92 (2)
Log-logistic	565.25 (4)	569.23 (4)
Log-normal	572.44 (5)	576.42 (5)
Weibull	557.47 (1)	561.45 (1)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; EU: Europe; PFS: Progression-free survival; US: United States

Figure 44: Pooled EU and US treatment-experienced parametric survival curves and Kaplan–Meier plots for OS



Abbreviations: EU: Europe; KM: Kaplan-Meier; OS: Overall survival; US: United States

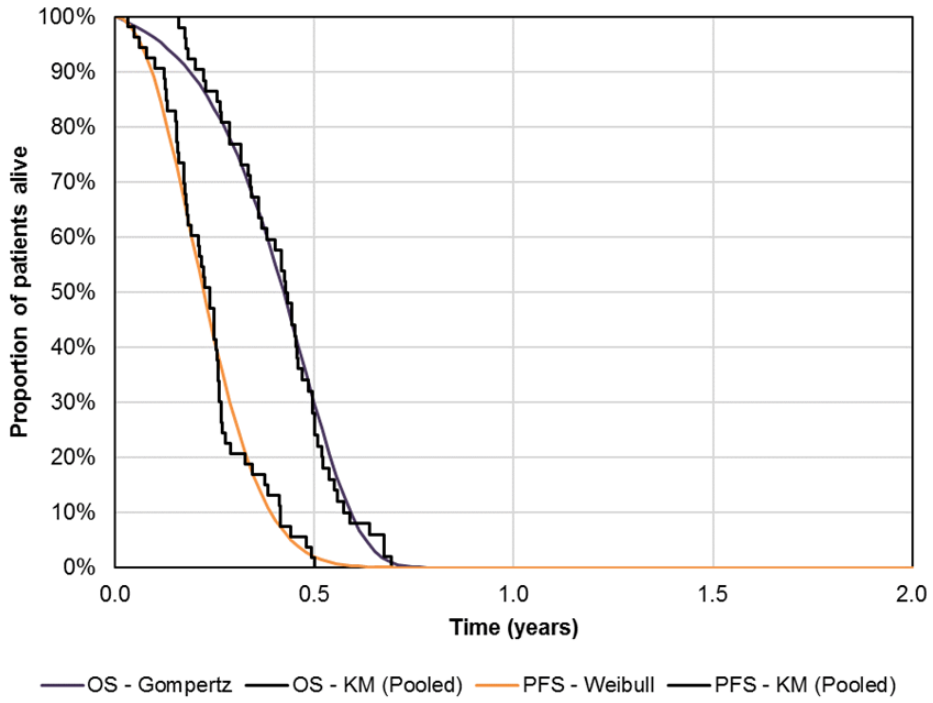
Table 37: Statistical goodness of fit for pooled EU and US parametric survival curves for OS

Model	*AIC (rank)*	*BIC (rank)*
Exponential	628.37 (6)	630.35 (6)
Generalised Gamma	568.65 (2)	574.61 (3)
Gompertz	565.88 (1)	569.86 (1)
Log-logistic	583.17 (4)	587.15 (4)
Log-normal	601.02 (5)	605.00 (5)
Weibull	569.76 (3)	573.74 (2)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; EU: Europe; OS: Overall survival; US: United States

In the base-case of the model, the Gompertz curve was selected for comparator OS, and the Weibull curve was selected for comparator PFS both due to superior visual and statistical fit. These base-case curve fits are presented in Figure 45.

Figure 45: Base-case OS and PFS curves applied – treatment-experienced metastatic MCC (comparator)

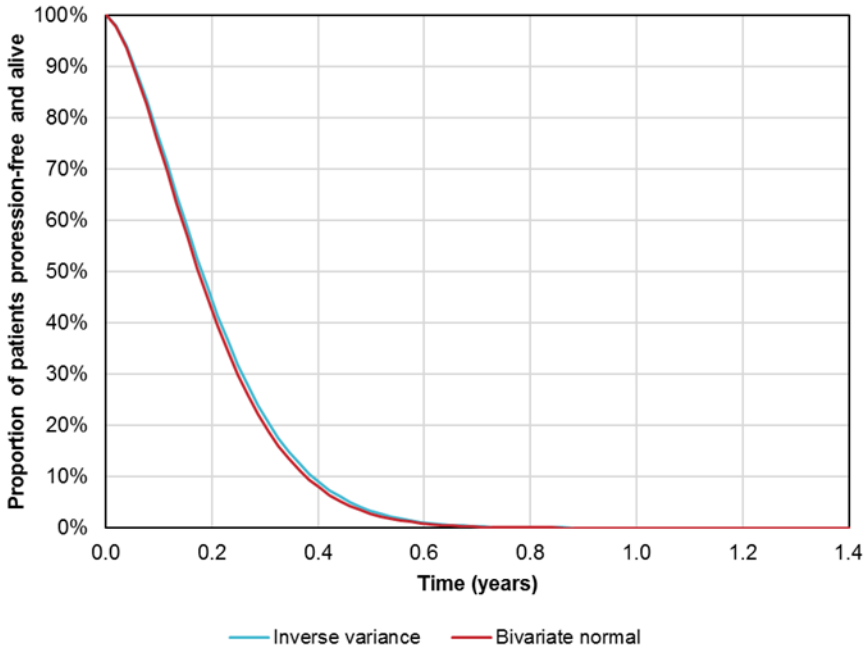


Abbreviations: KM: Kaplan-Meier; MCC: Merkel cell carcinoma; OS: Overall survival; PFS: Progression-free survival

A sensitivity analysis is then performed using the literature data and studies conducted by Merck KGaA/Pfizer, meta-analysed using the method of Ouwens et al. (Ouwens 2010). This is described in full in Appendix 10.

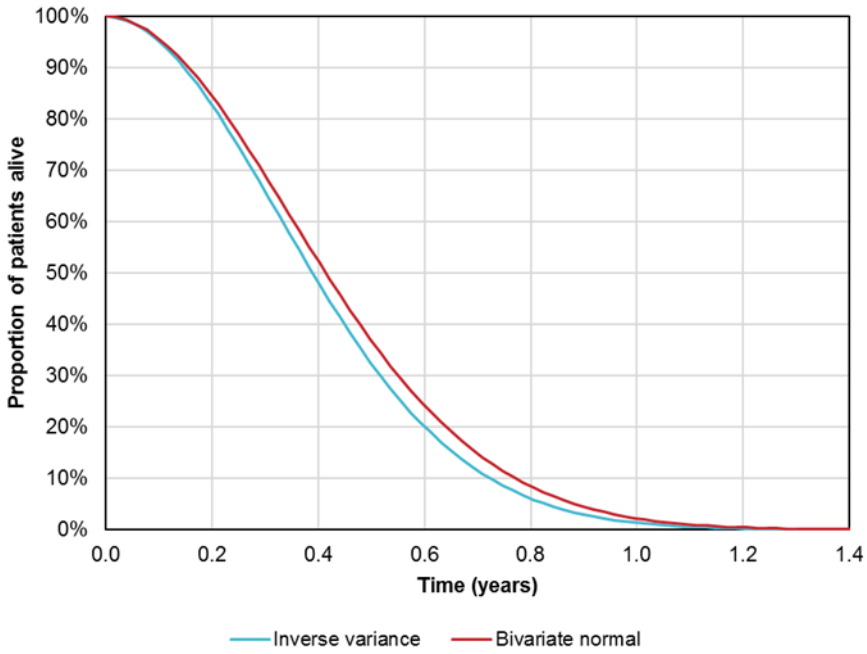
In order to combine data from all of the studies, parametric curve fitting was performed for each study, with the Weibull curve parameters used in analysis. As the Weibull curve has two parameters for each model these parameters were meta-analysed using the method of Arends (2008) – a bivariate normal distribution which accounts for the covariance between the two parameters (Arends 2008). The resulting meta-analysed curves are shown in Figure 46 and Figure 47 for PFS and OS, respectively.

Figure 46: Meta-analysed PFS for treatment-experienced metastatic MCC



Abbreviations: MCC: Merkel cell carcinoma; PFS: Progression-free survival

Figure 47: Meta-analysed OS for treatment-experienced metastatic MCC



Abbreviations: MCC: Merkel cell carcinoma; OS: Overall survival

As patient characteristics are not prognostic of outcomes beyond the line of treatment (as demonstrated in Appendix 10). There is no reason to attempt to match patient characteristics to the JAVELIN Merkel 200 trial using methods such as Matching Adjusted Indirect Comparison (MAIC), or Simulated Treatment Comparison (STC) – to do so would not adjust for bias, and may unintentionally

introduce further bias. This is as matching would be conducted on essentially random variables, introducing a large element of variability to the results.

Full details of the analyses on control data are given in Appendix 10. This includes analysis of the individual patient data collected by Merck KGaA/Pfizer, and literature analysis/synthesis.

Treatment-naïve metastatic MCC patients

For treatment-naïve metastatic MCC patients, an observational study was conducted by Merck KGaA/Pfizer with inclusion criteria similar to the JAVELIN Merkel 200 trial (Merck KGaA 2016a). This study is described in further detail in Section 4.3. The observational study enrolled 67 patients and collected data on PFS and OS. In addition, literature searches identified an additional six sources that contained information on PFS, OS, or both (detail given in Appendix 10) (Iyer 2016; Voog 1999; Satpute 2014; Santamaria-Barria 2013; Fields 2011; Allen 2005). The data described here are summarised in Table 38.

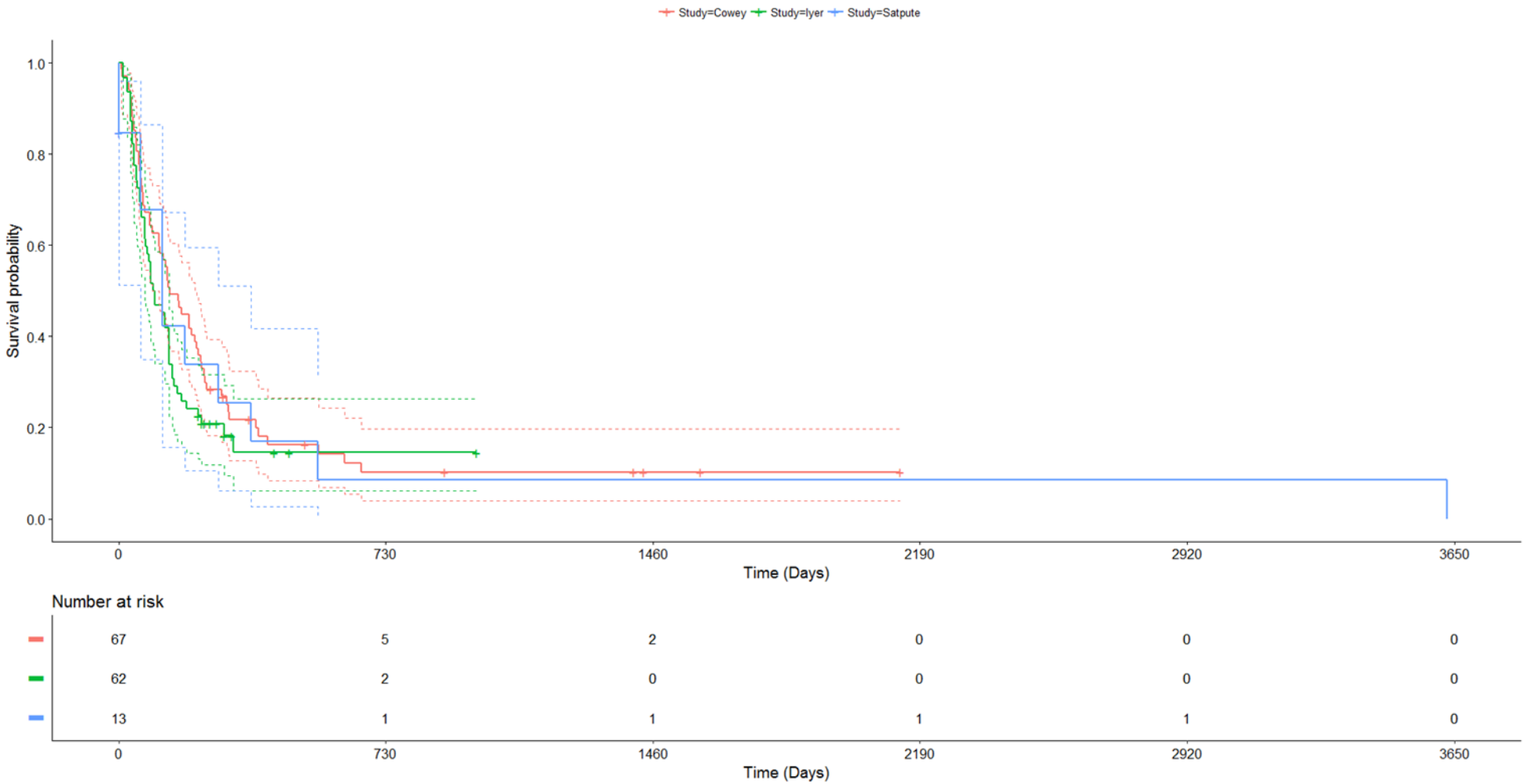
Table 38: Comparator data available for treatment-naïve metastatic MCC patients

Reference	*n*	*PFS*	*OS*	*Patient characteristics*
(Merck KGaA 2016a)	67	Yes	Yes	Yes
(Iyer 2016)	62	Yes	Yes	Yes
(Voog 1999)	101		Yes	Yes
(Satpute 2014)	13	Yes		Yes
(Santamaria-Barria 2013)	15		Yes	
(Fields 2011)	26		Yes	
(Allen 2005)	14		Yes	

Abbreviations: MCC: Merkel cell carcinoma; OS: Overall survival; PFS: Progression-free survival

The PFS and OS Kaplan-Meier curves for each of these studies (where available) are shown in Figure 48 and Figure 49, respectively.

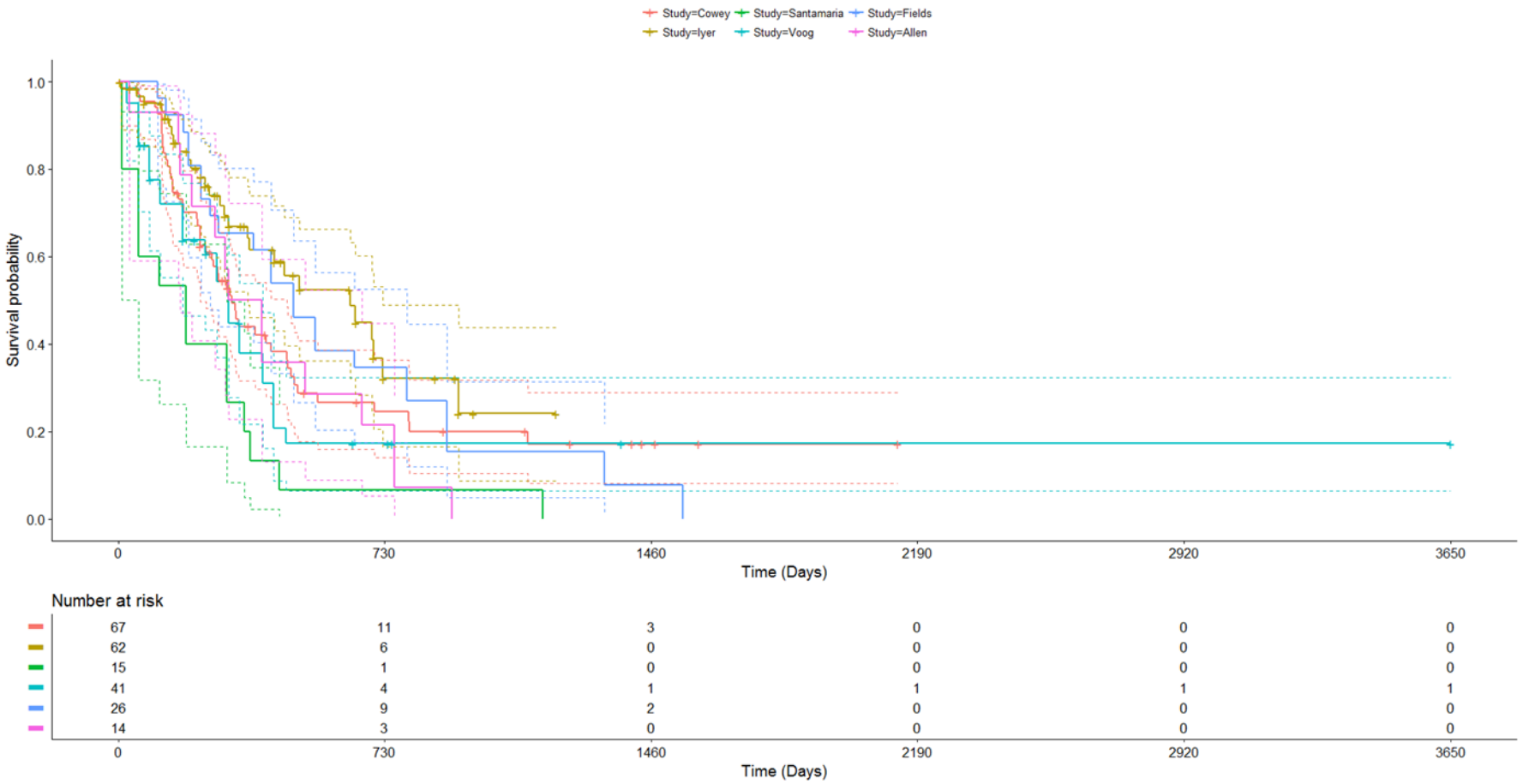
Figure 48: PFS for comparator data in treatment-naïve metastatic MCC patients



Note: Dotted lines represent 95% confidence intervals

Abbreviations: MCC: Merkel cell carcinoma; PFS: Progression-free survival

Figure 49: OS for comparator data in treatment-naïve metastatic MCC patients



Note: Dotted lines represent 95% confidence intervals

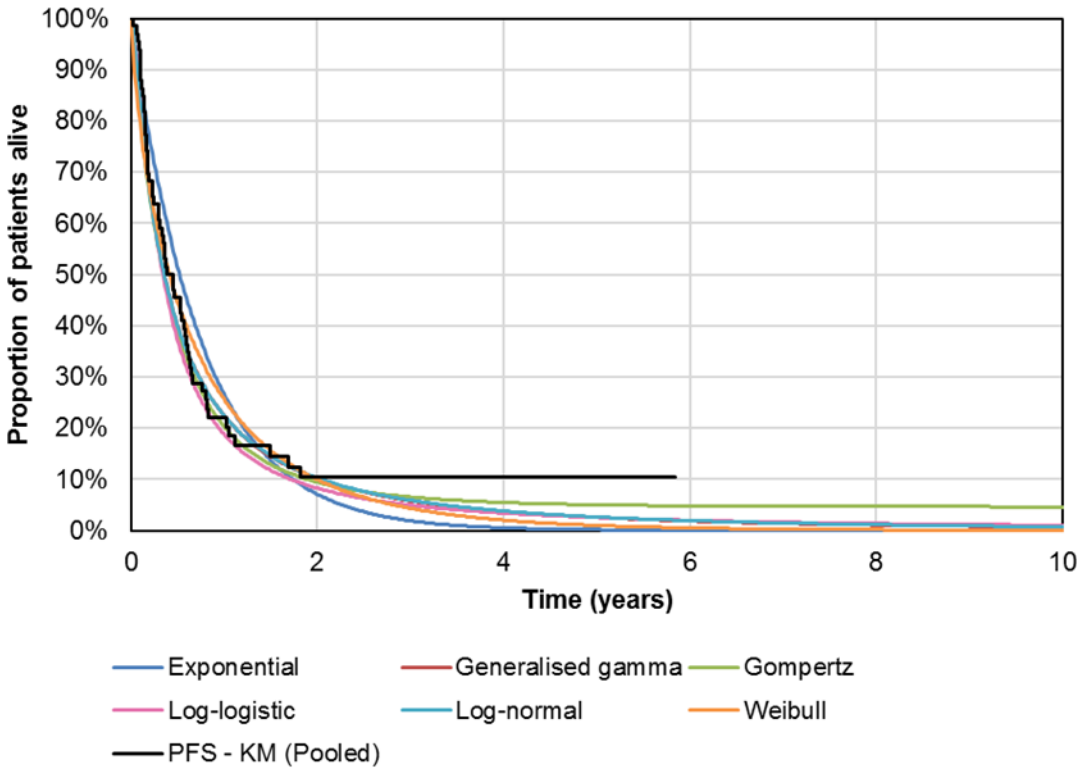
Abbreviations: MCC: Merkel cell carcinoma; OS: Overall survival

PFS and OS data appeared similar between the majority of studies (although studies are not perfectly aligned), with treatment-naïve patients showing substantially better outcomes than treatment-experienced patients and some (albeit few) patients exhibiting durable survival.

Analysis of individual patient data (age, ECOG, gender, immunosuppression status, stage at diagnosis) from the Merck KGaA/Pfizer sponsored study also indicated no patient characteristic of prognostic importance beyond line of therapy based on both regression analysis and visual inspection. Due to the similar outcomes seen (low between study variability) treatment-naïve data from both the Merck KGaA/Pfizer observational study and studies identified in the literature were naïvely pooled and parametric curves fit to inform the base-case analysis in treatment-naïve patients. This results in increased patient numbers for analysis, and likely the most generalisable results

Resulting parametric curve fits for the pooled analysis are presented in Figure 50 and Figure 51 for PFS and OS, respectively, with goodness of fit statistics presented in Table 39 and Table 40.

Figure 50: Pooled (all studies) treatment-naïve parametric survival curves and Kaplan–Meier plots for PFS



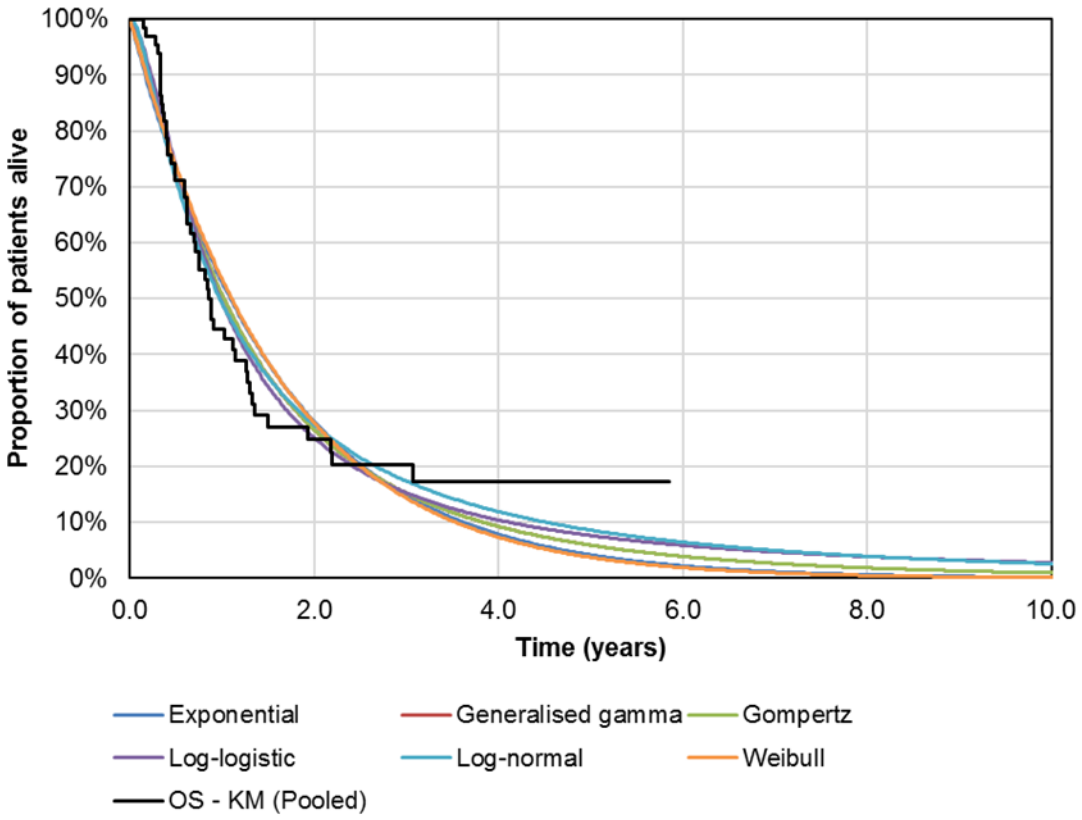
Abbreviations: KM: Kaplan-Meier; PFS: Progression-free survival

Table 39: Statistical goodness of fit for pooled (all studies) treatment-naïve parametric survival curves for PFS

Model	*AIC (rank)*	*BIC (rank)*
Exponential	1604.12 (6)	1607.08 (6)
Generalised Gamma	1561.53 (4)	1570.40 (4)
Gompertz	1557.71 (2)	1563.62 (2)
Log-logistic	1548.58 (1)	1554.49 (1)
Log-normal	1559.54 (3)	1565.46 (3)
Weibull	1585.73 (5)	1591.64 (5)

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: Progression-free survival

Figure 51: Pooled (all studies) treatment-naïve parametric survival curves and Kaplan–Meier plots for OS



Abbreviations: KM: Kaplan-Meier; OS: Overall survival.

Table 40: Statistical goodness of fit for pooled (all studies) treatment-naïve parametric survival curves for OS

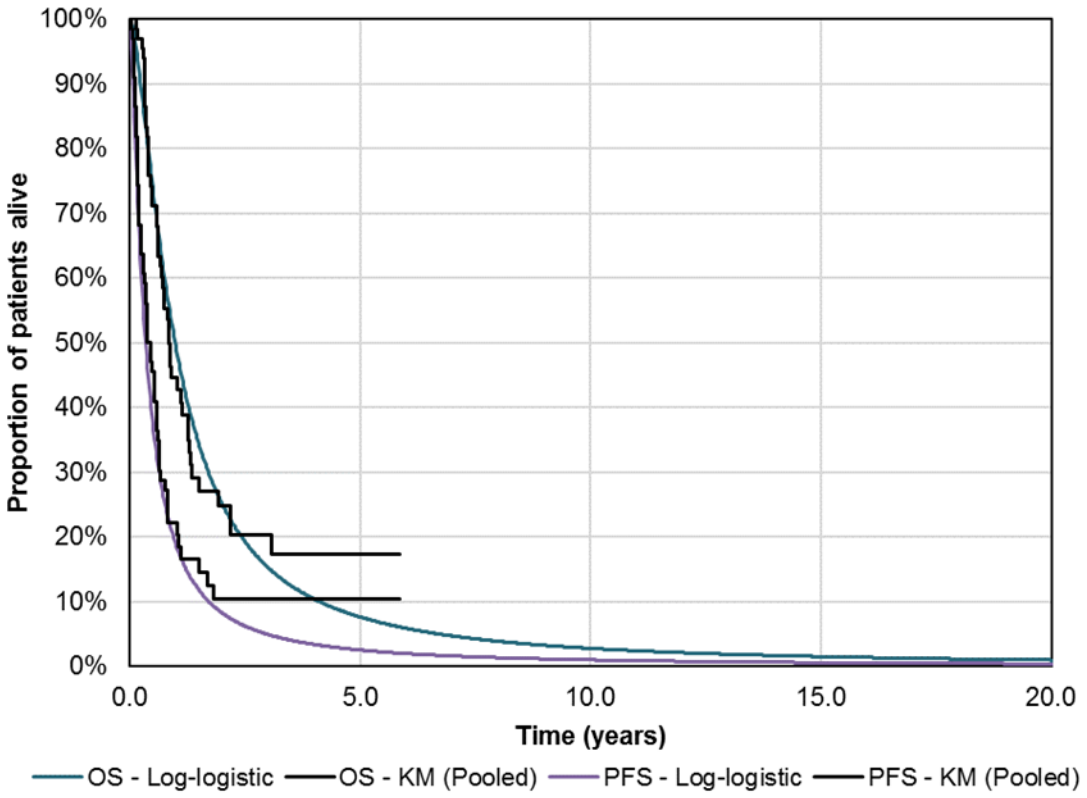
Model	*AIC (rank)*	*BIC (rank)*
Exponential	2,712.22 (4)	2,715.63 (4)
Generalised Gamma	2,699.20 (2)	2,709.45 (3)
Log-logistic	2,688.73 (1)	2,695.56 (1)
Log-normal	2,700.11 (3)	2,706.95 (2)
Weibull	2,714.03 (5)	2,720.86 (5)

Note: For OS, the Gompertz model did not converge hence is not presented.

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival

In the base-case model, the log-logistic model was used as this had the best statistical fit (according to AIC and BIC) and a good visual fit for both PFS and OS – clinician opinion also indicated that they seemed plausible. These base-case curve fits are presented in Figure 52.

Figure 52: Base-case OS and PFS curves applied – treatment-naïve metastatic MCC (comparator)



Abbreviations: KM: Kaplan-Meier; MCC: Merkel cell carcinoma; OS: Overall survival; PFS: Progression-free survival

Though the analysis described above considers a broad variety of data sources, patient-level data were not available for all studies and therefore the ability to explore the potential impact of prognostic factors was limited. Despite this all available patient characteristics and descriptions indicated the studies would be expected to have enrolled similar patients. As shown in Appendix 10, the data demonstrate that no observed patient characteristic is predictive of outcome (the reason for the pooling of the treatment-naïve data). For this reason, no statistical adjustments (such MAIC or STC) were attempted to match the data to JAVELIN Merkel 200 – and naïve comparisons between studies are consider reasonable.

5.3.4 Best supportive care: overall survival and progression-free survival

There is no literature which describes the outcomes of treatment-experienced or treatment-naïve metastatic MCC patients who are treated with BSC.

For treatment-experienced patients, clinical expert opinion at the advisory board and a one-to-one clinical validation meeting held with [redacted] both suggested that broadly the same survival outcomes were seen regardless of which treatment is given (BSC or chemotherapy). [redacted] emphasised the importance of stating that these data are the best proxy to use in the absence of data for patients treated with BSC, and that based on the data shown, there is no reason to believe that patients not receiving chemotherapy would perform significantly better or worse.

For treatment-naïve patients, a similar approach was used whereby data for chemotherapy were used to reflect outcomes for patients treated with either chemotherapy or BSC (Merck KGaA 2017d). For these patients this is an inherently conservative approach, as, in this cohort, chemotherapy is considered to have a beneficial effect on patient outcomes.

On this basis, comparisons versus BSC in the base-case for both patient cohorts rely on the chemotherapy data (described above and in Appendix 10). Although this is likely to bias against avelumab where BSC is a relevant comparator (as patients receive the benefits of chemotherapy, but not the costs) this is unlikely to be large. The reason is as the chemotherapies used are generic, unlikely to be used for a long period of time, or have substantive efficacy.

5.3.5 Chemotherapy and best supportive care: Time on treatment

The model assumes that up to a maximum of six treatment cycles for chemotherapy regimens can be given for patients with metastatic MCC for both treatment-experienced and treatment-naïve cohorts, and that a relative dose intensity (RDI) of two-thirds is most likely to apply (Merck KGaA 2017d). These assumptions have a clinical basis, with further discussion provided in Section 5.5.2.

For patients receiving BSC, no ToT data are required as no active treatment is administered. Details of the medical resource use patients incur as part of BSC are presented in Section 5.5.3.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

HRQL was assessed for patients at baseline, Week 7, every 6 weeks thereafter, and at the end-of-treatment visit in the JAVELIN Merkel 200 trial via the EQ-5D-5L questionnaire. The application of HRQL in the model is based on data for treatment-experienced patients in JAVELIN Merkel 200 (i.e. data from Part A), for both cohorts modelled (i.e. both treatment-experienced and treatment-naïve patients share the same health-state utility values). This was due to the immaturity and small sample size of the treatment-naïve cohort. The latest HRQL data from the 03 September 2016 data cut (minimum 12-months follow-up) was used for this analysis.

The EQ-5D encapsulates five domains of HRQL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and the 5L version has five levels for each domain: no problems, slight problems, moderate problems, severe problems and extreme problems or inability. The use of EQ-5D as a generic, preference-based HRQL measure aligns with the NICE reference case requirements (NICE 2013).

A description of the statistical methods used for analysing utility data are provided in Section 5.4.5. In this approach, there is no utility benefit attributed specifically to treatment with avelumab over standard care.

5.4.2 Mapping

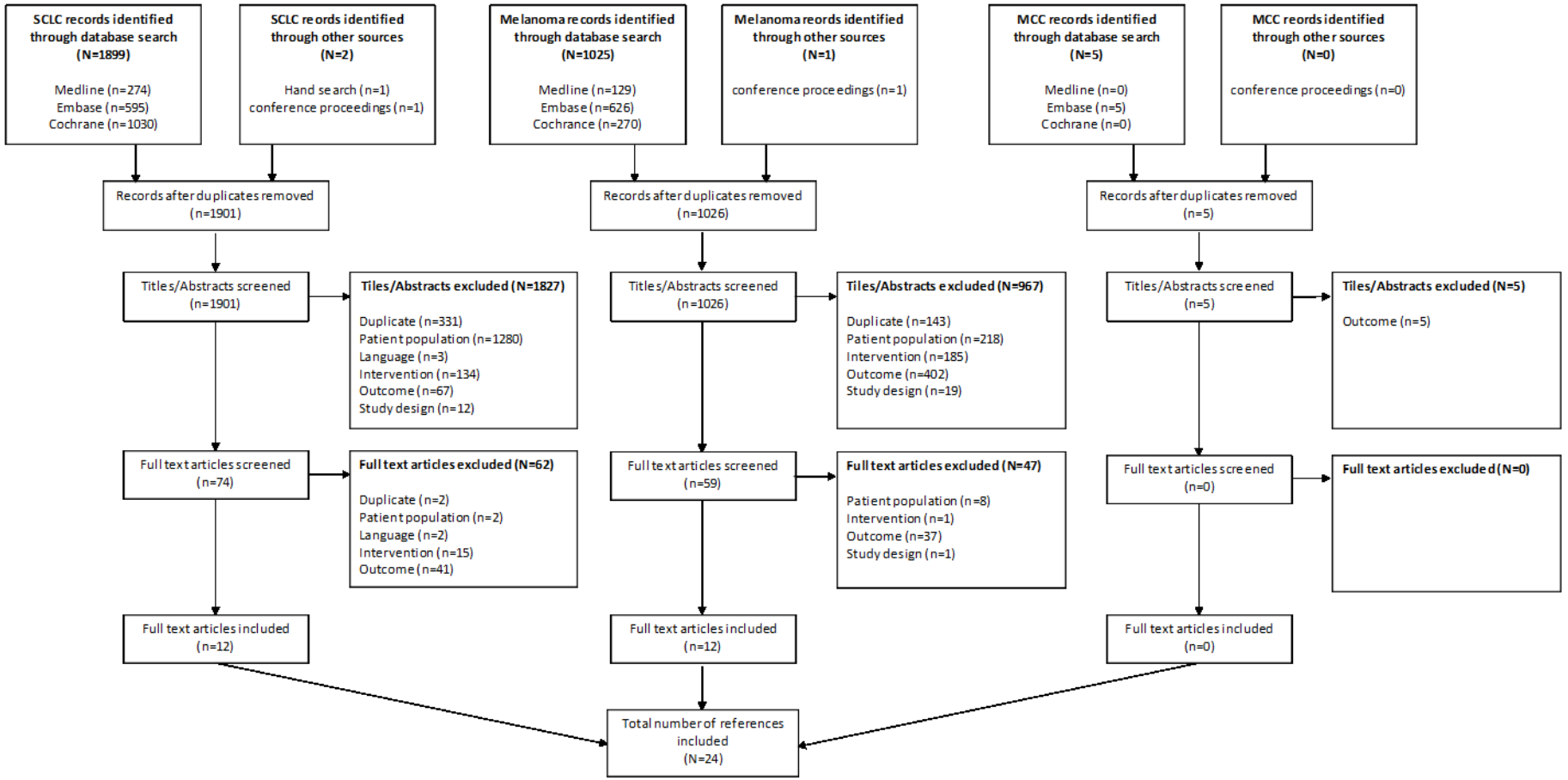
The EQ-5D-5L questionnaire was administered to patients in the JAVELIN Merkel 200 trial. As the value set for this HRQL measure has not been validated in the UK, the 'crosswalk' algorithm was used to convert EQ-5D-5L to EQ-5D-3L values (van Hout 2012). This algorithm converts EQ-5D-5L responses to UK EQ-5D-3L values, which are then used in analysis.

5.4.3 Health-related quality-of-life studies

An SLR was conducted to identify evidence on the HRQL of MCC patients. The same databases and conference proceedings were searched as with the search for previous cost-effectiveness studies. The search was originally performed on 28th July 2016 and subsequently updated on 16th May 2017. Due to the rarity of metastatic MCC and lack of published data, the search was broadened to include HRQL evidence for patients with SCLC or melanoma These other conditions were also included in anticipation of a dearth of literature on MCC and due to the similarities of SCLC and MCC in later stages of the disease. Full details of the search are provided in Appendix 12. The PRISMA diagram in Figure 53 presents the flow of studies identified in the HRQL review.

In total, 24 records were selected for data extraction (Appendix 13); however, no studies identified provided useful information on utilities for patients with metastatic MCC. Although HRQL data for patients with SCLC and melanoma were identified, it was agreed that caution should be exercised when comparing the HRQL for patients with these tumour types to metastatic MCC due to differences in demographics/characteristics and disease features. For instance, melanoma patients tend to be much younger than metastatic MCC patients, and the location of the disease varies and may considerably impact symptom burden. Therefore, it was suggested that there is no robust analogue disease area for MCC in terms of symptom burden and HRQL aspects. However, due to lack of information, data identified on AE prevalence for chemotherapy regimens, and disutility from non-metastatic MCC sources were utilised as the next best available approach. This is discussed further in Section5.4.4.

Figure 53: PRISMA diagram for identified HRQL studies



Abbreviations: HRQL: Survival-adjusted health-related quality of life, MCC: Merkel Cell Carcinoma, SCLC: Small Cell Lung Cancer

5.4.4 Adverse reactions

The impact of TRAEs on the HRQL of patients, and the costs incurred for associated treatment were incorporated into the economic model for all patients on treatment (determined by the time on treatment curve). For avelumab, AE rates in the model for both treatment-naïve and treatment-experienced cohorts were based on those reported in the JAVELIN Merkel 200 trial for the treatment-experienced cohort (Kaufman 2016c). For all chemotherapy regimens, data were extracted from studies identified in the SLR for each treatment matching patient characteristics, such as age and ECOG performance status as closely as possible with patients from the JAVELIN Merkel 200 trial.

Where evidence for the chemotherapies' use in metastatic MCC was unavailable, evidence related to their use in the treatment of small-cell lung cancer (SCLC) has been used as the best proxy for likely AE rates due to similarities in the neuroendocrine properties between the two diseases. Where SCLC data were unavailable, melanoma data have been used as a suitable alternative in the absence of more appropriate data, a fact that was supported by clinical experts as the issue of severe lack of data was broadly acknowledged (Merck KGaA 2017d).

A targeted review of previous NICE submissions was used to address AE duration data gaps, AE durations were subsequently validated by clinicians in England during an advisory board. Full details of the safety SLR are provided in Appendix 14. Evidence sources were identified for the prevalence of AEs (Socinski 2009; Flaherty 2013; Sun 2016; Dimitroulis 2008; Gervais 2015; McIllmurray 1989; O'Day 2013; Batchelor 2001; von Pawel 2014; Mau-Soerensen 2014), for the disutility values associated with AEs (Beusterien 2010; Doyle 2008; Nafees 2008; Ossa 2007; Tachi 2015; Tam 2013; Tolley 2013), and for the expected duration of AEs (NICE 2014a; NICE 2016b; NICE 2016d).

Disutilities due to the occurrence of TRAEs were included within the economic model if the TRAE occurred in ≥5% of patients in any treatment arm with a severity of either Grade 3 or 4. No AEs meeting these criteria were recorded as occurring in ≥5% of patients in the JAVELIN Merkel 200 trial, demonstrating avelumab's advantageous safety profile compared with the safety profiles associated with the chemotherapies that may be administered at this stage of disease.

The most commonly observed AEs for avelumab patients were increased liver enzymes and lymphopenia, occurring in 1% and 2% of patients, respectively. This is in contrast to typical chemotherapy regimens, which are commonly associated with anaemia, leucopenia, neutropenia, thrombocytopenia, fatigue and hair loss (Socinski 2009; Flaherty 2013; Sun 2016; Dimitroulis 2008; Gervais 2015; O'Day 2013; von Pawel 2014). The absence of Grade 3 or 4 AEs contributes to higher utility values for avelumab-treated patients versus those who may be treated with chemotherapy. Patients treated with BSC do not experience any AEs related to drug treatment.

As a result of the paucity of data to inform HRQL within the model for alternative treatment regimens, it has been assumed that non-AE adjusted health state utility values are the same across treatment arms (that is, the utility for a patient treated with chemotherapy with >100 days to live has the same utility as if the patient were treated with avelumab). Therefore, patients treated with BSC are assumed within the model to maintain higher HRQL (as a result of no TRAEs) compared with those treated with avelumab or chemotherapy. Though this application of utility values within the model fails to quantify the true benefit of treatment with avelumab in terms of HRQL versus BSC, the approach represents the most conservative application in consideration of the data available to inform this appraisal.

QALY decrements were calculated using AE prevalence, disutility and duration. These QALY decrements are applied only to patients on treatment – determined by the time on treatment curve. The probability of experiencing an AE per model cycle for each treatment was calculated using the following method:

- Grade 3 or 4 AEs occurring in > 5% of avelumab or chemotherapy combination-treated patients were included in the model
- These AEs are the most likely to have the largest impact on costs and utility losses.
- For simplicity, and a lack of data to suggest otherwise, it was assumed that AE prevalence is the same for patients whether they are treatment-experienced or treatment-naïve
- Furthermore, it was also assumed that any AEs for chemotherapy patients that were not reported in studies identified in the SLR had 0% prevalence
- Hair loss, although not a Grade 3 or 4 AE, was also included due to the large impact on patient (particularly female) utility.

For all patients treated with either avelumab or chemotherapy, QALY decrements associated with AEs were applied only to patients receiving active treatment. For chemotherapy, the decrements for each separate chemotherapy regimen were weighted according to their proportionate use. It was assumed that AEs are experienced at the same rate during the period over which patients receive treatment.

Full details of the calculations undertaken to derive AE rates for each modelled treatment are provided in Appendix 15.

Adverse event disutilities per event are presented in Table 41. The overall QALY decrements were applied per AE at each model cycle (i.e. per week while on treatment) are presented in Table 42. AE QALY decrements per model cycle by treatment are provided in Table 43. Table 44 provides the final QALY decrement per cycle weighted according to proportions of chemotherapy regimens used.

Table 41: Adverse event disutilities sourced from literature

Adverse event	***Mean***	***SE***	***Reference***
Anaemia	-0.090	0.020	Fatigue (Nafees 2008)
Dyspnoea	-0.050	0.012	Febrile Neutropenia (Nafees 2008)
Fatigue	-0.073	0.018	Fatigue (Nafees 2008)
Febrile Neutropenia	-0.090	0.016	Febrile Neutropenia (Nafees 2008)
Low haemoglobin	-0.080	0.016	Mild Anemia (Ossa 2007)
Hyponatremia	-0.090	0.015	Assume as Neutropenia
Infections	-0.120	0.012	(Tachi 2015)
Leukopenia	-0.090	0.015	Assume as Neutropenia
Lymphopenia	-0.090	0.015	Assume as Neutropenia
Muscle pain	-0.048	0.016	Assume as Nausea/vomiting
Nausea/Vomiting	-0.048	0.016	Nausea/vomiting (Nafees 2008)
Neutropenia	-0.090	0.015	Neutropenia (Nafees 2008)
Low platelets	-0.090	0.015	Assume as Neutropenia
Sensory neuropathy	-0.226	0.023	Assume neuropathy (Tam 2013)
Thrombocytopenia	-0.108	0.010	Thrombocytopenia (Tolley 2013)
Hair loss (any grade)*	-0.045	0.015	Hair Loss (Nafees 2008)

Notes: *Applied only to females.

Abbreviations: SE: Standard error

Table 42: Model cycle quality-adjusted life year decrement per adverse event, weighted by duration

AE	*QALY Decrement*
Anaemia	-0.0362
Dyspnoea	-0.0201
Fatigue	-0.0296
Febrile neutropenia	-0.0069
Low haemoglobin	-0.0322
Hyponatremia	-0.0033
Infections	-0.0343
Leucopenia	-0.0033
Lymphopenia	-0.0033
Muscle pain	-0.0066
Nausea/vomiting	-0.0028
Neutropenia	-0.0033
Low platelets	-0.0033
Sensory neuropathy	-0.1529
Thrombocytopenia	-0.0493
Hair loss (any grade)*	-0.0037

Notes: *Applied only to females.

Abbreviations: AE: Adverse event; QALY: Quality-adjusted life year

Table 43: Adverse event quality-adjusted life year decrements per cycle, by treatment

	Anaemia	*Dyspnoea*	*Fatigue*	*Febrile Neutropenia*	*Low haemoglobin*	*Hyponatremia*	*Infections*	*Leucopenia*	*Lymphopenia*	*Muscle pain*	*Nausea/ vomiting*	*Neutropenia*	*Low platelets*	*Sensory neuropathy*	*Thrombocytopenia*	*Hair loss (any grade)*
Avelumab									-0.000004							
Carboplatin + etoposide	-0.000154		-0.000052	-0.000018		-0.000002		-0.000016			-0.000001	-0.000113			-0.000296	-0.000413
Carboplatin + paclitaxel			-0.000315	-0.000019	-0.000157	-0.000005		-0.000056	-0.000010	-0.000025		-0.000144	-0.000020	-0.001631		-0.000494
Cisplatin + etoposide	-0.000185				-0.000130			-0.000052			-0.000014	-0.000137			-0.000277	-0.000191
Cisplatin + paclitaxel												-0.000039			-0.000060	-0.000765
Cyclophos-phamide + doxorubicin + vincristine	-0.000237										-0.000007	-0.000075			-0.000528	-0.002034
Paclitaxel	-0.000107	-0.000059	-0.000058								-0.000009	-0.000016				-0.001953
Doxorubicin + liposomal doxorubicin	-0.000237										-0.000004	-0.000075			-0.000528	-0.002271
Topotecan	-0.000985	-0.000105	-0.000293	-0.000016		-0.000014	-0.000266	-0.000061				-0.000182			-0.002783	-0.002919

Table 44: Total adverse event quality-adjusted life year decrement per cycle

Treatment	***Decrement***
Total avelumab	-0.000004
Total chemotherapy*	-0.001026
Total BSC	0.000000

Note: * Chemotherapy regimen dependent, base case: 50% carboplatin + etoposide, 50% cisplatin + etoposide

Abbreviations: BSC: Best supportive care

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

In the JAVELIN Merkel 200 trial, EQ-5D-5L data were collected at 6-weekly intervals. In total, 362 observations were collected from 71 patients. While this represents a substantial amount of data, EQ-5D-5L data were only collected while patients were receiving avelumab treatment, resulting in limited measurements in the post-progression setting. This is a common limitation of HRQL data in trials of oncology medications.

At baseline, average EQ-5D-5L utility scored via the crosswalk to EQ-5D-3L values was [redacted]. Considering median age at baseline, this utility value is comparatively high relative to general population utility. This may be explained by the expectation by patients that treatment will provide durable responses and long-term survival, as has been previously hypothesised to impact HRQL in previous NICE STAs of immuno-oncology therapies, though this is unclear (NICE 2016e). Furthermore, clinicians during an advisory board felt that these high utilities could be explained by the euphoria patients feel from less visible lesions on the skin and the impact a more effective and promising medicine may have on improving a patient's depression.

Given its ultra-rare disease classification, no data were identified as part of the SLR regarding the HRQL of metastatic MCC patients, and as such, validation of utility values against external data sources was not possible. However, EQ-5D data from the trial represent the "gold standard" of HRQL data to inform submissions of economic evidence to NICE and as such, these data were deemed most appropriate to inform the economic model.

Following an assessment of the options, the following approaches were available to incorporate trial utility data in the economic model:

- Utilities analysed by time to death, which is applied to patients treated with avelumab, chemotherapy or BSC (i.e. treatment independent). This approach has been used in previous appraisals of immunotherapy, most notably ipilimumab
- Data from the analysis of pre- and post-progression utilities from JAVELIN Merkel 200 trial. This approach is limited as the only post-progression values available are from patients receiving avelumab beyond progression (as utility was only collected whilst on treatment). As patients treated beyond progression are likely to have been judged to be responding by clinicians (the reason for continuing treatment), there may be some bias in these measures
- Data for pre-progression utility from the JAVELIN Merkel 200 trial with the application of a decrease in utility over time obtained from the literature to represent expected post-

progression utility decrement (O'Brien 2006)†††.Whilst sub-optimal, this allows the use of the pre-progression utilities from the JAVELIN Merkel 200 trial, with decrements taken from related literature

Time to death approach

EQ-5D-5L data were scored using the recommended 'crosswalk' algorithm between the EQ-5D-5L and EQ-5D-3L, to produce utility values (van Hout 2012). Data from the JAVELIN Merkel 200 trial were subsequently analysed using generalized estimating equation (GEE) regression. This technique accounts for multiple observations per patient (of which there are up to a maximum of 20), whereas simple means or Ordinary Least Squares (OLS) regression would produce biased results by not accounting for correlation between values at the patient level.

Due to the lack of quality of life data in the condition (and the limited numbers of patients treated by individual clinicians), it was not immediately clear what pattern utility values would take – with potentially multiple drops in utility as a patient approaches death. For this reason, models were constructed using up to three time periods before death

In order to estimate the appropriate time periods for each model, the "optim" function in R was used to identify the parameters (in this case the number of days before death observations were taken) to minimise the mean absolute error of the predicted utility. The result of the optimisation was groups of 30 days before death, and 30-100 days before death – whilst these are round numbers, this is as a direct result of the minimize function, and not artificially imposed.

Where observations were taken in the last 100 days before censoring (not necessarily death), these were assumed to fall in to the group furthest from death. Whilst the use of an algorithm to derive health states is novel (as opposed to clinician informed groupings), the results have face validity as they show a higher utility decrement in the final 30 days of life than for patients with between 30 days and 100 days to live, this improves over the use of the regression analysis which suggests a non-linear decrement in HRQL as patients approach the end of their lives. Furthermore, the groupings are driven by the best fit to the data and not subjective clinician views of the appropriate time period. The groupings have been discussed with a clinician who confirmed that whilst appearing arbitrary, they seem reasonable in light of the end of life experiences of these patients.

Results of the regression analysis of the time to death groups are presented in Regression 1 giving the coefficients and standard errors around the estimates.

Regression 1: Utility by time to death groups

```
Coefficients:
                          Estimate Std.err  Wald             Pr(>|W|)
(Intercept)               0.7744   0.0201   1447.87  <2e-16 ***
30 - 100         -0.0204  0.0304   0.45             0.502
<30                       -0.0662  0.0307   4.66             0.031 *
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Estimated Scale Parameters:
```

††† As no reliable and valid post-progression utility data could be identified for metastatic MCC patients (Section 5.4.3), SCLC utility values were used in the absence of suitable alternatives (Merck KGaA 2017d). Utilities were identified from O'Brien et al. (O'Brien 2006). Whilst from an unvalidated disease area, this provides a sensitivity analysis for utility data using the 'standard' pre- and post-progression utility approach.

```
                        Estimate Std.err
(Intercept)             0.0251   0.0044

Correlation: Structure = independence
Number of clusters: 71    Maximum cluster size: 15
```

Progression status approach

A linear mixed regression model was used to predict utility values according to disease progression status. The resulting model incorporates AE disutilities (unadjusted model). A further analysis was performed that adjusted for AE disutilities (adjusted model), which was applied within the model for patients treated with either BSC or chemotherapy so that AE utility decrements associated with avelumab were not applied to patients receiving other treatments.

Health state utility values applied in the model are presented in Table 45. Further details of the progression status approach are provided in Appendix 10.

Table 45: Summary of utility values for cost-effectiveness analysis

State	*Utility value: mean (SE)*	*Justification*
Progression-free	[redacted]	JAVELIN Merkel 200 patient-level data analysis
Post-progression	[redacted]	

Abbreviations: SE: Standard error

Progression status with external post-progression data approach

An alternative approach was taken for the estimation of post-progression utility using the results of a study by O'Brien et al. (O'Brien 2006). The study considered patients treated with BSC (+ topotecan) in SCLC, and reported a daily percentage change in utility upon progression of -0.056%. Using average durations of PFS and OS from the O'Brien study (of 16.3 and 23.3 weeks, respectively), an estimated percentage adjustment of 91.27% of pre-progression utility was calculated and subsequently applied.

Based on a progression-free utility of [redacted] (shown in Table 45), this equates to a utility of [redacted] for post-progression disease (similar to the value shown in Table 45 of [redacted]). As such, this approach provides an alternative application of progression-based utilities and is further explored in scenario analyses.

Summary of base-case approach

In the base-case we have utilised time to death utilities. This method is considered to be a robust approach in the context of this decision problem for several reasons. First, relatively fewer measures of the EQ-5D-5L are available for patients beyond progression compared to those with progression-free disease, and as such this approach has the advantage of considering the totality of utility evidence available without limiting analysis to progression status. Secondly as only patients on treatment had values taken beyond progression, the use of progression-based utilities may over-estimate the HRQL of patients who are in poor health – the use of time to death utilities sidesteps this issue by linking utility to a patient's health directly.

A previous study has noted that within the context of advanced or metastatic melanoma "analysis solely by progression status may not capture all predictive factors of patient utility and time to death may, as death approaches, be as or more important." (Hatswell 2014). Furthermore, the method has

been applied in a number of recent NICE STAs, particularly in the assessments of immuno-oncology therapies (NICE 2017c; NICE 2014b; NICE 2016a).

Given the immaturity of the utility data in the treatment-naïve cohort in JAVELIN Merkel 200, time-to-death utilities generated from the treatment-experienced analysis are applied in the treatment-naïve model too, i.e. it has been assumed that treatment-naïve patients would have at least the same HRQL as treatment-experienced patients. This is likely to be a conservative assumption given that equivalent patients treated at an earlier line are expected to be fitter and have improved prognosis versus those treated at later lines.

In summary, we have taken a comprehensive look at the alternative ways to approach utility analyses, however, all methods used make use of the "gold-standard" of EQ-5D data taken directly from the JAVELIN Merkel 200 trial.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

An SLR was conducted to identify all literature reporting resource use and/or unit costs for the comparators of interest among patients with metastatic MCC. The SLR was conducted alongside the SLR for previous cost-effectiveness studies originally performed on 28th July 2016 and subsequently updated on 16th May 2017. In anticipation of this review, and expecting that evidence pertaining to metastatic MCC would be limited as it is an ultra-rare disease, we asked clinical experts whether there were disease analogues that we could include in the search.

Clinicians present at the advisory board were in agreement that the pathology of metastatic MCC is similar to SCLC. Therefore, the search was broadened to studies reporting SCLC costs and resource use. We also included melanoma, however, cost and resource use data for patients with melanoma were only used where no data were identified in either metastatic MCC or SCLC patients. The search for cost and resource use studies was conducted using the same databases as for previous cost-effectiveness studies described in Section 5.1. Full details of the search are provided in Appendix 7.

Eligibility criteria are outlined in Table 46 to Table 48. The PRISMA diagram for identified cost/resource use studies is presented in Figure 54.

Table 46: Eligibility criteria for cost and resource use studies in metastatic MCC

Inclusion criteria		***Rationale***
Population	Age: adults aged ≥18 years Gender: any Ethnicity: any Disease: metastatic MCC	Consistent with the evidence base for avelumab and the anticipated marketing authorisation.
Interventions/Comparators	Any pharmacological treatment	This allows all relevant evidence to be identified
Outcomes	Cost-effectiveness, direct/indirect costs, resource use, BSC costs, costs, life years, QALYs, ICERs	The aim of the review was to identify relevant costs and data on resource use
Study design	Cost-effectiveness analyses, cost-minimisation analyses, cost-utility analyses, cost/burden of illness, costing studies	The aim of the review was to identify relevant costs and use of resources
Limits	No language restrictions	With limited data in MCC, all languages were included to identify all published literature
Exclusion criteria		
Intervention/Comparators	Studies exclusively focusing on the role of radiotherapy, chemo-radiotherapy, hormonal therapy, diagnostics, screening or surgery Studies investigating the role of maintenance/consolidation therapy after surgery Adjuvant or neo-adjuvant therapy Does not include chemotherapy regimens that are listed as comparators	In line with the anticipated NICE scope, studies were restricted to those evaluating the efficacy of comparators. Comparators were restricted to chemotherapies and BSC.
Population	Studies that included children and adults and did not provide subgroup analysis for the adult populations	Consistent with the avelumab evidence base
Outcomes	No relevant costs or resource use	Not part of the aims of the literature search
Study design	Systematic literature reviews and meta-analyses	Studies from systematic literature reviews and meta-analyses were cross checked to ensure all relevant publications were identified
Country	No country restriction	Review was kept broad considering the limited data

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; MCC: Merkel cell carcinoma; QALY: Quality-adjusted life year

Table 47: Eligibility criteria for cost and resource use studies in SCLC

Inclusion criteria		***Rationale***
Population	Age: adults aged ≥18 years Gender: any Ethnicity: any Disease: SCLC with an ECOG status of 0-1	Consistent with the evidence base for avelumab and the anticipated marketing authorisation
Interventions/Comparators	topotecan cyclophosphamide + doxorubicin + vincristine carboplatin + etoposide cisplatin + etoposide carboplatin alone carboplatin + paclitaxel cisplatin + paclitaxel doxorubicin liposomal doxorubicin paclitaxel pembrolizumab	Interventions were identified from an observational study as likely treatment options for patients with metastatic MCC.
Outcomes	Cost-effectiveness, direct/indirect costs, resource use, BSC costs, costs, life years, QALYs, ICERs	The aim of the review was to identify relevant costs and data on resource use
Study design	Cost-effectiveness analyses, cost-minimisation analyses, cost-utility analyses, cost/burden of illness, costing studies	The aim of the review was to identify relevant costs and use of resources
Limits	English language studies only	Time and resource required for translation and relevance for UK setting
Exclusion criteria		
Intervention/Comparators	Studies exclusively focusing on the role of radiotherapy, chemo-radiotherapy, hormonal therapy, diagnostics, screening or surgery Studies investigating the role of maintenance/consolidation therapy after surgery Adjuvant or neo-adjuvant therapy Does not include chemotherapy regimens that are listed as comparators	In line with the anticipated NICE scope, studies were restricted to those evaluating the efficacy of comparators. Comparators were restricted to chemotherapies and BSC.
Population	Studies that included children and adults and did not provide subgroup analysis for the adult populations	Consistent with the avelumab evidence base
Outcomes	No relevant costs or resource use	Not part of the aims of the literature search
Study design	Systematic literature reviews and meta-analyses	Studies from systematic literature reviews and meta-analyses were cross checked to ensure all relevant publications were identified
Country	No country restriction	Review was kept broad considering the limited data

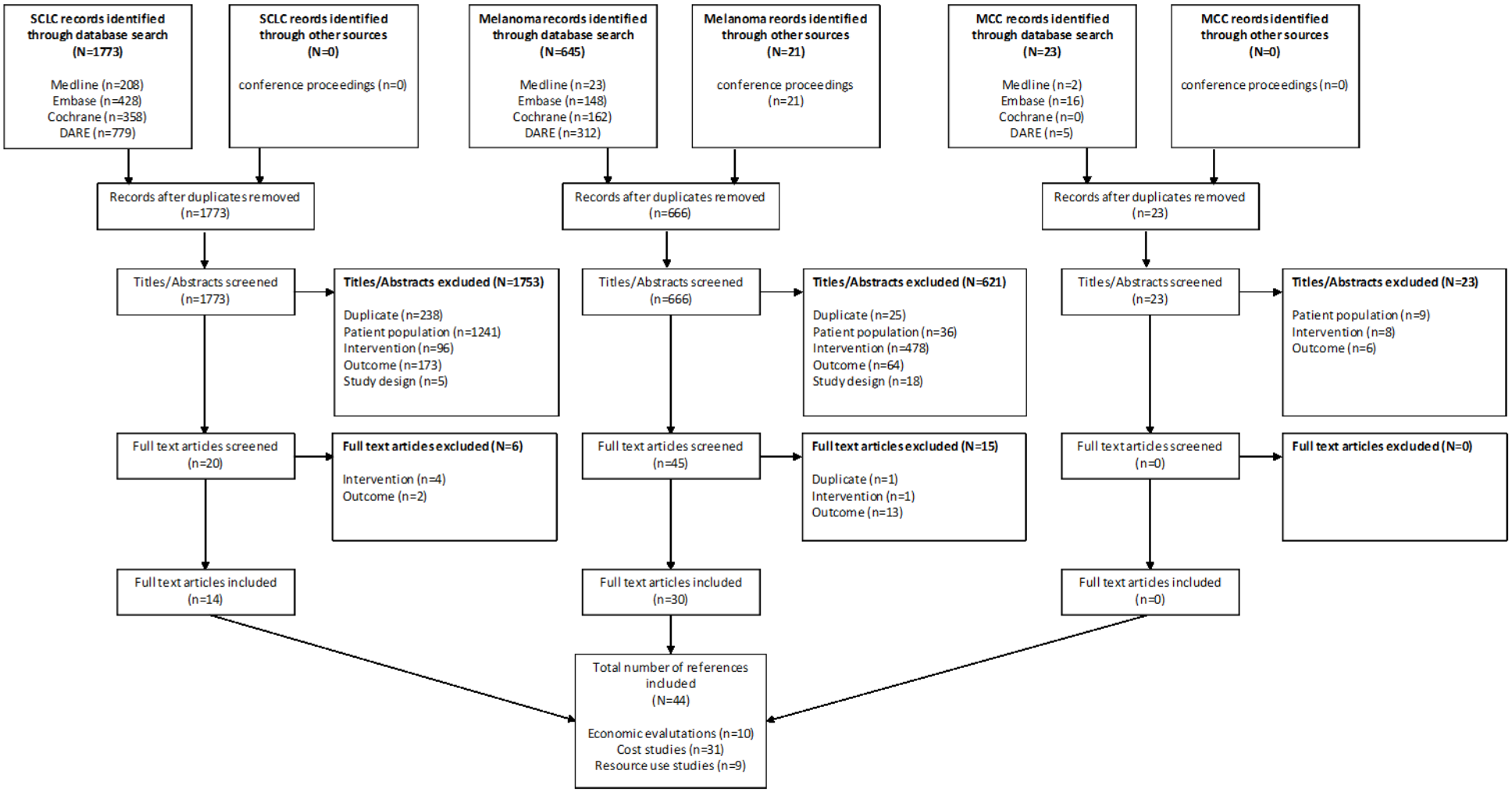
Table 48: Eligibility criteria for cost and resource use studies in melanoma

Inclusion criteria		***Rationale***
Population	Age: adults aged ≥18 years Gender: any Ethnicity: any Disease: melanoma	Consistent with the evidence base for avelumab and the anticipated marketing authorisation
Interventions/Comparators	topotecan cyclophosphamide + doxorubicin + vincristine carboplatin + etoposide cisplatin + etoposide carboplatin alone carboplatin + paclitaxel cisplatin + paclitaxel doxorubicin liposomal doxorubicin paclitaxel pembrolizumab	Interventions were identified from an observational study as likely treatment options for patients with metastatic MCC.
Outcomes	Cost-effectiveness, direct/indirect costs, resource use, BSC costs, costs, life years, QALYs, ICERs	The aim of the review was to identify relevant costs and data on resource use
Study design	Cost-effectiveness analyses, cost-minimization analyses, cost-utility analyses, cost/burden of illness, costing studies	The aim of the review was to identify relevant costs and use of resource
Limits	English language studies only	Time and resource required for translation and relevance for UK setting
Exclusion criteria		
Intervention/Comparators	Studies exclusively focusing on the role of radiotherapy, chemo-radiotherapy, hormonal therapy, diagnostics, screening or surgery Studies investigating the role of maintenance/consolidation therapy after surgery Adjuvant or neo-adjuvant therapy Does not include chemotherapy regimens that are listed as comparators	In line with the anticipated NICE scope, studies were restricted to those evaluating the efficacy of comparators. Comparators were restricted to chemotherapies and BSC
Population	Studies that included children and adults and did not provide subgroup analysis for the adult populations Studies focusing on patients with uveal or ocular melanoma	Consistent with the avelumab evidence base
Outcomes	No relevant costs or resource use	Not part of the aims of the literature search

Study design	Systematic literature reviews and meta-analyses	Studies from systematic literature reviews and meta-analyses were cross checked to ensure all relevant publications were identified
Country	None	Review was kept broad considering the limited data

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year

Figure 54: PRISMA diagram for identified cost and resource use studies



Abbreviations: HRQL: Survival-adjusted health-related quality of life, MCC: Merkel Cell Carcinoma, SCLC: Small Cell Lung Cancer

A summary of cost and resource use studies identified is provided in Appendix 7. These were the source of inputs for the economic model and a pragmatic approach was adopted where identified estimates were validated by the expert opinions of attendees of the UK advisory board, with further validation conducted with Consultant Medical Oncologist, [redacted]. Clinical input was particularly useful in informing treatment pathways as well as medical resource use relating to treatments and health states. Drug regimens applied for comparators in the model were sourced from published literature while also considering clinical feedback to ensure relevance to MCC. Estimates for drug and resource use costs were obtained from standard UK reference sources.

5.5.2 Intervention and comparators' costs and resource use

All health care costs including drug costs, administration costs, medical resource use costs and the cost of managing AEs, are considered are the same for both treatment-experienced and treatment-naïve cohorts. However, treatment-naïve patients can receive chemotherapy regimens, therefore the drug cost for the comparator arm in each cohort is different.

Drug costs

Intervention

Avelumab is available as a 200mg vial and is administered as an intravenous infusion once every 2 weeks at a target dose of 10 mg/kg (Kaufman 2016c). The list price for the cost per vial is £768 (as approved by the Department of Health). To calculate the average cost per treatment, information from various data sources has been utilised (Kaufman 2016c; Merck KGaA 2016f). As avelumab dosing is weight based, method of moments calculations were used in order to provide an accurate estimate of the average number of vials required per administration, and therefore the average cost of treatment per patient. The method of moments accounts for wastage by considering all patients who would require a given number of vials and applying the cost of that particular quantity in full. This method is preferred and literature has shown that the alternative - use of mean weight or BSA - underestimates drug costs (Hatswell 2014). Furthermore, the approach has also been widely utilised in previous submissions to NICE (NICE 2016e; NICE 2017b; NICE 2009).

Distributions of patient weights were obtained from the JAVELIN Merkel 200 trial. The two patient populations considered in the analysis were: all treated patients (n=88); and European patients only (n=29). Weight data for European patients was used in the base-case drug dosing calculations, as these patients are most representative of those treated in UK clinical practice. A log-normal distribution was fitted to patient weight data, and the proportion of patients requiring each number of vials based upon this distribution was obtained. The log-normal distribution was used as it is expected to most accurately reflect the weight of patients in clinical practice. Distribution of patient weight is positively skewed, with many patients at the upper end of the scale, and fewer patients at the lower end.

The log-normal distribution of patient weight was then used to establish the proportion of patients that would require each quantity of vials, with a range of one to 14 vials considered within the model (i.e. a range sufficiently large to consider all potential quantities of vials required per administration). The weighted average of all possible quantities of vials according to the proportions of patients that would receive them was then used to derive an estimate of the total number of vials required per administration.

The average dose required per administration was then calculated by multiplying the average number of vials by the vial size in milligrams. This is then multiplied by the cost per milligram to obtain a cost for each treatment, as there is only one vial size available for avelumab.

It should be noted that the target dose of 10 mg/kg was not achieved by all patients at all treatment visits within the JAVELIN Merkel 200 trial – an estimated 95.43% of planned treatment was

administered to patients (Merck KGaA 2016f) This estimate of the RDI for avelumab was used to inform the average dose administered to patients within the calculation of the average number of vials received (i.e. the target dose within the model was adjusted to reflect the RDI of avelumab to 9.543 mg/kg).

Avelumab has a relatively high RDI compared to typical chemotherapy regimens administered to metastatic MCC patients, which have an estimated RDI of 65% based on clinical expert opinion (Merck KGaA 2017d). This is expected to be due to avelumab being better tolerated by patients than traditional chemotherapy regimens (Merck KGaA 2017d).

Figure 55 presents the distribution of patients by the number of vials required per dose based on data from JAVELIN Merkel 200 data for all patients and for European patients only (Kaufman 2016c). Summary statistics are presented in Table 49.

Figure 55: Distribution of patients by number of vials used per dose

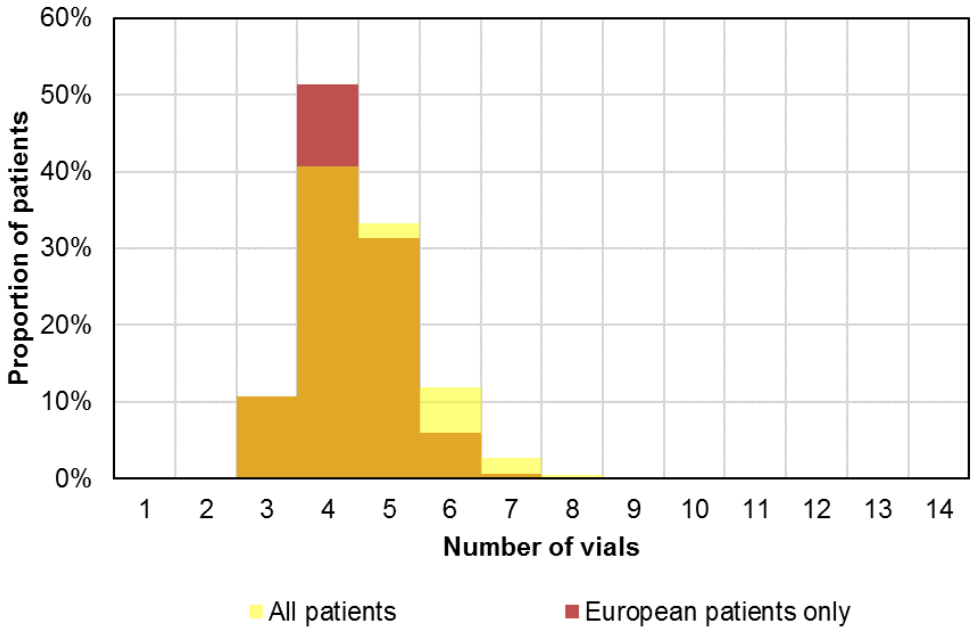


Table 49: Summary statistics, method of moments calculations for avelumab

	Patient population	
	All patients	***European patients only***
N	88	29
Mean weight (kg)	83.09	78.50
SD	19.15	14.99
SE	2.04	2.78
Average vials	4.46	4.25

Abbreviations: N: Number of patients; SD: Standard deviation; SE: Standard error

A summary of the dosing information for avelumab is provided in Table 50.

Table 50: Dosing information for avelumab

Dose	10 mg/kg
Vial size	200 mg
Cost per vial	£768.00 (Merck)
Cost per mg	£3.84
Average dose per treatment*	869 mg
RDI	95.43%
Average cost per treatment	£3,261.04
Administration information	IV infusion once every 2 weeks (Kaufman 2016c)

Note: *The average dose for avelumab is calculated via the method of moments and incorporates vial wastage.
Abbreviations: RDI: Relative dose intensity; IV: Intravenous

Comparators

For patients receiving BSC, no active treatment cost applies. Therefore, all costs attributable to BSC are discussed in Section 5.5.3 Chemotherapy costs are only relevant to treatment-naïve patients; however, for completeness these data are presented here given that they apply too in the model if chemotherapy is selected as a comparator for treatment-experienced patients.

At present, there are no metastatic MCC-specific treatment regimens licensed by the EMA or recommended by NICE for use in clinical practice in England. Instead, a combination of clinician and patient preference, AE profiles, as well as previous chemotherapy attempts often dictate which regimen is offered, along with the availability of drugs in specific localities. The retrospective observational study sponsored by Merck KGaA/Pfizer and conducted by Becker et al. to investigate outcomes of chemotherapy treatment for patients with treatment-experienced metastatic MCC was used to estimate individual chemotherapy regimens' proportionate usage or "market shares" in the treatment of treatment-experienced European metastatic MCC patients. Data consisted of anonymised patient level data extracted from a MCC specific registry in Europe (Becker 2016). The inclusion/exclusion criteria of this observational study were designed to match the inclusion/exclusion criteria of JAVELIN Merkel 200. Chemotherapy market shares from this study are outlined in Table 51.

Table 51: Market shares of chemotherapy regimens used in the treatment of metastatic MCC within Europe*

Chemotherapy regimen	***Market Share***
Carboplatin + etoposide	26.5%
Carboplatin + paclitaxel	5.9%
Cisplatin + etoposide	8.8%
Cisplatin + paclitaxel	2.9%
Cyclophosphamide + doxorubicin + vincristine (CDV)	5.9%
Paclitaxel	11.8%
Doxorubicin	8.8%
Liposomal doxorubicin	29.4%
Topotecan	0.0%

*Market shares were not used directly in the model in favour of expert opinion about chemotherapies utilised in practice in England
Abbreviations: MCC: Merkel cell carcinoma

Clinical validation elucidated the chemotherapy regimens' use in clinical practice in England. UK clinicians agreed that due to similarities in the pathology of Stage IV metastatcic MCC and SCLC, chemotherapy regimens used to treat patients with SCLC were often also used to treat metastatic MCC patients.

A combination of carboplatin and etoposide is used in many local NHS trusts for SCLC, and alternatively some patients are treated with a combination of cisplatin and etoposide. The choice of specific regimen would be largely dictated by the side effects experienced by the individual patient. Based on input from the UK advisory board, it was suggested that carboplatin and etoposide regimens are generally considered more straight forward to administer; however, they come with a greater risk of bone marrow toxicity.

For this reason, [redacted] supported the modelling assumption that a 50:50 split of carboplatin and etoposide/cisplatin and etoposide regimens would be a reasonable estimate of chemotherapy use in clinical practice in England. Despite the choice of chemotherapy regimen, clinicians agreed that the efficacy outcomes are broadly similar and that the choice of chemotherapy is dependent on the patient's level of fitness and the regimens associate side-effect profile. Clinicians at the advisory board were in agreement that most treatment-experienced patients would receive BSC. [redacted] further explained that chemotherapy is typically only offered to treatment-naïve patients, with approximately 95% of treatment-experienced patients expected to receive non-chemotherapy-based BSC. Treatment-experienced patients are often severely ill and survival outcomes are extremely poor regardless of treatment regimen received. The only differences between treatments are due to differing costs and AE profiles. The clinically validated market shares utilised in the base-case of the economic model are provided in Table 52, and these dosing regimens and costs are outlined in Table 53.

Table 52: Market shares of chemotherapy regimens used in metastatic MCC, clinically validated

Chemotherapy regimen	***Market share***
Carboplatin + etoposide	50%
Carboplatin + paclitaxel	0%
Cisplatin + etoposide	50%
Cisplatin + paclitaxel	0%
Cyclophosphamide + doxorubicin + vincristine (CAV)	0%
Paclitaxel	0%
Doxorubicin	0%
Liposomal doxorubicin	0%
Topotecan	0%

Abbreviations: MCC: Merkel cell carcinoma

Table 53: Dosing and cost information for the carboplatin & etoposide/cisplatin & etoposide chemotherapy regimens

Drug Regimen	*Dose*	*Administration information*	*Reference*	*Treatments per week*	*Cost per pack*	*N*	*SD*	*Pack size*	*Cost per mg*	*Weight*	*Cost per cycle*	*Reference*	*Assumptions (pack size)*
Carboplatin (IV) + Etoposide (IV) + Etoposide (oral)	Carboplatin 5 AUC	IV infusion on Day 1 of 3-week cycle	Clinical validation	0.33	£25.25	21,168	5.26	600 mg	£0.04	50%	£8.04	eMit (2016)	Carboplatin 600 mg/60 ml solution for infusion vials (1)
	Etoposide IV 100 mg/m²	IV infusion on Day 1 of 3-week cycle		0.33	£24.96	414	29.09	5,000 mg	£0.00			eMit (2016)	Etoposide 500 mg/125 ml solution for injection vials (10)
	Etoposide oral 200 mg/m²	PO on Days 2, 3 for 3-week cycle		0.67	£87.23	N/A	N/A	1,000 mg	£0.09			BNF Online (2017)	Etoposide 100 mg, (10)
Cisplatin + Etoposide (IV)	Cisplatin 80 mg/m²	IV infusion, once every 3 weeks	(Sun 2016)	0.33	£10.56	35,244	6.96	100 mg	£0.11	50%	£0.08	eMit (2016)	Cisplatin 100 mg/100 ml solution for infusion vials (1)
	Etoposide IV100 mg/m²	IV infusion, three times every 3 weeks	(Sun 2016)	1.00	£24.96	414	29.09	5000 mg	£0.00			eMit (2016)	Etoposide 500 mg/125 ml solution for injection vials (10)

Abbreviations: AUC: Area under curve; BNF: British National Formulary; eMit: Electronic Market Information Tool; IV: Intravenous; PO: Per os (by mouth); SD: Standard deviation

The base-case model assumes that patients receive intravenous carboplatin and intravenous etoposide on Day 1, followed by oral etoposide on Day 2 and Day 3. This regimen is given as a 3-weekly treatment cycle. It is also possible for a patient to receive intravenous etoposide on Day 2 and Day 3. However, in clinical practice this regimen is reserved for frailer patients where the treating clinician is concerned that the patient may not receive the full dose if oral medication was given (Merck KGaA 2017d). Based on this, the model incorporates the ability to treat a proportion of patients with intravenous etoposide on Day 2 and Day 3 as opposed to oral etoposide. Nevertheless, it is assumed that all patients receive oral etoposide in the base-case model, and this assumption is conservative owing to the high cost of intravenous medication administration.

Alternative chemotherapy regimens are outlined in Table 54. Dosage regimens were identified during the literature review and mirror regimens used to treat patients with SCLC, in the first instance, or melanoma were considered where data for MCC patients were unavailable. Dosage regimens for carboplatin and paclitaxel could not be identified so were assumed as cisplatin plus paclitaxel. Similarly, regimens for both doxorubicin and liposomal doxorubicin were assumed to be that of the doxorubicin component of CAV. Dosing regimens were presented to clinicians at an advisory board held by Merck KGaA/Pfizer in April 2017 to ensure treatment patterns for SCLC/melanoma patients were applicable to patients with metastatic MCC.

Dosing was calculated according to body surface area (BSA) or target AUC in the case of carboplatin. BSA was obtained from JAVELIN Merkel 200 patient level data, calculated using the DuBois approximation (Du Bois 1989). Average BSA in the JAVELIN Merkel 200 trial was 1.94 m^2. This was subsequently used to calculate doses for all drug treatments, with dose requirements in mg/m^2. AUC dosing was calculated using an estimated serum creatinine level of 0.9, average glomerular filtration rate (GFR) obtained from JAVELIN Merkel 200 patient level data and the target AUC of 5, for carboplatin regimens in SCLC. An average dose of 564.7 mg on Day 1 of each 3-weekly treatment cycle was required for carboplatin regimens.

All dosage regimens identified through literature searches were clinically validated. Due to the differences in cycle length between regimens, an administration frequency per weekly cycle was calculated due to the varying treatment cycle lengths of chemotherapy regimens. Due to the substantially larger drug cost for avelumab, this cost has been applied every 2 weeks in line with the frequency of administration; this method provides more accurate results compared to the method of calculating a drug cost for avelumab per weekly model cycle.

Costs of chemotherapy medications used in the model were obtained from the UK Department of Health's electronic market information tool (eMit). If drug costs were not listed on eMit, which is often the case for branded drugs, the Monthly Index of Medical Specialities (MIMS) or the British National Formulary (BNF) have been used as alternative cost sources. However, eMit prices were used where available as they are considered more reflective of the real prices paid for medications (Table 54).

Chemotherapy medications are available in a variety of different vial sizes. For simplicity, the vial size with the cheapest cost per mg has been used in the analysis. This is an inherently conservative approach. Furthermore, method of moments calculations have not been used to estimate the volume required; instead, an exact estimate using average patient BSA or target AUC has been used. This is also conservative as it assumes no drug wastage.

Total medication cost per model cycle is calculated by multiplying the average cost per administration with the average frequency of corresponding medication administrations per model cycle. The model applies the cost for chemotherapy regimens in accordance with the specified market shares.

The maximum durations of treatment for each chemotherapy regimen are provided in Table 55. Chemotherapy can be given for a maximum of six treatment cycles, and therefore is applied to patients in the first 18 cycles of the model. Paclitaxel has a slightly different regimen requiring

treatment every 4 weeks. If a paclitaxel regimen is given, the number of model cycles a cost is applied for reflects this.

Table 54: Dosing and cost information for other chemotherapy regimens

Drug regimen	*Dose*	*Administration information*	*Reference*	*Treatments per week*	*Cost per pack*	*N*	*SD*	*mg per pack*	*Cost per mg*	*Weight*	*Cost per cycle*	*Reference*	*Assumptions (pack size)*
Carboplatin + paclitaxel	Carboplatin 5 AUC	IV infusion, 1x every 3 weeks	Assumed carboplatin etoposide	0.33	£25.25	21,168	5.26	600 mg	£0.04	0.0%	£7.97	eMit (2016)	Carboplatin 600mg/60ml solution for infusion vials (1)
	Paclitaxel 225 mg/m²	IV infusion, 1x every 3 weeks	Assumed cisplatin paclitaxel	0.33	£11.50	13,664	19.80	150 mg	£0.08			eMit (2016)	Paclitaxel 150mg/25ml solution for infusion vials (1)
Cisplatin + paclitaxel	Cisplatin 80 mg/m²	IV infusion, 1x every 3 weeks	(Dimitroulis 2008)	0.33	£10.56	35,244	6.96	100 mg	£0.11	0.0%	£0.12	eMit (2016)	Cisplatin 100mg/100ml solution for infusion vials (1)
	Paclitaxel 175 mg/m²	IV infusion, 1x every 3 weeks	(Dimitroulis 2008)	0.33	£11.50	13,664	19.80	150 mg	£0.08			eMit (2016)	Paclitaxel 150mg/25ml solution for infusion vials (1)
CAV	C -1000 mg/m²	IV injection, 1x every 3 weeks	(Ettinger 1992)	0.33	£29.55	171	0.41	2,000 mg	£0.01	0.0%	£2.10	eMit (2016)	Cyclophosphamide 2g powder for solution for injection vials (1)
	D -50 mg/m²	IV injection, 1x every 3 weeks	(Ettinger 1992)	0.33	£4.04	43,156	3.07	50 mg	£0.08			eMit (2016)	Doxorubicin 50mg/25ml solution for injection vials (1)
	V- 1.4 mg/m²	IV injection, 1x every 3 weeks	(Ettinger 1992)	0.33	£15.71	995	4.26	5 mg	£3.14			eMit (2016)	Vincristine 1mg/1ml solution for injection vials (5)
Paclitaxel	80 mg/m²	IV injection, 3x every 4 weeks	(O'Day 2013)	0.75	£11.50	13,664	19.80	150 mg	£0.08	0.0%	£0.11	eMit (2016)	Paclitaxel 150mg/25ml solution for infusion vials (1)
Doxorubicin	50 mg/m²	IV injection, 1x every 3 week	Assume CAV	0.33	£4.04	43,156	3.07	50 mg	£0.08	0.0%	£0.05	eMit (2016)	Doxorubicin 50mg/25ml solution for injection vials (1)

Drug regimen	*Dose*	*Administration information*	*Reference*	*Treatments per week*	*Cost per pack*	*N*	*SD*	*mg per pack*	*Cost per mg*	*Weight*	*Cost per cycle*	*Reference*	*Assumptions (pack size)*
Liposomal doxorubicin	50 mg/m²	IV injection, 1x every 3 weeks	Assume CAV	0.33	£912.26	N/A	N/A	100 mg	£9.12	0.0%	£5.91	MIMS (2017)	Myocet 50mg vials (2)
Topotecan	1.5 mg/m²	IV infusion, 5x every 3 weeks	(von Pawel 2014)	1.67	£19.35	1,211	76.29	4 mg	£4.84	0.0%	£15.67	eMit (2016)	Topotecan 4mg/4ml concentrate for solution for infusion vials (1)

Abbreviations: AUC: Area under curve; CAV: Cyclophosphamide + doxorubicin + vincristine; eMit: Electronic Market Information Tool; IV: Intravenous; MIMS: Monthly Index of Medical Specialities; SD: Standard deviation

Table 55: Treatment cycle length and maximum duration, chemotherapy regimens

Drug Regimen	*Cycle length*	*Maximum*	*Assumptions*
Carboplatin (IV) + etoposide (IV) + etoposide (oral)	3 weeks	6 cycles	Advisory board assumption
Carboplatin + paclitaxel	3 weeks	6 cycles	
Cisplatin + etoposide	3 weeks	6 cycles	
Cisplatin + paclitaxel	3 weeks	6 cycles	
Cyclophosphamide + doxorubicin + vincristine (CAV)	3 weeks	6 cycles	
Paclitaxel	4 weeks	6 cycles	
Doxorubicin	3 weeks	6 cycles	Assumed as per CAV
Liposomal doxorubicin	3 weeks	6 cycles	
Topotecan	3 weeks	6 cycles	Advisory board assumption

Abbreviations: IV: Intravenous

Administration costs

Administration costs apply only to patients receiving drug treatment; therefore, patients on BSC or patients who have ceased treatment do not incur any costs for administration.

The cost for administering all regimens has been sourced from NHS reference costs (Department of Health 2016). Details are provided in Table 56.

Table 56: Administration costs, all drug treatments

Cost	*Description*	*Setting*	*Code*	*Reference*
£199	Deliver simple parenteral chemotherapy	Outpatient	SB12Z	NHS reference costs 2015-2016

Abbreviations: NHS: National Health Service

Avelumab and chemotherapy are both expected to be administered by intravenous infusion in an outpatient setting. This expectation was considered appropriate by [redacted] (Merck KGaA 2017d).

Avelumab is administered by intravenous infusion once every 2 weeks. For carboplatin plus etoposide regimens, a combination of intravenous and oral medication is given. On Day 2 and Day 3, where medication is taken orally, no administration cost has been applied. For other chemotherapy regimens, administration costs are applied in accordance with each individual drug regimen. Due to differing treatment cycle lengths for chemotherapy regimens, an administration frequency per week was calculated; this is then multiplied by the administration cost to give a cost of administration per model cycle. For avelumab, the cost of administration is applied every 2 weeks in accordance with the regimen used in JAVELIN Merkel 200 (Kaufman 2016c). Where more than one drug is given on the same day, it is assumed that the patient will incur only a single administration cost. The administration regimens and costs applied in the model are outlined in Table 57.

Table 57: Administration regimen, avelumab

Drug	Administration Information	Reference
Avelumab	IV infusion once every 2 weeks	(Kaufman 2016c)

Note: The administration cost as per Table 56 is applied every 2 weeks for patients on avelumab

Abbreviations: IV: Intravenous

Table 58: Administration regimen, carboplatin & etoposide/cisplatin & etoposide

Drug	***Administration Information***	***Reference***	***Treatments per week***	***Cost per week***	***Weight***
Carboplatin (IV) + Etoposide (IV) + Etoposide (oral)	Carboplatin IV infusion on Day 1 of 3-week cycle	Clinical validation	0.33	£66.33	50%
	Etoposide IV infusion on Day 1 of 3-week cycle	Clinical validation	0.33		
	Etoposide Orally on Day 2 and Day 3 for 3-week cycle	Clinical validation	0.67		
Cisplatin + Etoposide	Cisplatin IV infusion, once every 3 weeks	(Sun 2016)	0.33	£199	50%
	Etoposide IV infusion, three times every 3 weeks	(Sun 2016)	1.00		

Abbreviations: IV: Intravenous

Table 59: Administration regimen, other chemotherapy treatments

Drug Regimen	***Administration Information***	***Reference***	***Treatments per week***	***Cost per week***	***Weight***
Carboplatin + paclitaxel	Carboplatin IV infusion, once every 3 weeks	Assumed carboplatin etoposide	0.33	£66	0.0%
	Paclitaxel IV infusion, once every 3 weeks	Assumed cisplatin paclitaxel	0.33		
Cisplatin + etoposide	Cisplatin IV infusion, once every 3 weeks	(Sun 2016)	0.33	£199	50.0%
	Etoposide IV infusion, three times every 3 weeks	(Sun 2016)	1.00		
Cisplatin + paclitaxel	Cisplatin IV infusion, once every 3 weeks	(Dimitroulis 2008)	0.33	£66	0.0%
	Paclitaxel IV infusion, once every 3 weeks	(Dimitroulis 2008)	0.33		
Cyclophosphamide + doxorubicin + vincristine (CAV)	Cyclophosphamide IV injection, once every 3 weeks	(Ettinger 1992)	0.33	£66	0.0%
	Doxorubicin IV injection, once every 3 weeks	(Ettinger 1992)	0.33		
	Vincristine IV injection, once every 3 weeks	(Ettinger 1992)	0.33		
Paclitaxel	IV injection, three times every 4 weeks	(O'Day 2013)	0.75	£149	0.0%
Doxorubicin	IV injection, once every 3 weeks	Assume CAV	0.33	£66	0.0%
Liposomal doxorubicin	IV injection, once every 3 weeks	Assume CAV	0.33	£66	0.0%
Topotecan	IV infusion, five times every 3 weeks	(von Pawel 2014)	1.67	£332	0.0%

Abbreviations: IV: Intravenous

5.5.3 Health-state unit costs and resource use

Resource use and monitoring costs are the same for both treatment-experienced and treatment-naïve cohorts. Costs were taken from the Personal and Social Services Research Unit (PSSRU) Unit Costs for Health and Social Care (2016), and NHS reference costs (2015-2016) (Curtis 2015; Department of Health 2016). Costs applied in the model include the costs for personnel such as general practitioners (GPs), costs for monitoring and diagnostic tests, and radiotherapy.

The cost of resources applied in the model are outlined in Table 60 and Table 61.

Table 60: Resource use costs

Unit description	*Cost*	*Information*	*Model value*	*Reference*
GP visit	£36.00	Surgery consultation lasting 9.22 minutes	£36.00	PSSRU - Unit Costs of Health and Social Care 2016
CT scan	£120.99	Total HRGs - RD26Z - CT scan of 3 areas with contrast	£120.99	National Schedule of Reference Costs - 2015-16
Full blood count	£3.00	Haematology - DAPS05	£3.00	National Schedule of Reference Costs - 2015-16
Liver function test	£1.00	DAPS04 - Clinical Biochemistry	£1.00	National Schedule of Reference Costs - 2015-16
Renal function test	£1.00	DAPS04 - Clinical Biochemistry	£1.00	National Schedule of Reference Costs - 2015-16
Thyroid function test	£1.00	DAPS04 - Clinical Biochemistry	£1.00	National Schedule of Reference Costs - 2015-16

Abbreviations: GP: General practitioner; CT: Computed tomography; HRG: Healthcare resource group; PSSRU: Personal and Social Services Research Unit

Table 61: Resource use costs, radiotherapy

Unit description	*Cost*	*Information*	*Model value*	*Reference*
Radiotherapy	£126.60	Outpatient Attendance - 800 - Clinical Oncology	£126.60	National Schedule of Reference Costs - 2015-16

Data regarding the medical resource use frequencies for patients with metastatic MCC are lacking, due to the rarity of the disease. Therefore, estimates of resource use frequency were initially obtained via the literature review using SCLC as a suitable alternative before validating these estimates as applicable to MCC through clinical consultation. Resource use regimens differ in intensity depending on the patient's health state or current treatment. For patients on BSC, it is assumed that resource use would be minimal. During the advisory board meeting, clinicians expressed that the clinical tests outlined above would not be conducted for BSC patients. Therefore, BSC patients are conservatively assumed to incur the cost of one GP visit every 2 months. The cost for a 2-monthly GP visit also applies to all post-progression patients. Table 62 and Table 63 outline the resource use frequencies applied in the model.

To calculate a cost per model cycle, resource use per week was calculated; then subsequently multiplied by the corresponding resource use cost. Similar to drug costs and administration costs, the resource use cost applied in the model was weighted in accordance with market shares. The resulting resource use costs per model cycle are presented Table 64 and Table 65.

Table 62: Resource use frequencies for progression-free avelumab patients

Resource	***Avelumab***
GP visit	Every two treatment cycles
CT scan	Every 3 months
Full blood count	Every treatment cycle
Liver function test	Every treatment cycle
Renal function test	Every treatment cycle
Thyroid function test	Every treatment cycle

Abbreviations: CT: Computed tomography; GP: General practitioner

Table 63: Resource use frequencies for progression-free chemotherapy patients*

Resource	***Carboplatin + etoposide***	***Carboplatin + paclitaxel***	***Cisplatin + etoposide***	***Cisplatin + paclitaxel***	***CDV***	***Doxorubicin + liposomal doxorubicin***	***Paclitaxel***	***Topotecan***
GP visit	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle
CT scan	Every 2 months	Every 2 months	Every 2 months	Every 2 months	Every 2 months	Every 2 months	Every 2 months	Every 2 months
Full blood count	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle
Liver function test	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle
Renal function test	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle	Every treatment cycle
Thyroid function test	None	None	None	None	None	None	None	None

Notes: *Resource use estimates were obtained through clinical validation (Merck KGaA 2017d), estimates for topotecan were sourced from a publication identified in the literature review (Hartwell 2011)

Abbreviations: CDV: Cyclophosphamide + doxorubicin + vincristine; CT: Computed tomography; GP: General practitioner

Table 64: Resource use costs per model cycle, avelumab

Resource	***Avelumab***
GP visit	£9.00
CT scan	£10.08
Full blood count	£1.50
Liver function test	£0.50
Renal function test	£0.50
Thyroid function test	£0.50
Total	£22.08

Abbreviations: CT: Computed tomography; GP: General practitioner

Table 65: Resource use costs per model cycle, chemotherapy, weighted by estimated market share

Resource	***Chemotherapy***
GP visit	£12.00
CT scan	£15.12
Full blood count	£1.00
Liver function test	£0.33
Renal function test	£0.33
Thyroid function test	£0.00
Weighted total	£28.79

Abbreviations: CT: Computed tomography; GP: General practitioner

During the clinical validation process, it transpired that radiotherapy was a further treatment option for patients with Stage IV unresectable metastatic MCC.

The following radiotherapy regimen was clinically confirmed and was applied to patients on all treatments:

"Radiation therapy is received by approximately 75% of patients. For advanced MCC, palliative regimens are generally used. The regimens involve approximately 1-5 fractions, administered 1-2 times in total."

These estimates were used to calculate average duration of radiotherapy treatment of 3.75 days; which was then multiplied by the cost of radiotherapy to obtain an average cost estimate per patient. Cost information for radiotherapy is provided in Table 61.

[redacted] explained that patients would continue to receive radiotherapy providing there is a clinical need. For metastatic MCC patients, radiotherapy treatment regimens would be solely palliative, with no curative intent. [redacted] expected that a patient benefitting from treatment in terms of durable response and controlled disease would not receive radiotherapy (Merck KGaA 2017d). For this reason, the cost of radiotherapy was applied for 1 year for all patients, as after this time, patients receiving avelumab have achieved advantageous outcomes versus those treated with chemotherapy or BSC. The resulting cost of radiotherapy was calculated as £4.06 per model cycle. A summary of radiotherapy resource use information is provided in Table 66.

Table 66: Radiotherapy resource use summary

Duration of radiotherapy treatment (days)	3.75
Cost of average course of radiotherapy treatment	£474.75
Assuming average survival as per chemotherapy patients, number of cycles alive	87.74
Proportion of patients receiving radiotherapy per cycle	0.01
Radiotherapy cost per cycle	£4.06
Radiotherapy applied until (all patients)	1 year(s)

5.5.4 Adverse reaction unit costs and resource use

AE costs were identified from published literature sources, and were inflated to 2016 prices using the Hospital and Community Health Services (HCHS) index reported in Unit Costs for Health and Social Care (Curtis 2015). AE costs applied in the model are presented in Table 67. These costs were then multiplied by the corresponding model cycle probabilities presented in Appendix 15 to obtain a resulting cost per model cycle for each AE. Model cycle costs for AEs are presented in Table 68.

For chemotherapy regimens, costs were weighted by market shares of chemotherapy regimens. BSC patients are assumed not to incur any costs due to AEs. A summary of AE costs per model cycle by treatment is presented in Table 69.

Table 67: Adverse event costs, per event

Adverse event	*Source cost*	*Source SD*	*Cost year*	*Inflated cost*	*Inflated SD*	*Reference*
Anaemia	£64.28	91	2013	£66.45	£93.97	Grade 1 or 2 anaemia (Vouk 2016)
Dyspnoea	£251.00		2014	£256.62		Outpatient dyspnoea (Wehler 2017)
Fatigue	£64.28	91	2013	£66.45	£93.97	Assume as Grade 1 or 2 anaemia (Vouk 2016)
Febrile neutropenia	£4,444.00		2014	£4,543.44		Inpatient febrile neutropenia (Wehler 2017)
Low haemoglobin	£64.28	91	2013	£66.45	£93.97	Assume as Grade 1 or 2 Anaemia (Vouk 2016)
Hyponatremia	£64.28	91	2013	£66.45	£93.97	Assume as Grade 1 or 2 Anaemia (Vouk 2016)
Infections	£251.00		2014	£256.62		Outpatient infection (Wehler 2017)
Leucopenia	£272.47	289	2013	£281.67	£299.05	Assume as neutropenia / leucopenia (Vouk 2016)
Lymphopenia	£272.47	289	2013	£281.67	£299.05	Assume as neutropenia / leucopenia (Vouk 2016)
Muscle pain	£9.87	12	2013	£10.20	£12.83	Pain (extremity and back) Grade 1 or 2 (Vouk 2016)
Nausea/vomiting	£167.41	36	2013	£173.06	£36.72	Grade 1 or 2 nausea (Vouk 2016)
Neutropenia	£272.47	289	2013	£281.67	£299.05	Neutropenia / leucopenia (Vouk 2016)
Low platelets	£272.47	289	2013	£281.67	£299.05	Assume as neutropenia / leucopenia (Vouk 2016)
Sensory neuropathy	£432.00	0	2013	£446.59	£0.00	Assume as peripheral neuropathy (Vouk 2016)
Thrombocytopenia	£276.78	25	2013	£286.12	£25.53	Thrombocytopenia (Vouk 2016)
Hair loss (any grade)	£0.00	0	2013	£0.00	£0.00	Alopecia Grade 1 or 2 (Vouk 2016)

Abbreviations: SD: Standard deviation

Table 68: Adverse event costs, per model cycle

Treatment	*Anaemia*	*Dyspnoea*	*Fatigue*	*Febrile neutropenia*	*Low haemoglobin*	*Hyponatremia*	*Infections*	*Leucopenia*	*Lymphopenia*	*Muscle pain*	*Nausea/vomiting*	*Neutropenia*	*Low platelets*	*Sensory neuropathy*	*Thrombocytopenia*	*Hair loss (any grade)*	*Total*
Avelumab	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.38	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.38
Carboplatin + etoposide	£0.28	£0.00	£0.12	£11.54	£0.00	£0.04	£0.00	£1.35	£0.00	£0.00	£0.09	£9.76	£0.00	£0.00	£1.72	£103.70	£64.29
Carboplatin + paclitaxel	£0.00	£0.00	£0.71	£12.44	£1.37	£0.10	£0.00	£4.79	£0.82	£0.04	£0.00	£12.41	£1.73	£4.76	£0.00	£124.15	£0.00
Cisplatin + etoposide	£0.34	£0.00	£0.00	£0.00	£1.14	£0.00	£0.00	£4.45	£0.00	£0.00	£0.89	£11.84	£0.00	£0.00	£1.61	£47.91	£34.08
Cisplatin + paclitaxel	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£3.34	£0.00	£0.00	£0.35	£192.25	£0.00
Cyclophosphamide + doxorubicin + vincristine (CAV)	£0.43	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.44	£6.44	£0.00	£0.00	£3.06	£510.85	£0.00
Paclitaxel	£0.20	£0.76	£0.13	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.56	£1.36	£0.00	£0.00	£0.00	£490.44	£0.00
Doxorubicin + liposomal doxorubicin	£0.43	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.22	£6.44	£0.00	£0.00	£3.06	£570.27	£0.00
Topotecan	£1.81	£1.34	£0.66	£10.81	£0.00	£0.29	£1.99	£5.24	£0.00	£0.00	£0.00	£15.71	£0.00	£0.00	£16.16	£733.08	£0.00

Table 69: AE costs per model cycle

Total AE cost per cycle for avelumab	£0.38
Total AE cost per cycle for chemotherapy	£98.38
Total AE cost per cycle for BSC	£0.00

Abbreviations: AE: Adverse event; BSC: Best supportive care

5.5.5 Miscellaneous unit costs and resource use

End-of-life care costs have also been incorporated into the model. As no data are available on end of life care costs for metastatic MCC patients, an average cost of end of life care for terminal cancer patients has been obtained from the literature (Round 2015). This approach has been clinically validated (Merck KGaA 2017d). Costs for end-of-life care applied in the model are outlined in Table 70.

Table 70: End of life care costs, average

Category	***Model Value***
Health care	£4,761.00
Social care	£2,104.50
Total	£6,865.50

As the report by Round et al. reports end of life care costs across four cancer types (breast, colorectal, lung, and prostate) the option to apply the cost for one of these cancer types alone is incorporated within the model (Round 2015). The impact of varying this cost by cancer type is explored as sensitivity analysis.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

A summary of the base-case economic analysis inputs are provided in Table 71.

Table 71: Summary of variables applied in the economic model

Parameter	*Base-case value*	*Distribution for variation*	*Lower bound*	*Upper bound*	*Section in document*
Model Settings					
Discount rate, costs	0.035	Scenario analysis			Section 5.2
Discount rate, QALYs	0.035	Scenario analysis			
Discount rate, LYs	0	Scenario analysis			
Model cycle length (weeks)	1	Not varied			
Model time horizon	40.0	Not varied			
Patient age	69.3	Not varied			
Patient weight	78.50	Not varied			
Proportion male	79.31%	Not varied			
Survival and Progression					
HR: OS for avelumab at 1L	0.80	Log-normal	0.65	0.97	Section 5.3
HR: PFS for avelumab at 1L	1.00	Log-normal	0.82	1.21	
HR: TOT for avelumab at 1L	1.00	Log-normal	0.82	1.21	
HR: BSC versus chemotherapy - OS	1.00	Not varied			
HR: BSC versus chemotherapy - PFS	1.00	Not varied			
Dosing					
RDI: avelumab	0.95	Normal	0.94	0.97	Section 5.3, 5.5
RDI: chemotherapy	0.67	Normal	0.54	0.80	
Estimated discontinuation time for majority of patients	2 years	Scenario analysis			Section 5.3
Maximum plausible treatment duration	5 years	Scenario analysis			
Utilities					
Utility >100 days to death	0.77	Beta	0.73	0.81	Section 5.4
Utility decrement 30-100 days to death	-0.02	Beta	0.00	0.11	

Utility decrement <30 days to death	-0.07	Beta	0.02	0.14	
Utility avelumab, PF, JAVELIN Merkel 200	[redacted]	Beta	0.78	0.87	
Utility avelumab, Progressed, JAVELIN Merkel 200	[redacted]	Beta	0.69	0.79	
Utility chemotherapy, PF, JAVELIN Merkel 200	[redacted]	Beta	0.78	0.87	
Utility chemotherapy Progressed, JAVELIN Merkel 200	[redacted]	Beta	0.69	0.79	
Utility BSC PF, JAVELIN Merkel 200	[redacted]	Beta	0.78	0.87	
Utility BSC, Progressed, JAVELIN Merkel 200	[redacted]	Beta	0.69	0.79	
Utility avelumab, PF, custom	0.77	Beta	0.60	0.90	
Utility avelumab, PP, custom	0.72	Beta	0.57	0.85	
Utility chemotherapy, PF, custom	0.77	Beta	0.60	0.90	
Utility chemotherapy PP, custom	0.72	Beta	0.57	0.85	
Utility BSC, PF, custom	0.77	Beta	0.60	0.90	
Utility BSC, PP, custom	0.72	Beta	0.57	0.85	
Utility time to death (final month of life)	-0.06	Normal	-0.02	-0.13	
Admin Costs					
Admin cost, all drugs	199.00	Normal	198.81	199.19	Section 5.5
Resource Use Costs					
Cost, GP visit	£36	Normal	£29	£43	Section 5.5
Cost, CT scan	£121	Normal	£121	£121	
Cost, FBC	£3	Normal	£3	£3	
Cost, LFT	£1	Normal	£1	£1	
Cost, RFT	£1	Normal	£1	£1	
Cost, TFT	£1	Normal	£1	£1	
Cost, Radiotherapy	£127	Normal	£127	£127	
Cost, EoL, Health care	£4,761	Normal	£3,828	£5,694	
Cost, EoL, Social care	£2,105	Normal	£1,692	£2,517	

Resource Use Frequencies					
MRU frequency, GP visit, avelumab, PF	25%	Normal	20%	30%	Section 5.5
MRU frequency, CT scan, avelumab, PF	8%	Normal	7%	10%	
MRU frequency, FBC, avelumab, PF	50%	Normal	40%	60%	
MRU frequency, LFT, avelumab, PF	50%	Normal	40%	60%	
MRU frequency, RFT, avelumab, PF	50%	Normal	40%	60%	
MRU frequency, TFT, avelumab, PF	50%	Normal	40%	60%	
MRU frequency, Radiotherapy, avelumab, PF	0%	Normal	0%	0%	
MRU frequency, GP visit, chemotherapy, PF	33%	Normal	27%	40%	
MRU frequency, CT scan, chemotherapy, PF	13%	Normal	10%	15%	
MRU frequency, FBC chemotherapy, PF	33%	Normal	27%	40%	
MRU frequency, LFT, chemotherapy, PF	33%	Normal	27%	40%	
MRU frequency, RFT, chemotherapy, PF	33%	Normal	27%	40%	
MRU frequency, TFT, chemotherapy, PF	0%	Normal	0%	0%	
MRU frequency, Radiotherapy, chemotherapy, PF	0%	Normal	0%	0%	
Drug Costs					
Drug cost, avelumab	£768.00	Fixed			Section 5.5
Drug cost, carboplatin	£25.25	Normal	£25	£25	
Drug cost, etoposide IV	£24.96	Normal	£22	£28	
Drug cost, etoposide oral	£87.23	Fixed			
Drug cost, paclitaxel	£11.50	Normal	£11	£12	
Drug cost, cisplatin	£10.56	Normal	£10	£11	
Drug cost, cyclophosphamide	£29.55	Normal	£29	£30	
Drug cost, doxorubicin	£4.04	Normal	£4	£4	
Drug cost, vincristine	£15.71	Normal	£15	£16	
Drug cost, liposomal doxorubicin	£912.26	Fixed			

Drug cost, topotecan	£19.35	Normal	£15	£24	
Adverse Costs					
AE cost, anaemia	£66	Normal	£53	£79	Section 5.5
AE cost, dyspnoea	£257	Normal	£206	£307	
AE cost, fatigue	£66	Normal	£53	£79	
AE cost, febrile neutropenia	£4,543.44	Normal	£3,653	£5,434	
AE cost, low haemoglobin	£66.45	Normal	£53	£79	
AE cost, hyponatremia	£66.45	Normal	£53	£79	
AE cost, infections	£256.62	Normal	£206	£307	
AE cost, leucopenia	£281.67	Normal	£226	£337	
AE cost, lymphopenia	£281.67	Normal	£226	£337	
AE cost, muscle pain	£10.20	Normal	£8	£12	
AE cost, nausea/vomiting	£173.06	Normal	£139	£207	
AE cost, neutropenia	£281.67	Normal	£226	£337	
AE cost, low platelets	£281.67	Normal	£226	£337	
AE cost, sensory neuropathy	£446.59	Normal	£359	£534	
AE cost, thrombocytopenia	£286.12	Normal	£230	£342	
AE cost, hair loss	£0.00	Normal	£0	£0	
Adverse Events					
AE disutility, anaemia	-0.09	Beta	-0.05	-0.13	Section 5.4
AE disutility, dyspnoea	-0.05	Beta	-0.03	-0.08	
AE disutility, fatigue	-0.07	Beta	-0.04	-0.11	
AE disutility, febrile neutropenia	-0.09	Beta	-0.06	-0.12	
AE disutility, low haemoglobin	-0.08	Beta	-0.05	-0.11	
AE disutility, hyponatremia	-0.09	Beta	-0.06	-0.12	
AE disutility, infections	-0.12	Beta	-0.10	-0.14	

AE disutility, leucopenia	-0.09	Beta	-0.06	-0.12	
AE disutility, lymphopenia	-0.09	Beta	-0.06	-0.12	
AE disutility, muscle pain	-0.05	Beta	-0.02	-0.08	
AE disutility, nausea/vomiting	-0.05	Beta	-0.02	-0.08	
AE disutility, neutropenia	-0.09	Beta	-0.06	-0.12	
AE disutility, low platelets	-0.09	Beta	-0.06	-0.12	
AE disutility, sensory neuropathy	-0.23	Beta	-0.18	-0.27	
AE disutility, thrombocytopenia	-0.11	Beta	-0.09	-0.13	
AE disutility, hair loss	-0.04	Beta	-0.02	-0.08	
AE duration, anaemia	21.0	Normal	16.9	25.1	
AE duration, dyspnoea	21.0	Normal	16.9	25.1	
AE duration, fatigue	21.0	Normal	16.9	25.1	
AE duration, febrile neutropenia	4.0	Normal	3.2	4.8	
AE duration, low haemoglobin	21.0	Normal	16.9	25.1	
AE duration, hyponatremia	1.9	Normal	1.5	2.3	
AE duration, infections	14.9	Normal	12.0	17.8	
AE duration, leucopenia	1.9	Normal	1.5	2.3	
AE duration, lymphopenia	1.9	Normal	1.5	2.3	
AE duration, muscle pain	7.2	Normal	5.8	8.6	
AE duration, nausea/vomiting	3.0	Normal	2.4	3.6	
AE duration, neutropenia	1.9	Normal	1.5	2.3	
AE duration, low platelets	1.9	Normal	1.5	2.3	
AE duration, sensory neuropathy	35.3	Normal	28.4	42.2	
AE duration, thrombocytopenia	23.8	Normal	19.1	28.5	
AE duration, hair loss	21.0	Normal	16.9	25.1	

Abbreviations: AE: Adverse event; BSC; Best supportive care; CT: Computed tomography; EoL: End-of-life; FBC: Full blood count; GP: General practitioner; HR: Hazard ratio; LFT: Liver function test; LY: Life year; MRU: Medical resource use; OS: Overall survival; PF: Progression-free; PP: Post-progression; QALY: Quality-adjusted life year; RDI: Relative dose intensity; RFT: Renal function test; RPFS: Radiographic progression-free survival; TFT: Thyroid function test; TOT: Time on treatment

5.6.2 Assumptions

Assumptions are listed throughout the submission. However, the key assumptions considered in this submission are summarised in Table 72, with an overview of the key difference between the modelling of treatment-naïve and treatment-experienced cohorts provided in In summary, the inputs for both models are noted below in Table 73.

Table 73.

Table 72: Summary of key assumptions

Assumption	***Rationale***	***Section in document***
Applied to both 2L+ and 1L model		
Model cycle length of 1 week	A weekly cycle length is assumed to be sufficiently short enough to represent the frequency of clinical events and interventions (Siebert 2012)	Table 30
Outcomes with BSC are comparable to those with chemotherapy	No data are available to inform the efficacy of BSC for the treatment of metastatic MCC for treatment-naïve or treatment-experienced patients, and as such chemotherapy was chosen as a proxy for use within the economic model. This assumption was validated by clinical experts (Merck KGaA 2017d)	Section 5.3.4
Chemotherapy regimens are equally efficacious	Due to small patient numbers receiving each type of chemotherapy, it was assumed within the model that all chemotherapy regimens are associated with broadly similar outcomes. This assumption was validated by clinical experts (Merck KGaA 2017d)	Section 5.5.2
Only a proportion of patients on avelumab will continue treatment beyond 2 years	Based on clinical expert feedback, it is reasonable to assume that only one third (33.33%) of patients projected to be on treatment at 2 years will continue treatment beyond this time point. 2 years has strong support from clinical community, and precedence in other cancer types where immuno-oncology therapies are given.	Section 5.3.2
There is a maximum treatment duration for all patients	Based on clinical expert feedback, it is reasonable to expect that no patient will remain on treatment beyond 5 years; therefore treatment is capped in the model at this time point.	Section 5.3.2
Chemotherapy regimens reflect UK clinical practice	The most commonly administered chemotherapy regimens in clinical practice in England were suggested as carboplatin/etoposide and cisplatin/etoposide at the advisory board meeting. A 50:50 split of these regimens were assumed to apply within the model, validated at a further clinical validation meeting (Merck KGaA 2017d)	Section 5.5.2
Patients weight assumption is based on the EU patients in the JAVELIN Merkel trial	These patients are the most comparable patients to those likely to be treated in UK settings.	Section 5.5.2
Data from other cancers such as SCLC inform dosing regimens and adverse event rates for chemotherapy treatments, and medical resource use frequencies	SCLC was considered the best proxy by clinicians to MCC disease and SCLC data were utilised where there was a lack of data specifically for metastatic MCC patients	Section 5.4.3, Section 5.4.4, Section 5.5.1, Section 5.5.2, Section 5.5.3
Applied to 1L model only		

Proportionality or comparability of efficacy outcomes and time on treatment for treatment-naïve and treatment-experienced patients	Given the immaturity of data for patients with treatment-naïve metastatic MCC, data for treatment-experienced patients were utilised with an OS HR of 0.8 and a PFS and ToT HR of 1 applied to the treatment-experienced projections. This was informed by early clinical trial data and clinical expert opinion (Merck KGaA 2017d).	Section 5.3.2
Use of data from treatment-experienced patients to inform treatment-naïve modelling	Equivalent AE rates, medical resource use frequencies and utility values were assumed to apply to treatment-naïve patients, validated by clinical experts (Merck KGaA 2017d)	Section 5.4.1, Section 5.5.2, Section 5.5.3, Section 5.5.4

Abbreviations: AE: Adverse event; BSC: Best supportive care; EU: Europe; HR: Hazard ratio; MCC: Merkel cell carcinoma; SCLC: Small cell lung cancer

In summary, the inputs for both models are noted below in Table 73.

Table 73: Overview of modelling approaches by line of therapy

Feature	***Treatment-naïve***	***Treatment-experienced***	***Rationale***	***Section***
Comparators	Chemotherapy or BSC	BSC (~5% receive chemotherapy, comparison provided as a sensitivity analysis)	Clinical validation	Section 5.2.3
Comparator data sources	Merck KGaA studies/studies identified in literature	Merck KGaA studies only		Section 5.3.3
OS	HR of 0.8 applied to treatment-experienced data	Time to event analysis of JAVELIN Merkel 200: Part A data	Clinical validation	Section 5.3.15.3.2
PFS	HR of 1.0 applied to treatment-experienced data	Time to event analysis of JAVELIN Merkel 200: Part A data	Assumed same as lack of data to state otherwise	Section 5.3.1
ToT	HR of 1.0 applied to treatment-experienced data	Time to event analysis of JAVELIN Merkel 200: Part A data	Assumed same as lack of data to state otherwise	Section 5.3.2
HRQL	Same as for treatment-experienced	Time to death analysis of JAVELIN Merkel 200: Part A data		Section 0
Drug costs	Same as for treatment-experienced	Cost of avelumab: Supplied by Merck and approved by DoH Cost of chemotherapy*: eMit, MIMS, BNF	Cost of drugs remain the same for both cohorts	Section 5.5.2
Resource use costs (administration, radiotherapy, monitoring, GP costs, EoL, AE costs)	Same as for treatment-experienced	Costs taken from standard UK reference sources with frequencies confirmed via clinical validation	Clinical validation	Sections 0, 5.5.4, 5.5.5
AE rates	Same as for treatment-experienced	Avelumab - Taken from JAVELIN Merkel 200: Part A. Comparators – sourced from literature	Lack of data for treatment-naïve patients – data from first few months of treatment in this cohort would be	Section 0

			misrepresentative of AE rates as a whole	

Note:* Cost of chemotherapy is the same for both cohorts, however this cost only applies to treatment-experienced patients as part of the sensitivity analyses and not in the base-case analysis

Abbreviations: AE: Adverse event; BNF: British National Formulary; BSC: Best supportive care; DoH: Department of Health; eMit: Electronic Market information tool; EoL: End of life; GP: General Practitioner; HR: Hazard ratio; HRQL: Health-related quality of life; MIMS: Monthly Index of Medical Specialities; OS: Overall survival; PFS: Progression-free survival; ToT: Time on treatment; UK: United Kingdom.

5.7 Base case results

5.7.1 Base case incremental cost effectiveness analysis results

Treatment-experienced metastatic MCC patients

Discounted results for avelumab versus BSC in treatment-experienced metastatic MCC patients are presented in Table 74, with undiscounted results presented in Table 75. Compared with BSC, avelumab is associated with 3.11 life years (LYs) gained, 1.91 incremental quality-adjusted life years (QALYs), and incremental costs of £71,399 per patient. The incremental cost-effectiveness ratio (ICER) is £37,409 per additional QALY gained.

Table 74: Treatment-experienced patients, discounted incremental results (avelumab vs. BSC)

Treatment	***Total***			***Incremental***			***ICER***
	Costs	***LYs***	***QALYs***	***Costs***	***LYs***	***QALYs***	
Avelumab	£78,718	3.53	2.22				
BSC	£7,319	0.41	0.31	£71,399	3.11	1.91	£37,409

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LYs: Life years; QALYs: Quality-adjusted life years

Table 75: Treatment-experienced patients, undiscounted incremental results (avelumab vs. BSC)

Treatment	***Total***			***Incremental***			***ICER***
	Costs	***LYs***	***QALYs***	***Costs***	***LYs***	***QALYs***	
Avelumab	£82,680	3.53	2.72				
BSC	£7,319	0.41	0.31	£75,361	3.11	2.41	£31,260

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LYs: Life years; QALYs: Quality-adjusted life years

Treatment-naïve metastatic MCC patients

Discounted and undiscounted base-case results for avelumab versus BSC and chemotherapy are shown in Table 76 to Table 79 for treatment-naïve metastatic MCC patients. Compared with chemotherapy, avelumab is associated with 2.76 LYs gained, 1.56 incremental QALYs, and incremental costs of £68,104 per patient. The ICER is £43,633 per additional QALY gained. Compared with BSC, avelumab is associated with 2.76 LYs gained, 1.55 incremental QALYs, and incremental costs of £71,481 per patient. The ICER is £46,219 per additional QALY gained.

Table 76: Treatment-naïve patients, discounted full incremental analysis

Treatment	***Total***			***Incremental***			***ICER***
	Costs	***LYs***	***QALYs***	***Costs***	***LYs***	***QALYs***	
BSC	£7,103	2.02	1.38				
Chemotherapy	£10,480	2.02	1.37	£3,377	0.00	-0.01	Dominated
Avelumab	£78,584	4.78	2.93	£71,481	2.76	1.55	£46,219

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LYs: Life years; QALYs: Quality-adjusted life years

Table 77: Treatment-naïve patients, undiscounted full incremental analysis

Treatment	***Total***			***Incremental***			***ICER***
	Costs	***LYs***	***QALYs***	***Costs***	***LYs***	***QALYs***	
BSC	£7,450	2.02	1.56				
Chemotherapy	£10,933	2.02	1.54	£3,483	0.00	-0.01	Dominated
Avelumab	£83,057	4.78	3.69	£75,607	2.76	2.14	£35,409

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LYs: Life years; QALYs: Quality-adjusted life years

Table 78: Treatment-naïve patients, discounted results (avelumab vs.)

Treatment	***Total***			***Incremental***			***ICER***
	Costs	***LYs***	***QALYs***	***Costs***	***LYs***	***QALYs***	
Avelumab	£78,584	4.78	2.93				
Chemotherapy	£10,480	2.02	1.37	£68,104	2.76	1.56	£43,633
BSC	£7,103	2.02	1.38	£71,481	2.76	1.55	£46,219

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LYs: Life years; QALYs: Quality-adjusted life years

Table 79: Treatment-naïve patients, undiscounted results (avelumab vs.)

Treatment	***Total***			***Incremental***			***ICER***
	Costs	***LYs***	***QALYs***	***Costs***	***LYs***	***QALYs***	
Avelumab	£83,057	4.78	3.69				
Chemotherapy	£10,933	2.02	1.54	£72,124	2.76	2.15	£33,553
BSC	£7,450	2.02	1.56	£75,607	2.76	2.14	£35,409

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LYs: Life years; QALYs: Quality-adjusted life years

5.7.2 Clinical outcomes from the model

As part of the validation process, results from the model were compared with outcomes in the JAVELIN Merkel 200 trial. A summary of this comparison in terms of median OS and PFS is presented in Table 80.

Table 80: Avelumab model results compared with clinical data

Outcome	*Clinical study results*	*Model results*
Treatment-experienced patients		
OS	Median: 12.62 months Restricted mean: 15.63 months	Median: 12.30 months Restricted mean: 15.70 months
PFS	Median: 2.69 months Restricted mean: 10.14 months	Median: 2.18 months Restricted mean: 9.84 months
Treatment-naïve patients		
OS	Median: NR Restricted mean: [redacted] months	Median: 17.25 months Restricted mean: 8.67 months
PFS	Median: 9.10 months Restricted mean: [redacted] months	Median: 2.18 months* Restricted mean: 5.10 months

Key: NR, not reached; OS, overall survival; PFS, progression-free survival.

Note: Data cut off: 24-Mar-2017, follow-up ≥18 months for treatment-experienced patients, follow-up ≥3 months for treatment-naïve patients (n=14 with 6 months follow up).

*differs from clinical study results due to modelling approach used – hazard ratio of 1 has been applied rather than fitting curves directly to data from JAVELIN Merkel 200: Part B.

Abbreviations: NR: Not reached; OS: Overall survival; PFS: Progression-free survival

The comparison of model results with clinical data shown in Table 80 demonstrate similar values for treatment-experienced patients across the model and available trial data. For treatment-naïve patients, outcomes predicted by the model are lower than those reported in the available trial data most notably in the estimate of median PFS, which due to the initial drop noted in the PFS curve (shown in Figure 23 for treatment-experienced patients) should be interpreted with caution. The underestimate of 1L results is because conservative modelling assumptions informed by the 2L+ data and clinical input have been considered while the 1L data matures.

5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

Treatment-experienced metastatic MCC patients

Table 81: Summary of QALY gain by health state (treatment-experienced metastatic MCC)

QALYs	*Avelumab*	*BSC*
AE disutility	0.00	0.00
>100 days to death	2.05	0.13
30-100 days to death	0.12	0.13
<30 days to death	0.05	0.05
Total	2.22	0.31

Abbreviations: AE: Adverse event; BSC: Best supportive care; MCC: Merkel cell carcinoma; QALY: Quality adjusted life year

Table 82: Summary of costs by health state (treatment-experienced metastatic MCC)

Costs	***Avelumab***	***BSC***
PF On Tx	£67,371	£0
PF Off Tx	£1,903	£266
PP On Tx	£2,937	£0
PP Off Tx	£321	£187
EoL	£6,186	£6,866
Total	£78,718	£7,319

Abbreviations: BSC: Best supportive care; EoL: End of life; MCC: Merkel cell carcinoma; PF: Progression-free; PP: Post-progression; Tx: Treatment

Table 83: Summary of LY gain by health state (treatment-experienced metastatic MCC)

LYs	***Avelumab***	***BSC***
PF On Tx	0.75	0.00
PF Off Tx	2.24	0.24
PP On Tx	0.03	0.00
PP Off Tx	0.51	0.17
Total	3.53	0.41

Abbreviations: BSC: Best supportive care; LYs: Life years; MCC: Merkel cell carcinoma; PF: Progression-free; PP: Post-progression; Tx: Treatment

Table 84: Summary of predicted resource use by cost category (treatment-experienced metastatic MCC)

Costs	***Avelumab***	***BSC***
Drugs	£65,086	£0
Admin	£3,972	£0
RU	£3,459	£453
AEs	£15	£0
EoL	£6,186	£6,866
Total	£78,718	£7,319

Abbreviations: AEs: Adverse events; BSC: Best supportive care; EoL: End of life; MCC: Merkel cell carcinoma; RU: Resource use

Treatment-naïve metastatic MCC patients

Table 85: Summary of QALY gain by health state (treatment-naïve metastatic MCC)

QALYs	***Avelumab***	***Chemotherapy***	***BSC***
AE disutility	0.00	-0.01	0.00
>100 days to death	2.77	1.20	1.20
30-100 days to death	0.12	0.13	0.13
<30 days to death	0.05	0.05	0.05
Total	2.93	1.37	1.38

Abbreviations: AE: Adverse event; BSC: Best supportive care; MCC: Merkel cell carcinoma; QALY: Quality-adjusted life year

Table 86: Treatment-naïve, summary of costs by health state

Costs	*Avelumab*	*Chemotherapy*	*BSC*
PF On Tx	£67,078	£2,785	£0
PF Off Tx	£2,331	£866	£274
PP On Tx	£2,915	£0	£0
PP Off Tx	£290	£281	£281
EoL	£5,970	£6,547	£6,547
Total	£78,584	£10,480	£7,103

Abbreviations: BSC: Best supportive care; EoL: End of life; PF: Progression-free; PP: Post-progression

Table 87: Treatment-naïve, summary of life year gain by health state

LYs	*Avelumab*	*Chemotherapy*	*BSC*
PF On Tx	0.75	0.27	0.00
PF Off Tx	2.86	0.64	0.90
PP On Tx	0.03	0.00	0.00
PP Off Tx	1.13	1.12	1.12
Total	4.78	2.02	2.02

Abbreviations: BSC: Best supportive care; LYs: Life years; PF: Progression-free; PP: Post-progression

Table 88: First-line, summary of predicted resource use by category of cost

Costs	*Avelumab*	*Chemotherapy*	*BSC*
Drugs	£65,086	£173	£0
Admin	£3,972	£1,849	£0
RU	£3,541	£1,595	£555
AEs	£15	£315	£0
EoL	£5,970	£6,547	£6,547
Total	£78,584	£10,480	£7,103

Abbreviations: AEs: Adverse events; BSC: Best supportive care; EoL: End of life; RU: Resource use

5.8 Sensitivity analyses

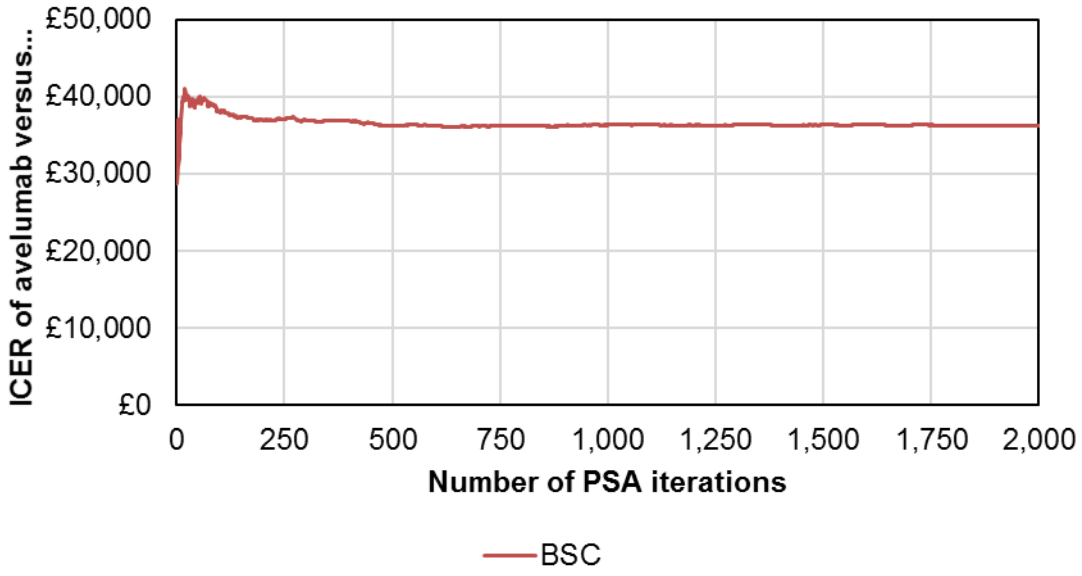
5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to establish the impact of model parameter uncertainty when all model parameters were varied simultaneously (parameters listed in section 5.6).

Treatment-experienced metastatic MCC patients

Model parameters were sampled within their respective bounds of uncertainty for 1,000 iterations, with the results recorded for each iteration. A total of 1,000 iterations were chosen as the mean ICER was shown to be suitably stable as shown in Figure 56.

Figure 56: Convergence of mean ICER by number of PSA iterations – treatment-experienced patients



Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; PSA: Probabilistic sensitivity analysis

The mean of these results was recorded, and the results from individual iterations were utilised to inform a PSA scatterplot and a cost-effectiveness acceptability curve. Mean probabilistic model results are presented in comparison to the deterministic results in Table 89.

Mean probabilistic and deterministic results are broadly comparable. However, due to the sensitivity in the ICER small changes in the total predicted QALYs for each treatment arm demonstrate notable differences in ICERs across both analyses – the ICER in the probabilistic analysis is reduced by approximately £1,000.

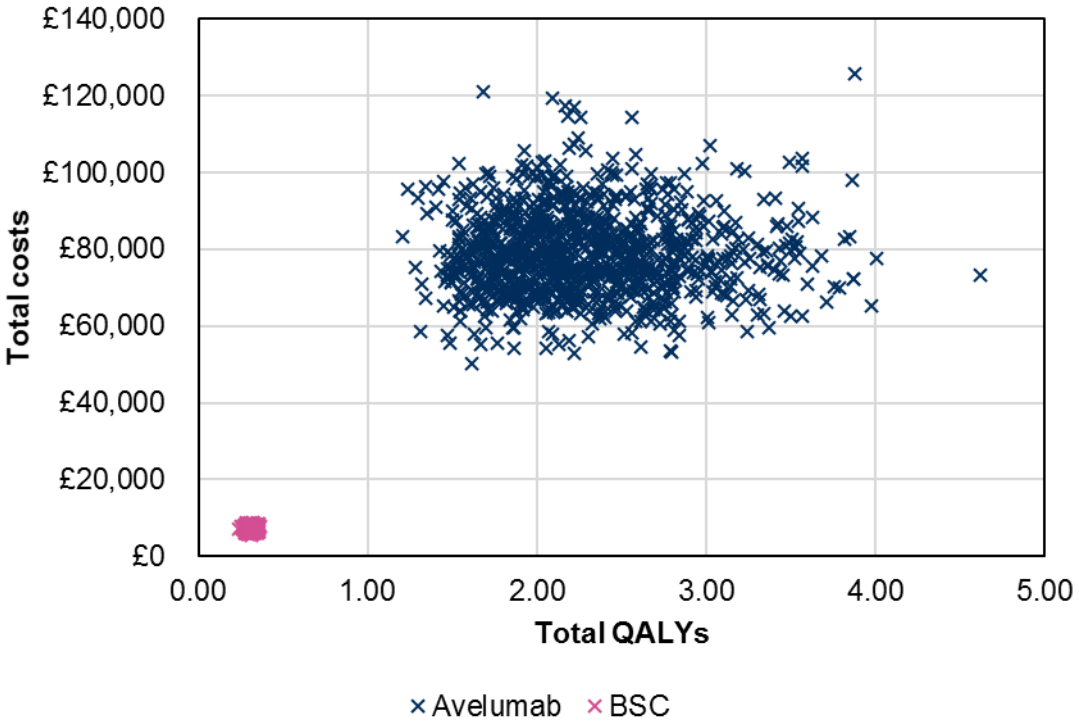
Table 89: Deterministic versus probabilistic base-case model results – treatment-experienced patients

Treatment	*Total costs*	*Total LYs*	*Total QALYs*	*ICER (avelumab vs.)*
Deterministic				
Avelumab	£78,718	3.53	2.22	
BSC	£7,319	0.41	0.31	£37,409
Probabilistic				
Avelumab	£79,060	3.66	2.29	
BSC	£7,312	0.41	0.31	£36,310

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LYs: Life years; QALYs: Quality-adjusted life years

The PSA scatter plot is presented in Figure 57. As expected, the majority of uncertainty is shown for the estimation of costs and outcomes relating to avelumab. In no simulation is avelumab predicted to be associated with poorer outcomes in comparison to treatment with BSC.

Figure 57: PSA scatter plot – treatment-experienced patients



Abbreviations: BSC: Best supportive care; PSA: Probabilistic sensitivity analysis; QALYs: Quality-adjusted life years

The cost-effectiveness acceptability curve (CEAC) is presented in Figure 58. The probability of avelumab being the most cost-effective treatment at a willingness to pay threshold of £50,000 per QALY gained is 84.0% compared to BSC.

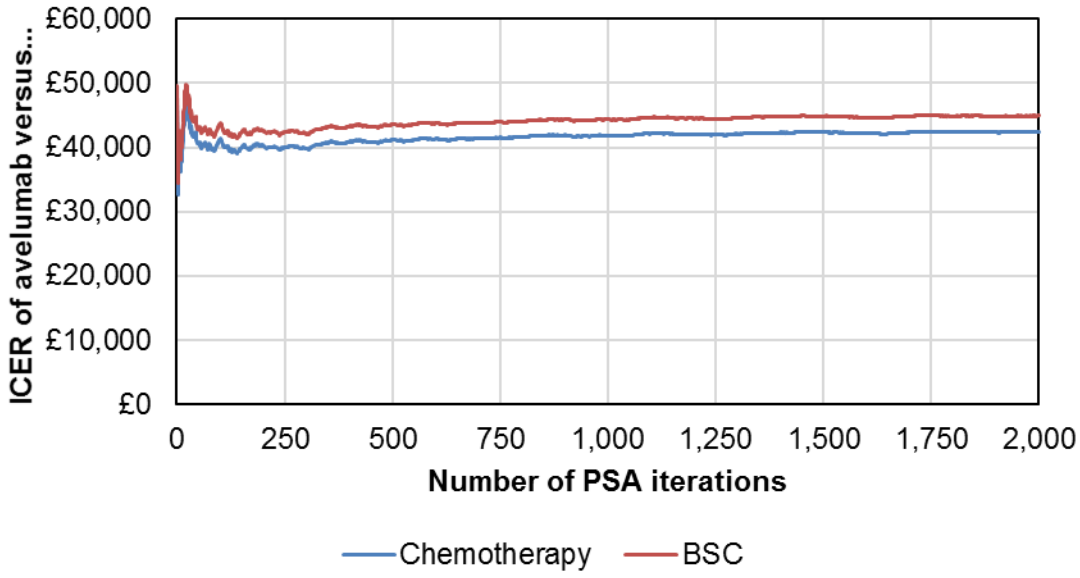
Figure 58: CEAC – treatment-experienced patients

Abbreviations: BSC: Best supportive care; CEAC: Cost-effectiveness acceptability curve

Treatment-naïve metastatic MCC patients

Model parameters were sampled within their respective bounds of uncertainty for 1,500 iterations, with the results recorded for each iteration. 1,500 iterations were chosen as the mean ICER was shown to be suitably stable as shown in Figure 59.

Figure 59: Convergence of mean ICER by number of PSA iterations – treatment-naïve patients



Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; PSA: Probabilistic sensitivity analysis

The mean of these results was recorded, and the results from individual iterations were utilised to inform a PSA scatterplot and a CEAC. Mean probabilistic model results are presented in comparison to the deterministic results in Table 90. Mean probabilistic and deterministic results are broadly comparable.

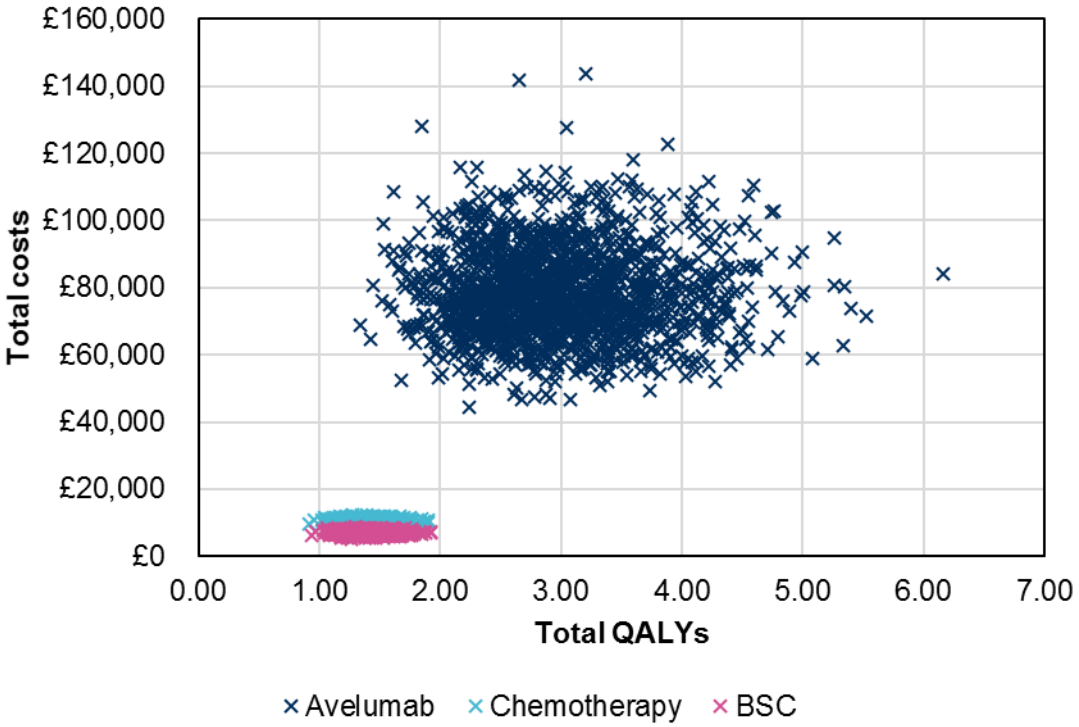
Table 90: Deterministic versus probabilistic base-case model results – treatment-naïve patients

Treatment	***Total costs***	***Total LYs***	***Total QALYs***	***ICER (avelumab vs.)***
Deterministic				
Avelumab	£78,584	4.78	2.93	
Chemotherapy	£10,480	2.02	1.37	£43,633
BSC	£7,103	2.02	1.38	£46,219
Probabilistic				
Avelumab	£78,802	4.90	2.99	
Chemotherapy	£10,473	2.04	1.38	£42,337
BSC	£7,078	2.04	1.39	£44,838

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LYs: Life years; QALYs: Quality-adjusted life years

The PSA scatter plot is presented in Figure 60. As expected, and as per outcomes for patients with treatment-experienced metastatic MCC, the majority of uncertainty is shown for the estimation of costs and outcomes relating to avelumab. Outcomes for BSC and chemotherapy are also shown to demonstrate more uncertainty than those in treatment-experienced metastatic MCC patients.

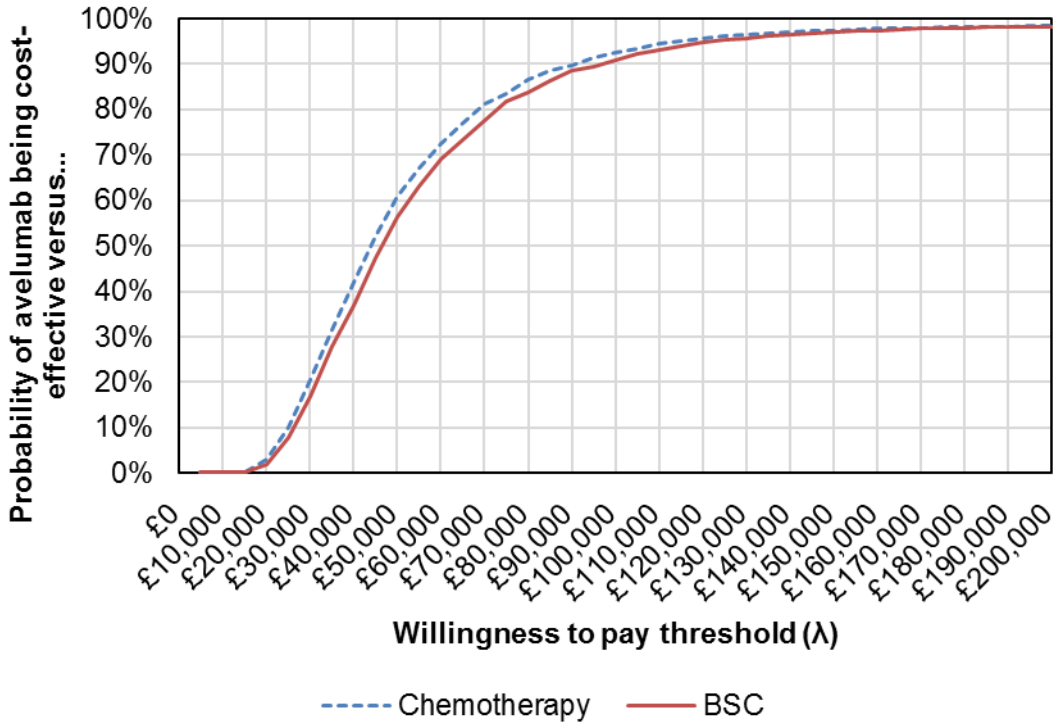
Figure 60: PSA scatter plot – treatment-naïve patients



Abbreviations: BSC: Best supportive care; PSA: Probabilistic sensitivity analysis; QALYs: Quality-adjusted life years

The CEAC is presented in Figure 61. The probability of avelumab being the most cost-effective treatment at a willingness to pay threshold of £50,000 per QALY gained is 56.4% compared to BSC, and 60.8% compared to chemotherapy.

Figure 61: CEAC – treatment-naïve patients



Abbreviations: BSC: Best supportive care; CEAC: Cost-effectiveness acceptability curve

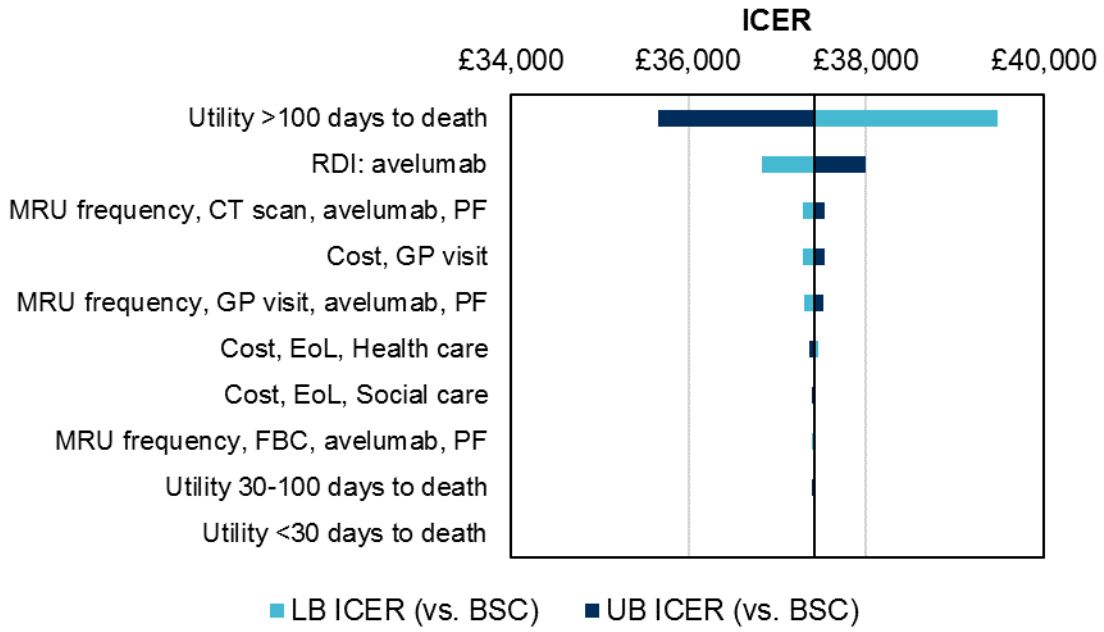
5.8.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to explore the sensitivity in the deterministic base-case model results when one parameter is varied at a time (Table 71). Each parameter was set to its lower and upper bound and model results were recorded. Parameters associated with direct correlation (e.g. curve fit parameters) and areas of structural uncertainty (e.g. choice of distribution) were not considered in this analysis, and are instead explored within the PSA (Section 5.8.1) and scenario analyses (Section 5.8.3).

Treatment-experienced metastatic MCC patients

The top ten influential parameters on the ICER are presented as a tornado diagrams in Figure 62.

Figure 62: OWSA tornado diagram, avelumab vs. BSC for patients with treatment-experienced metastatic MCC



Abbreviations: BSC: Best supportive care; CT: Computed tomography; EoL: End of life; FBC: Full blood count; GP: General practitioner; ICER: Incremental cost-effectiveness ratio; LB: Lower bound; LFT: Liver function test; MCC: Merkel cell carcinoma; MRU: Medical resource use; OWSA: One-way sensitivity analysis; PF: Progression-free; UB upper bound

The results of the OWSA demonstrate the most influential model parameters on cost-effectiveness results were related to the RDI of avelumab (and therefore the acquisition cost of avelumab) and HRQL. No other parameters explored within OWSA demonstrated notable impact of cost-effectiveness results.

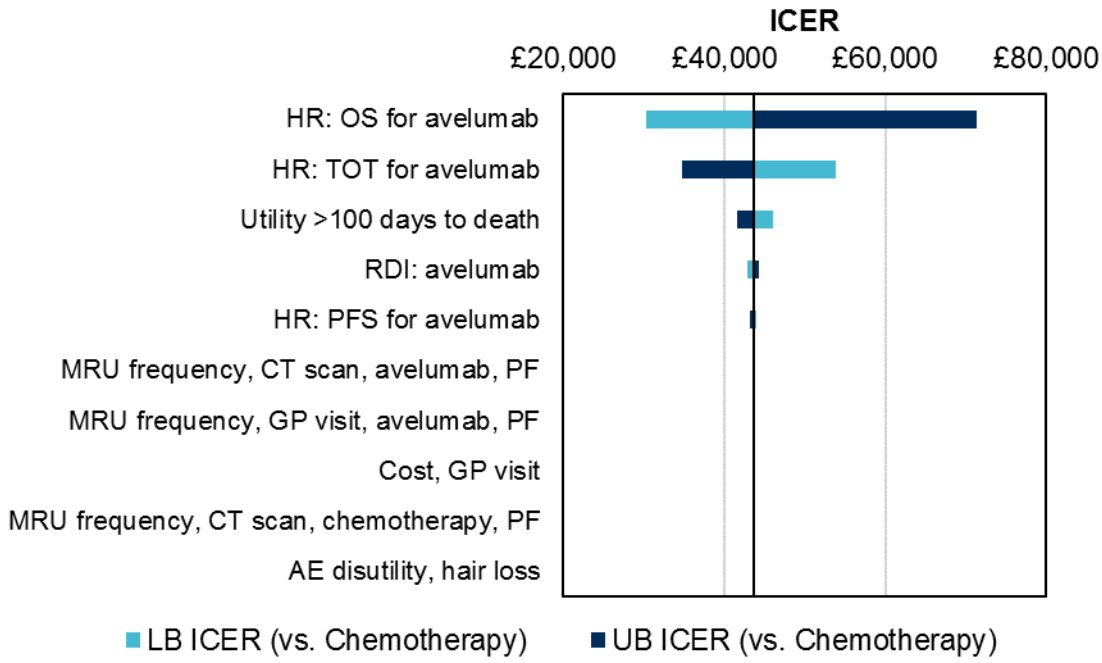
Treatment-naïve metastatic MCC patients

The top ten influential parameters on the ICER are presented as a tornado diagrams in Figure 63 for chemotherapy and Figure 64 for BSC.

Similar to the results of the OWSA for treatment-experienced metastatic MCC patients, OWSA results for treatment-naive metastatic MCC patients demonstrate the most influential model parameters on cost-effectiveness results were related to the RDI of avelumab and HRQL. Further to this, the application of a HR for the OS and ToT for avelumab demonstrates high uncertainty as expected. The HR for PFS is not associated with the same magnitude of influence on cost-effectiveness results, most likely due to the use of time to death based utilities in the model base-case, and the majority of benefit achieved for patients being driven by the OS curve.

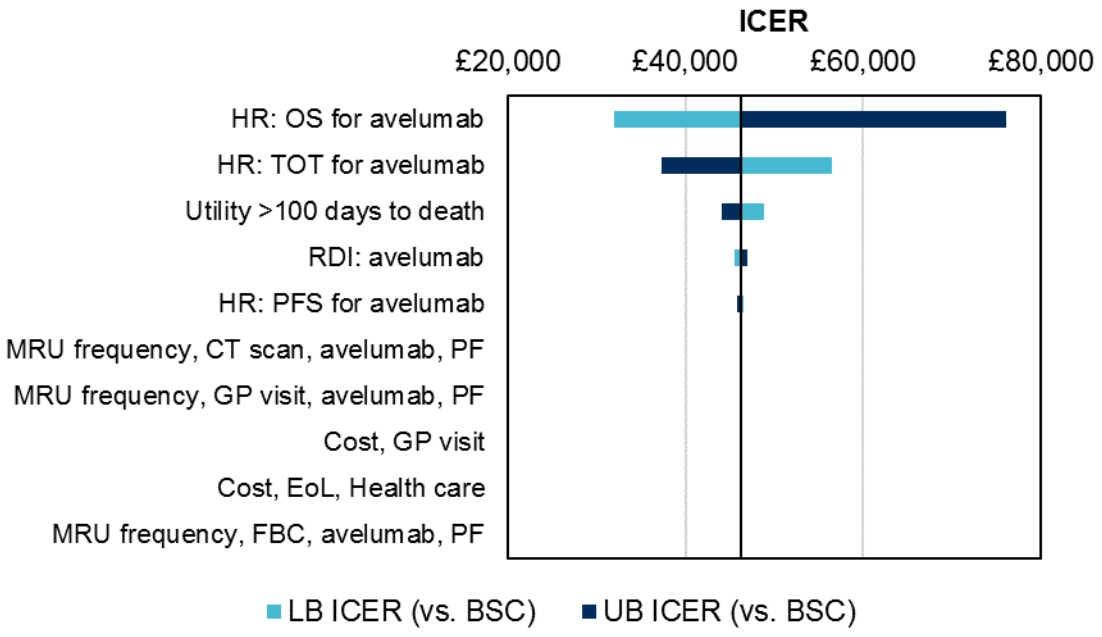
No other parameters explored within OWSA demonstrated notable impact of cost-effectiveness results.

Figure 63: OWSA tornado diagram, avelumab vs. chemotherapy for patients with treatment-naïve metastatic MCC



Abbreviations: AE: Adverse event; CT: Computed tomography; GP: General practitioner; HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; LB: Lower bound; MCC: Merkel cell carcinoma; MRU: Medical resource use; OS: Overall survival; OWSA: One-way sensitivity analysis; PF: Progression-free; PFS: Progression-free survival; RDI: Relative dose intensity; TOT: Time on treatment; UB upper bound

Figure 64: OWSA tornado diagram, avelumab vs. BSC for patients with treatment-naïve metastatic MCC



Abbreviations: CT: Computed tomography; EoL: End-of-life; FBC: Full blood count; GP: General practitioner; HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; LB: Lower bound; MCC: Merkel cell carcinoma; MRU: Medical resource use; OWSA: One-way sensitivity analysis; OS: Overall survival; PF: Progression-free; PFS: Progression-free survival; RDI: Relative dose intensity; TOT: Time on treatment; UB upper bound

5.8.3 Scenario analysis

In order to further assess the robustness of the economic analysis results, scenario analyses were performed. Base case model settings were changed and the impact of these changes on results were assessed. Scenarios explored included selecting varying time horizons, discount rates, survival assumptions, treatment duration assumptions, utility values and costs.

Treatment-experienced metastatic MCC patients

The full list of scenarios considered for patients with treatment-experienced metastatic MCC are presented in Table 91.

Table 91: Results of scenario analysis – treatment-experienced metastatic MCC patients

Base case input	***Scenario***	***ICER***
Time horizon 40 years	Time horizon of 5 years	£65,258
	Time horizon of 10 years	£47,186
	Time horizon of 20 years	£38,467
	Time horizon of 30 years	£37,418
Discounting: All 3.5%	Discounting: All 0%	£31,260
	Discounting: All 1.5%	£33,931
	Discounting: All 3.5%	£37,409
	Discounting: All 6%	£41,586
European patients (for derivation of average patient weight)	All patients	£39,274
OS: Extrapolation options – avelumab Spline – 1 knot - odds	Parametric - exponential	£74,659
	Parametric - generalised gamma	£38,944
	Parametric - Gompertz	£30,092
	Parametric - log-logistic	£48,587
	Parametric - log-normal	£49,240
	Parametric - Weibull	£70,712
	Spline - 1 knot - hazard	£45,903
	Spline - 1 knot - odds	£37,409
	Spline - 1 knot - normal	£42,017
	Spline - 2 knots - hazard	£44,452
	Spline - 2 knots - odds	£36,840
	Spline - 2 knots - normal	£38,303
	Spline - 3 knots - hazard	£42,844
	Spline - 3 knots - odds	£36,596
	Spline - 3 knots - normal	£38,449
	Mixture cure - exponential	£41,099
	Mixture cure - Weibull	£41,527
	Mixture cure - log-normal	£44,953
	Mixture cure - log-logistic	£29,003
	General population survival extrapolation	£31,588
OS: Extrapolation options - comparator Parametric - Gompertz	Parametric - exponential	£37,591
	Parametric - generalised gamma	£37,389
	Parametric - Gompertz	£37,409
	Parametric - log-logistic	£37,923
	Parametric - log-normal	£37,781
	Parametric - Weibull	£37,401

	Inverse variance (weibull - 2L only)	£37,580
	Bivariate normal (weibull - 2L only)	£37,980
PFS: Extrapolation options - avelumab Spline - 3 knots - hazard	Spline - 1 knot - hazard	£37,423
	Spline - 1 knot - odds	£37,409
	Spline - 1 knot - normal	£37,430
	Spline - 2 knots - hazard	£37,436
	Spline - 2 knots - odds	£37,438
	Spline - 2 knots - normal	£37,430
	Spline - 3 knots - hazard	£37,406
	Spline - 3 knots - odds	£37,409
	Spline - 3 knots - normal	£37,338
	Spline - custom	£37,243
PFS: Extrapolation options - comparator Parametric - Weibull	Parametric - exponential	£37,409
	Parametric - generalised gamma	£37,409
	Parametric - Gompertz	£37,409
	Parametric - log-logistic	£37,409
	Parametric - log-normal	£37,409
	Parametric - Weibull	£37,409
	Inverse variance (weibull - 2L only)	£37,409
	Bivariate normal (weibull - 2L only)	£37,409
ToT: Extrapolation options - avelumab Parametric – Log-logistic	Parametric - exponential	£35,811
	Parametric - generalised gamma	£36,733
	Parametric - Gompertz	£38,079
	Parametric - log-logistic	£37,409
	Parametric - log-normal	£38,390
	Parametric - Weibull	£36,194
	Spline - 1 knot - hazard	£36,635
	Spline - 1 knot - odds	£36,230
	Spline - 1 knot - normal	£36,386
	Spline - 2 knots - hazard	£36,754
	Spline - 2 knots - odds	£37,043
	Spline - 2 knots - normal	£36,992
	Spline - 3 knots - hazard	£36,754
	Spline - 3 knots - odds	£37,196
	Spline - 3 knots - normal	£38,144
ToT: Estimated discontinuation time for the majority of patients: 2 year(s)	1 year(s)	£31,334
	1.5 year(s)	£34,756
	2 year(s)	£37,409
	2.5 year(s)	£39,575

	3 year(s)	£41,402
ToT: Proportion of patients expected to remain on treatment after 2 years of treatment: 33%	5%	£33,459
	10%	£34,156
	15%	£34,853
	20%	£35,550
	25%	£36,247
	30%	£36,945
	35%	£37,642
	40%	£38,339
	45%	£39,036
	50%	£39,733
	55%	£40,430
	60%	£41,127
	65%	£41,824
	70%	£42,521
	75%	£43,218
	80%	£43,915
	85%	£44,612
	90%	£45,309
	95%	£46,006
	100%	£46,704
ToT: Maximum expected treatment duration: 5 year(s)	3 year(s)	£34,759
	4 year(s)	£36,240
	5 year(s)	£37,409
	6 year(s)	£38,369
	7 year(s)	£39,176
Utilities: Time to death (GEE)	Time to death (GEE)	£37,409
	Progression status	£35,568
	Time to death (decrement for final 30 days)	£35,464
Costs: End of life care costs Cancer type Average	Cancer type Lung	£37,531
	Cancer type Breast	£37,392
	Cancer type Colorectal	£37,436
	Cancer type Prostate	£37,277
	Cancer type Average	£37,409
Comparator: BSC	BSC	£37,409
	Chemotherapy	£35,949

Abbreviations: BSC: Best supportive care; GEE: Generalized estimating equation; ICER: Incremental cost-effectiveness ratio; MCC: Merkel cell carcinoma; OS: Overall survival; PFS: Progression-free survival; ToT: Time on treatment

Treatment-naïve metastatic MCC patients

The full list of scenarios considered for treatment-naïve metastatic MCC patients are presented in Table 92.

Table 92: Results of scenario analysis – treatment-naïve metastatic MCC patients

Base case input	***Scenario***	***ICER (avelumab vs.)***	
		Chemotherapy	***BSC***
Time horizon 40 years	Time horizon of 5 years	£127,507	£137,567
	Time horizon of 10 years	£66,209	£70,489
	Time horizon of 20 years	£45,142	£47,829
	Time horizon of 30 years	£43,380	£45,944
Discounting: All 3.5%	Discounting: All 0%	£33,553	£35,409
	Discounting: All 1.5%	£37,682	£39,827
	Discounting: All 3.5%	£43,633	£46,219
	Discounting: All 6%	£51,746	£54,983
European patients (for derivation of average patient weight)	All patients	£46,072	£48,698
OS: Extrapolation options – avelumab Spline – 1 knot - odds	Parametric - exponential	£375,007	£428,303
	Parametric - generalised gamma	£46,376	£49,156
	Parametric - Gompertz	£32,963	£34,836
	Parametric - log-logistic	£67,566	£71,960
	Parametric - log-normal	£70,157	£74,766
	Parametric - Weibull	£252,254	£280,071
	Spline - 1 knot - hazard	£61,669	£65,597
	Spline - 1 knot - odds	£43,633	£46,219
	Spline - 1 knot - normal	£52,372	£55,587
	Spline - 2 knots - hazard	£58,021	£61,665
	Spline - 2 knots - odds	£42,654	£45,173
	Spline - 2 knots - normal	£45,173	£47,868
	Spline - 3 knots - hazard	£54,281	£57,641
	Spline - 3 knots - odds	£42,239	£44,729
	Spline - 3 knots - normal	£45,435	£48,148
	Mixture cure - exponential	£50,358	£53,420
	Mixture cure - Weibull	£51,445	£54,585
	Mixture cure - log-normal	£57,483	£61,070
	Mixture cure - log-logistic	£30,371	£32,079
	General population survival extrapolation	£34,220	£36,174
	Parametric - exponential	£38,489	£40,671
	Parametric - generalised gamma	£39,714	£42,006

OS: Extrapolation options - comparator Parametric - Gompertz	Parametric - Gompertz	£39,714	£42,006
	Parametric - log-logistic	£43,633	£46,219
	Parametric - log-normal	£43,893	£46,497
	Parametric - Weibull	£38,270	£40,434
PFS: Extrapolation options - avelumab Spline - 3 knots - hazard	Spline - 1 knot - hazard	£43,755	£46,343
	Spline - 1 knot - odds	£43,725	£46,312
	Spline - 1 knot - normal	£43,751	£46,339
	Spline - 2 knots - hazard	£43,721	£46,309
	Spline - 2 knots - odds	£43,756	£46,344
	Spline - 2 knots - normal	£43,751	£46,339
	Spline - 3 knots - hazard	£43,570	£46,156
	Spline - 3 knots - odds	£43,633	£46,219
	Spline - 3 knots - normal	£43,404	£45,989
	Spline - custom	£43,322	£45,906
PFS: Extrapolation options - comparator Parametric - Weibull	Parametric - exponential	£43,504	£46,219
	Parametric - generalised gamma	£43,627	£46,219
	Parametric - Gompertz	£43,471	£46,219
	Parametric - log-logistic	£43,633	£46,219
	Parametric - log-normal	£43,622	£46,219
	Parametric - Weibull	£43,698	£46,219
ToT: Extrapolation options - avelumab Parametric – Log-logistic	Parametric - exponential	£41,678	£44,247
	Parametric - generalised gamma	£42,805	£45,384
	Parametric - Gompertz	£44,452	£47,046
	Parametric - log-logistic	£43,633	£46,219
	Parametric - log-normal	£44,832	£47,429
	Parametric - Weibull	£42,147	£44,720
	Spline - 1 knot - hazard	£42,686	£45,265
	Spline - 1 knot - odds	£42,191	£44,764
	Spline - 1 knot - normal	£42,382	£44,957
	Spline - 2 knots - hazard	£42,831	£45,411
	Spline - 2 knots - odds	£43,185	£45,767
	Spline - 2 knots - normal	£43,123	£45,705
	Spline - 3 knots - hazard	£42,832	£45,411
	Spline - 3 knots - odds	£43,372	£45,956
	Spline - 3 knots - normal	£44,531	£47,126
ToT: Estimated discontinuation time for the majority of patients: 2 year(s)	1 year(s)	£36,203	£38,721
	1.5 year(s)	£40,389	£42,946
	2 year(s)	£43,633	£46,219
	2.5 year(s)	£46,281	£48,892

	3 year(s)	£48,515	£51,147
ToT: Proportion of patients expected to remain on treatment after 2 years of avelumab treatment: 33%	5%	£38,803	£41,345
	10%	£39,655	£42,205
	15%	£40,507	£43,065
	20%	£41,360	£43,925
	25%	£42,212	£44,786
	30%	£43,064	£45,646
	35%	£43,917	£46,506
	40%	£44,769	£47,366
	45%	£45,621	£48,227
	50%	£46,474	£49,087
	55%	£47,326	£49,947
	60%	£48,179	£50,808
	65%	£49,031	£51,668
	70%	£49,883	£52,528
	75%	£50,736	£53,388
	80%	£51,588	£54,249
	85%	£52,441	£55,109
	90%	£53,293	£55,969
	95%	£54,145	£56,830
	100%	£54,998	£57,690
ToT: Maximum expected treatment duration: 5 year(s)	3 year(s)	£40,391	£42,948
	4 year(s)	£42,203	£44,776
	5 year(s)	£43,633	£46,219
	6 year(s)	£44,806	£47,403
	7 year(s)	£45,793	£48,400
Utilities: Time to death (GEE)	Time to death (GEE)	£43,633	£46,219
	Progression status	£41,064	£43,475
	Time to death (decrement for final 30 days)	£40,936	£43,338
Costs: End of life care costs Cancer type Average	Cancer type Lung	£43,759	£46,347
	Cancer type Breast	£43,615	£46,202
	Cancer type Colorectal	£43,661	£46,248
	Cancer type Prostate	£43,495	£46,081
	Cancer type Average	£43,633	£46,219

Abbreviations: BSC: Best supportive care; GEE: Generalized estimating equation; ICER: Incremental cost-effectiveness ratio; MCC: Merkel cell carcinoma; OS: Overall survival; PFS: Progression-free survival; ToT: Time on treatment

5.8.4 Summary of sensitivity analyses results

Sensitivity analyses were undertaken to explore key areas of uncertainty associated with the cost-effectiveness analysis. Parameter uncertainty was explored through probabilistic and deterministic OWSA, with structural uncertainty and key assumptions explored through scenario analyses.

Probabilistic sensitivity analysis results demonstrated that cost-effectiveness results were most sensitive to assumptions regarding the HRQL of patients and predicted long-term survival outcomes based on the shape of the cost-effectiveness scatterplots. OWSA showed the key parameters of influence on cost-effectiveness results were utility values and the HR applied to demonstrate OS and ToT for treatment-naïve patients. Scenario analyses highlighted key areas of uncertainty around the extrapolation of survival and anticipated duration of avelumab treatment.

5.9 Subgroup analysis

There are no subgroups of relevance to this appraisal, hence there are no subgroup analyses results produced by the economic model.

5.10 Validation

As stated in NICE DSU TSD 14, long-term extrapolated outcomes should be validated with the use of external data or clinical opinion (Faria 2015). Due to the poor prognosis of metastatic MCC patients along with the rarity of metastatic MCC, no external data sources with long-term follow-up were identified. Thus, validation of clinical benefit observed with avelumab depends upon comparison of outcomes between the model and clinical trials, whilst relying on expert opinion to confirm modelling assumptions. Predictions are reflective of clinical expectation and likely outcomes for patients in UK practice.

Comparison of outcomes - model and trial

As part of the validation process, results from the model were compared with outcomes in the JAVELIN Merkel 200 trial 2L+ cohort (Part A). A summary of this comparison in terms of median OS and PFS is presented in Table 80. Table 93 compares outcomes across time for both cohorts.

Table 93: Comparison of model and trial outcomes across time for both cohorts

Treatment-experienced					
Outcome	***Source***	***3 months (%)***	***6 months (%)***	***12 months (%)***	***18 months (%)***
OS	Trial	87.3	69.8	50.8	[redacted]
	Model	85.5	68.9	50.7	41.2
PFS	Trial	42.3	39.8	29.1	[redacted]
	Model	44.6	36.5	30.1	26.9
Treatment-naïve					
Outcome	***3 months***	***3 months (%)***	***6 months (%)***	***12 months (%)***	***18 months (%)***
OS	Trial	[redacted]	[redacted]	N/A	N/A
	Model	88.2	74.2	58.1	49.2
PFS	Trial	[redacted]	[redacted]	N/A	N/A
	Model	44.6	36.5	30.1	26.9

Abbreviations: N/A: Non-applicable; OS: Overall survival; PFS: Progression-free survival

Treatment-experienced metastatic MCC patients

In JAVELIN Merkel 200 2L+ cohort (Part A), avelumab was associated with a median OS of [redacted] months. This compares well with the median OS predicted by the model of 12.30 months. Similarly, for PFS, JAVELIN Merkel 200 2L+ cohort (Part A) showed a median PFS for treatment-experienced patients of 2.69 months, similar to the model's prediction of 2.18 months.

Treatment-naïve metastatic MCC patients

In JAVELIN Merkel 200 1L cohort (Part B), [redacted]; however, median OS predicted by the model is 17.25 months. Median PFS was 9.10 months in JAVELIN Merkel 200 1L cohort (Part B) and 2.18 months predicted by the model (owing to the conservatively applied HR for PFS See Section 5.3.2).

External validation

As we've discussed throughout the submission, we sought to validate our approaches and assumptions with clinical and health economic experts.

During model construction

In order to ensure the scientific rigour of this appraisal, Merck KGaA/Pfizer partnered with a number of Health Economic advisers. An independent health economic and outcomes research consultancy were commissioned to provide economic analysis and insight into best modelling practices. Additionally, a modelling steering committee comprising [redacted] were also consulted to advise on modelling methodologies used to inform the analysis, and took part in ad hoc meetings regarding economic model development, as well as a formal advisory board held by Merck KGaA/Pfizer on 10th April 2017. Clinical experts [redacted] advised on clinical assumptions and model inputs, both in the context of the advisory board and in frequent meetings as the modelling work was underway.

The specific aims of the advisory board meeting were:

- to better understand the disease background and current management pathway of MCC patients in England,
- to confirm that clinical trial evidence was applicable to patients in England, and
- to validate the clinical assumptions presented in the economic model.

The latter included full validation of comparators, resource use, costs and trial utility values.

During the meeting, the treatment pathway for patients with metastatic MCC was discussed. It was confirmed that, for treatment-naïve patients both chemotherapy and BSC are used, with the choice dependent on the health of the patient. For treatment-experienced patients almost no patients receive chemotherapy and most will receive BSC. In addition to this, 75% of patients across all lines will receive radiotherapy. Clinicians agreed that the trial population was a reasonable representation of clinical practice in England although the prior therapies used differ to standard practice. There was a consensus that the lack of UK data was not ideal, but was not prohibitive given the issues with trial recruitment.

With regards to the trial evidence from JAVELIN Merkel 200 2L+ cohort (Part A), there was a general agreement that the response data was approximately in line with what has been observed with other immuno-oncology therapies used in treatment-experienced patients in other cancers. Advisors agreed that the PFS pattern observed was in line with what is expected with other immuno-oncology therapies; that is, patients either drop off early on or achieve durable responses.

Clinicians agreed that carboplatin plus etoposide was the most relevant chemotherapy regimen for comparison where appropriate, with cisplatin and etoposide regimens used where carboplatin is not tolerated. It was agreed that the most common AE observed with carboplatin plus etoposide is fatigue. Clinicians agreed that the safety evidence from JAVELIN Merkel 200 is acceptable and that the low occurrence of grade 3 AEs and absence of Grade 4 AEs is favourable compared with other immuno-oncology therapies.

When asked about synthesising comparator evidence, clinicians agreed that the treatment regimens used in the EU and US observational studies conducted by Merck KGaA/Pfizer are not representative of clinical practice in England; however, it was expressed that the outcomes with regimens used in England are not likely to differ much to those seen in the observational data, and that outcomes for chemotherapy at this line would be very similar to those seen with BSC i.e. treatment is not effective.

Advisors recommended that the same utility values could be used for patients irrespective of treatment received, in the absence of sufficiently robust data for treatment-naïve patients – with disutilities applied for AEs.

Following the advisory board, a subsequent clinical validation meeting with [redacted], was undertaken on 4th May 2017 in order to validate further assumptions around the model base-case settings.

[redacted] confirmed the comparators for each line of treatment, and stated that for treatment-experienced patients, outcomes are the same for those treated with either chemotherapy or BSC. [redacted] explained that as such early signals in response rate would be seen it would be unlikely that a durable long-term OS benefit would not be observed. Model inputs such as AE rates, resource use frequencies and types along with the differences in these parameters between patient cohorts were also discussed.

Following model construction

Following model finalisation, meetings were held with three clinical experts: [redacted] to validate base-case model outputs: OS, PFS, treatment duration and the approach taken to model data for treatment-naïve patients.

OS

[redacted] stated that, based on the data seen, a durable benefit for patients treated with avelumab is implied, and it would therefore be unlikely not to observe a plateau in the OS curve in the long term given similar patterns seen for other checkpoint inhibitor treatments such as ipilimumab in melanoma. [redacted] further explained that with such high response rates, this would translate into long-term OS benefits, and, after 5 years, the hazard of death should be similar to that observed in the age-matched population.

[redacted] agreed that he would expect to see similar patient outcomes (in terms of long-term survival and durable response) for patients treated with avelumab compared to patients treated with other PD-1/PD-L1 drugs in other cancers.

[redacted] agreed with model OS predictions and further explained that a halving in survival rate from 10 years to 15 years is also reasonable.

PFS

[redacted] agreed that model estimates for PFS tie in with the OS projections. PFS and OS are closely correlated in MCC because patients who progress early on in their disease die rapidly soon after. [redacted] agreed that PFS and OS would correlate in the short term but long term those who have responded to treatment then subsequently progress may have better survival prospects.

Approach to modelling treatment-naïve patients

[redacted] explained that a HR for OS of 0.8 seemed reasonable for application to OS treatment-naïve patients, as he would expect a slightly lower proportion of patients to benefit in a treatment-experienced setting due to similar patterns seen with other immuno-oncology therapies such as pembrolizumab.

[redacted] and [redacted] both agreed that assuming a 20% OS benefit in 1L over 2L is a reasonable assumption to make.

Treatment duration

In the model it has been assumed that the majority of patients cease treatment at 2 years. [redacted] both agreed that it was reasonable for a third of patients to remain on treatment after this time, with [redacted] suggesting a realistic estimate would be between 30% and 40%. All clinicians agreed that a maximum treatment duration of 5 years, after which time all patients cease treatment, is reasonable. Furthermore, [redacted] predicted that, based on melanoma data, continued treatment benefit would be observed.

Model QC

The model was also subject to thorough quality-control checks by internal health economists not involved with the construction of the economic model. Quality-control checks covered, but was not limited to, a checklist of basic validity checks (e.g. setting all costs to zero and ensuring the model outputs zero costs), sheet by sheet check of model logic (e.g. checking patient flow sheet calculations), module by module check of VBA logic, validity assessment of outcomes (e.g. comparing available trial data with the outcomes of the model), and editorial checks (e.g. performing a spell check of model content).

Summary

A summary of the validation processes conducted are provided in Table 94.

Table 94: Validation of the de novo cost-effectiveness analysis

Validation performed by	*Nature of validation*	*Date(s)*	*Aspects covered*
Immuno-oncology (IO) steering committee	Model development	Jan-July 2017	Clinical data, economic model design and analyses
Advisory board including a range of clinical and economic experts	Clinical overview	10th April 2017	Disease background, current management, clinical data and economic inputs
[redacted]	Model base case	4th May 2017	Base case assumptions: comparators, clinical efficacy, treatment regimens, utilities, resource use
[redacted]	Model predictions	June-July 2017	Clinical assumptions: Treatment duration, 1L HRs and clinical outcomes
Independent internal health economists	Quality-control checks	April-July 2017	Cost-effectiveness model calculations

Abbreviations: IO: Immuno-oncologic

5.11 Interpretation and conclusions of economic evidence

Section 5 presents a comprehensive set of analyses undertaken to establish the cost-effectiveness of avelumab in the ultra-rare condition, metastatic Merkel Cell Carcinoma. The base-case results

demonstrate that avelumab is a cost-effective treatment option in patients with treatment-experienced metastatic MCC, with an ICER of £37,409 versus BSC. In treatment-naïve patients, avelumab is associated with an ICER of £43,633 versus chemotherapy.

The conclusion that avelumab is a cost-effective use of NHS resources for this small, under-served population, is based on a cost-utility analysis considering a NICE reference-case perspective, with structural features and clinical assumptions validated by clinical and economic experts. There are limitations in the analysis, ultimately related to the rarity of the underlying condition and the consequent trial design (single-arm) that was adopted following early discussions with regulators. While there were no UK patients enrolled in JAVELIN Merkel 200, the differences between patients in the trial and those potentially treated in England are considered inconsequential by clinical experts. Uncertainty linked to data maturity may diminish over time, but that resulting from the lack of controlled comparative data and associated with the sample size, will not, and is a direct consequence of this being an ultra-orphan condition.

In the absence of randomised data, it is challenging to generate accurate and unbiased estimates of effect in untreated patients. We have elected to utilise historical control data generated as part of the clinical development programme for avelumab. We are cognisant of the inherent challenges of working with historical control data but believe these are minimised, in so far as they can be, by the intentional match of inclusion and exclusion criteria of the observational studies to the interventional trial. Furthermore, a full assessment of the methods available to adjust for confounding preceded the use of these data in modelling.

Clinicians agree that patient outcomes today are poor and whilst the implemented evidence is from observational studies, the outcomes between studies are uniformly poor, such that even the most optimistic assumption would not markedly affect the cost-effectiveness of avelumab. The potential of avelumab to change this disease trajectory for patients is recognised by clinicians and acknowledged by regulators. Early evidence suggests that treatment with avelumab is associated with long-term survival in a proportion of patients and clinical experts are aligned in their expectation of an immune-response tail in OS which will become more evident as the data further mature. This is consistent with all other immuno-oncology therapies where there are long term data (Schadendorf 2015). The economic model projects mean survival gains of 1.6 - 1.9 QALYs with treatment, depending on prior therapy. These outcomes are not unreasonable in a treatment landscape where a small group of patients may achieve durable responses and a very different disease trajectory to that experienced with current standard of care.

In conclusion, our analyses support avelumab as a promising and innovative treatment for a small, under-served patient population, with limited unlicensed treatment options that deliver a poor benefit: risk ratio. Avelumab, therefore represents a step change in therapy to these patients, one that is also a cost-effective use of NHS resources with limited budget impact.

6 Assessment of factors relevant to the NHS and other parties

6.1 Number of people eligible for treatment in England

Metastatic MCC is an extremely rare disease with very few cases diagnosed annually; in Europe, the reported incidence of MCC is between 0.2 per 100,000 and 0.4 per 100,000 per year (average incidence of 0.3 per 100,000) (Kaufman 2016c).

Table 95: Calculations of the annual number of cases of metastatic MCC in England

		Reference
Incidence of MCC in Europe	0.3 per 100,000	(Kaufman 2016c)
Population of England	55,268,100	(ONS 2016)
Number of MCC cases in England per year	55,268,100/100,000 x 0.3 = **165 cases**	
Proportion of MCC cases metastatic at diagnosis	5% - 12%	(Stokes 2009; Fitzgerald 2015; Jackson 2015)
Number of MCC cases metastatic at diagnosis in England per year	(165 x 0.05) = **8 cases** (165 x 0.12) = **20 cases**	
Additional proportion of MCC cases relapsing with metastatic disease	37%	(Allen 2005; Stokes 2009; Santamaria-Barria 2013)
Number of MCC cases relapsing with metastatic disease in England per year	(165 x 0.37) = **61 cases**	
Total number of metastatic MCC cases in England per year	**70 - 81 cases**	

References: See appropriate row of table

Abbreviations: MCC: Merkel cell carcinoma

The number of patients eligible for treatment with avelumab was calculated as the proportions of metastatic MCC patients with stage IV disease from the overall incidence of MCC in Europe (Table 95). Approximately 37% of patients presenting with local or regional tumours subsequently develop recurrent disease (Allen 2005; Stokes 2009; Santamaria-Barria 2013).

The total estimated population of adults in England with the condition in year 1 is estimated to lie between 70 and 81. The estimates are detailed in Section 3.4. Clinicians during a UK advisory board confirmed that they expect patient numbers to be very small and that at most 100 patients would be diagnosed with metastatic MCC across the whole of England.

Table 96 below shows the total eligible patients over the next 5 years (2018-2022), assuming a population growth of 0.8% and stable disease epidemiology. The number of eligible patients is estimated to be approximately 75 (assuming an average proportion of MCC cases metastatic at diagnosis of 8.5%) in year 1.

Table 96: Maximum metastatic MCC population eligible for avelumab

Year	*2018*	*2019*	*2020*	*2021*	*2022*
Eligible patient population	75	76	76	77	77

Abbreviations: MCC: Merkel cell carcinoma

6.2 Assumptions made about current treatment options and uptake of technologies.

There are no alternative licensed therapies for metastatic MCC.

6.3 Assumptions of market share in England

For the purposes of this section, we assume 100% uptake of avelumab and present this as the maximum likely impact for the NHS of the introduction of this technology.

6.4 Other significant costs associated with treatment

Administration costs for the intravenous delivery of avelumab are incorporated in to the budget impact estimates below, as are costs of monitoring and managing adverse events. These estimates are derived from the economic model and therefore represent the total projected lifetime costs of patients.

6.5 Unit cost assumptions and calculations

Cost inputs for the budget impact model (BIM) are linked to the economic model and described fully in Section 5.

6.6 Estimates of resource savings

Given the comparators in the economic model are either chemotherapy or BSC no gross budget impact savings are realised. However, due to fewer AEs lower treatment management costs are expected compared with standard of care.

6.7 Estimated annual budget impact on the NHS in England.

The net budget impact for treating patients with metastatic MCC when avelumab is introduced is estimated to be between £3,271,984 to £3,139,341 and £4,292,500 to £4,321,054 in the years 2018-2022, respectively.

The detailed net budget impact, assuming 100% avelumab uptake for treatment-experienced and treatment-naïve metastatic MCC patients is shown in Table 97 and Table 98.

Table 97: Estimated net budget impact over 5 years for treatment-experiences patients (assuming 100% market share uptake)

	2018	***2019***	***2020***	***2021***	***2022***
Treatment costs	£3,083,799	£3, 764,335	£ 3,892,658	£ 3,979,326	£4,045,622
Administration costs	£188,184	£229,713	£237,713	£242,832	£246,878
Total costs	**£3,271,984**	**£3,994,048**	**£4,130,202**	**£4,222,159**	**£4,292,500**

Table 98: Estimated net budget impact over 5 years for treatment-naive patients (assuming 100% market share uptake)

	2018	***2019***	***2020***	***2021***	***2022***
Treatment costs	£3,072,438	£3,848,866	£ 4,001,901	£4,107,622	£4,189,201
Administration costs	£66,903	£113,449	£121,982	£127,645	£131,853
Total costs	**£3,139,341**	**£3,962,315**	**£4,123,883**	**£4,235,267**	**£4,321,054**

6.8 Other opportunities for resource savings or redirection of resources

None.

6.9 Limitations within the budget impact analysis

Any limitations of these assessments are linked to the underlying evidence base for MCC and the uncertainties surrounding the parameters in the economic model. Expert clinical opinion has been sought where possible to try and minimise these uncertainties.

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Single technology appraisal

Avelumab for treating metastatic merkel cell carcinoma

Dear Amerah,

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received on 1st August from Merck Serono/Pfizer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on 8th September**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

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Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Aminata Thiam, Technical Lead (Aminata.thiam@nice.ork.uk) Any procedural questions should be addressed to Thomas Feist, Project Manager Thomas.Feist@nice.org.uk

Yours sincerely

Joanna Richardson
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

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Section A: Clarification on effectiveness data

Matching-adjusted indirect comparisons (MAICs)

A1. **Priority question:** Please provide a matching-adjusted indirect comparison (MAIC) of JAVELIN Merkel 200 and Study 100070-Obs001 part A only for the outcomes of PFS and OS in the 1st line treatment for metastatic merkel cell carcinoma (MCC) population following the method presented in the NICE DSU Technical Support Document 18 (Methods for population-adjusted indirect comparisons in submission to NICE). Best practice guidance is to adjust for as many variables as possible, regardless of effect modifier status or level of imbalance. Please note that, in an "unanchored" indirect comparison (that is, an indirect comparison that does not rely on a common comparator), it is invalid to exclude a potential effect modifier or prognostic indicator because it results in a small effective sample size (unlike in an "anchored" indirect comparison). Please ensure that the adjustments made in the analysis include, at least, the following (please note this list is not exhaustive):

- Immunocompetency;
- Tumour PD-L1 expression status;
- Age;
- Tumour burden;
- ECOG status at baseline.

A2. **Priority question:** Please provide a MAIC of JAVELIN Merkel 200 trial and Study 100070-Obs001 overall (part A and part B) for the outcomes of PFS and OS in the 2nd and later lines treatment for metastatic MCC population following the method presented in the NICE DSU Technical Support Document 18 (Methods for population-adjusted indirect comparisons in submission to NICE). Best practice guidance is to adjust for as many variables as possible, regardless of effect modifier status or level of imbalance. Please note that, in an "unanchored" indirect comparison (that is, an indirect comparison that does not rely on a common comparator), it is invalid to exclude a potential effect modifier or prognostic indicator because it results in a small effective sample size (unlike in an "anchored" indirect comparison). Please ensure that the adjustments made in the analysis at least include the following (please note this list is not exhaustive):

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- Tumour burden;
- ECOG status at baseline.

A3. **Priority question:** Please provide a MAIC of JAVELIN Merkel 200 trial and Study 100070-Obs001 part B only for the outcomes of PFS and OS in the 2nd and later lines treatment for metastatic MCC population following the method presented in the NICE DSU Technical Support Document 18 (Methods for population-adjusted indirect comparisons in submission to NICE). Best practice guidance is to adjust for as many variables as possible, regardless of effect modifier status or level of imbalance. Please note that, in an "unanchored" indirect comparison (that is, an indirect comparison that does not rely on a common comparator), it is invalid to exclude a potential effect modifier or prognostic indicator because it results in a small effective sample size (unlike in an "anchored" indirect comparison). Please ensure that the adjustments made in the analysis at least include the following (please note this list is not exhaustive):

- Immunocompetency;
- Tumour PD-L1 expression status;
- Age;
- Tumour burden;
- ECOG status at baseline.

A4. Please provide a (MAIC of JAVELIN Merkel 200 trial and the Iyer et al. (2016) study for the outcomes of PFS and OS in the 1st line treatment for metastatic MCC population following the method presented in the NICE DSU Technical Support Document 18 (Methods for population-adjusted indirect comparisons in submission to NICE). Best practice guidance is to adjust for as many variables as possible, regardless of effect modifier status or level of imbalance. Please note that, in an "unanchored" indirect comparison (that is, an indirect comparison that does not rely on a common comparator), it is invalid to exclude a potential effect modifier or prognostic indicator because it results in a small effective sample size (unlike in an "anchored" indirect comparison). Where possible, please ensure that the adjustments made in the analysis include the following (please note this list is not exhaustive):

- Immunocompetency;
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- ECOG status at baseline.

Quality assessments

A5. Please provide a full quality assessment for JAVELIN Merkel 200 trial to supplement the assessment already provided in Appendix 8 of the company submission (CS). Please also provide a justification for the choice of quality assessment tool.

A6. Please provide a full quality assessment, using itemised criteria, for each of the systematic literature review including studies to supplement the information already provided in Appendix 4 of the CS. Please also provide a justification for the choice of quality assessment tool.

Immunosuppression

A7. Please provide the rationale for including immunosuppressed patients in Study100070-Obs001 when immunosuppressed patients were excluded from JAVELIN Merkel 200.

Baseline characteristics

A8. Please provide the following baseline characteristics for JAVELIN Merkel 200 – 2L+ cohort (part A):

a. Tumour size (median and range);

b. Number of patients from UK sites.

A9. Please provide the following baseline characteristics for JAVELIN Merkel 200 – 1L cohort (part B):

a. Presence of distal metastases;

b. Presence of lymph node metastases;

c. Tumour PD-L1 expression;

d. Tumour MCPyV status;

e. Number of patients from UK sites.

A10. Please provide the baseline characteristics, as presented in Table 15 page 64 of the CS, for:

a. Study 100070-Obs001 part A, 2L+ – all patients;

b. Study 100070-Obs001 part A, 2L+ – immunocompetent patients;

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c. Study 100070-Obs001 part B, 2L+ – all patients;

d. Study 100070-Obs001 part B, 2L+ – immunocompetent patients;

e. Study 100070-Obs001 part A, 1L – all patients;

f. Study 100070-Obs001 part A, 1L – immunocompetent patients.

Additional recruitment details

A11. Please provide the estimated date when recruitment is expected to be completed for JAVELIN Merkel 200 – part B.

Section B: Clarification on cost-effectiveness data

Additional analyses

B1. **Priority question.** Please use each set of results from the MAICs in questions A1 to A3 to fit a full range of parametric survival curves (including splines), for PFS and OS of avelumab and the comparator, and apply these curves as additional options in the economic model. Please also present, as a set of scenario analyses, the results of the economic model using your chosen best fitting curves for each of the comparisons in A1 to A3.

B2. **Priority question.** Please use the results of the MAIC in question A4 to fit a full range of parametric survival curves (including splines), for PFS and OS of avelumab and the comparator (where data are available), and apply these curves as additional options in the economic model.

B3. **Priority question.** Please fit all parametric survival curves (including splines) to the treatment-naïve PFS, OS and time on treatment (ToT) data from the JAVELIN 200 trial and present the results of the curve fits. Please add all these curves as options in the economic model and present the results as a scenario analysis using your chosen best fitting curves.

B4. **Priority question.** Please fit the spline curves to the comparator OS and PFS data used in the base case, in the same way that was done for the JAVELIN 200 trial data, and add these as options to the economic model.

Additional Kaplan-Meier data

B5. Please update the 'Lists' sheet to include the treatment-naïve Kaplan-Meier data for OS, PFS and ToT of the model along with the treatment-experienced data and comparator data.

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B6. Please update the 'Lists' sheet to include the additional Kaplan-Meier data from the MAICs requested in questions A1 to A4. Please include the adjusted avelumab data as well as the alternative comparator data.

Health-related quality of life

B7. Please provide the means and standard deviations of the mapped EQ-5D-5L data at each timepoint, for comparison against the EQ-5D-3L data collected in the JAVELIN 200 trial from which it was mapped.

B8. Please clarify why the disutilities associated with the adverse events are not applied in the time to death approach used in the base case analysis. Please amend the model to incorporate these.

Resource use and costs

B9. Please clarify whether the end-of-life care costs obtained from Round et al., 2015 were inflated to 2015-2016 prices in the model. If not, please inflate them using the Hospital and Community Health Services index (as done for the adverse reaction unit costs).

B10. Please clarify why many of the costs applied in the model for the treatment of adverse events are estimates based on grade 1 or 2 events (e.g. anaemia, muscle pain, nausea/vomiting) when the model is based on grade 3 or 4 events (with the exception of hair loss). Please consider using costs related to grade 3 or 4 events where applicable.

B11. Where applicable, please correct the calculations in the economic model that incorrectly estimate the number of weekly cycles for which a monthly cost is applied. For example, in cell D47 of the 'Resource Use Costs' sheet, it is assumed that 3 months equates to only 12 weeks. Further examples are in cell C73 and E94 of the same sheet.

Time on treatment

B12. Please clarify whether deaths were considered as events or censoring in the ToT data from the JAVELIN 200 trial.

<u>Section C: Textual clarifications and additional points</u>

C1. Please clarify whether Figures 5 and 6 of Appendix 10 show regression results using a Weibull distribution or a generalised Gamma distribution. The preceding text states

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generalised Gamma but the table headings state Weibull. Please update with the generalised Gamma regression results if necessary.

C2. Please update the line of therapy button in model to ensure all inputs are reset to the appropriate base case inputs. Currently avelumab survival curves do not reset.

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Single technology appraisal

Avelumab for treating metastatic merkel cell carcinoma

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The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **12 midday on 12th September**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial in-confidence information clearly marked and one with this information removed.

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Yours sincerely

Joanna Richardson
Technical Adviser – Appraisals
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Dear Joanna,

We would like to thank NICE and the ERG group for granting Merck/Pfizer extra time to address the clarification questions received on 24th August 2017. We have made every effort to provide the ERG group with the analyses requested although some of the requests seem less relevant given the data provided and even more so in the context of an ultra-orphan disease with limited data and small patient numbers.

The response to each question is provided below the relevant question unless stated otherwise.

The cost-effectiveness model has been updated as part of the response to these clarification questions. The impact of each change made to the model is reported within the response to each question. The changes made to the cost-effectiveness model following the response to questions B9, B10 and B11 have been fully incorporated within the updated model, and form part of the revised base case settings. As a result of these changes (to resource use and costs), the revised ICER for treatment- experienced metastatic MCC is £37,350 (avelumab vs. BSC) per additional QALY gained and for treatment-naïve metastatic MCC is £43,553 (avelumab vs. chemotherapy) per additional QALY gained. Other changes to the model that consider alternative scenarios or settings may be found within the updated model, but do not form part of the revised base case settings.

Please do not hesitate to get in touch if you have any further questions.

Yours sincerely,

Amerah Amin
Health Economist
Merck Serono Ltd.

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Section A: Clarification on effectiveness data

Matching-adjusted indirect comparisons (MAICs)

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A2. Priority question: Please provide a MAIC of JAVELIN Merkel 200 trial and Study 100070-Obs001 overall (part A and part B) for the outcomes of PFS and OS in the 2nd and later lines treatment for metastatic MCC population following the method presented in the NICE DSU Technical Support Document 18 (Methods for population-adjusted indirect comparisons in submission to NICE). Best practice guidance is to adjust for as many variables as possible, regardless of effect modifier status or level of imbalance. Please note that, in an "unanchored" indirect comparison (that is, an indirect comparison that does not rely on a common comparator), it is invalid to exclude a potential effect modifier or prognostic indicator because it results in a small effective sample size (unlike in an "anchored" indirect comparison). Please ensure that the adjustments made in the analysis at least include the following (please note this list is not exhaustive):

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A3. Priority question: Please provide a MAIC of JAVELIN Merkel 200 trial and Study 100070-Obs001 part B only for the outcomes of PFS and OS in the 2nd and later lines treatment for metastatic MCC population following the method presented in the

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> NICE DSU Technical Support Document 18 (Methods for population-adjusted indirect comparisons in submission to NICE). Best practice guidance is to adjust for as many variables as possible, regardless of effect modifier status or level of imbalance. Please note that, in an "unanchored" indirect comparison (that is, an indirect comparison that does not rely on a common comparator), it is invalid to exclude a potential effect modifier or prognostic indicator because it results in a small effective sample size (unlike in an "anchored" indirect comparison). Please ensure that the adjustments made in the analysis at least include the following (please note this list is not exhaustive):
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Questions A1-A3 and B1-B2 have been answered jointly as they request that the same method be applied to different data sources, and that the associated results be considered. More specifically, they request the use of Matching Adjusted Indirect Comparison (MAIC) between the JAVELIN Merkel 200 trial of avelumab and the manufacturer-conducted observational studies, discussed at length in Appendix 10 of the manufacturers submission.

MAIC is a method to reweight patient characteristics from one study to aggregate data from another study where individual level data (ILD) are unavailable – its use (alongside Simulated Treatment Comparisons [STC]) is discussed in NICE Technical Support Document (TSD) 18 (Phillippo D, 2016). The use of MAIC is recommended with some reservations where ILD are not available from both studies – if data are available from both studies then the methods used are discussed in TSD 17 (estimating efficacy from observational data) (Faria R, 2015).

In this instance, ILD are available for both the JAVELIN Merkel 200 trial (as apparent from the curve fitting and trial reanalysis performed), and the manufacturer-sponsored observational studies – as stated on page 3 of Appendix 10: *"As these studies were commissioned by Merck/Pfizer, patient-level data are available for analysis."* and apparent from the reanalysis and regression analysis performed on the data. As such, we question the appropriateness of conducting MAIC between JAVELIN Merkel 200 and the observational studies. We communicated these concerns during our call with the Evidence Review Group, but as they have elected not to revise the questions, we present our rationale below.

The NICE TSD series highlights two reasons why MAIC analyses are inappropriate in this situation, and there is a further reason in the literature of propensity scoring and standardisation.

1. **The availability of ILD for both studies.**

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The creation of MAIC was motivated by the availability of only aggregate-level data (ALD) for published studies – as stated in the original paper proposing the method: *"If* [ILD] *were available from all trials of interest, biases stemming from differences between trial populations could be mitigated by regression adjustment"* (Signorovitch JE, 2010).

In the case of MCC, the appropriate method (based on TSD 17) would appear to be propensity score-based methods – either reweighting or matching, as highlighted to the Evidence Review Group. Propensity score methods would allow the balancing of trials where ILD are available, which would inherently have a higher degree of accuracy in using all available data and not merely summary characteristics of aggregated data.

2. **The requirement for included matching variables *to be prognostic*.**

The ERG highlight recommendation 4 of TSD 17 (to include all relevant prognostic and predictive variables, even if apparently well matched), however do not address the issue of what constitutes a 'relevant' characteristic.

Much of Appendix 10 in the Merck/Pfizer submission focuses on our efforts to establish which characteristics were 'relevant'; there we analysed – through both univariate and multivariate regression, the variables highlighted by the Evidence Review Group, and more, demonstrating that the only predictive variable in MCC appears to be the line of treatment. Due to limited patient numbers (as metastatic MCC is an ultra-rare cancer) and to ensure no erroneous conclusions are drawn, Kaplan-Meier plots by characteristic group (e.g. age, sex) were also presented, which – similarly – show no clear pattern to the suggested variables.

We believe ours to be a robust, stepwise approach to determining which variables could be relevant/prognostic. As an example, in multivariate regression immunosuppression was a predictor of longer progression-free survival (Appendix 10, Regression 2) but not statistically significant (p=0.28). In univariate regression it remained insignificant, and the subsequent examination of the Kaplan-Meier plot showed that the survival curves for immunosuppressed and immunocompetent patients overlapped, crossing 6 times over the period for which data are available (Figure 5).

A similar pattern was apparent for all other characteristics available, leaving no predictive or prognostic variables for matching, or to use the words linked to propensity scoring, these variables are *"strongly ignorable"* in the outcomes seen.

We consider that the base case in Merck's submission is appropriate; it applied no balancing/matching methods as there were no characteristics predictive/prognostic of progression-free survival or overall survival identified in the observational data. We also

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provided alternative curve fits to the data, and fits to each individual set of data, in our sensitivity analyses.

In an effort to provide the ERG with some matching / balancing of the treatment and control arms, we have considered applying propensity scoring and regression adjustment (akin to STC).

Literature suggests that matching methods typically require large numbers of patients for valid inferences to be drawn. For propensity scoring, this is recommended to be a minimum of 10 events for every characteristic to be included (Austin, 2011). Given the small number of patients in the treatment-naïve patient cohorts (39 in JAVELIN Merkel 200 (PFS events n=15, [redacted]), 67 in the observational dataset (PFS events n=58, OS events n=49), we attempt this only for the treatment-experienced patients. Here we have 88 patients from JAVELIN Merkel 200 ([redacted]) and 54 from the observational dataset (PFS events n=54, OS events n=52). Whilst it is technically possible to conduct these analyses for treatment-experienced patients, we would underline the exploratory nature of the analyses, and stress the limitations and high degree of uncertainty.

Propensity matching

In the propensity matching method, patients in the observational study (n=54) were matched on a 1:1 basis with patients in JAVELIN Merkel 200 – Part A (n=88) based on their propensity score using optimal matching across the whole dataset (minimising the overall distance between matches). Age and gender were available in both datasets to calculate this score. The matched units demonstrate a lose match across both treatment arms with a good overlap between studies. The limited number of variables (2) for matching should be considered.

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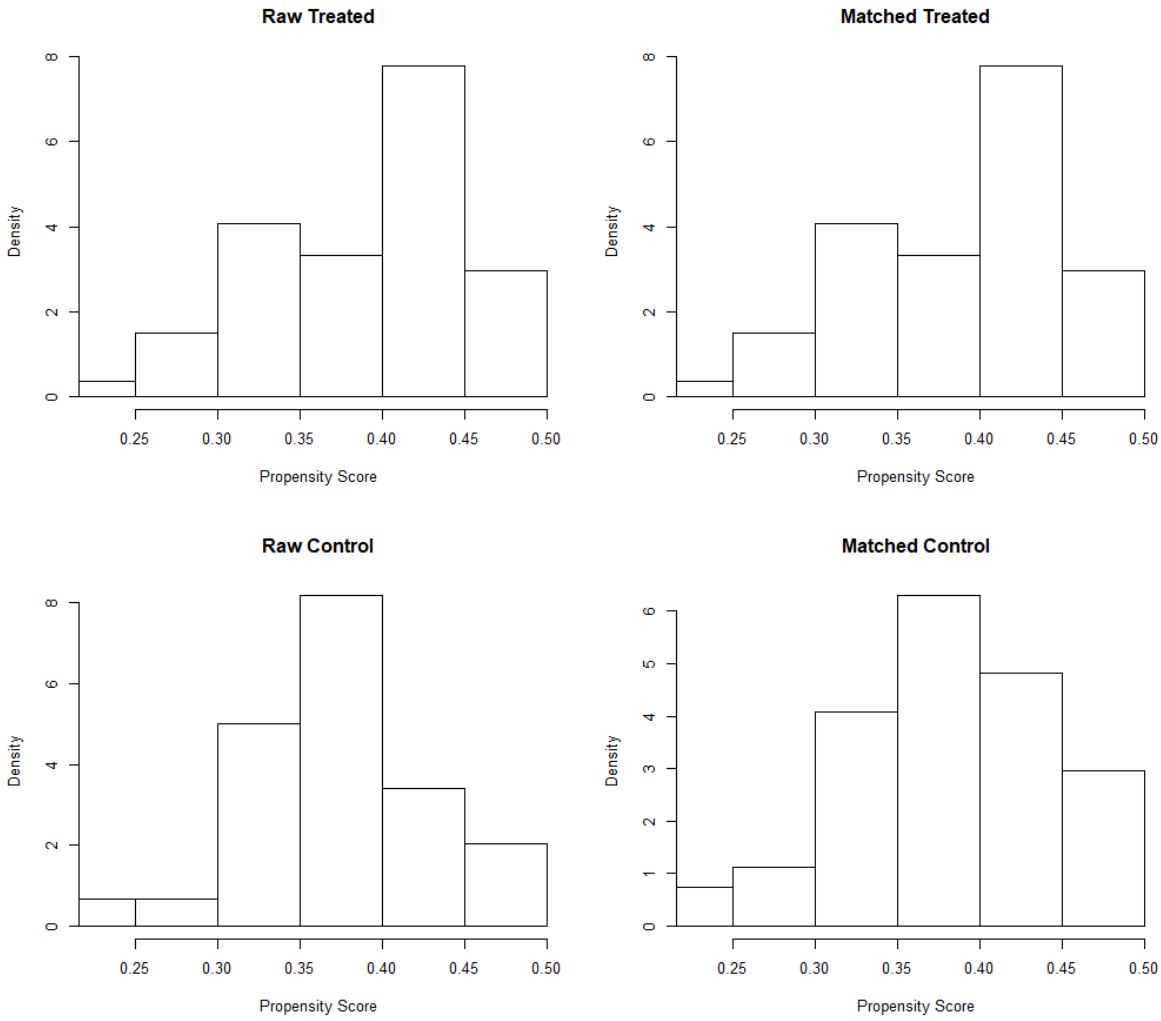
Figure 1. Histogram of raw and matched patients



A jitter plot of the matched patients and excluded patients (for whom no match was available, [redacted]) is shown in Figure 2.

Each circle demonstrates an individual's propensity score. The top row is blank as all the control patients are matched as there are more control units. The bottom row shows the unmatched patients from the avelumab study not considered within the analysis as a match was not available due to patient numbers.

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Figure 2: Jitter plot of matched and unmatched patients

NB: Avelumab patients are classed as 'control' patients by the software, as they are more numerous

The resultant Kaplan-Meier curves for overall survival and progression-free survival are presented in Figure 3. The 95% confidence intervals for each curve demonstrate that with the reduced sample size, additional uncertainty is present for each curve.

Figure 3: Propensity score matched Kaplan-Meier curves

Key: OS, overall survival; PFS, progression-free survival.
Note: The solid lines (——) demonstrate the full patient population, with the darker shaded areas denoting the associated 95% confidence interval. The dashed lines (- - -) demonstrate the propensity matched population, with the lighter shaded areas denoting the associated 95% confidence interval.

In order to incorporate the analysis within the cost-effectiveness calculations, the base-case survival curves for avelumab were refit using only the matched patients. The resultant curves are presented in Figure 4.

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Figure 4: Propensity score matched base-case curves

Key: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

This led to the cost-effectiveness results shown in Table 1. Using the propensity score matched curves, the base case ICER reduced from £37,409 to £33,796.

Table 1: Cost-effectiveness results – propensity score matching analysis

Treatment	Total costs	Total LYs	Total QALYs	ICER (avelumab vs.)
Submitted base case				
Avelumab	£78,718	3.53	2.22	
BSC	£7,319	0.41	0.31	£37,409
Propensity weighted analysis				
Avelumab	£79,051	3.87	2.44	
BSC	£7,319	0.41	0.31	£33,796

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

Regression analysis

Survival regressions were performed on the ILD for treatment-experienced patients from the manufacturer-sponsored observational studies. These data were used in preference to the JAVELIN Merkel 200 trial data as, although there are fewer patients, more events were observed and the data fits standard parametric regressions – in this case, the Weibull regression (data for patients treated with avelumab follow more complex shapes due to the mechanism of action).

In the regressions for progression-free survival and overall survival, predictive variables of age, gender and immunosuppression were used – in contrast to matching where no patients could be matched due to a lack of overlap in including immunosuppression,

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multivariate regression allows the impact of immunosuppression to be estimated. The results of the regressions are presented in Regression 1 and Regression 2, respectively.

Regression 1: Progression-free survival

```
Estimates:
                data mean  est        L95%       U95%       se         exp(est)   L95%       U95%
shape                 NA    2.16929    1.75683    2.67859    0.23341         NA         NA         NA
scale                 NA   76.93740   53.84810  109.92705   14.00698         NA         NA         NA
as.numeric(Age)   14.29630    0.00968   -0.00616    0.02553    0.00808    1.00973    0.99386    1.02586
gendermale         0.66667    0.12426   -0.14892    0.39744    0.13938    1.13231    0.86163    1.48801
immunosup          0.12963   -0.01875   -0.42404    0.38654    0.20679    0.98142    0.65440    1.47188

N = 54,  Events: 54,  Censored: 0
Total time at risk: 4626
Log-likelihood = -275, df = 5
AIC = 561
```

Key: AIC, Akaike Information Criterion.

Regression 2: Overall survival

```
Estimates:
                data mean  est        L95%       U95%       se         exp(est)   L95%       U95%
shape                 NA    3.16e+00   2.53e+00   3.95e+00   3.58e-01         NA         NA         NA
scale                 NA    1.42e+02   1.09e+02   1.86e+02   1.96e+01         NA         NA         NA
as.numeric(Age)   1.43e+01   1.00e-02  -8.93e-04   2.09e-02   5.57e-03   1.01e+00   9.99e-01   1.02e+00
gendermale        6.67e-01  -3.91e-02  -2.39e-01   1.61e-01   1.02e-01   9.62e-01   7.88e-01   1.17e+00
immunosup         1.30e-01   1.87e-01  -1.13e-01   4.88e-01   1.53e-01   1.21e+00   8.93e-01   1.63e+00

N = 54,  Events: 52,  Censored: 2
Total time at risk: 7895
Log-likelihood = -281, df = 5
AIC = 571
```

Key: AIC, Akaike Information Criterion.

Survival parameters for Weibull curves were then estimated for data matched to the aggregate data from the avelumab treatment-experienced patients who had a mean age of 69.7, were 73.9% male, and 100% immunocompetent, as compared to the mean age of 72, 66.7% male and 13% with immunosuppression in the observational data.

Adjusting the survival in the model for the comparator arm resulted in an increase in estimated survival for the comparator arm, and the cost-effectiveness results shown in Table 2. The results demonstrate an increase in the ICER of approximately £235 versus the submitted base case.

Table 2: Cost-effectiveness results – regression analysis

Treatment	Total costs	Total LYs	Total QALYs	ICER (avelumab vs.)
Submitted base case				
Avelumab	£78,718	3.53	2.22	
BSC	£7,319	0.41	0.31	£37,409
Propensity weighted analysis				
Avelumab	£78,718	3.53	2.22	
BSC	£7,278	0.43	0.32	£37,645

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

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We would again stress the exploratory nature of these analyses.

A4. Please provide a (MAIC of JAVELIN Merkel 200 trial and the Iyer et al. (2016) study for the outcomes of PFS and OS in the 1st line treatment for metastatic MCC population following the method presented in the NICE DSU Technical Support Document 18 (Methods for population-adjusted indirect comparisons in submission to NICE). Best practice guidance is to adjust for as many variables as possible, regardless of effect modifier status or level of imbalance. Please note that, in an "unanchored" indirect comparison (that is, an indirect comparison that does not rely on a common comparator), it is invalid to exclude a potential effect modifier or prognostic indicator because it results in a small effective sample size (unlike in an "anchored" indirect comparison). Where possible, please ensure that the adjustments made in the analysis include the following (please note this list is not exhaustive):

- Immunocompetency;
- Tumour PD-L1 expression status;
- Age;
- Tumour burden;
- ECOG status at baseline.

The combined answer to questions A1-A3 and B1-B2 are relevant to our response to this question, however the context is slightly different. The requested methodology of MAIC is appropriate here, however the conduct of such analysis as requested by the Evidence Review Group is problematic.

There are two reasons for this.

1. The characteristics requested by the ERG are either not present, not collected, or not reported in two trials – of the four characteristics listed by the Evidence Review Group all patients in the avelumab clinical study program were immunocompetent (making matching difficult), tumour PD-L1 expression status was not reported in Iyer *et al.* (nor was tumour burden or ECOG), leaving only age, which was shown in Appendix 10 of the manufacturers submission not to be a significant predictor of either progression-free survival or overall survival.
2. The number of patients available for analysis is very small. With only 39 patients in JAVELIN Merkel 200 – Part B trial, the outcomes for such matching are extremely questionable, and unlikely to be informative.

Although not requested, conducting an MAIC to the data available for treatment-experienced patients (avelumab n=88, chemotherapy n=54) would have equally large caveats around the figures due to the low patient numbers.

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Quality assessments

A5. Please provide a full quality assessment for JAVELIN Merkel 200 trial to supplement the assessment already provided in Appendix 8 of the company submission (CS). Please also provide a justification for the choice of quality assessment tool.

The quality assessment of the clinical trials provided in Appendix 4 of the company submission includes the JAVELIN Merkel 200 trial. This has been identified by its publication author Kaufman (Kaufman H, 2016) and is highlighted in the copy of Table 40 (including in Appendix H) below. The Downs and Black checklist was chosen given the evidence base identified in the clinical systematic review. The Downs and Brown checklist is a validated checklist for assessing the risk of bias in observational studies, single arm studies, and RCTs (Downs S, 1998). This information is in addition to the critical appraisal already provided for the JAVELIN Merkel 200 trial in Appendix 8 of the company submission.

H.1 Results of critical appraisal using Downs and Black checklist

Table 40: Summary of critical appraisal using Downs and Black checklist for observation studies, single arm trials, and non-RCTs

Study name	Metastasis site	Study design	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total score
Bhatia 2015	Distant	nRCT	1	1	1	1	0	1	0	1	1	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	1	**12**
Iyer 2014	Distant	Cohort	1	1	1	1	0	1	1	1	1	0	1	0	1	0	0	0	1	1	1	1	1	0	0	0	0	1	**16**
Satpute 2014	Distant	Cohort	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	**7**
Nghiem 2016	Distant	Single arm	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	0	1	1	1	1	1	0	0	0	1	**16**
Becker 2016	Distant	Observational	1	1	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	**8**
Sabol 2016	Distant	Observational	1	0	1	1	0	1	0	0	0	1	1	0	1	0	0	0	0	0	0	1	1	0	1	0	0	0	0	**10**

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Study name	Metastasis site	Study design	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total score
Kaufman 2016	Distant	Single arm	1	1	1	1	2	1	1	1	1	1	1	0	1	0	0	0	0	1	1	1	1	1	0	0	0	1	**19**
Cowey 2016	Distant	Observational	1	1	1	1	0	1	1	0	0	0	1	0	1	0	0	0	0	0	1	1	0	1	0	0	0	0	**11**
Timmer 2016	Distant	Observational	1	1	1	1	0	1	0	0	0	0	1	0	1	0	0	0	0	1	0	1	1	1	0	0	0	0	**11**
Bhatia 2016b	Distant	Cohort	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	**5**
Di 1995	Metastatic MCC	Single arm	1	1	1	1	0	1	0	0	0	0	1	1	1	0	0	1	0	0	0	1	1	0	0	0	0	0	**11**
Samlowski 2010 (S0331 study)	Metastatic MCC	Single arm	1	1	1	1	0	1	1	1	1	0	1	0	1	0	0	1	0	1	0	1	0	0	0	0	0	0	**13**
Savage 1997	Metastatic MCC	Observational	1	1	1	1	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	**9**
Shah 2009	Metastatic MCC	Single arm	1	1	1	1	0	1	0	1	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	**9**
Woll 2009	Metastatic MCC	Single arm	1	0	0	1	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	**5**
Nathan 2016	Metastatic MCC	Single arm	1	1	1	1	0	1	1	1	1	0	1	0	1	0	0	0	0	1	0	1	1	0	0	0	0	0	**13**
Bhatia 2016a	Metastatic MCC	Single arm	1	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	**7**
Shah 2016	Metastatic MCC	Single arm	1	1	1	1	0	1	1	1	0	0	1	0	1	0	0	0	0	1	0	1	0	1	0	0	0	0	**12**

MCC: Merkel Cell Carcinoma

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1: Is the hypothesis/objective of the study clearly described?; **2**: Are the main outcomes to be measured clearly described in the introduction or methods section?; **3**: Are the characteristics of the patients included in the study clearly described?; **4**: Are the interventions of interest clearly described?; **5**: Are the distributions of principal confounders in each group of subjects to be compared clearly described?; **6**: Are the main findings of the study clearly described?; **7**: Does the study provide estimates of the random variability in the data for the main outcomes?; **8**: Have all important adverse events that may be a consequence of the intervention been reported?; **9**: Have the characteristics of patients lost to follow-up been described?; **10**: Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?; **11**: Were the subjects asked to participate in the study representative of the entire population from which they were recruited?; **12**: Were those subjects who were prepared to participate representative of the entire population from which they were recruited?; **13**: Were the staff, places and facilities where the patients were treated representative of the treatment the majority of the patients receive?; **14**: Was an attempt made to blind study subjects to the intervention they received?; **15**: Was an attempt made to blind those measuring the main outcomes of the intervention?; **16**: If any results of the study were based on "data dredging" was this made clear?; **17**: In trials and cohort studies, do the analyses adjust for different lengths of follow up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?; **18**: Were the statistical tests used to assess the main outcomes appropriate?; **19**: Was compliance with the interventions reliable?; **20**: Were the main outcomes measures used accurate (valid and reliable)?; **21**: Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case control studies) recruited from the same population?; **22**: Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case control studies) recruited over the same period of time?; **23**: Were study subjects randomized to intervention groups?; **24**: Was the randomized intervention assignment concealed from both patients and healthcare staff until recruitment was complete and irrevocable?; **25**: Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?; **26**: Were losses of patients to follow-up taken into account?

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A6. Please provide a full quality assessment, using itemised criteria, for each of the systematic literature review including studies to supplement the information already provided in Appendix 4 of the CS. Please also provide a justification for the choice of quality assessment tool.

Quality assessment of the RCT and non-RCT evidence is provided in the pdfs embedded below. Quality assessment of RCTs was based on the checklist by NICE (NICE, 2013). Quality assessment of the non-RCT studies were evaluated using the checklist by Downs and Black.

Quality assessment of RCT's

Appendix I: Quality assessment of RCTs

Quality assessment of non-RCTs

Appendix J: Quality assessment of non-I

Quality assessment of the economic studies were based on the checklist by Drummond et al. (Drummon MF, 1996) This is presented in the embedded file below. The Drummond checklist is a validated quality assessment tool, and has been used in previous NICE submissions to evaluate the quality of the economic evaluations.

Quality assessment of economic studies

A systematic review was undertaken to identify economic evaluations in MCC. Through the literature review, no economic studies in MCC were identified however, the review included identifying studies that could be used to source resource use and cost data for input into a cost-utility and budget impact model. A quality assessment of these studies is provided in the embedded file below.

Appendix K: Quality assessment of econ

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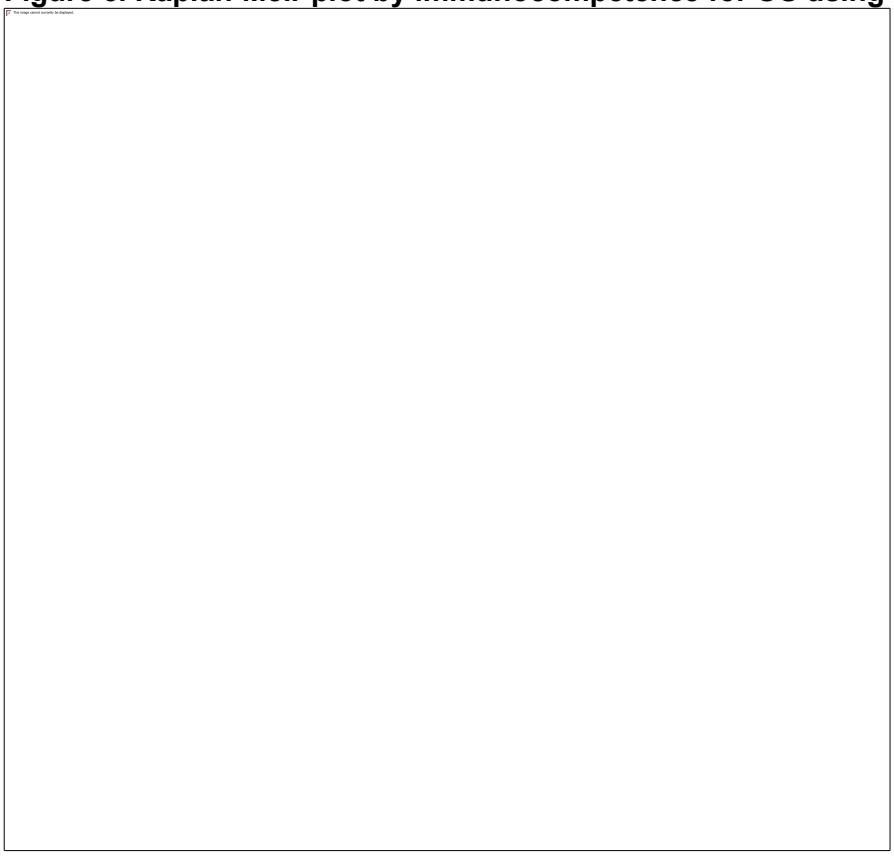
Immunosuppression

A7. Please provide the rationale for including immunosuppressed patients in Study100070-Obs001 when immunosuppressed patients were excluded from JAVELIN Merkel 200.

Immunosuppressed patients are not anticipated to achieve different survival outcomes from immunocompetent patients for both patient populations (that is, treatment-naïve and treatment-experienced patients), as evidenced in the manufacturer submission Appendix 10, and detailed in clarification questions A1-A3. Furthermore, given the rarity of the disease and difficulty in obtaining patient data, all patients were included in the Study 100070-Obs001.

The analysis performed in Appendix 10 showed that immunosuppression was not a significant predictor of outcomes (PFS or OS) in either univariate or multivariate regression analysis. Kaplan-Meier curves are also presented, reproduced below for the most relevant data (2L overall survival) from Figure 14 (in Appendix 10). The curves indicate that the survival curves split by immunosuppression cross multiple times appear to be similar. The lack of significance in regression analysis is therefore unlikely to be due to low patient numbers and instead indicates it is not a significant predictor of outcome.

Figure 5. Kaplan-Meir plot by immunocompetence for OS using pooled 2L MCC data



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Baseline characteristics

A8. Please provide the following baseline characteristics for JAVELIN Merkel 200 – 2L+ cohort (part A):

a. Tumour size (median and range);

Median tumour size: 1.8cm; range: 0.6-17.0cm

b. Number of patients from UK sites.

Zero patients from a UK site were included in the JAVELIN Merkel 200 study (003-part A)

A9. Please provide the following baseline characteristics for JAVELIN Merkel 200 – 1L cohort (part B):

a. Presence of distal metastases;

Distal metastases have not been collected. Instead, the trial collected visceral metastases at baseline N=39, n (%):

- Present [redacted]
- Absent [redacted]
- Missing [redacted]

b. Presence of lymph node metastases;

Lymph node disease at baseline N=39, n (%)

- Yes [redacted]
- No [redacted]
- Missing [redacted]

c. Tumour PD-L1 expression;

Not yet available in the interim analysis with cut off March 2017

d. Tumour MCPyV status;

Not yet available in the interim analysis with cut off March 2017

e. Number of patients from UK sites.

Zero patients from a UK site were included in the JAVELIN Merkel 200 study (003-part B)

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A10. Please provide the baseline characteristics, as presented in Table 15 page 64 of the CS, for:

a. Study 100070-Obs001 part A, 2L+ – all patients;

Table 3: Baseline characteristics for Study 100070-Obs001 part A, 2L+ – all patients

Baseline characteristic	***100070-Obs001 part A, 2L+ All patients***
	(N=20)
Age	
<75 years, n (%)	11 (55)
≥75 year, n (%)	9 (45)
Median, years (range)	73.5 (66.0-81.1)
Gender, n (%)	
Male	14 (70)
Female	6 (30)
ECOG PS, n (%)	
0	1 (5.0)
1	16 (80.0)
2	1 (5.0)
Unknown	2 (10.0)
Weight (kg)	
Median (range)	NA
Region, n (%)	
Midwest or Northeast	5 (25.0)
South or west	15 (75.0)
Site of primary tumour, n (%)	
Face	5 (25.0)
Lower limb or trunk	7 (35.0)
Scalp and neck	2 (10.0)
Upper limb	5 (25.0)
Unknown primary	1 (5.0)
Arm	NA
Leg	NA
Trunk	NA
Missing	NA
Metastatic involvement at study entry, n (%)*	
Yes	NA
No	NA

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Baseline characteristic	***100070-Obs001 part A, 2L+ All patients***
	(N=20)
Number of prior systemic cancer therapies received, n (%)	
1	NA
2	NA
≥3	NA
Number of prior systemic cancer therapies received for metastatic disease, n (%)	
1	NA
2	NA
≥3	NA
Prior anticancer therapy, n (%)	
Chemotherapy for metastatic disease	NA
Chemotherapy for non-metastatic disease	NA
Antibody therapy	NA
Experimental T cell co-regulator therapy	NA
Kinase inhibitors	NA
Other	NA
Prior chemotherapy for metastatic disease, n (%)	
Etoposide	NA
Carboplatin	NA
Cisplatin	NA
Doxorubicin	NA
Visceral disease at study entry, n (%)	
Present	14 (70.0)
Absent	4 (20.0)
Not noted or missing	2 (10.0)
Lymph node disease only at study entry, n (%)	
Yes	4 (20.0)
No	16 (80.0)
Sum of target lesion diameters (SLD) at baseline	
Median SLD, mm (range)	NA
Tumour PD-L1 expression, n (%)[+]	
PD-L1+	NA
PD-L1-	NA
Not evaluable	

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Baseline characteristic	***100070-Obs001 part A, 2L+ All patients***
	(N=20)
Tumour MCPyV status, n (%)	
MCPyV+	NA
MCPyV-	NA
Not evaluable	NA

NA: Not available
*Patients identified were diagnosed with metastatic MCC on or any time before September 2014- determined initially through structured data (i.e. mention of metastatic in line of therapy or stage IV at initial/current diagnosis) and then confirmed by radiology reports and physician notes.

b. Study 100070-Obs001 part A, 2L+ – immunocompetent patients;

Table 4: Baseline characteristics for Study 100070-Obs001 part A, 2L+ – immunocompetent patients

Baseline characteristic	***100070-Obs001 part A, 2L+ immunocompetent patients***
	(N=14)
Age	
<65 years, n (%)	7 (50.0)
≥65 year, n (%)	7 (50.0)
Median, years (range)	75.2 (63.6, 81.1)
Gender, n (%)	
Male	11 (78.6)
Female	3 (21.4)
ECOG PS, n (%)	
0	0
1	13 (92.9)
2	0
Unknown	1 (7.1)
Weight (kg)	
Median (range)	NA
Region, n (%)	
Midwest or Northeast	4 (20.0)
South or west	10 (80.0)

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Baseline characteristic	***100070-Obs001 part A, 2L+ immunocompetent patients***
	(N=14)
Site of primary tumour, n (%)	
Face	3 (21.4)
Lower limb or trunk	7 (50.0)
Scalp and neck	1 (7.1)
Upper limb	2 (14.3)
Unknown primary	1 (7.1)
Arm	N/A
Leg	N/A
Trunk	N/A
Missing	N/A
Metastatic involvement at study entry, n (%)*	
Yes	NA
No	NA
Number of prior systemic cancer therapies received, n (%)	
1	NA
2	NA
≥3	NA
Number of prior systemic cancer therapies received for metastatic disease, n (%)	
1	NA
2	NA
≥3	NA
Prior anticancer therapy, n (%)	
Chemotherapy for metastatic disease	NA
Chemotherapy for non-metastatic disease	NA
Antibody therapy	NA
Experimental T cell co-regulator therapy	NA
Kinase inhibitors	NA
Other	NA
Prior chemotherapy for metastatic disease, n (%)	
Etoposide	NA
Carboplatin	NA
Cisplatin	NA
Doxorubicin	NA

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Baseline characteristic	***100070-Obs001 part A, 2L+ immunocompetent patients***
	(N=14)
Visceral disease at study entry, n (%)	
Present	10 (71.4)
Absent	2 (14.3)
Not noted or missing	2 (14.3)
Lymph node disease only at study entry, n (%)	
Yes	2 (14.3)
No	12 (85.71)
Sum of target lesion diameters (SLD) at baseline	
Median SLD, mm (range)	NA
Tumour PD-L1 expression, n (%)[+]	
PD-L1+	NA
PD-L1-	NA
Not evaluable	
Tumour MCPyV status, n (%)	
MCPyV+	NA
MCPyV-	NA
Not evaluable	NA

*Patients identified were diagnosed with metastatic MCC on or any time before September 2014- determined initially through structured data (i.e. mention of metastatic in line of therapy or stage IV at initial/current diagnosis) and then confirmed by radiology reports and physician notes.

c. Study 100070-Obs001 part B, 2L+ – all patients;

Table 5: Baseline characteristics for Study 100070-Obs001 part B, 2L+ – all patients

Baseline characteristic	***100070-Obs001 part B, 2L+ All patients***
	(N=34)
Age	
<65 years, n (%)	12 (35.3)
≥65 year, n (%)	22 (64.7)
Median, years (range)	67.5 (61.0-72.0)
Gender, n (%)	
Male	22 (64.7)
Female	12 (35.3)

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Baseline characteristic	***100070-Obs001 part B, 2L+ All patients***
	(N=34)
ECOG PS, n (%)	
0	NA
1	NA
2	NA
Unknown	34 (100)
Weight (kg)	
Median (range)	NA
Region, n (%) Observational data 56 European clinical sites: Germany (53), Austria (2) and Switzerland (1)	34 (100)
Site of primary tumour, n (%)	
Face	NA
Lower limb or trunk	NA
Scalp and neck	8 (23.5)
Upper limb	NA
Unknown primary	1 (2.9)
Arm	9 (25.5)
Leg	5 (14.7)
Trunk	6 (17.7)
Missing	5 (14.7)
Metastatic involvement at study entry, n (%)	
Yes	10 (29.4)
No	24 (70.6
Number of prior systemic cancer therapies received, n (%)	
1	0
2	29 (85.3)
≥3	5 (14.7)0
Number of prior systemic cancer therapies received for metastatic disease, n (%)	
1	NA
2	NA
≥3	NA

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Baseline characteristic	***100070-Obs001 part B, 2L+ All patients***
	(N=34)
Prior anticancer therapy, n (%)	
Chemotherapy for metastatic disease	NA
Chemotherapy for non-metastatic disease	NA
Antibody therapy	NA
Experimental T cell co-regulator therapy	NA
Kinase inhibitors	NA
Other	NA
Prior chemotherapy for metastatic disease, n (%)	
Etoposide	NA
Carboplatin	NA
Cisplatin	NA
Doxorubicin	NA
Visceral disease at study entry, n (%)	
Present[a]	20 (58.8)
Absent	7 (20.6)
Not noted or missing	7 (20.6)
Lymph node disease only at study entry, n (%)	
Yes[b]	7 (20.6)
No	27 (79.4)
Sum of target lesion diameters (SLD) at baseline	
Median SLD, mm (range)	NA
Tumour PD-L1 expression, n (%)[+]	
PD-L1+	NA
PD-L1-	NA
Not evaluable	
Tumour MCPyV status, n (%)	
MCPyV+	NA
MCPyV-	NA
Not evaluable	NA

a: Visceral metastases and/or elevated lactate dehydrogenase according to classification of malignant melanoma.

b: Distant soft tissue and lymph node metastases according to classification of malignant melanoma.

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d. Study 100070-Obs001 part B, 2L+ – immunocompetent patients;

Table 6: Baseline characteristics for Study 100070-Obs001 part B, 2L+ – immunocompetent patients

Baseline characteristic	***100070-Obs001 part B, 2L+ immunocompetent patients***
	(N=29)
Age	
<65 years, n (%)	11(37.9)
≥65 year, n (%)	18 (62.1)
Median, years (range)	67.0 (61.0-73.0)
Gender, n (%)	
Male	18 (62.1)
Female	11 (37.9)
ECOG PS, n (%)	
0	NR
1	NR
2	NR
Unknown	29 (100.0)
Weight (kg)	
Median (range)	NA
Region, n (%)Observational data 56 European clinical sites: Germany (53), Austria (2) and Switzerland (1)	29 (100)
Site of primary tumour, n (%)	
Face	N/A
Lower limb or trunk	N/A
Scalp and neck	6 (20.7)
Upper limb	N/A
Unknown primary	1 (3.5)
Arm	9 (31.0)
Leg	4 (13.8)
Trunk	5 (17.2)
Missing	4 (13.8)
Metastatic involvement at study entry, n (%)	
Yes	7 (24.)
No	22 (75.9)

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Baseline characteristic	***100070-Obs001 part B, 2L+ immunocompetent patients***
	(N=29)
Number of prior systemic cancer therapies received, n (%)	
1	0
2	24 (82.8)
≥3	5 (17.2)
Number of prior systemic cancer therapies received for metastatic disease, n (%)	
1	NA
2	NA
≥3	NA
Prior anticancer therapy, n (%)	
Chemotherapy for metastatic disease	NA
Chemotherapy for non-metastatic disease	NA
Antibody therapy	NA
Experimental T cell co-regulator therapy	NA
Kinase inhibitors	NA
Other	NA
Prior chemotherapy for metastatic disease, n (%)	
Etoposide	NA
Carboplatin	NA
Cisplatin	NA
Doxorubicin	NA
Visceral disease at study entry, n (%)	
Present [a]	16 (55.2)
Absent	6 (20.7)
Not noted or missing	7 (24.1)
Lymph node disease only at study entry, n (%)	
Yes[b]	7 (24.1)
No	22 (75.9)
Sum of target lesion diameters (SLD) at baseline	
Median SLD, mm (range)	NA
Tumour PD-L1 expression, n (%)[+]	
PD-L1+	NA
PD-L1-	NA
Not evaluable	

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Baseline characteristic	***100070-Obs001 part B, 2L+ immunocompetent patients***
	(N=29)
Tumour MCPyV status, n (%)	
MCPyV+	NA
MCPyV-	NA
Not evaluable	NA

[a]: Visceral metastases and/or elevated lactate dehydrogenase according to classification of malignant melanoma.
[b]: Distant soft tissue and lymph node metastases according to classification of malignant melanoma.

e. Study 100070-Obs001 part A, 1L – all patients;

Table 7: Baseline characteristics for Study 100070-Obs001 part A, 1L+ – All patients

Baseline characteristic	***100070-Obs001 part A, 1L+ All patients***
	(N=67)
Age	
<65 years, n (%)	14 (20.9)
≥65 year, n (%)	53 (79.1)
Median, years (range)	75.8 (67.1-82.3)
Gender, n (%)	
Male	53 (79.1)
Female	14 (20.9)
ECOG PS, n (%)	
0	14 (20.9)
1	32 (47.8)
2	8 (9.0)
Unknown	13 (19.4)
Weight (kg)	
Median (range)	NA
Region, n (%)	
Midwest or Northwest	11 (16.4)
South	42 (62.7)
West	14 (20.9)
Site of primary tumour, n (%)	
Face	16 (23.9)
Lower limb or trunk	22 (32.8)
Unknown primary	2 (3.0)
Scalp and neck	12 (17.9)
Upper limb	15 (22.4)

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Baseline characteristic	***100070-Obs001 part A, 1L+ All patients***
	(N=67)
Metastatic involvement at study entry, n (%)	
Yes	7 (10.4)
No	18 (71.6)
Unknown	12 (17.9)
Number of prior systemic cancer therapies received, n (%)	
1	0
2	NA
≥3	NA
Number of prior systemic cancer therapies received for metastatic disease, n (%)	
1	NA
2	NA
≥3	NA
Prior anticancer therapy, n (%)	
Chemotherapy for metastatic disease	NA
Chemotherapy for non-metastatic disease	NA
Antibody therapy	NA
Experimental T cell co-regulator therapy	NA
Kinase inhibitors	NA
Other	NA
Prior chemotherapy for metastatic disease, n (%)	
Etoposide	NA
Carboplatin	NA
Cisplatin	NA
Doxorubicin	NA
Visceral disease at study entry, n (%)	
Present [a]	46 (68.65)
Absent	14 (20.90)
Not noted or missing	7 (10.45)
Lymph node disease only at study entry, n (%)	
Yes[b]	14 (20.90)
No	53 (79.1)
Sum of target lesion diameters (SLD) at baseline	
Median SLD, mm (range)	NA

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Baseline characteristic	***100070-Obs001 part A, 1L+ All patients***
	(N=67)
Tumour PD-L1 expression, n (%)[+]	
PD-L1+	NA
PD-L1-	NA
Not evaluable	
Tumour MCPyV status, n (%)	
MCPyV+	NA
MCPyV-	NA
Not evaluable	NA

f. Study 100070-Obs001 part A, 1L – immunocompetent patients.

Table 8: Baseline characteristics for Study 100070-Obs001 part A, 1L+ – immunocompetent patients

Baseline characteristic	***100070-Obs001 part A, 1L+ immunocompetent patients***
	(N=51)
Age	
<65 years, n (%)	10 (19.6)
≥65 year, n (%)	41 (80.4)
Median, years (range)	78.1 (67.9-83.7)
Gender, n (%)	
Male	43 (84.3)
Female	8 (15.7)
ECOG PS, n (%)	
0	11 (21.6)
1	25 (49.0)
2	5 (5.9)
Unknown	10 (19.6)
Weight (kg)	
Median (range)	NA
Region, n (%)	
Midwest or Northwest	6 (11.8)
South	37 (72.5)
West	8 (15.7)

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Baseline characteristic	***100070-Obs001 part A, 1L+ immunocompetent patients***
	(N=51)
Site of primary tumour, n (%)	
Face	12 (23.5)
Lower limb or trunk	18 (35.3)
Unknown primary	2 (3.9)
Scalp and neck	8 (15.7)
Upper limb	11 (21.6)
Metastatic involvement at study entry, n (%)	
Yes	6 (11.8)
No	35(68.6)
Unknown	10 (19.6)
Number of prior systemic cancer therapies received, n (%)	
1	NA
2	NA
≥3	NA
Number of prior systemic cancer therapies received for metastatic disease, n (%)	
1	NA
2	NA
≥3	NA
Prior anticancer therapy, n (%)	
Chemotherapy for metastatic disease	NA
Chemotherapy for non-metastatic disease	NA
Antibody therapy	NA
Experimental T cell co-regulator therapy	NA
Kinase inhibitors	NA
Other	NA
Prior chemotherapy for metastatic disease, n (%)	NA
Etoposide	NA
Carboplatin	NA
Cisplatin	NA
Doxorubicin	NA
Visceral disease at study entry, n (%)	
Present [a]	34 (66.67)
Absent	10 (19.61)
Not noted or missing	7 (13.72)

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Baseline characteristic	***100070-Obs001 part A, 1L+ immunocompetent patients***
	(N=51)
Lymph node disease only at study entry, n (%)	
Yes[b]	10 (19.6)
No	41 (80.4)
Sum of target lesion diameters (SLD) at baseline	
Median SLD, mm (range)	NA
Tumour PD-L1 expression, n (%)[+]	
PD-L1+	NA
PD-L1-	NA
Not evaluable	
Tumour MCPyV status, n (%)	
MCPyV+	NA
MCPyV-	NA
Not evaluable	NA

Additional recruitment details

A11. Please provide the estimated date when recruitment is expected to be completed for JAVELIN Merkel 200 – part B.

Recruitment of the last patient in the study is expected [redacted] with primary analyses planned for [redacted].

Section B: Clarification on cost-effectiveness data

Additional analyses

B1. **Priority question.** Please use each set of results from the MAICs in questions A1 to A3 to fit a full range of parametric survival curves (including splines), for PFS and OS of avelumab and the comparator, and apply these curves as additional options in the economic model. Please also present, as a set of scenario analyses, the results of the economic model using your chosen best fitting curves for each of the comparisons in A1 to A3.

B2. **Priority question.** Please use the results of the MAIC in question A4 to fit a full range of parametric survival curves (including splines), for PFS and OS of avelumab and the comparator (where data are available), and apply these curves as additional options in the economic model.

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Responses to questions B1 and B2 are provided in response to questions A1-A3.

B3. **Priority question.** Please fit all parametric survival curves (including splines) to the treatment-naïve PFS, OS and time on treatment (ToT) data from the JAVELIN 200 trial and present the results of the curve fits. Please add all these curves as options in the economic model and present the results as a scenario analysis using your chosen best fitting curves.

Within the submitted cost-effectiveness model, the outcomes of overall survival, progression-free survival and time on treatment were not based on data for treatment-naïve patients (from Part B of the JAVELIN Merkel 200 trial), as these data were considered too immature for long-term extrapolation, and contribute a relatively small sample of patients (n=39). Over the observed period (based on the 39 enrolled patients[redacted]. Minimum follow-up for these patients was 3 months, with a maximum follow up of approximately 11 months.

An overview of the data for treatment-naïve patients is provided in Figure 32 and Figure 40 of the company submission, for overall survival/progression-free survival and time on treatment, respectively. For ease of comparison, these data are represented in Figure 6 alongside data for treatment-experienced patients.

Figure 6: 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.

In order to directly address the ERG's question, we fit parametric curves to the 1L data set directly and discuss them in the context of the base case we presented.

Progression-free survival

Parametric survival models

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Five-year parametric progression-free survival curves are provided in Figure 7 alongside the current base-case model setting, and the available Kaplan-Meier data from JAVELIN Merkel 200 – Part B. The statistical goodness of fit for each of these curves are provided in Table 9.

Figure 7: 5-year progression-free survival – JAVELIN Merkel 200: Part B (parametric survival curves)

Key: KM, Kaplan-Meier; PFS, progression-free survival.

Table 9: Statistical goodness of fit – parametric survival curves for progression-free survival (JAVELIN Merkel 200: Part B)

Distribution	AIC	BIC
Exponential	97.62	99.28
Generalised Gamma	93.24	98.23
Gompertz	98.00	101.33
Log-logistic	97.93	101.26
Log-normal	96.38	99.71
Weibull	99.27	102.60

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

The curves predict 5-year progression-free survival to be between 0.00% and 31.67%, dependent on the choice of parametric survival curve. The base-case setting considered within the cost-effectiveness model estimates five-year survival at approximately 18.71%.

By fitting the parametric curves, inappropriate curve fits are observed for the Gompertz and generalised gamma curves. The Gompertz curve predicts no events to occur beyond approximately 3 years, whereas the generalised gamma curve shows a sudden drop in progression-free survival just before 3 years (most likely due to convergence issues based on the relatively small sample size). Both of these extrapolations are clearly unfounded. All

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other parametric curve fits demonstrate 5-year progression-free survival estimates of less than 10%.

To provide an overview of the long-term progression-free survival estimates, the exponential, Weibull, log-logistic and log-normal curves are presented for the entire modelled time horizon in Figure 8. Any curves demonstrating a hazard of death lower than that of the age- and gender-adjusted general population were capped accordingly (i.e. curves were associated with a hazard of progression or death greater than or equal to the hazard of death for the age- and gender-adjusted general population).

Figure 8: 40-year progression-free survival – JAVELIN Merkel 200: Part B (parametric survival curves)

Key: KM, Kaplan-Meier; PFS, progression-free survival.

The long-term survival estimates demonstrate an over-fitting to the tail-end of the Kaplan-Meier data. For the currently available data cut, seven patients are at risk for a progression-free survival event beyond 6 months, and by the time of the last recorded event occurs at approximately 9 months, only five patients are at risk. The best statistical fit (according to Akaike and Bayesian Information Criteria) would be either the exponential or log-normal curves – both of these curves predict different long-term estimates of survival.

Based on the findings of this exploratory analysis, no choice of parametric curve provided an estimation of long-term progression-free survival in line with the base case, nor are they aligned with the clinical expectation of outcomes to be at least as good as those observed for treatment-experienced patients. All parametric curves provide estimates of average progression-free survival lower than the most pessimistic extrapolation for treatment-experienced patients (using a 3-knot normal spline) of 2.81 progression-free life years.

The reasons for the relatively pessimistic estimates of progression-free survival may be due to the fact that none of the extrapolations are able to appropriately take into consideration

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the emergent plateau noted in the data for treatment-experienced patients, as follow up is simply not long enough for treatment-naïve patients. Furthermore, enrolment for this trial is still ongoing, and therefore data for the remaining 60+ patients who have yet to enrol are likely to affect the estimates of progression-free survival to date based on the current sample of 39 patients, as well as future long-term estimates.

Spline-based models

Spline-based models were also fitted to the observed data for treatment-naïve patients, as shown in Figure 9. The statistical goodness of fit for each of these curves are provided in Table 10.

Figure 9: 5-year progression-free survival – JAVELIN Merkel 200: Part B (spline-based curves)

Key: haz, hazard; KM, Kaplan-Meier; nor, normal; odd, odds; PFS, progression-free survival.

Table 10: Statistical goodness of fit – spline-based curves for progression-free survival (JAVELIN Merkel 200: Part B)

Distribution	AIC	BIC
1-knot, odds	96.18	101.17
1-knot, normal	95.48	100.47
1-knot, hazard	96.36	101.35
2-knot, odds	97.77	104.42
2-knot, normal	97.36	104.01
2-knot, hazard	97.70	104.35
3-knot, odds	94.22	102.54
3-knot, normal	94.48	102.80
3-knot, hazard	93.82	102.14
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.		

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Several of the curves are shown to over-fit the observed Kaplan-Meier data (such as the 3-knot normal spline). However, the 1- and 2-knot splines show reasonable fit to the observed data and are therefore considered over a longer timeframe (Figure 10). Any curves demonstrating a hazard of death lower than that of the age- and gender-adjusted general population were capped accordingly (i.e. curves were associated with a hazard of progression or death greater than or equal to the hazard of death for the age- and gender-adjusted general population).

Figure 10: Forty-year progression-free survival – JAVELIN Merkel 200: Part B (spline-based curves)

Key: haz, hazard; KM, Kaplan-Meier; nor, normal; odd, odds; PFS, progression-free survival.

Overall survival

Parametric survival models

Five-year parametric overall survival curves are provided in Figure 11 alongside the current base-case model setting, and the available Kaplan-Meier data from JAVELIN Merkel 200 – Part B. The curves predict 5-year survival to be between 0.01% and 33.37%, dependent on the choice of parametric survival curve. The base-case setting considered within the cost-effectiveness model estimates 5-year survival at approximately 26.33%.

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Figure 11: 5-year overall survival – JAVELIN Merkel 200: Part B (parametric survival curves)

Key: KM, Kaplan-Meier; OS, overall survival.

Table 11: Statistical goodness of fit – parametric survival curves for overall survival (JAVELIN Merkel 200: Part B)

Distribution	AIC	BIC
Exponential	54.44	56.10
Generalised Gamma	58.36	63.35
Gompertz	56.36	59.69
Log-logistic	56.43	59.76
Log-normal	56.37	59.70
Weibull	56.38	59.71
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.		

Survival estimates for the entire modelled time horizon were considered to establish the plausibility of long-term estimates. Where required, any curves demonstrating a hazard of death lower than that of the age- and gender-adjusted general population were capped accordingly (i.e. curves were associated with a hazard of death greater than or equal to the age- and gender-adjusted general population).

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Figure 12: 40-year overall survival – JAVELIN Merkel 200: Part B (parametric survival curves)

Key: KM, Kaplan-Meier; OS, overall survival.

By considering a longer time horizon over which the parametric survival curves may be compared, a clear division of the curves may be observed. The exponential, Gompertz and Weibull curves all predict the majority of patients to have died by approximately 10 years. The generalised gamma, log-logistic and log-normal curves predict a proportion of patients to live longer, in line with the expected immune-response mechanism of action of avelumab.

Given the clinical expectation of patients treated with avelumab at first line to live longer than patients treated with avelumab at later lines, the exponential, Gompertz and Weibull curves should be considered as inappropriate for use within the cost-effectiveness model. Each of these curves produce average life year estimates of 1.44 to 2.42 – much lower than the life year estimate predicted in the model base case for treatment-experienced patients of 3.53 and for treatment-naïve patients of 4.78.

However, the generalised gamma, log-logistic and log-normal parametric curves produce a range of survival curves with associated survival estimates of 4.14 to 5.69 life years. These curves provide survival estimates above and below the base-case curve (which used a hazard ratio applied to data for treatment-experienced patients).

Spline-based models

Spline-based models were also fitted to the observed data for treatment-naïve patients, as shown in Figure 13. The statistical goodness of fit for each of these curves is provided in Table 12.

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Figure 13: 5-year overall survival – JAVELIN Merkel 200: Part B (spline-based curves)

Key: haz, hazard; KM, Kaplan-Meier; nor, normal; odd, odds; OS, overall survival.

Table 12: Statistical goodness of fit – spline-based curves for overall survival (JAVELIN Merkel 200: Part B)

Distribution	AIC	BIC
1-knot, odds	58.43	63.42
1-knot, normal	58.32	63.31
1-knot, hazard	58.38	63.37
2-knot, odds	60.29	66.95
2-knot, normal	60.08	66.74
2-knot, hazard	60.27	66.92
3-knot, odds	56.90	65.22
3-knot, normal	56.30	64.62
3-knot, hazard	56.98	65.30
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.		

The 3-knot splines provide erroneous extrapolations, as noted with the early “bump” in the survival curve. Therefore, these models should be discounted from consideration. However, the 1- and 2-knot splines show reasonable fit to the observed data and are therefore considered over a longer timeframe (Figure 14). Any curves demonstrating a hazard of death lower than that of the age- and gender-adjusted general population were capped accordingly (i.e. curves were associated with a hazard of progression or death greater than or equal to the hazard of death for the age- and gender-adjusted general population).

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Figure 14: 40-year overall survival – JAVELIN Merkel 200: Part B (spline-based curves)

Key: haz, hazard; KM, Kaplan-Meier; nor, normal; odd, odds; OS, overall survival.

The 1-knot normal and odds splines provide long-term estimates of overall survival similar to those used to inform the model base case. The 2-knot versions of these splines provide lower estimates of long-term survival, whereas the hazard-based splines provide similar extrapolations to those seen by the exponential, Gompertz and Weibull extrapolations (which were considered clinically implausible).

Time on treatment

Parametric survival models

For time on treatment, spline-based models were not considered in the submitted cost-effectiveness model. Based on the clinical expectation of treatment discontinuation for the majority of patients at 2 years, and for all patients at 5 years, the estimation of long-term time on treatment was unnecessary for incorporation within the model, and therefore as the parametric models demonstrated reasonable visual fit within the observed period, these models were considered sufficient for informing time on treatment.

For consistency with the submitted cost-effectiveness model, spline-based models were not fitted to time on treatment data for the treatment-naïve cohort, as spline-based models were not fitted to time on treatment data for the treatment-experienced cohort. However, parametric models for time on treatment were fitted (and were also subject to the same assumptions regarding treatment discontinuation as per the submitted base case). The curves are presented in Figure 15, with the statistical goodness of fit for each of these curves provided in Table 13.

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Figure 15: Time on treatment – JAVELIN Merkel 200: Part B (parametric curves)

Key: KM, Kaplan-Meier; On Tx, on treatment.

Table 13: Statistical goodness of fit – parametric survival curves for time on treatment (JAVELIN Merkel 200: Part B)

Distribution	AIC	BIC
Exponential	96.35	98.01
Generalised Gamma	92.45	97.44
Gompertz	93.17	96.50
Log-logistic	90.65	93.98
Log-normal	90.46	93.78
Weibull	90.88	94.21
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.		

The Gompertz curve does not converge, and should therefore be discounted from further consideration. Of the parametric models that are not associated with convergence issues, the log-normal is shown to exhibit the lowest AIC and BIC scores, though the Weibull model appears to show good visual fit most similar to the base-case settings used in the submitted cost-effectiveness model.

Summary of analysis

As discussed, fitting survival curves to data from JAVELIN Merkel 200 – Part B trial is associated with numerous caveats and limitations. Data from this trial are immature and are therefore not considered an accurate basis from which long-term extrapolation may be considered to inform the cost-effectiveness analysis.

However, the extrapolation options presented in response to this question are available for selection within the updated cost-effectiveness model. The curves will only apply to the avelumab arm of the model, and will only change if the model is set to consider the treatment-naïve patient population.

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The preferred base case of the manufacturer remains unchanged – that is, the use of a hazard ratio applied to more mature follow-up data for treatment-experienced patients. However, several combinations of the aforementioned survival curves have been explored, with results provided in Table 14.

Table 14: Scenario analysis: avelumab versus chemotherapy for treatment-naïve patients using data from the JAVELIN Merkel 200: Part B trial

Description	ICER
Submitted base case (HR applied to data from JAVELIN Merkel 200 – Part A)	*£43,633*
Same parametric model for each outcome (log-normal for OS, PFS and ToT)	£51,312
Splines for OS and PFS (spline 1-knot hazard for OS, PFS, log-normal for ToT)	£46,978
Most plausible parametric estimates (log-normal for OS, PFS, Weibull for ToT)	£42,935
Most plausible overall estimates (spline 1-knot hazard for OS, PFS, Weibull for ToT)	£39,409
Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; ToT, time on treatment. **Note:** Plausibility of estimates were established based on long-term outcomes and comparison to clinical expectation (e.g. low number of patients on treatment at 5 years, immune-response tail in OS etc.)	

We would again stress the immature nature of the available data for treatment-naïve patients treated with avelumab, and how these results should be interpreted with caution.

B4. **Priority question.** Please fit the spline curves to the comparator OS and PFS data used in the base case, in the same way that was done for the JAVELIN 200 trial data, and add these as options to the economic model.

Spline-based models were not considered necessary for comparator data as our assessment of the hazard function concluded there is no apparent need for a flexible modelling. Further to this, Kaplan-Meier data available for the comparator are complete and therefore complex extrapolation methods should only be required for the purpose of improving the fit to the observed data.

To address the ERG's request, spline curves have now been fitted to the comparator overall survival and progression-free survival data considered in the model base case. These spline models are presented alongside the associated Kaplan-Meier data in Figure 16.

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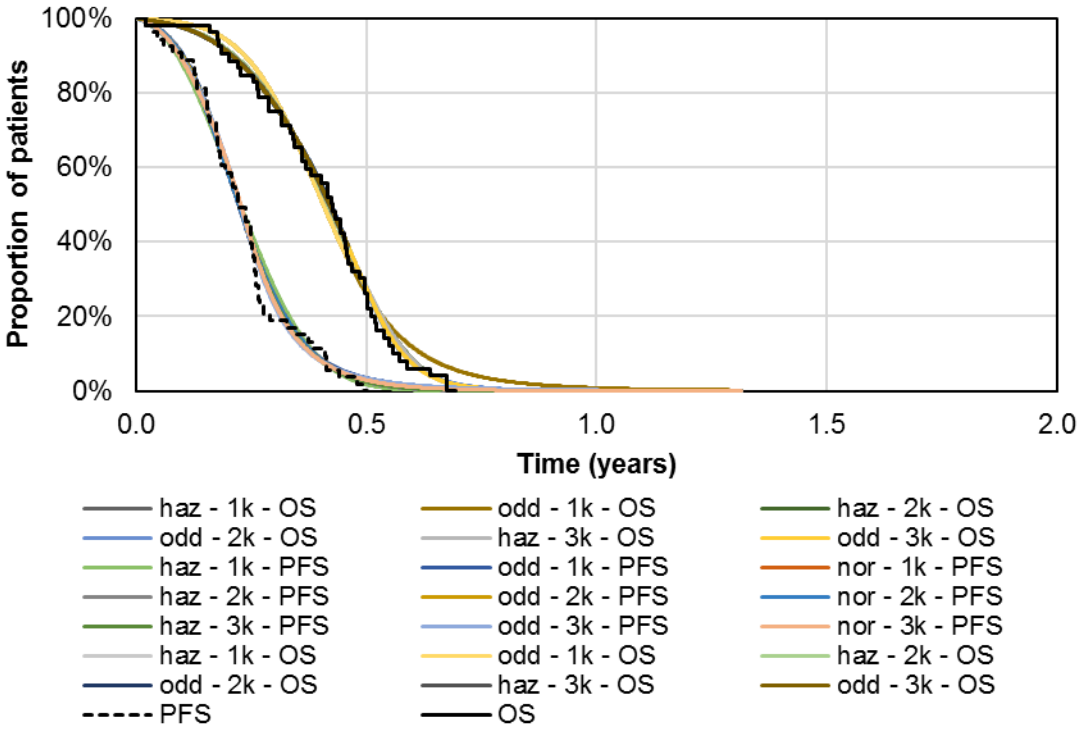
Figure 16: Comparator survival – treatment-experienced patients (spline-based models)



Key: haz, hazard; nor, normal; odd, odds; OS, overall survival; PFS, progression-free survival.
Note: The normal-based spline models for overall survival did not converge, hence are not provided.

The parametric models are presented in Figure 17. The base-case models considered within the cost-effectiveness model was the Gompertz for overall survival and the Weibull for progression-free survival – these curves are presented separately in Figure 18. Compared to the parametric models, there is no clear advantage of using these new spline-based models over the better-fitting parametric models, and as such these models are not considered further.

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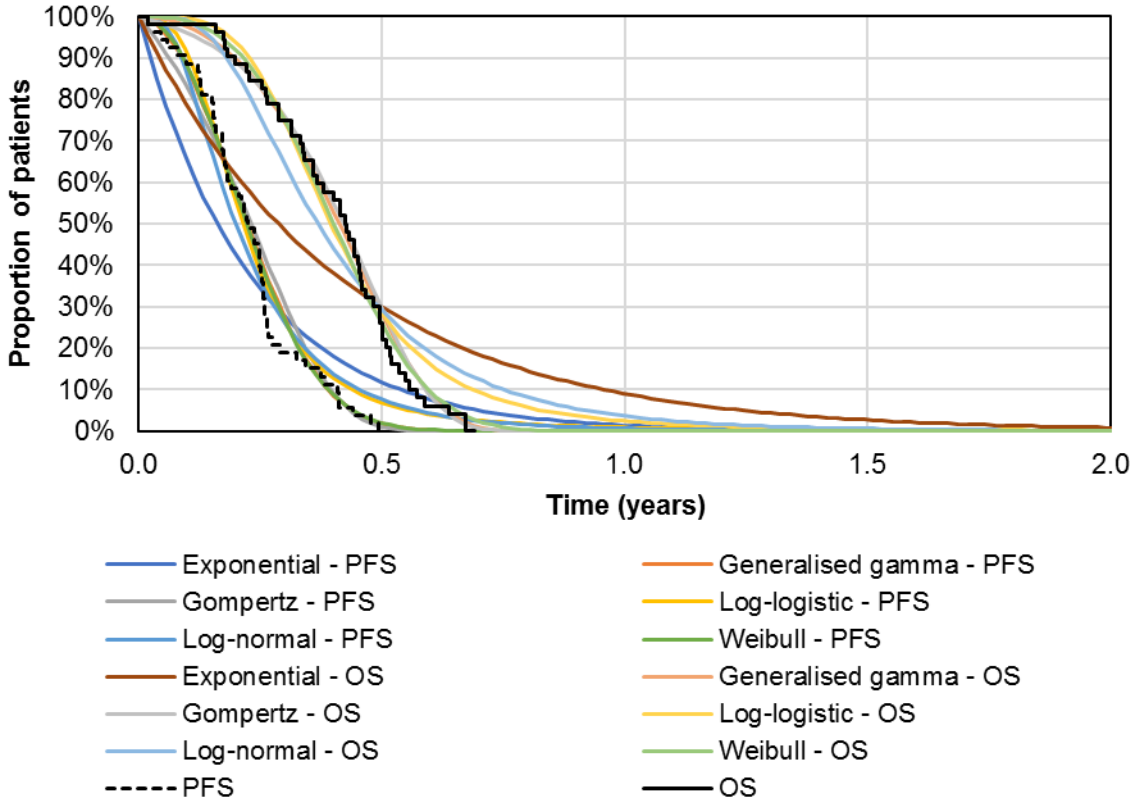
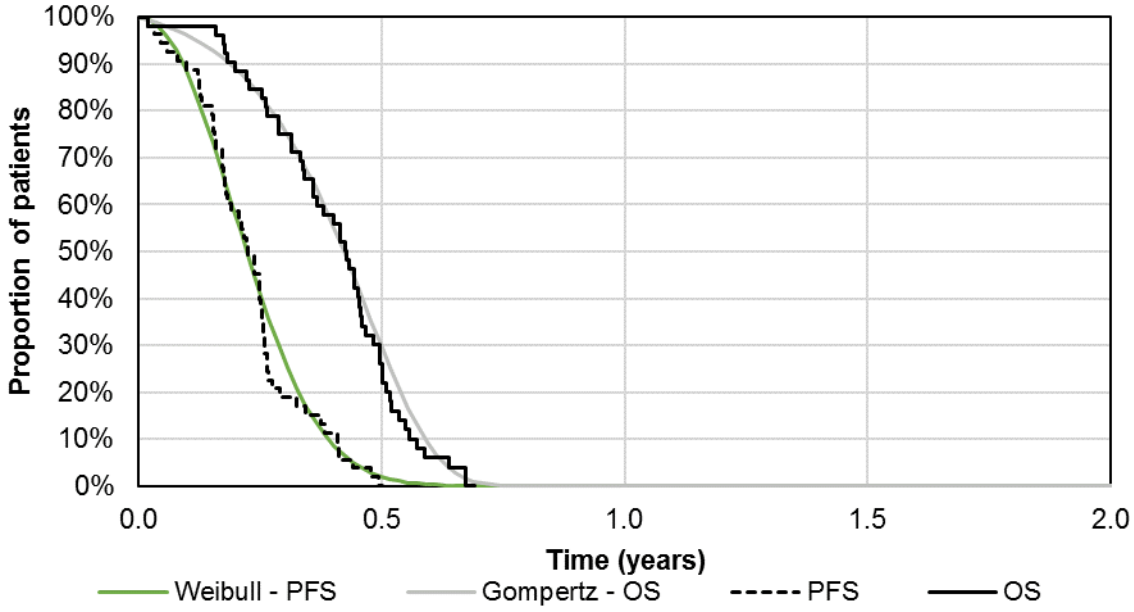
Figure 17: Comparator survival – treatment-experienced patients (parametric models)



Key: OS, overall survival; PFS, progression-free survival.

Figure 18: Comparator survival – treatment-experienced patients (parametric models used in model base case)



Key: OS, overall survival; PFS, progression-free survival.

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Additional Kaplan-Meier data

B5. Please update the 'Lists' sheet to include the treatment-naïve Kaplan-Meier data for OS, PFS and ToT of the model along with the treatment-experienced data and comparator data.

The model has been updated to include Kaplan-Meier data based on JAVELIN Merkel 200 – Part B. These data are made visible when the model is set to consider treatment-naïve patients, and are presented alongside data for treatment-experienced patients. It should be noted that these data are immature, and therefore the data for treatment-experienced patients are of pivotal importance to consider alongside the data for treatment-naïve patients when determining the plausibility of short- and long-term survival estimates for treatment-naïve patients.

The Kaplan-Meier data for treatment-naïve patients may be found on the 'Lists' sheet in the range CD104:CN185. The data are presented for each outcome (overall survival, progression-free survival and time on treatment) with survival times reported in years and months.

B6. Please update the 'Lists' sheet to include the additional Kaplan-Meier data from the MAICs requested in questions A1 to A4. Please include the adjusted avelumab data as well as the alternative comparator data.

The updated model includes the Kaplan-Meier data based on the propensity score matching analysis. To avoid confusion with the Kaplan-Meier data already present within the model, and because these data are from a purely exploratory analysis, these data are provided in the *"ERG requested curves"* sheet in cells R24:V132.

Health-related quality of life

B7. Please provide the means and standard deviations of the mapped EQ-5D-5L data at each timepoint, for comparison against the EQ-5D-3L data collected in the JAVELIN 200 trial from which it was mapped.

The JAVELIN Merkel 200 trial collected EQ-5D-5L data at 6-weekly intervals while patients were receiving avelumab treatment. The question as written is difficult to interpret, however the output believed to be requested is provided – a summary of the EQ-5D-5L crosswalk utility values from the latest data cut of JAVELIN Merkel 200 – Part A. These data are presented in Table 15.

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Table 15: Mean and standard deviations of utility scores at each timepoint

Visit	n	Mean	SD
Baseline	71	0.739	0.224
Week 7 Day 43	52	0.774	0.167
Week 13 Day 85	39	0.789	0.146
Week 19 Day 127	30	0.755	0.128
Week 25 Day 169	28	0.796	0.130
Week 27 Day 183	1	0.533	NA
Week 31 Day 211	20	0.815	0.120
Week 33 Day 225	1	0.796	NA
Week 37 Day 253	21	0.770	0.119
Week 43 Day 295	21	0.780	0.131
Week 49 Day 337	14	0.781	0.155
Week 51 Day 351	1	0.837	NA
Week 55 Day 379	16	0.771	0.149
Week 57 Day 393	1	0.837	NA
Week 61 Day 421	9	0.690	0.105
Week 63 Day 435	1	0.837	NA
Week 67 Day 463	11	0.725	0.114
Week 69 Day 477	1	0.837	NA
Week 73 Day 505	9	0.720	0.113
Week 75 Day 519	1	0.837	NA
Week 79 Day 547	10	0.722	0.107
Week 81 Day 561	1	0.708	NA
Week 85 Day 589	11	0.720	0.102
Week 91 Day 631	7	0.758	0.076
Week 97 Day 673	6	0.759	0.083
Week 103 Day 715	6	0.759	0.083
Week 109 Day 757	3	0.773	0.119
Week 115 Day 799	3	0.773	0.119
Week 121 Day 841	2	0.741	0.148
At end of treatment	27	0.797	0.163
Key: NA, not applicable; SD, standard deviation.			

B8. Please clarify why the disutilities associated with the adverse events are not applied in the time to death approach used in the base case analysis. Please amend the model to incorporate these.

The *"time-to-death"* utilities do not differentiate between those patients receiving active treatment and those not receiving active treatment. As such, incorporating adverse event-related disutilities (which by definition do not apply for patients not receiving treatment) was not possible while disaggregating expected time to death. However, these adverse event-related disutilities were still important to capture within the cost-effectiveness model when *"time-to-death"* utilities were used.

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The application in the model therefore considers the following approach:

- Health-state utility values for patients according to their estimated *"time-to-death"* were calculated excluding adverse event-related disutilities.
- Adverse event-related disutilities were incorporated within the *"progression-free disease and on treatment"* and *"progressed disease and on treatment"* health states, but were calculated as quality-adjusted life year decrements.

For patients receiving avelumab, these quality-adjusted life year decrements are negligible for treatment-experienced patients (-0.000166 and -0.00000745 for the *"progression-free disease and on treatment"* and *"progressed disease and on treatment"* health states, respectively). Therefore, within the manufacturer's submission the combined value appears to be 0.00 (rounded to two decimal places).

However, for treatment-naïve patients receiving chemotherapy, the impact of adverse events on health-related quality of life is greater – estimated at -0.01 (rounded to two decimal places). Adverse events for treatment-naïve patients receiving avelumab are estimated at 0.00 (rounded to two decimal places), as per the estimate for treatment-experienced patients.

To allow the ERG to investigate further the impact of adverse event related disutilities on the cost-effectiveness results, a switch has been implemented on the *"Controls"* sheet to disable the application of adverse event related disutilities.

In summary, the model does include adverse event-related disutilities within the model base case using the *"time-to-death"* approach. However, the impact of adverse events on health-related quality of life is small for patients receiving avelumab, and is only noticeable (when rounded to two decimal places) for treatment-naïve patients receiving chemotherapy.

Resource use and costs

B9. Please clarify whether the end-of-life care costs obtained from Round et al., 2015 were inflated to 2015-2016 prices in the model. If not, please inflate them using the Hospital and Community Health Services index (as done for the adverse reaction unit costs).

The end-of-life care costs obtained from Round *et al.*, 2015 were not inflated using the Hospital and Community Health Services index in the submitted cost-effectiveness model. This was unintentional, as the costs reported in the publication are stated as 2013-2014 prices. As such, the updated model incorporates an inflation factor of 297/290.5 ≈ 1.02 – derived from the PSSRU.

By correcting this within the model, the ICER for avelumab versus BSC for treatment-experienced patients decreases from £37,409 to £37,401. The ICER for avelumab versus chemotherapy for treatment-naïve patients decreases from £43,633 to £43,624.

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B10. Please clarify why many of the costs applied in the model for the treatment of adverse events are estimates based on grade 1 or 2 events (e.g. anaemia, muscle pain, nausea/vomiting) when the model is based on grade 3 or 4 events (with the exception of hair loss). Please consider using costs related to grade 3 or 4 events where applicable.

The Grade 1 and Grade 2 costs considered within the model are for anaemia, muscle pain and nausea/vomiting. The publication identified for adverse event costs (Vouk *et al.*, 2016) did not report Grade 3 or Grade 4 costs for these adverse events as they were not commonly experienced in clinical practice.

Treatment-related anaemia, muscle pain and nausea/vomiting adverse events were not experienced by any of the patients treated with avelumab, and hence rates of 0% are applied within the cost-effectiveness model. Therefore, as these adverse events are only experienced by patients treated with chemotherapy, the use of lower grade costs within the model was considered a conservative modelling assumption.

However, the cost of resolving these adverse events may be higher, as highlighted by the Evidence Review Group. NICE TA319 of ipilimumab for previously-untreated (treatment-naïve) advanced melanoma and TA357 of pembrolizumab for advanced melanoma after disease progression with ipilimumab provide costs for each of the three aforementioned adverse events. As these submissions were based on 2012 and 2014 prices, each cost was inflated using the Hospital and Community Health Services index. A summary of these costs is provided in Table 16.

Table 16: Updated adverse event costs

Adverse event	Original cost	Inflated cost	Source and assumptions
Anaemia	£728.62 for ipilimumab patients, £792.10 for vemurafenib or BSC patients.	£799.39	NICE TA319. Oxford Outcomes: Anaemia. Average across both treatment arms assumed to apply.
Muscle pain	£146.00	£153.49	NICE TA319. HRG service code: 191, Pain management, multi-professional non-admitted face-to-face.
Nausea/ vomiting	£213.49	£218.27	NICE TA357. Assumed the same as diarrhoea from NICE TA319 (Oxford Outcomes: Diarrhoea).
Key: BSC, best supportive care; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.			

The impact of including these costs on the ICER for avelumab versus BSC for treatment-experienced patients is zero, as no patients experience these adverse events. However, for treatment-naïve patients, the ICER for avelumab versus chemotherapy decreases from £43,633 to £43,601.

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B11. Where applicable, please correct the calculations in the economic model that incorrectly estimate the number of weekly cycles for which a monthly cost is applied. For example, in cell D47 of the 'Resource Use Costs' sheet, it is assumed that 3 months equates to only 12 weeks. Further examples are in cell C73 and E94 of the same sheet.

Within the cost-effectiveness model, the following costs on the *"Resource Use Costs"* sheet were affected by the use of 28 days to reflect the duration of a month:

- Frequency of a CT scan for avelumab-treated patients with progression-free disease (D47),
- Frequency of CT scans for chemotherapy-treated patients with progression-free disease (C73:J73), and
- Frequency of GP visits for patients treated with best supportive care post-progression (E94).

The model has been updated to appropriately reflect the monthly costs using the value of 365.25/12 days (approximately 30.44 days) instead of 28 days. By correcting this within the model, the ICER for avelumab versus BSC for treatment-experienced patients decreases from £37,409 to £37,358. The ICER for avelumab versus chemotherapy for treatment-naïve patients decreases from £43,633 to £43,593.

Time on treatment

B12. Please clarify whether deaths were considered as events or censoring in the ToT data from the JAVELIN 200 trial.

Death was considered an event in the analysis of treatment discontinuation data from the JAVELIN 200 trial, as patients who had died could no longer receive treatment. Of the 88 patients in JAVELIN Merkel 200 – Part A, [redacted] patients discontinued treatment by the end of follow up. [redacted] patients discontinued treatment due to death.

Section C: Textual clarifications and additional points

C1. Please clarify whether Figures 5 and 6 of Appendix 10 show regression results using a Weibull distribution or a generalised Gamma distribution. The preceding text states generalised Gamma but the table headings state Weibull. Please update with the generalised Gamma regression results if necessary.

The tables presented in Figure 5 and Figure 6 of Appendix 10 are mistitled – the preceding text discusses the generalised Gamma regression results, and the regression results show the results from the generalised Gamma regression which can be seen by having three parameters (mu, sigma and Q) as opposed to the two that would be expected with a Weibull regression (rate or shape, and scale). As this is only a text change to two table titles, the

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report has not been updated so as to avoid confusion in the documentation history that NICE will make available as part of the single technology appraisal process.

C2. Please update the line of therapy button in model to ensure all inputs are reset to the appropriate base case inputs. Currently avelumab survival curves do not reset.

In the submitted cost-effectiveness model, the *"Set model to…"* button changes the settings that differ across treatment lines. As discussed in the manufacturer's submission, the survival curves for chemotherapy differ according to the line of therapy. However, for avelumab patients the choice of survival model does not change by line of therapy – rather, hazard ratios are applied to the survival curves for treatment-experienced patients. Therefore, while the *"Set model to…"* button does not change the choice of survival model, this is deliberate as no change is intended to apply.

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Downs S, B. N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of heath care intervenstions. *Journal of Epidemiol Community Heath* , 377-84.

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Appendix G – patient/carer organisation submission

About you and your organisation
Name : [redacted]
Name of organisation : NET Patient Foundation
Position in the organisation : Patient Support Manager (RGN)
Brief description of the organisation : The NET Patient Foundation is the only UK wide charity established for the advocacy, education and support of those diagnosed and living with malignant neuroendocrine tumours (NETs) . We provide research and evidence based information resources for patients, carers and family members, as well as over 100 NHS hospitals - including relevant medical and scientific communities. We are members of both the European and International NET communities – working collaboratively to raise awareness, fund research and most importantly advocate for and support NET patients. We are donation dependent – details and confirmation of this and our charity status can be found on the Charity Commission website : https://www.gov.uk/government/organisations/charity-commission
The NET Patient Foundation has a small staff, comprising of co-founder/CEO, Patient Support Manager (RGN) and Operations Manager. Through fixed term contracts we also have a community support nurse and counselling/psychotherapy team.
Our "membership" exceeds 1000 : nb Over 4,000 neuroendocrine neoplasms (8 per 100,000 persons) are diagnosed per year. They are found at a mixture of sites in the body with a varying relationship between stage at diagnosis and survival. 573 of the 8,726 neuroendocrine neoplasms diagnosed in England, 2013 and 2014 have been coded as Merkel Cell Carcinoma. (**PHE data 2016**).
|Reflecting its rarity (and possible aggressive nature) we have only a few people, amongst the 1000+ who have contacted us, with this particular form of NET – our experience is informed by their conversations – and information from within the European and International communities, as well as research and trial data.

Living with the condition
Malignant neuroendocrine tumours (NETs) are considered rare or at least uncommon. Most NETs are presumed to be indolent, that is, non-aggressive. Merkel Cell carcinoma (MCC) does not fall into this category – patients describe lesions that change "almost before my eyes", with one young woman reporting a "pea-size lump that became a golf ball within 2 weeks".
MCC presents, primarity, as a firm, painless, rapidly enlarging, (often) red-violet , dome-shaped lump of unbroken skin : usually, but not exclusively, in areas of skin that are exposed to direct sunlight.
Though signifiantly less common than melanoma, MCC has a threefold death rate (comparison)
It is reported as a cancer that predominantly occurs within the older population (>65yrs), but is also seen in those with immunocompromised health states . Post-transplant patients are reported to have a tenfold higher risk than the general population (8% of MCC population are post transplant), positive HIV status can further raise this risk to thirteen fold. Post transplant patients with MCC have a median age of 53years.
5year survival based on disease/lymph node staging : S1 – 76%; S2 (1LN) 50%: >1 LN 0-18%
>40% have non-localised disease
Schadendorf et al 2017
2010 (NCIN) incident rate in England : between 53 – 106 people per year
2013-2014 (PHE) incident rate in England : 286 people per year (reflecting global increase reports)

Given the rarity of incidence there is little information on patient experience however patients (and their families) tell us of the fear, uncertainty, despair of diagnosis – compounded by a perceived lack of knowledge and experience amongst healthcare professionals of this disease. Prognosis is poor – especially beyond stage 1 disease : even treated disease has a high recurrence rate.
Family members describe the pain of watching loved ones go through exhausting toxic treatments

hoping for response only to find the disease unresponsive or recur "within weeks".

Current practice in treating the condition

Current guidelines, due for review next year, exist – and recommend wide excision surgery for localised primary site disease with radical lymphadenectomy (or at least sentinel node biopsy) +/- adjuvant radiotherapy to excision beds. Where complete excision is not possible chemotherapy is advised – despite high remission rates, responses are short-lived and the disease has a high recurrence rate.

Avelumab offers a more durable response – and lower toxicity (according to available trial data).

Patients and carers want cure. If cure cannot be achieved then quality of life dominates – high toxicity is only seen as endurable if short-term and treatment is effective and sustainable.

"My grand-daughter told me she only remembers nanny being sick . . .she's 8, my wife was only on chemo for 6 weeks. . ."

For primary contained disease current guidelines for treatment provide the best chance of cure. However once lymph node or other secondary disease occurs prognosis is abysmal – with current treatments providing little in the way of tolerance or sustainability, nb people with MCC are often older and /or are already immunocompromised (post transplant, HIV, etc).

What advantages do patients or carers consider to be the advantages of the treatment being appraised ?

Disease control, tolerability and sustained response – in essence, hope. Hope for a treatment that not only provides the high remission rate of chemotherapy but does this with fewer side effects and longer lasting effects. A tolerable treatment – some with MCC do not necessarily experience pain or other cancer related symptoms unless or until it affects secondary site function or their daily activity – for others lethargy, impairment of usual daily activities or hospitalisation (due to disease burden, obstruction) is reported. Psychologically, the emotional burden of living with an aggressive and largely untreatable cancer is exhausting, overwhelming, "its despair . . .", "hopeless", or as one woman put it " I felt like I'd lost him already . . .".

The reports emerging from the JAVELIN trial would suggest that the psychological improvements reported by patients were as important as the physical : "Patients feel like getting back to their previous activities, they feel good and are optimistic and positive about their future".

Despite the travelling and time required at hospital to complete the trial / receive the medication – "Patient satisfaction was high relative to their previous negative experiences with chemotherapy and radiotherapy, which patients described as highly debilitating, both physically and mentally"

Abstract 67556 Kaufman et al ISPOR Congress 2016

What do patients and / or carers consider to be the disadvantages of the treatment being appraised ?

Availability/accessibility – would this be specialist centre only (for some this would then necessitate extra travel – though this in itself would not deter them)

Age – all reports assume this to be a disease of the older person – "it wont be age restricted will it?"

With currently available treatments – tolerance and toxicity is an issue. In relatively low symptom symptom disease, the side effects of cytotoxic treatment can be incredibly debilitating – even more so in the older population – or in those already immunocompromised.

Avelumab "by all reports actually stimulates your immune system, . . .", "helps your white cells fight back . . .isn't that what it does?"

Patient population
MCC is rare as previously stated. Clinical experience and knowledge limited – however, we do have information about current practice and guidance.

We believe that Avelumab offers a real innovative step change, in treatment, for those with residual or inoperable disease.
It may also, in the future, have a role in adjuvant therapy – either post surgery or in the neoadjuvant setting – for those with operable disease. But this would need clinical / research / trial evidence.

Research evidence on patient or carer views of the treatment
We are familiar with the published research for Avelumab – as well as poster presentations and abstracts.

Avelumab is not available as part of routine NHS care

Patient experience has been undertaken – as part of the JAVELIN study - utility scores and quantitive assessment abstracts. Drop out from the quantitative study is attributed to poor health – these patients may have reported less positively.

Other issues

We do consider the treatment to be innovative, the first immunotherapy treatment for MCC – and that it provides a step change in the treatment of metastatic Merkel cell carcinoma and what is more services the unmet clinical need for a safe, effective and durable therapy for those diagnosed.

Key Messages

Unmet needs
Quality of life impact – psychologically as well as physically
Safe, effective and durable
Innovation

References :

- PHE : Incidence and survival in neuroendocrine tumours and neuroendocrine carcinomas (NETs/NECs) in England, 2013-2014 . PHE publications gateway number: 2016360 . Published: October 2016
- Schaedendorf et al (2017) Merkel Cell Carcinoma : Epidemiology, Prognosis, Therapy and Unmet Medical Needs. European Journal of Cancer (71) 53-69 : http://dx.doi.org/10.1016/j.ejca.2016.10.022
- National Cancer Intelligence Network (2010) Rare skin cancer in England.
- Kaufman et al (2016) Patient perspectives on Merkel Cell carcinoma (MCC) and its treatment with a noval agent (Avelumab) : findings from in-depth qualitative interviews.

Abstract 67557 Poster presentation at the ISPOR 19th Annual European Congress 29 October-2 November Vienna

- Kaufman et al (2017) Non-progression during treatment with avelumab contributes to gains in helath utility scores in patients with metastatic Merkel cell carcinoma

Poster PCN180 presented at the ISPOR 22nd Annual International Meeting May20-24 Boston, Mass. USA

- Lebbe et al (2015) European Dermatology Forum : Guidlines on the diagnosis and treatment of Merkel Cell Carcinoma. Eur J Cancer. 2015 Nov;51(16):2396-403. doi: 10.1016/j.ejca.2015.06.131.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Avelumab for treating metastatic merkel cell carcinoma ID1102

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: NCRI-ACP-RCP

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Avelumab for treating metastatic merkel cell carcinoma ID1102

What is the expected place of the technology in current practice?

Avelumab is an intravenously administered programmed cell death ligand-1-blocking human antibody developed for the treatment of various tumours.

It has received accelerated approval in the USA for the treatment of metastatic Merkel cell carcinoma (mMCC) in adults and paediatric patients aged ≥12 years.

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The expected place for avelumab is within its expected marketing authorisation i.e. the treatment of people with mMCC, to palliate symptoms and prolong life.

MCC is a high grade, locally invasive, highly metastatic neuroendocrine skin cancer in older people (median 76 years with 62% between 50-80 years and 34% >80 years) [1, 2]. It is very rare: 1515 cases reported centrally in England in the decade to 2008 but with incidence rising from 0.1 to 0.2/100000 across that time [3].

MCC can disseminate loco-regionally as in-transit, satellite and nodal metastases and more widely to distant skin, lung, central nervous system, bone and liver [4].

The natural history of MCC is described in retrospective case reviews, searches of the United States national cancer database and in a prospective registration study of a single-centre cohort [1, 2, 5]. Two-thirds of patients present with primary lesions only (stage I and II), one-quarter have clinical or radiological evidence of regional nodal involvement (stage III), and fewer than 10% present with disseminated disease (stage IV). Primary MCC is amenable to surgical control and is also radiosensitive. Recurrence rates are high, with relapse-free survival at 5 years for stage I-III patients reported as 48%, median time to recurrence 9 months and >90% recurrences manifest within 2 years.

Note that some patients present with locally or regionally advanced disease which is not amenable to radiotherapy or surgery as primary treatment and these patients also need access to effective systemic therapy, grouping them together with patients with metastatic MCC as 'advanced MCC'.

Many chemotherapeutic agents have activity against MCC, including cyclophosphamide, doxorubicin (or epirubicin) plus vincristine or etoposide plus cisplatin. Response rates are reported around 55-60% but note this is based on retrospective note review and grouped case reports not prospective trials [6-10].

Duration of clinical benefit is variable between individuals and depends very much on the degree of initial response.

For example, in a retrospective case review [10] of 62 patients with distant mMCC, the response rate to a diverse chemotherapy regimens (two thirds based on platinum agents) was 55% and median progression free survival (PFS) was 94 days (range 12-983 days).

Among the 8 patients with a complete response, median PFS was much longer, 303 days (range 139-983 days) and among those with partial response median PFS was 145 days (range 26-721 days).

The median duration of response from time of best response was 85 days (range 12-942 days) and for complete responders it was median 190 days (range 18-942 days) and for partial responders it was 63 days (12-666 days).

In the second line context, agents such as topotcan or paclitaxel collectively achieved a response rate of only 23%, a median PFS of just 61 days (range 11-354 days). The median duration of response after best response to second line treatment was 101 days (range 6-255 days).

Median overall survival after diagnosis of mMCC in these 62 treated patients was 13 months (range 58 days to 3.2 years). Median survival was 9.5 months after start of first line therapy and 5.7 months after start if second line therapy.

Taken together, this detailed retrospective review and the other aggregated case studies are in line with clinical experience.

First, cytotoxic chemotherapy has a good probability of response which can be useful in palliating symptoms

Second, duration of response is highly variable between individuals and much longer if complete response is achieved. Clearly a few patients achieve benefit for upwards one or two years. However, half of patients have responses which last under three months.

Third, half of first-line treated patients have progressed or died by three months, or by five months even if they achieved partial response.

Fourth, response rate is low and progression or death rapid in the second line context.

Cytotoxics have not been compared to best supportive care and selection of best agents has not been undertaken in randomised trials.

From discussion with colleagues, I understand in the UK the most widely used regiment is the combination of carboplatin and etoposide.

The variable outcomes - moderately high probability of response skewed towards short duration of benefits - contribute to a willingness of oncologists to offer at least first line cytotoxic chemotherapy in the hope of complete response which may prove durable, tempered by an awareness of possible futility which has to be weighed against the harms caused by treatment.

There is a consensus among UK oncologists and SSMDT members, that cytotoxic chemotherapy should be offered to people with mMCC but the decisions on whether to use it are made on an individual basis, balancing risk and benefit.

Importantly, there is also consensus that there is an unmet need for effective well-tolerated treatments to improve symptom control from unresectable loco-regional disease and to prolong survival from disseminated MCC.

There is real interest among clinicians in clinical trials in this setting as the options are limited, and trial entry would also be regarded as standard of care.

Some patients might be offered regional chemotherapy, typically isolated limb infusion, for example for an unresectable MCC primary or extensive in transit metastases. This is only undertaken in limited centres in the UK.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Management of patients with advanced MCC can be challenging because the age rage is wide, including middle aged fit individuals and many elderly patients with co-morbidities affecting treatment tolerability.

Younger and fitter patients are more likely to be offered and accept treatment with cytotoxic chemotherapy.

Patients in their late seventies and older, and people with co-morbidities, are more likely to be spared cytotoxic chemotherapy or decline it, judging the risks of prolonged morbidity from adverse events to outweigh the benefits of tumour response to treatment without proven survival advantage. Such patients might instead be offered best supportive care, with surgical or radiation treatment for selected symptomatic lesions.

However, this is an individual choice based on balance of risk and benefit. To give an example from my practice, a patient with multiple co-morbidities but with a large unresectable MCC mass on his face was treated with 4 cycles of carboplatin and etoposide. The resulting partial response enabled him to proceed first to radiotherapy and then finally to surgery for this lesion. Although disease has progressed at other sites many months later, he

maintained good control of this previously symptomatic facial disease which is was of great palliative benefit.

MCC has a recognized association with iatrogenic or natural immune suppression [11], including coincidental chronic lymphocytic leukaemia (CLL) [12], organ transplantation [13], HIV infection [14] and auto-immune disease [15]. Immune suppression also appears to predict a more aggressive clinical course [13, 16]. Lower absolute lymphocyte count (ALC) at diagnosis is associated with more advanced stage and, independently, with poorer survival in a retrospective single centre series [17].

In the series discussed above, 14/62 (23%) of patients treated with chemotherapy for mMCC had immune compromise including lymphoid malignancy, HIV infection, organ transplantation and iatrogenic immune suppression. These 14 patients had outcomes through the full range from early progressive disease to response with PFS approaching a year [10]. Currently, there is no reason to use immune suppression to select patients for different standard of care treatment options other than as a co-morbiditiy factored into the individualised balance of risk and benefit.

Most MCC have the skin commensal, Merkel cell polyomavirus (MCPyV), integrated in the malignant cell genome [18, 19]. There is currently no data indicating patients with virus-positive advanced MCC should be treated differently to virus negative MCC, although the latter do have a somewhat different profile of driver mutations.

A significant minority of MCC patients have additional cancers sequentially or concurrently, including those sharing UV light exposure as a risk factor (melanoma and non-melanoma skin cancers) and CLL. There is no good evidence for selecting patients for treatment for MCC on the basis of presence or absence of other cancers except as part of individual balance of risk and benefit.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Avelumab for MCC should be offered exclusively in the context of clinical services provided by consultant medical or clinical oncologists trained in the use of systemic therapy for malignant disease.

The oncologists should be members of a SSMDT or similar framework. Management of such patients can be multidisciplinary, including the use of surgery or radiotherapy. MCC is rare: it is important that patients in local hospitals are directed for a specialist opinion within the SSMDT so a critical level of knowledge and experience can be maintained and trials accessed.

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Advanced MCC is a potentially lethal disease. Patients should have a key worker supporting them, typically a skin cancer clinical nurse specialist.

The oncology services should include patient access to an Acute Oncology Service (AOS), for 24/7 management of adverse events. AOS are experienced in managing cytotoxic chemotherapy complications and are gaining experience in managing Immune related Adverse Events (IrAE) through the use of immune checkpoint inhibitors for melanoma, lung cancer and renal cancer.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Immune checkpoint inhibition is not currently available as standard of care in the NHS.

Currently there is a clinical trial of combination nivolumab and ipilimumab. This is an umbrella design trial covering a range of cancers positive for viruses (https://clinicaltrials.gov/ct2/show/NCT02488759). Entry to this trial is standard of care in Birmingham and the other contributing centres, and cross-regional referrals are taken.

Paraxel operate an expanded access scheme for avelumab for patients with advanced refractory MCC following cytotoxic chemotherapy. The scheme does exclude some patients for example if they have prior auto-immune disease.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

https://merkelcell.org/wp-content/uploads/2015/10/MccNccn.pdf - the US National Clinical Practice Guideline in Oncology has been updated in 2017.

For metastatic melanoma the guidelines state that a clinical trial if available is the preferred option, and other options include systemic therapy, radiation therapy or surgery (i.e. under highly selective circumstances, in the context of multidisciplinary consultation, resection of oligometastases can be considered)

With regard to systemic therapy, it lists as options cisplatin +/- etoposide, carboplatin +/- etoposide, topotecan, CAV (cyclophosphamide, doxorubicin and vincristine)

It also lists pembrolizumab, a monoclonal antibody targeting PD-1, commenting that non-randomised trials show response rates similar to those for chemotherapy. It is not clear to me from searching that pembrolizumab is licensed for this indication in the United States.

The data supporting the use of pembrolizumab are from a trial of pembrolizumab 2mg/kg intravenously 3-weekly up to progression, limits of tolerance or 2 years, in 26 systemic therapy-naïve adult patients with advanced with MCC performance status 0-1, without immune deficiency or ongoing systemic immunosuppressive therapy, active autoimmune disease, second cancers or active central nervous system metastases. The response rate was 14/25 (4 complete) giving a response rate of 56% (95% CI 35-76%). Responses occurred in virus positive and negative disease. Response duration was from at least 2.2 to at least 9.7 months (responses ongoing) and the progression free survival rate at 6 months was 67% (95% CI 49-86%). The grade 3-4 adverse event rate was 15%, similar to use of the same agent in patients with melanoma [20].

Whereas the response rate is similar to that achieved for cytotoxic chemotherapy in retrospective review, the progression free survival seems promisingly longer.

The European consensus based guidelines were published in 2015 and included UK representation [21].The following are quoted from this source: Except for surgery of isolated metastasis, there is no established curative treatment for metastatic MCC.

Regimens combine in various ways carboplatin, cisplatin and etoposide, cyclophosphamide with vincristine, doxorubicin, prednisone, bleomycin or 5-fluorouracil.

Initial regression is frequent with a response rate up to 75%
Responses are of short duration with a median overall survival rate of 9 months and high toxicity in elderly patients.

Among these regimens, one of the most frequently used for patients with good performance status is a combination of cisplatin and etoposide (cisplatin 60–80 mg/m2 IV on day 1 plus etoposide 80–120 mg/m2 IV on days 1–3 every 21–28 days or carboplatin AUC 5 IV on day 1 plus etoposide 80–100 mg/m2 IV on days 1–3 every 28 days.

Enrolment in clinical trials should be encouraged and should aim to evaluate innovative therapies such as immunotherapy including anti CTLA4 and anti PDL1/PD-1, pan tyrosine kinase inhibitors and somatostatin analogues.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Advantages

Avelumab has proven efficacy in mMCC in a prospective trial whereas cytotoxic chemotherapy has not been formally tested in a trial for this indication and data is based on retrospective case series. In this setting, chemotherapy is not really regarded as a standard of care more a default position for lack of better options.

A central piece of evidence to NICE will be the data in the following paper [22].

In this single arm trial, patients with stage IV MCC refractory to prior chemotherapy, performance status 0-1, not on immunosuppressive agents nor with CLL or other immunosuppressive conditions and without inflammatory bowel disease, were treated with avelumab 10 mg/kg by 1 h intravenous infusion once every 2 weeks until confirmed disease progression or unacceptable toxicity.

In 88 patients, 28 responded including 8 complete responses, response rate was 31.8% (95% CI 21.9-43.1%).

Ninety two percent of these responses had durations exceeding 6 months and duration ranged up to 17.5 months.

Although median PFS was 2.7 months, 40% were alive without progression at 6 months indicating a flattened tail to this curve. In most cases responses were apparent <2 months from starting.

Treatment related grade 3 events affected 5% patients.

Thus, in this unpromising second-line context, response rate was higher than that reported for chemotherapy in a small retrospective series [10], and responses appeared considerably more durable.

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In summary, based on published data, avelumab offers an excellent option for treatment after chemotherapy failure, with rapid kinetics of benefit, a solid response rate in about a third of patients, durable responses and overall 40% patients alive and free of progression at 6 months.

Our experts' general experience is that monoclonal antibodies targeting the PD-1 PD-L1 checkpoint are generally well tolerated including in elderly and less fit people, as documented for avelumab in the trial.

The scope of the appraisal is wider and includes avelumab as first line option. Data are not in the public domain on the outcomes of first line avelumab treatment for mMCC. However, many patients are not suitable for first-line chemotherapy because of advanced age and/or co-morbidities. It is entirely appropriate to consider the use of avelumab as first -line therapy even based on the current second line data. Avelumab is likely better tolerated than chemotherapy and looks to be at least as good if not better based on the second line PFS even though the first-line response rate and PFS are unknown. A response rate of around 30% still offers a better chance of palliation of symptoms at least for some months than the other standard alternative, best supportive care. Therefore, clinicians would wish for the opportunity to offer avelumab first as well as second line, discussing with patients the evidence as it becomes available, balancing probability of response (remembering that data for chemotherapy does not come from a formal prospective trial so cannot be regarded as standard of care) against tolerability for each individual.

Disadvantages
If a patient is sufficiently fit for either chemotherapy or avelumab and symptomatic from high volume mMCC, clinicians will tend to prioritise in first line the regimen with most rapid reduction of burden and highest probability of response. Our experts look forward to knowing the response rate and kinetics of response in the first line setting to guide its use in comparison to cytotoxic chemotherapy.

Although avelumab is well tolerated, in established practice of low level and longer term adverse events from immune checkpoint inhibitors which can compromise quality of life. Therefore, tolerability should continue to be monitored.

Administration
Avelumab is given intravenously every 2 weeks until confirmed progression or intolerance. This is more frequent than most chemotherapy regimens and potentially continues for longer than a standard 4-6 cycles of standard 3-weekly chemotherapy.

Additional treatments

Typically immune checkpoints do not require additional treatments in the absence of IrAE.

Starting or stopping rules
Stopping rules in relation to IrAE are becoming well established through experience with pembrolizumab and nivolumab.

Sub groups
The trial of avelumab in chemo-refractory patients excluded patients with immune compromise [22]. Thus, we do not know the benefits in this significant sub-group. It is plausible that such patients fail to benefit, lacking appropriate immune effectors. It is equally plausible that the mMCC is more immunogenic in immune suppressed patients and avelumab might have a greater chance of inducing response. For this reason, the decision to use avelumab as opposed to best supportive care or chemotherapy should be individualised taking into account all factors rather than in excluding patients with immune compromise from access to avelumab. However, data on outcomes should continue to be collected.

Exploratory post-hoc analysis of tumour PD-L1 expression and Merkel cell virus positivity were undertaken on the trial population [22]. The simple summary is that responses were seen in patients with either PD-L1 positive (1% threshold) or negative MCC, and in virus positive or negative mMCC. Neither test is routine standard of care in the UK. These should not be used as predictive biomarkers to limit access to avelumab based on the current data but might be subject to further research.

Assessment of response
It is likely that clinicians will undertake cross sectional imaging at 12-week intervals and outcome will be evaluated using iRECIST 1.1 (i.e. modified per the immune related response criteria) [23] (albeit less formally than in a trial). This approach is an adaptation of assessment of response for cytotoxic chemotherapy, essentially in requiring radiological progression to be confirmed in two successive scans prior to treatment discontinuation because transient increase in tumour volume (pseudo-progression) is a recognised phenomenon for people treated with immune checkpoint inhibitors and does not necessarily indicate treatment failure.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Patients with mMCC are managed in SSMDT in which oncologists are now experienced in the use of immune checkpoint inhibitors for advanced melanoma. Therefore, we do not anticipate major barriers to implementation.

It is important to permit use of avelumab on an individualised basis for people with mMCC in the context of this rare cancer and to encourage data collection, and not to permit funding restrictions to be placed arbitrarily by NHS England preventing access for individual subgroups.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

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The only issue I anticipate regarding access is that many elderly patients find travelling for treatment at a specialist centre onerous, and travel can be expensive such that poverty may be a barrier to travel. This is a difficult issue to balance and extends more widely than this setting alone: the need for specialist care for a population with a rare cancer versus improving accessibility for older patients or those lacking the means to travel.

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Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Avelumab for treating metastatic merkel cell carcinoma ID1102

NICE National Institute for Health and Care Excellence

Clinical expert statement

Avelumab for treating metastatic merkel cell carcinoma [ID1102]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]

2. Name of organisation	[redacted]
3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To control the progression of individual's Merkel Cell carcinoma & try to provide improve better survival & quality of life.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Stabilisation of disease with a lack of progression
9. In your view, is there an unmet need for patients and	Yes – patients with metastatic Merkel cell cancer have really only 1 line of therapy which lasts a very limited period of time. Often chemotherapy works for only a short period (<6 months) and progression of disease occurs far too quickly for them & their family/ friends. The uncontrollable nature of the

healthcare professionals in this condition?	disease combined with the fact that chemotherapy is highly toxic (carboplatin-etoposide combination as standard) is of great concern to clinicians treating this condition.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Carboplatin +/- etoposide chemotherapy in the first line, beyond this I personally do not feel that there is a standard of care. Some clinicians may use other system cytotoxic treatments but these are of limited value & efficacy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	None that have been reviewed regularly – this has historically been due to a lack of good data relating to this condition. It is treated on the basis of extrapolation from other neuroendocrine tumours (the commonest being small cell lung cancer). There are now NCCN (National Comprehensive Cancer Network, USA based) guidelines that were first published for Merkel Cell Cancer in October 2016. These were published prior to the data relating to this application. This is due to historical poor limited options available to us as treating clinicians. As indicated the preferred option for treatment of disseminated disease is for consideration of clinical trial. https://www.merkelcell.org/wp-content/uploads/2015/10/MccNccn.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	For metastatic disease it is standard for patients to receive carboplatin-etoposide chemotherapy or best supportive care as the only 2 options in first line. As indicated above further lines of therapy are of limited value and do vary across the country. Patients may receive other lines of treatment (perhaps topotecan or CAV (cyclophosphamide/ Doxorubicin/ Vincristine) although

• What impact would the technology have on the current pathway of care?	Use of systemic therapy is not available for many patients due to the considered toxicity of treatment with cytotoxic chemotherapy. Therefore discussions that I have in clinic are often concentrating upon limiting impact of toxic treatment & not exposing patients to chemotherapy options available. Those that do receive treatment are treated as standard cytotoxic therapies with reviews within chemotherapy clinic, treated on chemosuites and admitted with toxicities to the oncology wards. The use of avelumab would 1. Increase the proportion of patients able to receive treatment if available in the first line setting. 2. Reduce the impact of toxicity related admissions to the wards. 3. Reduce the time patients spent on chemotherapy unit (avelumab infusion time is short than current standard of care). 4. As avelumab is effective treatment then the expectation is that patients would benefit both in their symptoms and longevity. It is my expectation that the clinician group that would be prescribing & utilising this drug (avelumab) under consideration is the same group that currently treat metastatic malignant melanoma. As a cohort we are well trained in utilising these drugs & managing the patients in their course of treatment. Therefore training would not be a concern for the NHS.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes the patients being considered for avelumab would be the same cohort of patients as currently being seen by oncologists for system therapy
• How does healthcare resource use differ	None that I am aware of.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist treatment centres with Consultant Oncologists who specialise in the treatment of skin malignancies.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None – as indicated this type of treatment (immunotherapy) is routinely being given for other tumour sites (e.g. including melanoma, renal and lung cancers) across the country.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – undoubtedly this treatment has the potential to offer patients better outcomes compared to the standard of care. It is less toxic & better tolerated with fewer admissions to hospital – patients feel better on this type of treatment.
• Do you expect the technology to increase length of life more than current care?	Yes The second-line data that is published for avelumab (Kaufmann et al. Lancet Oncol. 2016 Oct;17(10):1374-1385) shows that ~1/3 of patients achieved a response whilst most tolerate this treatment with few admissions (6%). This is the type of expected response for immunotherapy – there are generally perceived to be a proportion of patients who gain benefit with some doing very well. The response rates in other tumour types with immunotherapy varies but is generally between 30 and 50% depending upon tumour site

	& treatment regimen. It would be the aim of clinicians to try to achieve this type of response in those being treated. In the first line setting avelumab would be expected (in my opinion) to achieve perhaps a slightly better response rate to that seen in the second line setting but the increase would be modest. The main impact of this group of patients having access would be a) more patients being able to be offered treatment & b) that this treatment would be less toxic. I would be surprised if the overall disease control rate of patients in the first line setting achieve substantially more benefit. My expectation is that the disease control rate would remain between 35 – 50%. In my opinion it is important to start these treatments as soon as possible to allow these drugs time to be effective – unlikely chemotherapy it can take as few months to be effective and therefore dially we would have access to this drug in the first-line setting to allow the most opportunity to achieve the best possible outcome.
• Do you expect the technology to increase health-related quality of life more than current care?	Of the published data for Avelumab in this group of patients the trial showed that few patients were admitted to hospital with significant toxicities. Certainly if we could avoid first line chemotherapy then many of the admissions associated with the standard chemotherapy regimen would be avoided. My experience of immunotherapy (including avelumab) is that patients tolerate these well, with few toxicity associated admissions. Indeed I have had no patients (even those who experience toxicities) that have preferred chemotherapy to single agent PD-1 or PD-L1 targeted immunotherapy.
13. Are there any groups of people for whom the technology would be more or	None that can be identified at this current time.

less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Immunotherapy is generally easier to deliver than cytotoxic chemotherapy - no risk of extravasation damage. Few supportive medication is required (I do not routinely give antiemetics or other drugs alongside this class of treatment).

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment would be stopped at the time of a lack of clinical benefit – this would be determined either clinically or on the basis of cross-sectional imaging (usually CT Scan). No other tests would be required as far as I'm aware.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Patients are routinely able to carry on working or looking after family members whilst on this type of drug. I have a patient, on avelumab, who has continued to look after her 2 grandchildren and work parttime as an actress whilst on this drug. I am unsure about if this is taken into account.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes it is innovative – the ability of the pharmaceutical company to get phase 2 data is to be commended. This is a difficult tumour site to either set up a trial, achieve data & identify a drug that is effective. As indicated the drug is less toxic than standard and maintains patients well being to allow them to continue the 'rest of their life'

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Definitely – this has the potential to allow a minority of patients to achieve reasonable outcomes (rather than the standard poor ones).
• Does the use of the technology address any particular unmet need of the patient population?	Yes – this is a rare tumour type in which no specific good data has been seen until now. This opens the door to allow better management of their cancer.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As indicated the treatment is generally very well tolerated.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Disease control in ~30% of patients and that this may achieve durable response in some patients with little exposure to toxicity.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I'm aware of.

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA457]?	No
22. How do data on real-world experience compare with the trial data?	Unsure but have no reason to expect this to be significantly different
Equality	
23a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	
Key messages	
24. In up to 5 bullet points, please summarise the key messages of your statement. • Treatment to achieve better long term outcomes for Merkel Cell patients • Very well tolerated treatment with few significant grade 3-4 toxicities • Novel treatment that may transform a small proportion of patients lives • Need to be used as early in the pathway as possible for potential maximisation of beneficial outcomes •	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Avelumab for treating metastatic merkel cell carcinoma [ID1102]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Kate Fife**

2. Name of organisation	**Cambridge University Hospitals NHSFT**
3. Job title or position	
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prolong the life of patients with metastatic Merkel's cancer whilst maintaining quality of life.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically significant:RECIST Complete or partial response, and stable disease (ie lack of progression; tumour control rate)
9. In your view, is there an unmet need for patients and	Yes. In this predominantly elderly population, chemotherapy has significant toxicity and only a short duration of response.

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patients who are fit enough are offered chemotherapy, usually with carboplatin or cisplatin and etoposide, or topotecan. Occasionally patients may receive second line chemotherapy. Palliative radiotherapy can be used for symptoms. Supportive care is instituted in patients unfit for chemotherapy or following failure of chemotherapy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No; it is a relatively rare condition
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is not defined. There is agreement amongst oncologists that platinum based chemotherapy can offer short term palliative benefit in selected patients.

• What impact would the technology have on the current pathway of care?	It would replace chemotherapy as first line treatment.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes; avelumab is given as an intravenous infusion for 1 hour every 2 weeks in a chemotherapy day unit. This compares with intravenous chemotherapy , which is usually given 3 weekly, but infusion times are longer (typically 2-3 hours for carboplatin/etoposide or 6-8 hours for cisplatin /etoposide).
• How does healthcare resource use differ between the technology and current care?	See above
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary/tertiary care oncology departments
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new facilities. Most staff are now familiar with the use of immune checkpoint inhibitors owing to their use in melanoma, lung cancer and renal cancer.

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not that we are currently aware of.
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Patients: generally easier in terms of toxicity (no risk of neutropenic sepsis or hair loss and other chemo related effects), but more frequent infusions (q 2 weeks) and longer duration of treatment in terms of months. Healthcare professionals: generally easier for oncologists, especially if they have immunotherapy experience. Antihistamine premedication required (compared with antiemetics for chemotherapy)
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Informal: stopping when patients have had a confirmatory (second) scan showing progression, or progression with clinical deterioration.

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Likely to be included
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes; lower toxicity than chemotherapy, safer to use and likely to produce longer lasting responses in a subset of patients.
• Is the technology a 'step-change' in the management of the condition?	Yes

• Does the use of the technology address any particular unmet need of the patient population?	Yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Patients may require steroids for immune related adverse events; the side effects usually improve with appropriate use of steroids.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, although patients in the UK may be performance status 2 (excluded from the trial). They are unlikely to have had 2 previous courses of chemotherapy, and may be chemotherapy naive
• If not, how could the results be extrapolated to the UK setting?	UK patients may do better if avelumab used earlier in the course of disease
• What, in your view, are the most important	Duration of response is most important and this has been measured in the trials

outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Complete responses and partial responses predict for long term response
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the	No

publication of NICE technology appraisal guidance [TA457]?	
22. How do data on real-world experience compare with the trial data?	Little available
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	

Key messages
24. In up to 5 bullet points, please summarise the key messages of your statement. • Immunotherapy is a step change in the management of metastatic Merkel cell cancer • Prolonged responses may be seen, particularly in patients in complete response • The treatment is less toxic for the patient and safer • Chemotherapy results in a short response duration and higher risk of treatment related morbidity and mortality •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Avelumab for treating metastatic Merkel cell carcinoma

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 16/134/09

BMJ Technology Assessment Group

Title: Avelumab for treating metastatic Merkel cell carcinoma

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Kayleigh Kew	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Peter Cain	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Fatima Salih	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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Abbreviation	In full
1L	First-line population (untreated)
2L+	Second-line and later population (pretreated)
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AIC	Akaike information criterion
BOR	Best overall response
BSC	Best supportive care
CENTRAL	Cochrane© Center Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTLA	Cytotoxic T-lymphocyte-associated protein
DARE	Database of Abstracts of Reviews of Effects
DoR	Duration of response
DRR	Durable response rate
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EoT	End-of-Treatment
EQ-5D	EuroQoL - 5 dimensions
ERG	Evidence Review Group
EU	Europe
FACT-M	Functional Assessment of Cancer Therapy - Melanoma
FDA	Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IERC	Independent Endpoint Review Committee
IHC	Immunohistochemistry
IPD	Individual patient data
irAE	Immune-related adverse event
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
MAA	Marketing authorisation application
MAIC	Matching Adjusted Indirect Comparison

MCC	Merkel cell carcinoma
mMCC	Metastatic Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MEDLINE	Medical Literature Analysis and Retrieval System Online
NE	Non-estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SCLC	Small cell lung cancer
SD	Stable disease
SE	Standard error
SLD	Sum of the longest diameter
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
STC	Simulated Treatment Comparison
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse events
TSD	Technical Support Document
TTP	Time to progression
UK	United Kingdom
US	United States
VAT	Value-added tax

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of avelumab (BAVENCIO®; Merck Serono/Pfizer) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of avelumab for treating metastatic Merkel cell carcinoma (mMCC).

The company submission (CS) states that a European marketing authorisation application (MAA) for avelumab to treat mMCC in adults was submitted to the European Medicines Agency (EMA) in October 2016 and avelumab received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 21 July 2017 for avelumab as a monotherapy for the treatment of adult patients with mMCC. The company [redacted] The ERG notes that avelumab has received accelerated approval by the FDA (23 March 2017) for the treatment of adults and paediatric patients (over 12 years) with mMCC.

The key clinical trial informing the safety and efficacy of avelumab in patients with mMCC is the JAVELIN Merkel 200 trial. Avelumab was administered in the trial at a dose of 10 mg/kg as a 60-minute intravenous (IV) infusion once every 2 weeks with the dose of avelumab calculated based on the weight of the patient on the day of administration. Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab was mandatory in JAVELIN Merkel 200 in line with the anticipated SmPC guidance.

JAVELIN Merkel 200 was conducted in two parts, Part A comprised patients at second-line or beyond treatment (2L+) and Part B comprised patients at first-line treatment (1L) for mMCC. The two parts of JAVELIN Merkel 200 restricted trial entry to adults with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 who had mMCC meeting the trial entry criteria. The final scope issued by NICE specified the population of interest to be patients with mMCC with different comparators requested for the 1L and 2L+ populations. The Evidence Review Group (ERG) considers the populations in JAVELIN Merkel 200 Part A and Part B to be relevant to the decision problem. In addition, all clinically relevant outcomes were reported in the CS, with the exception of health-related quality of life (HRQoL) data for 1L patients.

In the final scope issued by NICE, the comparator of interest was identified as chemotherapy for the 1L population and best supportive care (BSC) for the 2L+ population. The ERG notes that no trial level data were presented in the CS for BSC. The company presented the results of studies of chemotherapy

as a surrogate for BSC, reporting that these were the best available equivalent and were likely to over-estimate the efficacy of BSC. The company presented naïve comparisons of avelumab versus chemotherapy in the CS and reported that they considered this to be an appropriate method of comparison. The company reported that this was because the statistical analyses that were undertaken for the purposes of the economic modelling, suggested that there were no patient characteristics that were prognostic of outcomes in mMCC and for this reason they did not consider that statistical adjustments (such as Matching Adjusted Indirect Comparison [MAIC], or Simulated Treatment Comparison [STC]) were necessary to match the observational data to the relevant cohorts within JAVELIN Merkel 200. In response to clarification questions (CQs), the company provided a propensity score matching analysis for OS and PFS in the 2L+ population, and multi-variate regression analyses with covariates of age, gender and immunosuppression. The ERG considers the data presented by the company do not explore all potential covariates for the comparison of avelumab versus BSC.

There were no subgroups other than 1L and 2L+ requested in the final scope issued by NICE. The ERG notes that some subgroup data from a *post hoc* analysis are reported in the CS for the 2L+ population.

1.2 Summary and critique of clinical effectiveness evidence submitted by the company

JAVELIN Merkel 200 was the key study used in the EMA application to gain the positive CHMP opinion for avelumab. It was a multicentre international, open-label, single-arm, two-cohort clinical study comprising patients with mMCC at 1L and 2L+ therapy. Part A and Part B are still ongoing, with Part B still recruiting patients. In the analyses presented in the CS there were 88 2L+ patients in the intention-to-treat (ITT) population with a minimum of 18-months follow-up. For the 1L population, a pre-planned interim analysis of a data-cut from 24 March 2017 (n=39) was presented in the CS, which was used for three analyses; efficacy for patients with ≥3-month follow-up (n=29), efficacy for patients with 6-month follow-up (n=14); and efficacy and safety endpoints for the full 39 patients. The ERG notes that the planned sample size for the primary analysis of the 1L cohort is 112 patients, and further analyses are planned for [redacted]. Patients in JAVELIN Merkel 200 were enrolled across study sites in North America, Europe, Australia and Asia, although those in Part B (1L) were only in the USA and Europe. Avelumab was given IV at the expected EU licensed dose in JAVELIN Merkel 200 with the recommended paracetamol and antihistamine premedications. Treatment with avelumab was continued for between 6 and 12 months, or longer in agreement with the Sponsor if there was a complete response (CR). Treatment was discontinued on disease progression or study withdrawal for any reason including intolerable toxicity. In the 2L+ cohort, [redacted] Out of the 39 1L patients in the ITT population, there were [redacted] patients [redacted] still on avelumab at ≥3 months.

[redacted] The primary efficacy endpoint in JAVELIN Merkel 200 Part A was confirmed best overall response (BOR), defined as complete response (CR) or partial response (PR) according to RECIST 1.1, as determined by an IERC. The primary efficacy endpoint in Part B was durable response which was defined as an objective response (CR or PR) according to RECIST version 1.1, determined by IERC, with a duration of at least 6 months.

The median age of the 2L+ population is [redacted] (72.5 years versus [redacted] years, respectively). The ERG's clinical experts reported that this is broadly consistent with the median age expected of 2L+ mMCC patients in England, although it is possibly slightly younger. The inclusion criteria of JAVELIN Merkel 200 restricted patients to those with an ECOG PS of 0 or 1. The ERG's clinical experts reported that the ECOG PS of patients in both Part A and Part B was slightly better than expected in clinical practice in England, with more patients expected to be ECOG 1 and some ECOG 2 at 2L+. In addition, they reported that patients at later lines of therapy (i.e. at 2L at beyond) generally have worse ECOG PS and are less able to tolerate the side effects of therapies and so are more likely to have worse outcomes. The ERG notes that 30.7% of patients in JAVELIN Merkel 200 Part A were at third line therapy and 4.5 % of patients were fourth line and beyond. The ERG considers that subgroups by line of therapy would be useful and that the efficacy for the whole 2L+ population may be underestimated for the equivalent 2L population in England likely to receive avelumab.

Median PFS for the 2L+ cohort (Part A) of JAVELIN Merkel 200 was 2.7 months (95% CI: 1.4 to 6.9) at the 18-month follow-up analysis and the same proportion of patients who were progression-free at 12 months remained progression free at 18 months ([redacted]. The ERG considers that the OS data are still relatively immature for the 2L+ cohort although at 18-months follow-up, [redacted] had died at data cut-off and median OS was reported to be [redacted]. The ORR for the 2L+ cohort at the 18-month analysis was [redacted] and the proportion of patients with a BOR of stable disease was [redacted]. The estimate of the proportion of patients with ≥6 months duration of response (DoR) was [redacted] in the 18-month analysis for the 2L+ cohort) and the 18-month DRR was 30.7%. The HRQoL data from the 2L+ cohort comprised of EQ-5D data, FACT-M questionnaire responses and qualitative patient interviews. In general, the HRQoL data suggest a trend of improvement in HRQoL over time with avelumab treatment although there were no data reported in the CS that reached statistical significance.

The 2L+ subgroup analyses reported in the CS for the subgroups of number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status were highlighted by the company in the forest plot in the CS. The ERG considers these highlighted subgroups suggest there may be within

subgroup differences in ORR with avelumab although the ERG acknowledges the differences were not statistically significant but some subgroups comprised a very low number of patients.

In the 1L cohort (Part B) of JAVELIN Merkel 200, the median PFS was 9.1 months (95% CI: 1.9 to not reached) in the ≥3-month follow-up analysis. The ERG considers the OS data from the 1L cohort should be interpreted with caution as they are immature and based on small patient numbers in an interim analysis. Median OS had not been reached at the 3-month analysis for the 1L cohort; the KM estimates for OS in the 1L population suggested a 3-month OS rate of [redacted]. The 6-month results for ORR in the 1L cohort suggest they have [redacted]. The 6-month DRR in the 1L patients with ≥6 months follow-up (n=14) was [redacted], and [redacted]) of responses had a duration of ≥6 months. No HRQoL data were reported for the 1L population in the CS.

The median duration of therapy for the 2L+ cohort was [redacted] with a median number of infusions of [redacted]. The median duration of therapy in the 1L cohort was [redacted] with a median number of infusions of [redacted]. The ERG notes that as of 3 March 2016, 97.7% (86/88) of the 2L+ patients experienced an AE during JAVELIN Merkel 200 and 75.0% of the 2L+ patients (66/88) experienced an AE that was deemed to be a treatment-related AE (TRAE). In the 1L cohort, as of 30 December 2016, 71.8% (28/39) patients had experienced a TRAE. The ERG notes that the most common treatment-emergent adverse (TEAE) was [redacted]. In terms of serious TEAEs, [redacted] in the 2L+ cohort experienced a serious TEAE and [redacted] of the serious TEAEs were deemed to be related to treatment with avelumab based on the 18-month follow-up data set. In the 1L cohort, [redacted]) of patients experienced a serious TEAE and [redacted] of these were attributed to avelumab (3-month follow-up data set). Deaths due to any TEAE were reported in [redacted] in the 2L+ cohort and [redacted] in the 1L cohort; [redacted]. Given the mechanism of action of avelumab, the ERG considers that immune-related AEs (irAEs) are of clinical importance. Data were provided on irAEs for only the 2L+ cohort; the most common immune-mediated reactions in the 2L+ cohort were [redacted].

In the clinical section of the CS, the company provided a naïve comparison of avelumab versus chemotherapy in the 1L and 2L+ populations using a retrospective observational study that they conducted specifically for the comparison (Study 100070-Obs001), and Iyer 2016, a study identified through the company's systematic literature reviews (SLRs). In addition, a further six studies were explored for use in the economic modelling.

The company provided an appendix to the CS (CS appendix 10) detailing a series of analyses which were presented as evidence to show there are no patient characteristics that are prognostic of outcomes (including factors such as ECOG PS and stage at diagnosis in mMCC). The company conducted separate regression analyses for the 1L and 2L+ populations using the Study 100070-Obs001 chemotherapy data for the following baseline characteristic subgroups:

- stage at diagnosis,
- age,
- gender,
- immunosuppression status, and
- ECOG PS.

The company used these regression analyses and visual inspections of KM plots, as the basis for their assertion that it was not necessary to adjust for prognostic factors or use treatment effect modifier techniques such as matching adjusted indirect comparison (MAIC) or simulated treatment comparison (STC). The ERG considers the small number of patients in the regression analyses presented by the company in CS appendix 10 means that there is a large amount of uncertainty around the results purely based on an initial small sample size. The ERG, therefore, considers that caution should be taken when drawing conclusions from the statistically non-significant results from the regression analyses, as they could be a result of the small patient numbers rather than the absence of a subgroup effect (prognostic indicator). The ERG considers that subgroups identified in the subgroup analyses (CS page 83, Figure 18), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, the company should have adjusted outcomes appropriately.

Study 100070-Obs001 was a retrospective, observational study conducted by Merck KGaA/Pfizer in two parts; one in the EU (EU2L; n=34), and one in the US (US2L; n=20, and US1L; n=67). The company reported that Study 100070-Obs001 was designed to investigate clinical outcomes in mMCC patients with chemotherapy treatment and to provide comparator data on PFS and OS for the avelumab data from JAVELIN Merkel 200. Study 100070-Obs001 included adult patients with distant mMCC and was conducted in two parts: Part A was conducted in the US and included both 1L and 2L+ patients, whereas Part B was conducted in Europe and only included 2L+ patients. The pooled data from the US and EU 2L+ cohorts were used in the economic analyses and therefore the ERG critique will focus on the pooled dataset. However, the ERG and the company considered the EU study most likely to best

reflect clinical practice in England as the US studies are likely to be associated with more aggressive treatments, resulting in improved outcomes.

In terms of baseline characteristics for the 2L+ populations, the ERG notes that 30.0% of the US 2L+ patients and 14.7% of the EU 2L+ patients in Study 100070-Obs001 were immunocompromised, in contrast to 0% of the JAVELIN Merkel 200 patients. The ERG considers immunosuppression to be a potential confounder and that results of Study 100070-Obs001 that include the immunosuppressed patients should be interpreted with caution. The median age in the EU 2L+ cohort of Study 100070-Obs001 was substantially younger compared to the US cohort and the JAVELIN Merkel 200 2L+ patients (67.5 years, 72.5 years and 73.5 years, respectively). Baseline ECOG performance status data were only available for the US part of Study 100070-Obs001, but this suggests that the patients in JAVELIN Merkel 200 had a better baseline ECOG status compared to the patients in Study 100070-Obs001 with more ECOG 0 patients in JAVELIN Merkel 200 (ECOG 0: 55.7% vs 5.0%; JAVELIN Merkel 200 and Study 100070-Obs001, respectively).

Similar to the 2L+ cohort of Study 100070-Obs001, the 1L cohort included immunosuppressed patients (23.9%), whereas none of the 1L JAVELIN Merkel 200 avelumab patients were immunosuppressed. The ERG considers that 1L patients had a better baseline ECOG status in JAVELIN Merkel 200 compared to in Study 100070-Obs001 (79.5% vs 20.9%; JAVELIN Merkel 200 and Study 100070-Obs001, respectively). In addition, there were no ECOG 2 patients in JAVELIN Merkel 200, compared to 9% of patients in Study 100070-Obs001.

The ERG is unclear why the Iyer 2016 paper was selected from the other chemotherapy papers identified by the SLR. The ERG considers the Iyer 2016 study population to be younger than that of the Study 100070-Obs001 and JAVELIN Merkel 200 populations. In addition, the ERG notes Iyer 2016, similar to Study 100070-Obs001, contains immunosuppressed patients that were excluded from JAVELIN Merkel 200.

The results for avelumab in the 2L+ mMCC population of the JAVELIN Merkel 200 trial, relative to chemotherapy (surrogate for BSC) in Study 100070-Obs001 and Iyer 2016, indicate that avelumab is associated with a higher 6-month DRR (30.6% [JAVELIN Merkel 200] vs 0.0% [Study 100070-Obs001] and 6.7% [Iyer 2016]), longer 12-month PFS (29.0% vs 0.0%), longer 12-month OS (50.0% vs 0.0%), and a higher CR rate (11.4% vs 0.0% to 3.3%).

The company considered it appropriate to combine the chemotherapy data from Study 100070-Obs001, Iyer 2016 and Samlowski 2010 (a study identified in the SLRs) in a meta-analysis in the economic modelling for the 2L+ population. The meta-analysis results for both OS and PFS suggest chemotherapy is associated with longer OS and PFS compared to chemotherapy in the pooled data from Study 100070-

Obs001 (OS approximately 1.25 years versus approximately 0.75 years, respectively; and PFS approximately 0.75 years versus approximately 0.5 years, respectively). However, the ERG is concerned that the inclusion of Samlowski 2010 introduces clinical heterogeneity as the Samlowski trial population comprises a mix of 1L (n=9) and 2L+ (n=14) patients.

The results for the 1L population of the naïve comparison of avelumab from JAVELIN Merkel 200 Part B with chemotherapy suggest avelumab is associated with improved ORR, PFS and OS outcomes compared to chemotherapy in Study 100070-Obs001 and in Iyer 2016. [redacted] In total, there were seven studies that the company identified from the SLRs and their own observational studies with OS or PFS (or both) data on chemotherapy in 1L mMCC patients (Study 100070-Obs001; Iyer 2016; Voog 1999; Satpute 2014; Santamaria-Barria 2013; Fields 2011; Allen 2005) that were used in a naïve pooling in the economic modelling. The company reported that, "this results in increased patient numbers for analysis, and likely the most generalisable results". The ERG considers that the approach is likely to introduce unnecessary heterogeneity into the analysis although it is not possible to predict the likely direction of the resulting bias. The ERG considers it difficult to draw any conclusions relating to OS or PFS for avelumab compared to chemotherapy in 1L mMCC because the data for avelumab are extremely limited due to the lack of long-term follow-up and small number of patients in the analysis (maximum n=29, and only 14 patients with 6 months or longer follow-up). [redacted] In response to clarification questions, the company conducted a propensity score matching analysis and a regression analysis for PFS and OS for the 2L+ population. In the propensity score matching analysis, the 2L+ patients from Study 100070-Obs001 (US 2L - Part A and EU 2L - Part B; n=54) were matched on a 1:1 basis with 2L+ patients in JAVELIN Merkel 200 (Part A; n=88). The only variables which the company used in the matching process to calculate the propensity score, were age and sex, [redacted] The ERG is unclear why the company did not explore using alternative variables for matching. The ERG considers that subgroups identified in the subgroup analyses (CS page 83, Figure 18), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, included as characteristics for matching. The ERG considers there to be a notable difference in the propensity scores of the unmatched and matched patients between the two studies (Study 100070-Obs001 and JAVELIN Merkel 200). However, the [redacted]

[redacted]

The regression analysis was used to match the Study 100070-Obs0012L+ patients to the JAVELIN Merkel 200 2L+ patients baseline age, gender and immunosuppression status. [redacted]. The ERG considers the regression analysis to be a more robust analysis of avelumab versus chemotherapy compared to the naïve comparison and propensity score matching because it adjusts for a greater range of likely covariates. However, the ERG would have preferred an analysis with further potential prognostic factors adjusted for such as line of therapy 2L or third line and beyond (3L+), and PD-L1 status. The ERG considers that the inclusion of further covariates would confirm the robustness of the company's preferred option, the naïve comparison of study level data from JAVELIN Merkel 200 for avelumab with pooled data from Study 100070-Obs001 for chemotherapy if the results of both analyses were similar.

The company did not conduct any propensity score matching or regression analyses for the IL population using the JAVELIN Merkel 200 and Study 100070-Obs001 data as they considered the patient numbers and PFS and OS event rates in JAVELIN Merkel 200 were too small (n = 39; [redacted]). The later data cut that the company anticipates taking place in [redacted], is likely to have an increase in patient number and an increase in the events of interest. The ERG considers this later dataset is likely to provide the basis for a more robust assessment of avelumab versus chemotherapy in 1L patients. However, the ERG also considers that any analysis should be adjusted for potential observed treatment-effect modifiers with justification provided for the variables used.

No safety data were provided for chemotherapy studies in mMCC in the CS; surrogate data from studies in melanoma and small cell lung cancer were used to inform inputs in the economic model.

The ERG considers it important to highlight that the results of JAVELIN Merkel 200 and the naïve comparisons, propensity score matching analyses and regression analyses, all comprise evidence on avelumab from single arm studies that are at high risk of bias and thus should be interpreted with caution.

[redacted]

1.3 Summary of cost effectiveness evidence submitted by the company

The company submitted an economic model to assess the cost effectiveness of avelumab in two populations of patients with Merkel cell carcinoma: treatment-naïve patients and treatment-experienced patients. The model uses a partitioned survival structure with health states of progression-free, progressed disease and death. Within each of these states are three sub-states in which different health state utility values are applied based on the expected time to death. These sub-states are defined as '>100 days until death', '30 to 100 days until death' and '<30 days until deaths'. These states were identified statistically as being key times at which quality of life changed.

The treatment effectiveness was estimated using separate data sources because there were no head-to-head trials comparing avelumab with relevant comparators. The effectiveness of avelumab was informed by the JAVELIN Merkel 200 trial for both the treatment-naïve and treatment-experienced populations, while comparator evidence for chemotherapy/BSC was informed by observational studies conducted by Merck KGaA/Pfizers, which, for the treatment-naïve population, was pooled naïvely with additional studies identified through a systematic review. These data were used to form a naïve comparison between avelumab and chemotherapy/BSC, which the company considered reasonable because of the similarity in the inclusion/exclusion criteria in both JAVELIN Merkel 200 trial and the Merck KGaA/Pfizer sponsored observational studies. The additional studies pooled for the treatment-naïve population were considered to have similar outcomes.

For the treatment-experienced population, the company fitted a range of survival curves to the JAVELIN Merkel 200 overall survival (OS) data including standard parametric distributions and more flexible spline models, while for the progression-free survival (PFS) data only splines were considered because of the non-monotonic hazard function identified through log cumulative hazard plots. The observational data were only fitted with standard parametric survival models as they were not considered to require more flexible models after assessing the log-cumulative hazard plots.

For the treatment-naïve analysis, a Cox proportional hazards model was fitted to PFS and OS data in both populations of the JAVELIN Merkel 200 trial to estimate a relative effect as a hazard ratio (HR). However, the company considered the analysis too uncertain to be used in the model so instead elicited HRs from clinical experts. The elicited value for OS was 0.8, which was a more conservative estimate than the value from the Cox model. For PFS, a HR of 1 was assumed, i.e. no difference between populations.

Time on treatment for treatment-experienced avelumab patients was estimated using data from the JAVELIN Merkel 200 trial. A range of standard parametric survival were fitted to the data and the best statistical fit, the log-logistic distribution, was chosen as a basis to estimate time on treatment. However, the company considered the extrapolation to be implausible and, based on clinical expert opinion, truncated the curve so that two thirds of patients remaining on treatment at two years would immediately

discontinue, and all patients still on treatment at 5 years would also discontinue immediately. The company assumed the same time on treatment for the treatment-naïve population because of the limited data available for that population. Treatment duration for the chemotherapy group was fixed at six cycles of treatment.

1.4 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG's key concerns lie fundamentally with the available data used to inform the estimates of treatment effectiveness. The lack of a randomised head-to-head trial makes the relative treatment effectiveness uncertain, and the ERG considers the lack of adjustment for patient characteristics to be unjustified. The treatment effectiveness is a key input of the economic model and can be very influential on the results of the economic model. This is, therefore, a key point for consideration when assessing the likelihood of avelumab being cost effective in either of the two populations presented.

For the treatment-experienced population, the company conducted a propensity score matched analysis in response to clarification questions, which adjusted for age and gender. The ERG did not consider this to be a sufficiently adjusted analysis, however, the company also performed a Weibull regression analysis on the comparator data, that also included for immunosuppression status, and this was adjusted to the mean values of these covariates in the JAVELIN Merkel 200 trial. The ERG considered this analysis to be preferable given the adjustment for more variables, but still considers the lack of adjustment for other important variables such as ECOG status and stage of disease at diagnosis to be a potentially serious limitation. The Weibull regression model was incorporated in the ERG's preferred base case analysis.

Another influential part the model is the estimation of time of treatment for avelumab, which can seriously impact the cost effectiveness results if not estimated correctly. The ERG considered the company's approach to estimating time on treatment for the treatment-experienced population to be flawed. They chose to use the log-logistic survival curve based on optimal statistical fit, however, this curve had an implausible extrapolation. The company chose to truncate the curve at two years, where they assumed two thirds of the patients remaining in treatment would immediately discontinue, and then all patients remaining on treatment at five years also discontinue immediately. The ERG's clinical experts considered it to be unethical to discontinue treatment for patients who may still receiving benefit until there is evidence to suggest that no further benefit would be gained beyond this time. The ERG's clinical experts did not consider this to reflect what is likely to occur in clinical practice and therefore the ERG consider the preferred approach to be selecting a similarly good fitting curve but with a more plausible extrapolation. This was chosen to be the Weibull curve, which had similar statistical fit to the data but without the extended implausible tail, and was included as part of the ERG's preferred base case.

The ERG also considered it to be implausible to assume that the time on treatment for patients in the treatment-naïve population would be equivalent to that of those in the treatment-experienced population. This was evident when assessing the independently fitted time on treatment curves for the treatment-naïve population, which demonstrated higher expected treatment costs than the treatment-experienced population. However, the ERG acknowledges the uncertainty in this estimation given the limited data in the treatment-naïve population.

For the treatment effectiveness estimation in the treatment-naïve population, the ERG considered the assumption of proportional hazards (PHs) to be unfounded, which potentially leads to the overestimation of both progression-free survival (PFS) and overall survival (OS). The ERG's preferred approach is to use the independently fitted survival curves that the company provided in response to clarification questions. This showed a much lesser benefit in terms of PFS and OS indicating that the PH assumption may be flawed. This analysis is of course highly uncertain given the limited data.

1.5 ERG commentary on the robustness of evidence submitted by the company

1.5.1 Strengths

Clinical

The CS contained a systematic review that addressed the population specified in the decision problem outlined in the final scope issued by NICE.

At the request of the ERG, the company attempted to adjust the outcomes of interest in the 2L+ population for potential confounders, albeit with a limited selection.

Economic

The economic model was of a high standard and relatively easy to use and validate. The model contained a range of modelling approaches that could be selected by the user and displayed inputs and results clearly both numerically and graphically.

The company submission was thorough and generally clear in describing and justifying the approaches taken. In particular, the company were very clear in defining what was part of the base case and what was considered as a scenario analyses.

1.5.2 Weaknesses and areas of uncertainty

Clinical

A key limitation of the submission is the lack of direct randomised evidence comparing avelumab versus chemotherapy and the total absence of trial-level data for avelumab versus BSC. In addition, the ERG considers that the process of selecting appropriate comparative evidence from studies included in the clinical effectiveness SLR was non-systematic, and differs from the SLR described in Appendix 10 of the CS to identify effectiveness data for the economic model. The ERG is not qualified to comment on the feasibility of an RCT of avelumab in the population of interest in this decision problem, although the ERG does consider a comparative randomised study design to be preferable in accounting for observed and unobserved differences in patient populations.

There are no data on the long-term safety and efficacy of avelumab, and the data on OS in 1L mMCC are immature and are based on small patient numbers (n=39).

Overall, the ERG considers that the available evidence on the clinical efficacy of avelumab for the treatment of 2L+ and 1L mMCC is of limited quantity and quality due to the single-arm non-randomised study design of JAVELIN Merkel 200 Part A and Part B. However, the ERG also acknowledges that JAVELIN Merkel 200 Part A and Part B at this time, represent the best available evidence on the clinical effectiveness of avelumab.

The ERG has concerns around the generalisability of JAVELIN Merkel 200 Part A and Part B results to the population in England most likely to be eligible for treatment with avelumab as there were no study sites in England. In addition, it is considered that a high proportion of patients in both studies had an ECOG PS of 0 compared to that expected in mMCC patients in England and there was no information on subsequent treatments received following study drug discontinuation.

The company reported that to address the comparison of avelumab with BSC requested in the 2L+ population in the NICE final scope they have assumed that the efficacy data from chemotherapy regimens are equal to those of BSC. The company cited clinical experts' opinion stating that, "efficacy outcomes with BSC and chemotherapy are likely to be very similar due to very poor patient performance with both".

Based on guidance from the FDA, the ERG is concerned that single-arm studies shouldn't be used for capturing time-to-event data such as OS and PFS. In addition, the ERG considers that OS data in JAVELIN Merkel 200 are likely confounded by the use of subsequent treatment, although no data on subsequent treatments were reported in the CS for either Part A or Part B of JAVELIN Merkel 200.

The ERG notes that there were high levels of TRAEs in Part A and Part B of JAVELIN Merkel 200: as of 3 March 2016, 75.0% of the 2L+ patients had experienced an AE that was deemed to be a TRAE, and in the 1L cohort, as of 30 December 2016, 71.8% patients had experienced a TRAE.

The 2L+ subgroup analyses reported in the CS for the subgroups of number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status were highlighted by the company in the forest plot in the CS. The ERG considers these highlighted subgroups suggest there may be within subgroup differences in ORR with avelumab although the ERG acknowledges the differences were not statistically significant but some subgroups comprised a very low number of patients.

The ERG considers the small number of patients in the regression analyses presented by the company in CS appendix 10 means that there is a large amount of uncertainty around the results purely based on an initial small sample size. The ERG, therefore, considers that caution should be taken when drawing conclusions from the statistically non-significant results from the regression analyses, as they could be a result of the small patient numbers rather than the absence of a subgroup effect (prognostic indicator). The ERG considers that subgroups identified in the subgroup analyses (CS page 83, Figure 18), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, the company should have adjusted outcomes appropriately.

The ERG is concerned that Study 100070-Obs001 included immunosuppressed patients, whereas none of the JAVELIN Merkel 200 avelumab patients were immunosuppressed. In addition, the ERG considers that 1L and 2L+ patients had a better baseline ECOG status in JAVELIN Merkel 200 compared to in Study 100070-Obs001. The ERG is concerned that these differences in baseline characteristics are not accounted for in the naïve comparisons presented in the CS.

The ERG considers the regression analysis to be a more robust analysis of avelumab versus chemotherapy compared to the naïve comparison and propensity score matching because it adjusts for a greater range of likely covariates. However, the ERG would have preferred an analysis with further potential prognostic factors adjusted for such as line of therapy 2L or third line and beyond (3L+), and PD-L1 status. The ERG considers that the inclusion of further covariates would confirm the robustness of the company's preferred option, the naïve comparison of study level data from JAVELIN Merkel 200 for avelumab with pooled data from Study 100070-Obs001 for chemotherapy if the results of both analyses were similar.

The later data cut that the company anticipates taking place in [redacted], is likely to have an increase in patient number and an increase in the events of interest. The ERG considers this later dataset is likely to provide the basis for a more robust assessment of avelumab versus chemotherapy in 1L patients. However, the ERG also considers that any analysis should be adjusted for potential observed treatment-effect modifiers with justification provided for the variables used.

Economic

The lack of adjustment for imbalances in potential effect modifiers or prognostic indicators between the data sources was a key limitation of the company's analysis. The justification that there were no statistically significant prognostic effects from the variables included in a regression analysis was not considered sufficient by the ERG due to the small sample size included in the analyses.

The assumptions applied for time on treatment were considered implausible by the ERG and clinical expert opinion suggested that there was no evidence to suggest discontinuation at two years was suitable and believed it would be unethical without that evidence.

The key issue for the treatment-naïve population is the limited data, but the use of a Cox proportional hazards model to estimate a relative treatment effect between populations was considered to be potentially implausible without evidence to justify a constant relative effect.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

The ERG's preferred base case ICERs, presented cumulatively as each change is applied to the company's base case, are presented in Table 1 and Table 2 for the treatment-naïve and treatment-experienced populations, respectively. The results differ from the company's base case analyses as a result of changes to the company's approach for the estimation of treatment effectiveness and time on treatment, as well as the addition of premedication costs for avelumab, which were not considered in the company's model.

Table 1. ERG base case ICER (treament-naïve)

	Avelumab	BSC	Incremental value
Company's base case			
Total costs (£)	£78,588	£7,217	£71,371
QALYs	2.93	1.38	1.55
ICER			£46,148
Weibull time on treatment curve (without truncation)			
Total costs (£)	£92,392	£7,217	£85,176
QALYs	2.93	1.38	1.55
ICER			£55,075
Parametric curves for PFS and OS			
Total costs (£)	£159,375	£7,217	£152,158
QALYs	2.65	1.38	1.27
ICER (compared with base case)			£75,430
ICER with all changes incorporated			£120,228
Addition of pre-medication costs			
Total costs (£)	£159,570	£7,217	£152,353

QALYs	2.65	1.38	1.27
ICER (compared with base case)			£46,206
ICER with all changes incorporated			£120,383
ERG's alternative base case ICER			
ICER with all changes incorporated			**£120,383**
Abbreviation used in the table: BSC, best supportive care; ERG, evidence review group; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year.			

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Table 2. ERG base case ICER (treatment experienced)

	Avelumab (1)	Chemotherapy (2)	BSC (3)	Incremental value (1-2)	Incremental value (1-3)
Company's base case					
Total costs (£)	£78,752	£9,838	£7,465	£68,914	£71,287
QALYs	2.22	0.30	0.31	1.92	1.91
ICER				£35,873	£37,350
Weibull time on treatment curve (without truncation)					
Total costs (£)	£92,557	£9,838	£7,465	£82,718	£85,091
QALYs	2.22	0.30	0.31	1.92	1.91
ICER				£43,060	£44,584
Weibull regression models for PFS and OS					
Total costs (£)	£92,537	£9,630	£7,413	£82,906	£85,124
QALYs	2.22	0.31	0.32	1.91	1.90
ICER (compared with base case)				£36,199	£37,582
ICER with all changes incorporated				£43,432	£44,857
Addition of pre-medication costs					
Total costs (£)	£92,644	£9,630	£7,413	£83,014	£85,232
QALYs	2.22	0.31	0.32	1.91	1.90
ICER (compared with base case)				£35,920	£37,397
ICER with all changes incorporated				£43,488	£44,914
ERG's alternative base case ICER					
ICER with all changes incorporated				**£43,488**	**£44,914**

Abbreviation used in the table:

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Section 3 of the company submission (CS) provides an overview of the key aspects of Merkel cell carcinoma (MCC) and metastatic MCC (mMCC). The Evidence Review Group (ERG) notes the population outlined in the final scope issued by the National Institute for Health and Care Excellence (NICE) for this Single Technology Appraisal (STA) is people who have mMCC.[1]

The ERG considers the information in the CS to provide a reasonable overview of mMCC and to be relevant to the NICE final scope.[1] The CS provides an overview of what MCC is, its aetiology and a brief summary of the staging and prognosis of mMCC. In addition, the company details the effects of mMCC on patient's health-related quality of life (HRQoL) with some of this detail based on clinical expert opinion. The ERG's clinical advisors agree with the company's description of mMCC and the company's advisors' views on its impact on patients' HRQoL. In summary, MCC is a rare neuroendocrine skin cancer that is more common in the elderly and on sun-exposed sites, and it tends to metastasise at an early stage. The visible appearance of the cancer can cause considerable psychosocial distress to patients with symptoms dependent on the site of the primary tumour and metastases. There are currently very few treatment options for patients with mMCC and it is generally associated with a poor prognosis.

2.1.1 Epidemiology

The company presented estimates of life expectancy for patients with mMCC using data sourced from published literature, and reported that England specific data for this exact population were unavailable (CS page 42, Section 3.4). The data presented in the CS suggest that median life expectancy of mMCC patients is between 4 and 13 months. One of the ERG's clinical experts noted that a recent study published by Harms *et al.* reported median survival of patients with distant mMCC was 12 months, whereas over 70% of the patients with local or nodal mMCC survived longer than 12 months from diagnosis.[2] Harms *et al.* reported that estimated 5-year overall survival was 51%, 35%, and 14%, respectively for local, nodal, and distant mMCC.[2]

The company estimated that there are between 70 and 81 people with mMCC in England each year. This estimated prevalence of mMCC in England was calculated using published data on the incidence of MCC in Europe sourced for one of the journal publications of the JAVELIN Merkel 200 trial[3] and the Office for National Statistics data on the population of England in 2016.[4] The company reported that although their clinical experts consider these estimates of mMCC incidence to be reflective of clinical practice, they may be an under-estimation. The justification for this statement was that approximately 20% of patients may not be treated by specialist physicians (e.g. patient's ineligible for

chemotherapy) and therefore are not accounted for within these calculations. The ERGs clinical experts reported that most mMCC patients presenting for treatment would be referred for oncology review at a skin cancer multidisciplinary team meeting even if they may be ineligible for chemotherapy, and that in England, the decision on chemotherapy eligibility is usually made by an oncologist. The ERG and its experts consider that if patients are not seen at specialist centres then they are unlikely to receive avelumab. The ERG considers that the omission of these patients from the estimates of incidence is unlikely to have an impact on the company's estimate of the number of patients eligible for avelumab which is based on these data, and discussed in Section 2.2.

The company identified three studies to provide data on the proportion of MCC patients who have metastatic disease at diagnosis.[5-7] Two of the three studies[6, 7] were US-based studies and the third[5] was a small UK-based study (n = 37). In the UK-based study, 8% of patients had mMCC at diagnosis.[5] This value lies within the US study values of 5–12% and so appears to be a reasonable estimate. The company used both the higher and lower figures (i.e. 5% and 12%) to provide a range of values for the number of patients with mMCC at diagnosis in England per year (8–20 patients). The company sought published data from three US-based studies for the proportion of MCC patients who relapse with metastatic disease each year;[6, 8, 9] however, the ERG is unclear how the company reached the figure of 37% of patients relapsing with metastatic disease from these studies and due to time constraints were unable to fully investigate the three studies. The ERG's clinical experts report that 37% is probably a reasonable estimate for the UK, but the ERG considers it important to highlight that this figure is subject to a high degree of uncertainty. The ERG's clinical experts do, however, report that UK data on incidence and prevalence of mMCC are lacking and agree with the approach taken by the company to generate estimates for mMCC in the UK.

The company's estimate of the number of mMCC patients in England per year combines the proportion with mMCC at diagnosis with the number relapsing with mMCC (Table 3). The ERG notes that the lower value of 70 cases should possibly be 69 based on the numbers provided in Table 6 of the CS (8 new mMCC cases + 61 relapsing cases) but acknowledges that this a minor difference.

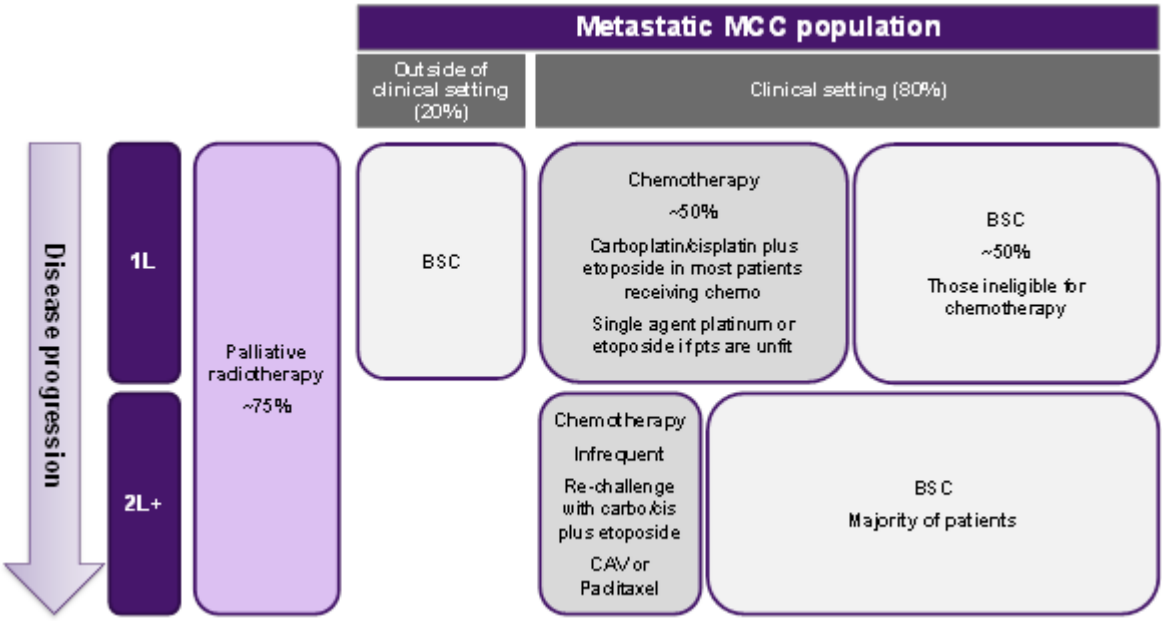
Table 3. Company's estimate of the number of patients with metastatic MCC in England per year (adapted from CS page 43, Table 6)

		Reference
Incidence of MCC in Europe	0.3 per 100,000	(Kaufman 2016)[3]
Population of England	55,268,100	(ONS 2016)[4]
Number of MCC patients in England per year	55,268,100/100,000 x 0.3 = **165 cases**	
Proportion of MCC patients metastatic at diagnosis	5% – 12%	(Stokes 2009;[6] Fitzgerald 2015;[7] Jackson 2015[5])
Number of patients with metastatic MCC in England per year	(165 x 0.05) = **8 cases** (165 x 0.12) = **20 cases**	
Additional proportion of MCC patients relapsing with metastatic disease	37%	(Allen 2005;[8] Stokes 2009;[6] Santamaria-Barria 2013[9])
Number of patients relapsing with metastatic disease in England per year	(165 x 0.37) = **61 cases**	
Total number of metastatic MCC patients in England per year	**70 – 81 cases**	
Abbreviations: MCC: Merkel cell carcinoma		

2.2 Critique of company's overview of current service provision

The company reported that there are no England-specific guidelines for mMCC or MCC. The ERG notes that, in the CS, the company reported that the NICE skin cancer pathway and London Cancer guidelines are not specific for MCC.[10, 11] However, the ERG also notes that the London Cancer guidelines comprise of skin cancer radiotherapy guidelines[10] and do provide some guidance on treatment of mMCC, which the company summarised in the CS. In addition, the company summarised the European guidelines for MCC recommendations for mMCC.[12] The company also consulted clinical experts to help depict the current treatment pathway for mMCC patients specifically in England and presented a pictorial representation of the pathway (Figure 1). The ERG's clinical experts are generally in agreement with the treatment pathway in Figure 1, reporting that around half of mMCC patients will receive chemotherapy and half will receive palliative care/best supportive care (BSC) at first line and most patients will receive BSC at second line. The ERG's clinical experts reported that the most commonly used chemotherapy regimen in the UK is probably carboplatin plus etoposide.

Figure 1. Company's representation of the current clinical pathway for the treatment of metastatic MCC in England according to their MCC experts (reproduced from CS page 41, Figure 3)



*Defined as patients who do not receive treatment at a specialised clinic or skin MDT.
Abbreviations: 1L: First-line; 2L+: Second-line plus; BSC: Best supportive care; CAV: Cyclophosphamide + doxorubicin + vincristine; MCC: Merkel cell carcinoma; MDT: Multidisciplinary team

The ERG notes that there is no existing NICE technology appraisal guidance in mMCC and its clinical experts confirm the absence of England and UK specific national guidance. The company reports that, if approved, avelumab will be offered as a treatment option for both treatment-naïve and treatment-experienced patients with mMCC. The company does not present any further details on the proposed new treatment pathway with avelumab incorporated. The ERG's clinical advisors report that if approved, avelumab may be used as an alternative to chemotherapy at first line. In these patients second line treatment would probably still be BSC unless their performance status remained good enough for them to be considered for chemotherapy at second line. Avelumab would also provide a treatment option for some patients who may not be eligible for chemotherapy in the first-line setting. Alternatively, avelumab may be used at second line or later in pre-treated patients, where again following discontinuation patients are likely to receive BSC.

The company reported in Section 2.4 of the CS (page 35) that they do not expect the resource use associated with the administration of avelumab to be any greater than that required for the current administration of chemotherapy. However, the ERG's clinical experts reported that as avelumab is given 2-weekly and chemotherapy is 3-weekly it will result in more hospital visits. In addition, chemotherapy is only given for 6 cycles whereas avelumab treatment is continued until disease progression or unacceptable toxicity. However, the ERG's clinical experts also reported that etoposide chemotherapy regimens often rely on patient compliance to take oral drugs at home, and carboplatin or cisplatin require longer infusion times than avelumab.

Avelumab is an immunotherapy and in keeping with other immunotherapies will require monitoring for immunotherapy-related side effects. The main additional tests required during treatment are blood tests which are likely to include thyroid function tests, glucose, cortisol and more frequent liver function tests (2-weekly instead of 3-weekly). Table 4 summarises the drug-related and administration costs estimated by the company for avelumab. The ERG notes from the summary of product characteristics (SmPC) that avelumab also requires premedication with an antihistamine and acetaminophen before the first four infusions as a minimum to prevent potential infusion-related reactions and these costs have not been included by the company. The use of antihistamines and acetaminophen for premedication of the fifth or later avelumab infusion is based on clinician judgement. The ERG, therefore, considers the cost of associated with the use of avelumab are likely to be higher than that reported in Table 4. The ERGs clinical experts reported that in England, the premedication is likely to be 1g of paracetamol given orally (or intravenously [IV]), and 10mg of IV (or oral equivalent dose) chlorpheniramine. The ERGs clinical experts also reported that the costs associated with these are likely to be relatively low as they are both available as generic formulations.

Table 4. Company summary of the costs associated with avelumab (adapted from CS page's 33-34, Table 5)

	Description	Cost	Source
Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate); one vial of 10 mL contains 200 mg of avelumab		SmPC[13]
Acquisition cost (excluding VAT)		£768 per 200 mg (list price; confirmed by DH as subject to MAA)	Merck KGaA/Pfizer
Method of administration	Intravenous infusion	£199 (simple parenteral chemotherapy) every two weeks - outpatient; SB12Z - NHS reference costs 2015-2016	SmPC[13]
Doses	10 mg/kg over 60 minutes	£3,261.04 (per dose)	SmPC[13]; CS Table 50
Dosing frequency	Every 2 weeks	-	SmPC[13]
Average length of a course of treatment	The recommended dose of avelumab is to be administered intravenously over 60 minutes every 2 weeks. Average duration of treatment calculated via the area under the curve within the model yields a mean ToT of 9.4 months (for both treatment-experienced and treatment-naïve patients).	-	SmPC[13] JAVELIN Merkel 200 CSR[14]
Average cost of a course of treatment	The average dose per treatment is estimated to be 849mg; an average cost per course of £65,086	£65,086	CS Section 5

Anticipated number of repeat courses of treatments	Administration of avelumab should continue until disease progression or unacceptable toxicity. Patients with radiological disease progression not associated with significant clinical deterioration, defined as no new or worsening symptoms, no change in performance status for greater than two weeks, and no need for salvage therapy, could continue treatment. Median PFS in the JAVELIN Merkel 200 2L+ cohort was 2.7 months and 9.1 months in the 1L cohort.	-	Advised by clinical experts
Dose adjustments	Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability, as detailed in the SmPC. The median dose intensity in the 2L+ cohort from JAVELIN Merkel 200 was 9.92 mg/kg/cycle The median dose intensity in the 1L cohort was 10mg/kg/cycle.		SmPC[13] JAVELIN Merkel 200 CSR[14]
Anticipated care setting	Secondary care: dispensed by hospital pharmacy		Merck KGaA/Pfizer
Abbreviations: DH: Department of Health; SmPC: Summary of Product Characteristics; VAT: Value-added tax			

The company estimated the number of patients eligible for treatment with avelumab over the next 5 years (2018–2022) using their estimate of people with MCC presented in Table 3 and the average of the estimates of the proportion of MCC patients with metastatic disease at diagnosis (8.5%). A population growth of 0.8% and stable disease epidemiology were assumed, although the source of the 0.8% population growth figure was not referenced. The resulting estimates are reported to be the maximum number of patients eligible for avelumab and are presented in Table 5. The ERG assumes that the reason that they are the maximum number, is a result of patients who would not be eligible for avelumab also being included; based on clinical expert opinion, the ERG does not consider the inclusion of these patients likely to have a substantial impact on the estimates.

Table 5: Maximum metastatic MCC population eligible for avelumab (adapted from CS table 96, page 210)

Year	2018	2019	2020	2021	2022
Eligible patient population	75	76	76	77	77
Abbreviations: MCC: Merkel cell carcinoma					

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company submission (CS) provides a summary of the decision problem and tabulates a comparison with the National Institute for Health and Care Excellence (NICE) final scope[1] together with the rationale for any deviation from the NICE final scope (Table 6) as outlined in the CS. The NICE final scope[1] requested a different comparator for untreated metastatic Merkel cell carcinoma (mMCC) from that for previously treated mMCC, and the company has addressed this in the CS by providing separate data on avelumab for the first-line (1L) and second-line or beyond (2L+) populations.

Table 6. Summary of decision problem as outlined in the company's submission (adapted from CS, pages 18-19, Table 1)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with metastatic MCC	As per scope	-
Intervention	Avelumab	As per scope	-
Comparator(s)	Untreated metastatic MCC Chemotherapy (such as cisplatin or carboplatin with or without etoposide) BSC Previously treated metastatic MCC BSC	Untreated metastatic MCC Chemotherapy (cisplatin or carboplatin plus etoposide- option to select a chemotherapy "basket" is also available) BSC Previously-treated metastatic MCC BSC Chemotherapy (cisplatin or carboplatin plus etoposide- option to select a chemotherapy "basket" is also available)	UK clinical expert opinion is that a 50:50 split of carboplatin plus etoposide and cisplatin plus etoposide is used for treatment-naïve patients with no expected differences in efficacy between regimens In the 2L the majority of patients will receive BSC with a minority of patients who are fit enough receiving chemotherapy. The choice of cytotoxic agent in 2L is dependent on the choice of chemotherapy a patient received at 1L. In some instances, patients, may be re-challenged with cisplatin or carboplatin with or without etoposide- The option of selecting a chemotherapy "basket" has also been included.
Outcomes	Overall survival Progression-free survival Response rate Adverse effects of treatment Health-related quality of life	As per scope	-
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY.	As per scope	-

	The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	No subgroups were identified	As per scope	-
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per scope	-

Abbreviations: 1L, first line; 2L, second line; BSC, best supportive care; CS, company submission; MCC, Merkel cell carcinoma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; UK, United Kingdom

3.1 Population

Clinical effectiveness data on avelumab in the CS are derived from the JAVELIN Merkel 200 trial, which was designed to evaluate the efficacy and safety of avelumab in patients with mMCC. JAVELIN Merkel 200 is an international, single-arm study, conducted in 72 sites across North America, Europe, Australia and Asia. However, the Evidence Review Group (ERG) notes that there were no patients recruited from UK sites in JAVELIN Merkel 200.

JAVELIN Merkel 200 comprises of two parts: Part A which included patients with metastatic MCC who had failed at least one prior line of chemotherapy (referred to from here-in as the second-line plus [2L+] or treatment-experienced cohort) and Part B which included patients with no prior therapy (referred to from here-in as the first-line [1L] or treatment-naïve cohort).

The final scope issued by NICE[1] specifies the population of interest to be people with mMCC although the comparators in the final scope require separate analyses for the 1L and 2L+ populations. The company provided data from Part B and Part A of JAVELIN Merkel 200 to address these two populations, respectively.

Part A of JAVELIN Merkel 200 included 88 2L+ patients. Part B of JAVELIN Merkel 200 is still recruiting 1L patients; March 2017 data cut included only 39 patients although target enrolment is 112, which is expected to be achieved in [redacted]. Part B was a later addition to the JAVELIN Merkel 200 trial and is critical for assessing the clinical efficacy of avelumab in the 1L setting which is a key part of the NICE final scope.[1] The ERG is concerned that the small sample size for the 1L and

2L+ cohorts in JAVELIN Merkel 200 may lead to uncertain and imprecise estimates of safety and efficacy.

The ERG's clinical experts consider the inclusion criteria for JAVELIN Merkel 200 are generally consistent with the expected eligibility criteria for avelumab in clinical practice in England. A possible exception is the restriction on performance status in the trial to patients with an Eastern Cooperative Oncology Group performance score (ECOG PS) of less than 2, whereas patients in clinical practice may have higher scores at baseline, particularly in the 2L+ population. In terms of baseline characteristics of the patients in JAVELIN Merkel 200, there are no other major concerns reported by the ERG's clinical experts in terms of comparability with the equivalent mMCC patient population in England. The ERG notes that 35.2% of the 2L+ cohort were third line or beyond (3L+) at study baseline and the ERGs clinical experts considered that this is possibly a reflection of the more aggressive treatment approach used in non-UK countries. The ERGs clinical experts also considered that most UK patients would be expected to receive avelumab first or second line, and would be unlikely to receive an active treatment at third line or beyond.

The observational study (Study 100070-Obs001) used to provide data on the comparator of chemotherapy in the CS, comprised patients with mMCC who had received one or more lines of prior chemotherapy treatment. Study 100070-Obs001 had similar inclusion and exclusion criteria to JAVELIN Merkel 200 except for the observational study including immunocompromised patients. The ERG's clinical experts reported that depending on the reason for patients being immunocompromised, these patients may not be eligible for avelumab (e.g. solid organ transplant patients) or may be substantially younger than the typical mMCC patient (e.g. HIV infected patients). The ERG is unsure as to the baseline characteristics for this subset of Study 100070-Obs001 patients and thus is unable to comment further on them in relation to the overall study population. In the company response to clarification questions, the company stated that immunosuppressed patients are not anticipated to achieve different survival outcomes from immunocompetent patients in either the 1L or 2L+ populations. The company reference the univariate and multivariate regression analyses they conducted to explore this characteristic in Appendix 10 of the CS that demonstrate no statistical significance in progression-free survival (PFS) or overall survival (OS) based on immunocompetency. The company also reported that they consider, "The lack of significance in regression analysis is therefore unlikely to be due to low patient numbers and instead indicates it is not a significant predictor of outcome". In addition, they report that due to, "the rarity of the disease and difficulty in obtaining patient data, all patients were included in the Study 100070-Obs001". The ERG is concerned that immunocompetency could still potentially be a prognostic indicator and that the low patient numbers in the analysis may be masking any potential relationship.

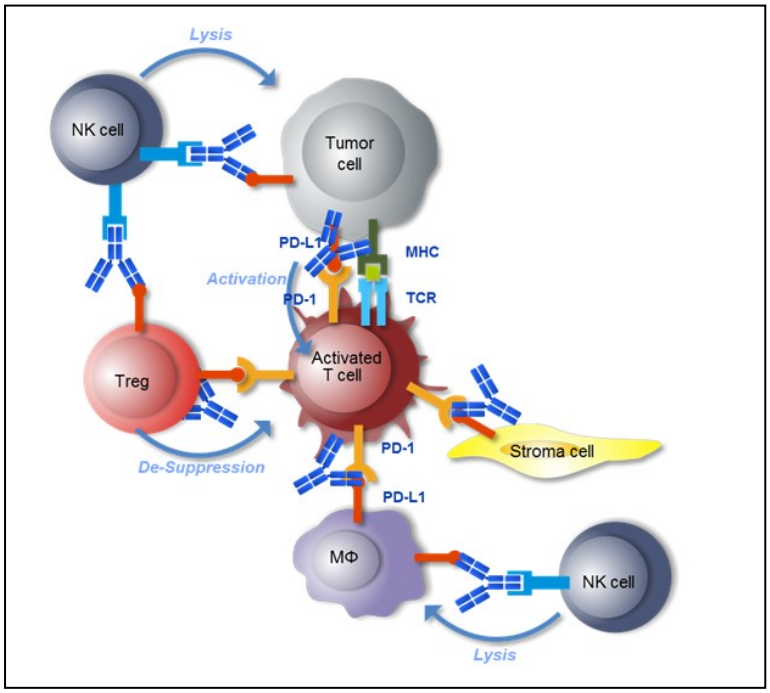
In summary, the ERG considers the data presented within the submission for avelumab to be representative of UK patients with mMCC, and to be relevant to the decision problem that is the focus of this single technology appraisal (STA). The ERG is concerned that the inclusion of immunocompromised patients in Study 100070-Obs001 may be a confounder in any unadjusted analyses where this study is included to provide data on chemotherapy outcomes.

3.2 Intervention

The intervention specified in the final scope issued by NICE,[1] and that was the focus of the CS for this STA, was avelumab. Avelumab (BAVENCIO®), is reported to be a human IgG1 lambda monoclonal antibody that inhibits an immune checkpoint protein known as PD-L1. The company reported that if approved, avelumab will be the first licensed treatment for mMCC in Europe. The ERG's clinical experts state that the current main pharmaceutical treatment in the UK for mMCC is chemotherapy.

Tumour cells and tumour-infiltrating immune cells may express PD-L1 and can contribute to the inhibition of the anti-tumour response through binding to PD-1 and B7.1 receptors which are located on T-cells and antigen presenting cells. Avelumab works through binding to PD-L1 and thus blocking the interaction between PD-L1 and the PD-1 and B7.1 receptors. This results in the restoration of normal anti-tumour activity (Figure 2). In addition, avelumab has also been shown *in vitro* to induce antibody-dependent cell-mediated cytotoxicity (ADCC),[15] which is a process associated with the direct killing of antigen-expressing cancer cells.[15, 16] The company reported that this ADCC property of avelumab is not seen with other PD-1/PD-L1 inhibitors, such as pembrolizumab, nivolumab, durvalumab, and atezolizumab.

Figure 2. Proposed mechanism of actions of avelumab (reproduced from the CS page 31, Figure 1)



Abbreviations: ADCC: Antibody-dependent cell-mediated cytotoxicity; ADCP: Antibody-dependent cellular phagocytosis; MHC: Major histocompatibility complex; NK: Natural killer; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1; TCR: T-cell receptor

The company reported that, "avelumab was granted Orphan Drug designation for the treatment of metastatic MCC by the Food and Drug Administration (FDA) (25 September 2015) and the European Medicines Agency (EMA) (6 June 2016; EU Orphan designation number: EU/3/15/1590), as well as Fast Track and Breakthrough Therapy Designations in October 2015 and November 2015, respectively[17, 18]". The company stated that these designations reflect the efficacy of avelumab in patients with mMCC, the poor outcomes associated with mMCC, and the limited treatment options available.

The CS states that a European marketing authorisation application (MAA) for avelumab to treat mMCC in adults was submitted to the European Medicines Agency (EMA) in October 2016 and avelumab received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 21 July 2017 for avelumab as a monotherapy for the treatment of adult patients with mMCC. The company anticipated that final approval would be received on 23 September 2017; however, the ERG notes that on 5 October 2017, avelumab was still on the pending European Commission decisions list on the EMA website.[19]

The ERG notes that avelumab has received accelerated approval by the FDA (23 March 2017) for the treatment of adults and paediatric patients (over 12 years) with mMCC. This approval is reported by the company to be based on 1L and 2L+ data from JAVELIN Merkel 200. The ERG also notes that avelumab for mMCC treatment will be submitted to the Scottish Medicines Consortium (anticipated

date [redacted]) and the National Centre for Pharmacoeconomics (anticipated date [redacted]). In addition, Form A is planned to be submitted to the All Wales Medicines Strategy Group in [redacted].

As discussed in Section 2.2, avelumab is anticipated to be administered as a 10 mg/kg IV infusion over 60 minutes every 2 weeks, which is more frequent than the 3-weekly chemotherapy regimens currently used as the main active treatment for mMCC. In addition, premedication with an antihistamine and acetaminophen is required prior to the first four avelumab infusions, and subsequent use is at the discretion of the treating clinician. Monitoring of patients for immunological adverse effects (AEs) is also necessary and involves regular clinical reviews and blood tests. The most frequently experienced AEs are managed by the temporary discontinuation of avelumab, administration of corticosteroids and supportive care.

The clinical efficacy and safety data presented in the CS for avelumab are from the Phase II, international, single-arm, open-label JAVELIN Merkel 200 trial of avelumab in mMCC. It is reported in the CS to be the largest registration trial in mMCC to date. Patients in JAVELIN Merkel 200 received avelumab at a dose of 10 mg/kg as a 60-minute intravenous (IV) infusion once every 2 weeks with the dose of avelumab calculated based on the weight of the patient on the day of administration. The ERG notes from the clinical study report (CSR) that the infusion duration could vary from 50 to 80 minutes and considers this variation may potentially have an impact on the acute infusion related AE rates experienced by patients as well as the resource use involved. The ERG's clinical experts reported that even at 80 minutes, the avelumab infusion time is quicker than that of a carboplatin plus etoposide chemotherapy regimen. Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab was mandatory in JAVELIN Merkel 200 in line with the anticipated SmPC guidance. The ERG notes that the suggested premedication regimen in the trial (diphenhydramine 50 mg IV, or equivalent, and acetaminophen 650 mg oral or IV) could be modified based on local treatment standards and guidelines. The ERG is unsure whether these local variations in premedication regimens would have any impact on the safety of avelumab. The ERGs clinical experts reported that premedication in England is likely to be with 1g of oral paracetamol and chlorpheniramine 10mg intravenously (IV). The ERGs clinical experts also reported that the local variations in premedication regimens is unlikely to have any impact on the safety of avelumab. The CS also reports that, "any medications (other than those excluded by the clinical study protocol) that were considered necessary for the patients' welfare and would not interfere with avelumab could be given at the Investigator's discretion". No further details were reported in the CS on what these medications were though and so the ERG is unable to comment on the potential impact of them on the safety and efficacy of avelumab. The ERG otherwise considers the administration of avelumab in JAVELIN

Merkel 200 to be in accordance with its anticipated EU marketing authorisation and the final scope issued by NICE[1] for this STA.

3.3 Comparators

The comparators specified in the final scope issued by NICE[1] were chemotherapy (such as cisplatin or carboplatin with or without etoposide) or best supportive care (BSC) for untreated mMCC (i.e. 1L) and only BSC for previously treated mMCC (i.e. 2L+). The study used to provide the clinical data for the intervention that is the focus of this STA, avelumab, was a single-arm study (JAVELIN Merkel 200) with no RCTs of avelumab in mMCC identified by the company's systematic literature review (SLR). The company reported that, as a result of the lack of comparative and non-comparative clinical data in mMCC and concerns around reporting bias in existing literature, a retrospective observational study (Study 100070-Obs001) comprising of two parts was conducted by Merck KGaA (the company) and Pfizer Inc in Europe and the US to investigate the clinical efficacy of chemotherapy in mMCC.[20, 21] The aim of the observational study (Study 100070-Obs001) was to establish the efficacy of chemotherapy, and to facilitate interpretation of the JAVELIN Merkel 200 trial results. The ERG notes that the CHMP also recommended that good quality comparative control data should be generated given the lack of a comparator arm in JAVELIN Merkel 200. Study 100070-Obs001 comprised patients with mMCC who had received one or more lines of prior chemotherapy treatment and had similar inclusion/exclusion criteria to JAVELIN Merkel 200, except for immunocompromised patients, which were also included in Study 100070-Obs001.

The chemotherapy drugs used by patients at different lines of therapy in the 2L+ cohort of Study 100070-Obs001

[redacted] The ERG notes that it is reported in the CSR that, "[redacted]

[redacted] In addition, it is reported in the CS and agreed by the ERG's clinical experts that different chemotherapy regimens are not known to be associated with significant differences in treatment efficacy in mMCC, although the ERG notes that there are no clinical study data provided to support this assertion.

The ERG considers it important to highlight that like JAVELIN Merkel 200, Study 100070-Obs001 was a single-arm study and so an indirect comparison was still required to generate estimates of efficacy for avelumab versus chemotherapy. The company reported that the statistical analyses that were undertaken for the purposes of the economic modelling, suggested that there were no patient characteristics that were prognostic of outcomes in mMCC and for this reason they did not consider that statistical adjustments (such as Matching Adjusted Indirect Comparison [MAIC], or Simulated Treatment Comparison [STC]) were necessary to match the observational data to the relevant cohorts within JAVELIN Merkel 200. The company presented data from each of the two single-arm studies side-by-side in the CS as a naïve comparison. In addition, in response to a clarification request, the company did provide a comparison of JAVELIN Merkel 200 Part A avelumab data with chemotherapy using Study 100070-Obs001 data and a propensity score matching method for the 2L+ population. The company also provided a regression analysis for the 2L+ population using the Study 100070-Obs001 data with age, gender and immunosuppression as predictive variables. The company did not undertake the MAICs requested by the ERG during the clarification stage claiming that this was due to the availability of individual patient data (IPD) from both JAVELIN Merkel 200 and Study 100070-Obs001 and the requirement for matching variables to be prognostic. The company considered that the univariate and multivariate regression analyses that they conducted in Appendix 10 of the CS demonstrated no patient-level factors were associated with differences in the efficacy of avelumab. The ERG considers that the small number of patients in the analyses would not necessarily demonstrate statistically significant differences. As such, ERG considers it important to highlight that the absence of statistical significance does not exclude the possibility that the patient characteristic is associated with a difference in avelumab efficacy. The ERG would therefore have preferred to see analyses with

adjustments for differences in patient baseline characteristics between JAVELIN Merkel 200 and Study 100070-Obs001 presented for both the 1L and 2L+ populations as the primary analyses.

In terms of BSC, no clinical data were presented in the CS for BSC and so the clinical comparison of avelumab versus BSC is not possible. The company reported that they found no literature describing the outcomes of treatment-experienced or treatment-naïve mMCC patients treated with BSC suitable for inclusion in the CS. The company therefore decided to use chemotherapy as a proxy of BSC in both the 1L and 2L+ populations in the economic model, reporting that it is conservative for 1L as it assumes the benefits of chemotherapy without the associated costs. The company cited clinical expert opinion as the basis for this decision in the 2L+ population, reporting that an expert advisor ([redacted]) suggested that broadly the same survival outcomes were seen regardless of which treatment is given (BSC or chemotherapy) at 2L+. The company stated that the bias associated with this assumption in both the 1L and 2L+ populations is likely to be against avelumab and is unlikely to be large because the chemotherapies used are generic (thus relatively inexpensive), unlikely to be used for a long period, and unlikely to have substantive efficacy. The ERG agrees with the company's assertions regarding the efficacy but considers there may be differences in safety outcomes for a BSC treatment arm compared with a chemotherapy treatment arm, which could have an impact on the overall results from the economic modelling.

In summary, the ERG does not consider the comparison with BSC to have been covered in the clinical effectiveness section of the CS and the ERG has concerns that the comparison with chemotherapy is subject to a high degree of uncertainty as it is based on naïve comparison of single-arm studies or analyses with limited adjustments for between-study differences in patient characteristics at baseline.

3.4 Outcomes

The company presents no direct evidence for avelumab versus chemotherapy or avelumab versus BSC; however, evidence for avelumab is presented for all of the outcomes listed in the final scope issued by NICE:[1]

- Overall survival;
- Progression-free survival;
- Response rate;
- Health-related quality of life (HRQoL); and
- Adverse effects of treatment.

It is noted that guidance from the FDA[22] reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and OS although they provide an accurate assessment of overall response rate (ORR). The ERG recommends that the PFS and OS estimates from JAVELIN Merkel 200 are interpreted with caution.

Comprehensive data on response rate were presented in the CS for avelumab from JAVELIN Merkel 200 that included ORR, best overall response (BOR), duration of response (DoR) and durable response rate (DRR; defined as an objective response of complete response [CR] or partial response [PR] according to Response Evaluation Criteria in Solid Tumours [RECIST] 1.1 lasting at least 6 months). In addition, tumour shrinkage in target lesions at each time point from baseline was reported; these data are not discussed further in this report as they are not, strictly speaking, response rate data and numerous other data on response rate are available.

The HRQoL data presented in the CS were also from JAVELIN Merkel 200 although only for the 2L+ population. The HRQoL data were collected using the EuroQol 5-dimensions 5-level (EQ-5D-5L) and the Functional Assessment of Cancer Therapy for Melanoma (FACT-M) questionnaires, in addition to qualitative, semi-structured patient interviews. FACT-M is a disease-specific instrument that was originally developed for melanoma. FACT-M was selected by the company in the absence of an MCC-specific tool due to the similarities between MCC and melanoma.[23] In the JAVELIN Merkel 200 trial, EQ-5D-5L data were collected only while patients were receiving avelumab treatment, thus resulting in limited measurements in the post-progression setting. The company reported that this is a common limitation of HRQoL data in oncology studies. EQ-5D results were not reported in the clinical section of the CS, and only utility values derived from the UK EQ-5D-3L values generated from the EQ-5D-5L data were presented in the cost-effectiveness section. The EQ-5D-5L data were provided in response to a question at the clarification stage (question B7). The use of qualitative, semi-structured patient interviews in the 2L+ patients from JAVELIN Merkel 200 was reported to be a method of acquiring a comprehensive picture of the impact of mMCC and its management on patients' lives, but again it was limited by the number of patients agreeing to participate in the interviews (n=33) and a high drop-out rate in terms of the number completing the final interview (n=17).

Based on advice from clinical experts, the ERG considers that the outcomes presented in the submission are clinically relevant to the decision problem; however, there is a lack of direct comparative data for any of the outcomes for avelumab and the comparators specified in the NICE final scope.[1] There are no clinical outcome data presented for BSC in the CS and outcome data for chemotherapy are limited to measures of response rate, PFS and OS. Data from the propensity score matching and regression analyses in the 2L+ population provided in the clarification response document are limited to PFS and OS. There was also no HRQoL data presented in the CS for the 1L population.

3.5 Timeframe

The CS reported the latest data available from each of the two parts of JAVELIN Merkel 200, although the ERG considers it important to highlight that recruitment is still ongoing for Part B. In the company response to clarification questions it was reported that recruitment of the last patient for Part B was not expected to be until [redacted].

The data in the CS were from a data cut on the 24 March 2017 and comprised a minimum of 18-months follow-up for Part A (2L+ cohort, n=88) and 29 (out of a total of 39) 1L patients (Part B) with ≥3 months follow-up with a response status recorded. In addition, there were 14 patients in the 1L cohort with ≥6 months follow-up. The safety outcomes reported in the CS included the full patient cohort (Part A n=88 and Part B n=39) who received at least one dose of avelumab. The company reported that an additional data cut was expected at the [redacted] with further data cuts in 2018. The planned date of study completion is June 2025 and the estimated primary completion date in September 2019 (final data collection date for primary outcome measure). The ERG notes that the median OS reported in the CS for both the 1L and 2L+ cohorts of JAVELIN Merkel 200 is immature.

In summary, the ERG considers the duration of follow-up in Part A of JAVELIN Merkel 200 to be suitable for assessing the short-term safety and efficacy outcomes of treatment with avelumab. However, the ERG has concerns that the number of patients currently recruited to Part B is extremely small and the follow-up of those recruited is relatively short. The ERG also considers that further trial data are required to assess the long-term effects of avelumab in the 1L and 2L+ populations, both in terms of efficacy and safety.

3.6 Other relevant factors

The company reported in the CS that there are no anticipated equality issues with avelumab. Current treatment options for mMCC are limited and the introduction of an immuno-oncology therapy would provide a licensed therapeutic option with a different mode of action from those treatments currently used in mMCC.

No subgroups were requested in the final scope issued by NICE and the company provided limited subgroup data within the CS in addition to the data for the 1L and 2L+ populations requested in the comparators section of the NICE final scope.[1] The additional subgroup data were only for the 2L+ population and included site of primary tumour, tumour MCPyV (Merkel cell polyomavirus) status, number of prior systemic treatments, presence of visceral metastases at baseline, disease burden at baseline and tumour PD-L1 expression status at baseline. These additional subgroup data for the 2L+ population are reported to be *post hoc* analyses and limited to the outcome of objective response rate. They are discussed further in Section 4.3.5.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

In the absence of any direct comparative studies of avelumab against the comparators of interest for metastatic Merkel cell carcinoma (mMCC), the company conducted multiple systematic literature review (SLR) processes for effectiveness, safety, cost-effectiveness, cost and resource use, and health-related quality of life (HRQoL). The effectiveness SLR and safety SLR are discussed in this section, and the cost-effectiveness, cost and resource use, and HRQoL SLRs are discussed in Section 5. An SLR detailed in Appendix 10 of the company submission (CS) was conducted to inform treatment effectiveness in the economic model, and thus overlaps significantly with the effectiveness SLR; studies identified in either process are discussed in this section.

The purpose of the effectiveness SLR was to identify studies of avelumab and the relevant comparators within the final scope issued by the National Institute for Health and Care Excellence (NICE)[1] to derive comparative estimates of their effectiveness for people with mMCC. The effectiveness SLR also sought safety and tolerability outcomes from relevant mMCC studies. The purpose of the safety SLR was to find evidence of avelumab and the chemotherapy comparators in the treatment of small cell lung cancer (SCLC) and melanoma where safety data specific to mMCC was not found in the effectiveness SLR.

4.1.1 Searches

4.1.1.1 Effectiveness SLR

The company provided the search terms and strategies implemented in the effectiveness SLR as Appendix 3 of the CS. The first set of searches was conducted on 21 September 2015 and sought to identify randomised controlled trials (RCTs), cohort studies and case series of any pharmacological intervention for mMCC. Subsequent update searches on 27 January 2016 and 27 March 2017 also included terms to identify case reports because insufficient evidence was identified in the original search.

The evidence review group (ERG) considers the electronic databases used for the company's electronic database searches for the effectiveness SLR appropriate and comprehensive. The electronic database searches were run in Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (EMBASE), MEDLINE (R) In-process, (via PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL). Databases, search dates and, where reported, number of hits are summarised in Table 7.

Table 7. Summary of searches conducted for the company's effectiveness systematic literature review (SLR)

Database/source	Platform	Purpose	Hits		
			21/09/15	27/01/16	27/03/17
MEDLINE + Embase	EMBASE	Cohorts and case series	1,974	85	307
MEDLINE + Embase	EMBASE	Case reports	N/A	927	96
CENTRAL	Cochrane	Cohorts, case series, case reports	16	16	30
MEDLINE In process	PubMed	Cohorts, case series, case reports	256	167	360
Bibliographies	N/A	Cohorts, case series, case reports	NR	NR	NR
Conference proceedings*	EMBASE and handsearching	Unpublished studies and supplementary results	NR	NR	NR
CDSR	Cochrane	Trials in progress	NR	NR	NR
DARE	Not stated	Trials in progress	NR	NR	NR
Orphanet	http://www.orpha.net	Trials in progress	NR	NR	NR
GLOBOCAN	http://globocan.iarc.fr/	Trials in progress	NR	NR	NR

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects; Embase, Excerpta Medica Database; N/A, not applicable; NR, not reported; MEDLINE, Medical Literature Analysis and Retrieval System Online

*CS Appendix 3 lists the following conferences handsearched from 2011 to 2016: American Academy of Dermatology, American Head and Neck Society, American Society of Clinical Oncology, British Association of Dermatologists, European Association of Dermato Oncology, European Cancer Congress/European Society for Medical Oncology, International Federation of Head and Neck Oncologic Societies, International Society for Pharmacoeconomics and Outcomes Research, Society for Melanoma Research, World Congress of Dermatology.

Search strategies for MEDLINE, Embase and CENTRAL provided in Appendix 3 of the CS included appropriate disease terms and MESH headings. Intervention terms were not included because the searches sought to identify studies of any pharmacological intervention for mMCC, meaning that the searches are broader than the decision problem in the NICE final scope.[1] No language or date restrictions were used for the database searches. Study design filters for RCTs, cohort studies and case series were applied to the Embase and MEDLINE searches, and separate searches were run in these databases to identify case reports (see Table 7). It is not clear whether the study design filters are validated because they are not cited. Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases, but considers the strategies to be reasonable.

The company report that included study bibliographies were searched to supplement the electronic database searches for RCTs, cohort studies, case series and case reports. Conference proceedings were handsearched for unpublished studies, and searches were conducted in the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), and the Orphanet and GLOBOCAN websites for trials in progress (Table 7). The Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) diagram provided in the CS (CS Figure 4, page 49; Figure 3) shows that 5 records were included from searches of conference proceedings and 1 reference

from searches of study bibliographies, but no information is provided about the number of records screened from these sources. Similarly, search terms and number of records assessed, retrieved and included (if any) from CDSR, DARE, Orphanet and GLOBOCAN is not described.

The ERG notes that no trial registries were searched for unpublished or ongoing studies (e.g. clinicaltrials.gov and the International Clinical Trials Registry Platform [ICTRP]). Trials registries are recognised as an increasingly important source of ongoing and unpublished studies, and can sometimes provide additional effectiveness and safety data that are not available in the published literature.[24, 25] A basic unrestricted search performed by the ERG in clinicaltrials.gov for 'merkel cell carcinoma' returned 46 records: 22 are listed as recruiting or in the pre-recruitment stage, 13 are completed, 5 are active but not recruiting, and 5 have either unknown, withdrawn or terminated status. An equivalent search in the ICTRP returned 31 studies, 24 of which were found in the clinicaltrials.gov search; of the 7 unique records, 3 are listed as 'authorised', '3 as recruiting', and 1 as 'not recruiting'. Not all studies were designed to assess mMCC and some included patients with other solid tumours.

The ERG noted some descriptive inconsistencies between the CS and Appendix 3 with regards to the searches conducted to identify studies for the effectiveness SLR. First, the list of sources provided in the CS lists the electronic database searches of MEDLINE, EMBASE, MEDLINE In-process and CENTRAL, and supplementary searches of conference proceedings, but does not mention the bibliography searching, CDSR, DARE, Orphanet or GLOBOCAN. Second, the CS states that conference proceedings were handsearched for the last 5 years from 2013 to 2017, whereas Appendix 3 states that the handsearching covered 6 years from 2011 to 2016.

In summary, the ERG considers the company's electronic database searches for the effectiveness SLR to be sufficiently broad and sensitive to identify published RCT and non-RCT evidence relevant to the decision problem that is the focus of this Single Technology Appraisal (STA). Supplementary searches are not described in detail and no trial registry searches were conducted, so evidence from ongoing or unpublished studies may have been overlooked.

4.1.1.2 Safety SLR (SCLC and melanoma)

The company provided the search terms and strategies implemented for the safety SLR as Appendix 14a of the CS. The safety searches were conducted on 2 August 2016 and were not updated. Searches were run in MEDLINE, Embase and the Cochrane Library, separately for SCLC and melanoma. Additional searches included conference proceedings, bibliographies and clinicaltrials.gov. Dates and terms for additional searches of conference proceedings, bibliographies and clinicaltrials.gov were not provided.

The search strategies provided in CS Appendix 14a combined disease terms for either SCLC or melanoma with treatment terms, study design (for RCTs, cohorts and observational studies, and to exclude animal studies and case reports) and outcomes (e.g. safety and adverse effects). Treatment terms were topotecan, cyclophosphamide, doxorubicin, vincristine, carboplatin, etoposide, cisplatin, paclitaxel, liposomal doxorubicin and pembrolizumab. Avelumab terms were not included, which may be because avelumab safety data were available from the key mMCC study; the ERG considers that terms to identify avelumab studies conducted in SCLC and melanoma population should have been included to provide context for the comparator treatments in these populations. In addition, the electronic database searches were limited to records with safety terms in the title or abstract, which is likely to be overly restrictive because relevant studies not mentioning safety in these fields will have been excluded. Results were also limited to those in English language.

4.1.2 Inclusion criteria

4.1.2.1 Effectiveness SLR

Eligibility criteria for the effectiveness SLR were predefined and are reproduced in Table 8. The company conducted one search and sift process to identify studies of avelumab and the relevant comparators. In accordance with guidance from Cochrane[25] and the Centre for Reviews and Dissemination,[24] two independent reviewers appraised the titles and abstracts of citations identified through the searches and discrepancies were resolved by a third reviewer (CS, Appendix 4).

Table 8. Key eligibility criteria used in the search strategy (adapted from CS page 47, Table 8)

Criteria		Rationale
Inclusion criteria		
Population	•Age: adults (≥18 years) •Gender: any •Ethnicity any •Disease: metastatic MCC o Distant metastatic MCC o Regional or lymph node metastatic MCC	Consistent with evidence base for avelumab and the anticipated marketing authorisation.
Intervention	•Avelumab	Intervention defined by the NICE decision problem for treatment of patients with metastatic MCC
Comparator	•Any pharmaceutical intervention	Since the primary objective of the clinical review was to assess the clinical efficacy, QoL, safety, and tolerability associated with pharmacological interventions for the treatment of patients with metastatic MCC, no restriction on pharmaceutical interventions was applied
Study design	•All RCTs irrespective of blinding status •Non-RCTs •Single-arm trials •Observational studies (retrospective analysis, prospective studies, cohort studies, case control studies, case series, case reports)	RCTs are considered as the gold standard of clinical evidence, minimising the risk of confounding factors and allowing the comparison of the relative efficacy of the interventions Other studies will supplement evidence provided by RCTs

		Observational studies include wider patient population and present real-life effectiveness data
Language restrictions	•Both English and non-English language studies for all study designs except case reports •Inclusion of case reports was restricted to studies published in English language	Considering the paucity of data in the population, articles in both English and non-English language were included
Exclusion criteria		
Population	•Studies including a mixed population of Stage I, II, IIIa, and Stage IIIB/IV MCC, with no specific subgroup analysis for metastatic MCC	Only studies focusing on metastatic MCC were considered to align to the decision problem
Comparator	•Studies exclusively focusing on the role of radiotherapy, chemo-radiotherapy, hormonal therapy, or surgery were excluded •Studies investigating the role of maintenance/consolidation therapy after surgery were excluded •Adjuvant or neo-adjuvant therapy were excluded	In line with the anticipated NICE scope, studies were restricted to those evaluating the efficacy of comparators. Comparators were restricted to chemotherapies and BSC.

Abbreviations: BSC, best supportive care; NICE, National Institute for Health and Care Excellence; MCC, Merkel Cell Carcinoma; QoL, quality of life; RCT, randomised controlled trial.

The ERG considers the population defined by the company to be appropriate and relevant to the decision problem outlined in the NICE final scope,[1] which is in line with the proposed marketing authorisation for avelumab. The SLR sought to include studies of adults with distant, regional or lymph node metastatic MCC, and excluded studies with a mixed population of stage I, II, IIIa and IIIB/IV MCC without subgroup analysis, which the ERG considers appropriate. However, the definitions of first-line (1L) and second-line and above (2L+) populations are not given (e.g. whether patients are only considered second line after a course of systemic therapy) and so it is unclear how study populations were classified.

In the inclusion criteria, avelumab is listed as the only included intervention and 'any pharmacological intervention' as the comparator (Table 8). However, in the exclusion criteria it is stated that studies were restricted to those evaluating the efficacy of the comparators listed in the NICE final scope[1] (i.e. chemotherapies and best supportive care [BSC]). Studies exclusively focusing on radiotherapy, chemoradiotherapy, hormonal therapy or surgery, those investigating the role of maintenance or consolidation therapy after surgery, and studies of adjuvant or neo-adjuvant therapy were not eligible; the ERG considers these exclusions reasonable. The ERG considers the SLR intervention and comparator eligibility criteria to reflect the decision problem. As with the population inclusion criteria, comparators are not listed separately for 1L (chemotherapy or BSC) and 2L+ (BSC), which creates a lack of transparency in the selection process.

The ERG considers the company's criteria regarding study designs and language appropriate given the size of the evidence base for mMCC. A minimum study population size was not predefined which led to the inclusion of several single case reports and very small studies. Studies listed as 'included' in the

PRISMA diagram were subsequently excluded if they had less than 10 participants, which is not detailed in the PRISMA diagram for the SLR (discussed further in Section 4.1.3).

Overall, the ERG considers the company's inclusion criteria for the clinical effectiveness SLR appropriate to the decision problem outlined in the NICE final scope,[1] although there is a lack of transparency regarding the definition and application of criteria for the 1L and 2L+ populations.

4.1.2.2 Safety SLR (SCLC and melanoma)

Eligibility criteria are not provided explicitly for the safety SLR but search strategies and reasons for exclusion listed in the PRISMA diagram (Figure 4) indicate that RCTs and non-RCTs (cohort, longitudinal, retrospective, prospective and observational studies) of relevant comparator treatments for SCLC or melanoma were included. The searches were designed to identify studies in SCLC as a proxy due to its similar neuroendocrine properties to MCC. Searches for melanoma were undertaken in case no evidence was identified for MCC or for SCLC.

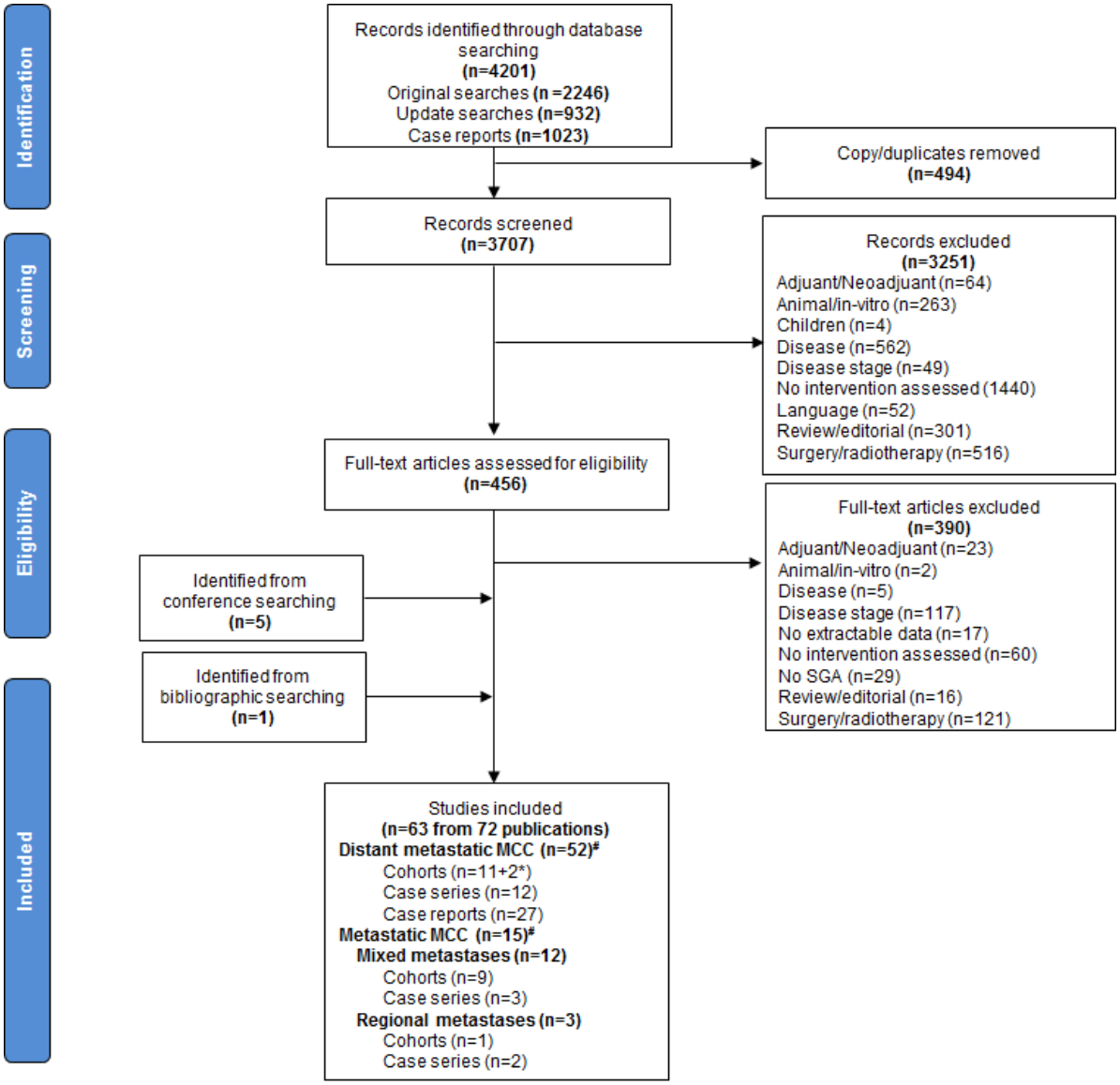
As described in Section 4.1.1.2 avelumab was not part of the eligibility criteria, and the searches may have been overly restrictive by the way safety outcomes were incorporated into the searches. Overall, the omission of explicit eligibility criteria makes it difficult to assess the robustness of the safety SLR, including the reasoning behind eligibility criteria and how they were applied in the study selection process.

4.1.3 Critique of data extraction

4.1.3.1 Effectiveness SLR

A PRISMA diagram was provided in the CS to illustrate the results of the literature searches and sifting process for the effectiveness SLR (CS, Figure 4; reproduced in Figure 3). Overall, 4,201 titles and abstracts were identified from the database searches, of which 3,707 were screened after 494 duplicates were removed. The PRISMA diagram does not detail how many records were retrieved and screened from conference proceedings and bibliographies, only that 5 and 1 (respectively) were assessed at the full text stage, along with 456 from the main database searches (a total of 462). The PRISMA diagram indicates that 390 records were excluded after full text review, leaving 72 to be included in the SLR which relate to 63 studies. The ERG notes that only two of these 63 studies relate to avelumab,[3, 26] although they both relate to JAVELIN Merkel 200 Part A (2L+). Kaufman 2016[3] is a journal publication of JAVELIN Merkel 200 Part A, and Femia 2016[26] is a case report of the first patient in JAVELIN Merkel 200 Part A to achieve a complete response (CR) with avelumab. No publications specific to JAVELIN Merkel 200 Part B (1L) were reported to be identified as part of the effectiveness SLR depicted in Figure 3.

Figure 3. PRISMA flow diagram for the effectiveness SLR (reproduced from CS page 49, Figure 4)



Reasons for exclusion at the full text stage are summarised in the PRISMA diagram and a full list of excluded studies was provided as CS Appendix 6. The most common reasons for exclusion at the full text stage of the effectiveness SLR were: surgery or radiotherapy (n = 121) and wrong disease stage (n = 117). Other reasons were: no intervention assessed (n = 60), no subgroup analysis (n = 29), adjuvant or neoadjuvant therapy (n = 23), no extractable data (n = 17), review or editorial (n = 16), wrong disease (n = 5) and animal or *in vitro* study (n = 2). The ERG considers the reasons for exclusion reasonable and in line with the eligibility criteria.

Appendix 5 lists all 63 included studies[3, 20, 26-85] and refers to CS, Appendix 11 (although they actually appear in CS, Appendix 10) for details on which studies provided suitable control data for the economic analysis. The search detailed in Appendix 10 was conducted to find studies suitable for providing data

to inform the economic analysis, and includes four studies excluded from the effectiveness SLR (Allen 2005,[8] Cowey 2016 [US 1st line],[33] Fields 2011,[86] and SantaMaria-Barria 2013[9]). The ERG is uncertain why the separate search process described in Appendix 10 was required in addition to the effectiveness SLR described in the CS and Appendix 5, and why the included studies differ.

Of the shorter list of included studies described in Appendix 10 (48 rather than 63), 34 were excluded for having less than 10 people to avoid reporting biases of rare cases, 6 because they did not report outcomes relevant to the NICE final scope,[1] and one because the treatment is not considered standard of care in the National Health Service (NHS). Three additional studies were identified in supplementary searches. The ERG considered these reasons for exclusion appropriate but could not reconcile the inconsistency between this process and the SLR described in the CS.

Ultimately, 10 studies with 10 or more patients and relevant outcomes, either from the effectiveness SLR or the SLR described in Appendix 10, were assessed for suitability as control data for avelumab (Table 9). The company did not provide data extraction forms for these studies. Three studies included a 2L+ population (Becker 2016 [EU2L],[20] Cowey 2017 [US2L],[21] and Samlowski 2010[54]), 6 studies included a 1L population (Allen 2005,[8] Merck KGaA 2016,[87] Fields 2011,[86] Santamaria-Barria 2013,[9] Satpute 2014[56] and Voog 1999[67]), and one included both 1L and 2L+ populations (Iyer 2016[88]). The suitability of these studies as comparative data for JAVELIN Merkel 200 is discussed in Section 4.4.

Table 9. Studies from the effectiveness SLR and Appendix 10 assessed for suitability as comparative evidence

	Line	Outcomes	N
Allen 2005[8]	1L	OS	14
Becker 2017 [EU2L][20]	2L+	PFS, OS	34
Merck KGaA 2016 [US1L] [33]	1L	PFS, OS	67
Cowey 2016a [US2L][89]	2L+	PFS, OS	20
Fields 2011[86]	1L	OS	26
Iyer 2016[88]	1L	PFS, OS	32
	2L+	PFS, OS	30
Samlowski 2010[54]	2L+*	PFS, OS	14
Santamaria-Barria 2013[9]	1L	OS	15
Satpute 2014[56]	1L	PFS	13
Voog 1999[67]	1L	OS	101

Abbreviations: 1L, first line; 2L+, second line or above; OS, overall survival; PFS, progression-free survival US1L, United States first line study; US2L, United States second line study; EU2L, European Union second line study; SLR, systematic literature review.

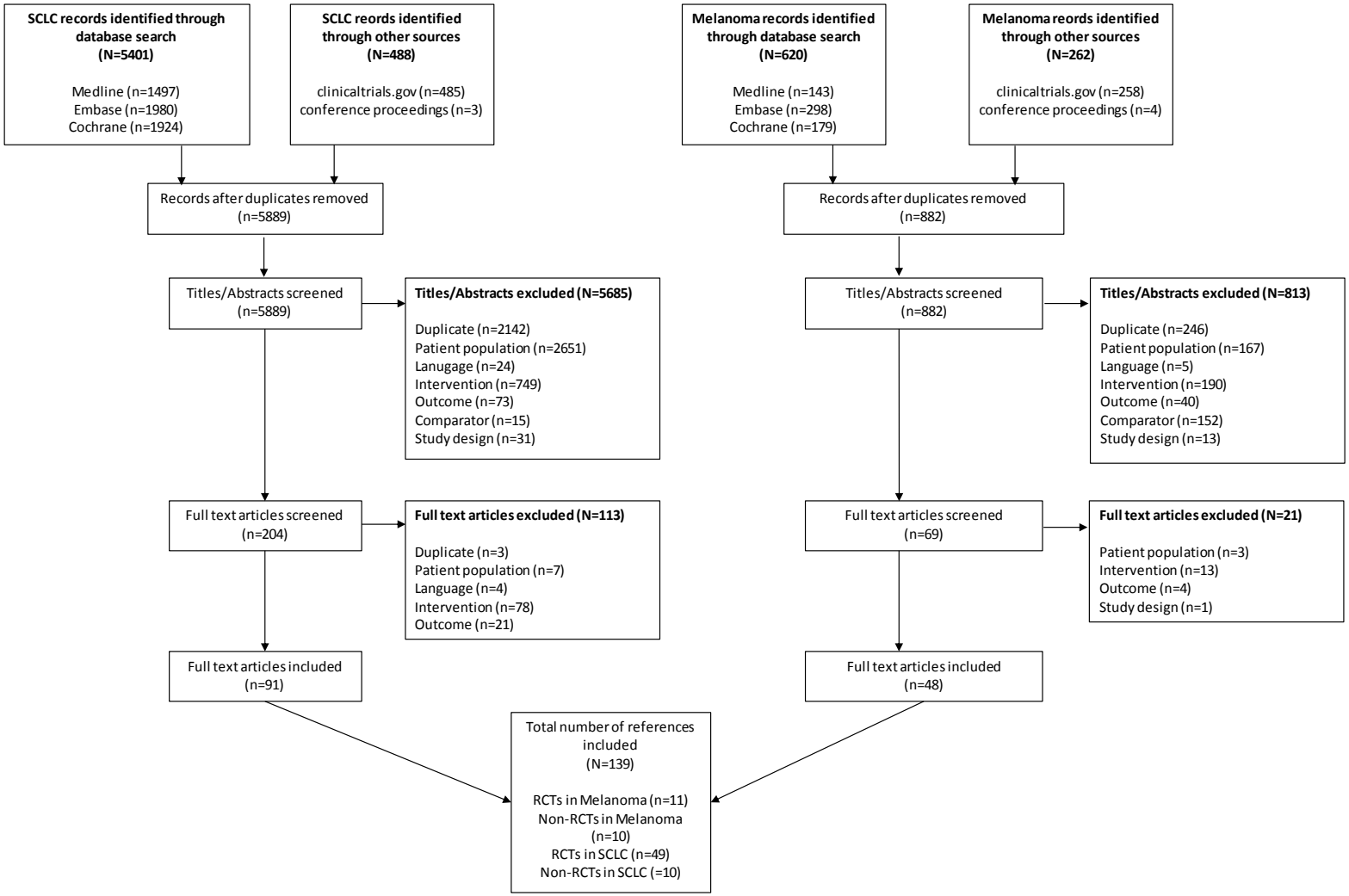
In summary, the ERG is uncertain why the separate search processes described in Appendix 10 were required in addition to the effectiveness SLR described in the CS and Appendix 5, and why the included studies differ. Data extraction forms were not provided. There is a lack of transparency around the process of deciding which study data were included for comparison with JAVELIN Merkel 200 given

the large number of studies identified in the effectiveness SLR; however, the ERG's clinical experts did not highlight that relevant studies have been omitted from the list shown in Table 9.

4.1.3.2 Safety SLR (SCLC and melanoma)

A PRISMA flow diagram is provided illustrating the sifting process for the safety SLR (CS Appendix 14, Figure 2). The diagram shows details of the sift separately for SCLC and melanoma, whereas the text in Appendix 14 combines the two, but the numbers match. Overall, 6,771 titles and abstracts were screened across SCLC and melanoma: 6,021 from the database searches in MEDLINE, Embase and the Cochrane Library (5,401 SCLC and 620 melanoma), 743 from trial registries (485 SCLC and 258 melanoma) and 7 from conferences (3 SCLC and 4 melanoma). Of those screened, 273 full texts were assessed (204 SCLC and 69 melanoma) and 139 were included, relating to 80 studies (59 SCLC[90-142] and 21 melanoma[137, 143-166]).

Figure 4. PRISMA flow diagram for the safety SLR of small cell lung cancer and melanoma (reproduced from CS Appendix 14, Figure 2)



The company provided extraction forms including study design, patient characteristics and adverse event (AE) data for all 80 studies (CS Appendix 14b). The information is also summarised in Tables 19–22 of Appendix 14. However, the CS does not describe in detail the process of selecting study data from this SLR to compare with safety data for avelumab (Section 4.4.6).

In summary, as with the effectiveness SLR, the SLR process is well documented up to the point studies were listed as included but there the process of deciding which study data contributed to the economic modelling is not well described.

4.1.4 Quality assessment

4.1.4.1 Effectiveness SLR

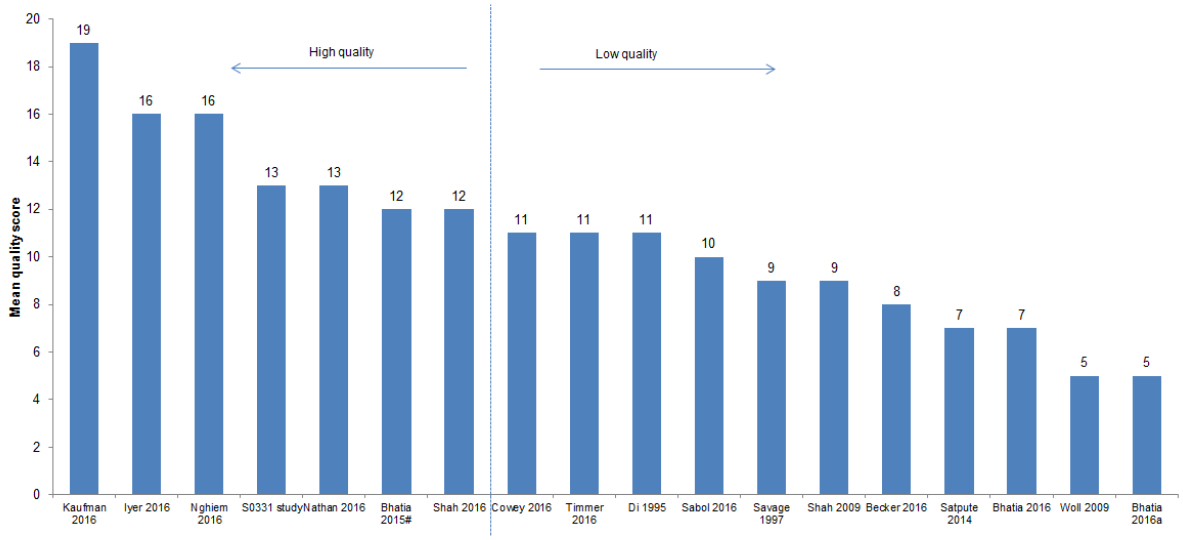
The company used the Downs and Black Checklist[167] to assess 18 cohort studies[3, 20, 30-33, 36, 43, 46, 47, 52, 54, 56, 57, 60, 61, 66, 73] identified in the effectiveness SLR, including the four studies on which the indirect treatment comparison was based. The 26-item checklist was designed to be used for both randomised and non-randomised studies and gives both an overall score and a profile of scores across four domains: reporting (10 items), external validity (3 items), bias (7 items) and confounding (6 items). Each item is rated 0 or 1 and the tool allows for them to be added to provide an overall score.

A separate basic quality assessment for Part A and Part B of JAVELIN Merkel 200 is provided in CS Appendix 8, which is referenced in Section 4.6 of the main CS document (CS, pg. 67). The assessment includes yes/no answers to 10 questions. The tool used is not cited and no reasoning behind the judgements provided, but the ERG broadly agrees with the responses. The ERG provides a full critique of JAVELIN Merkel 200 in Section 4.2.

The company did not quality-assess the 45 other studies listed as included in CS Appendix 5, or the four additional studies mentioned in Appendix 10.[8, 9, 33, 86] The ERG requested full quality assessments for each of the SLR included studies but no additional assessments were provided for the efficacy SLR. The company state that cohorts and single-arm studies were assessed but does not provide a rationale for the decision to omit case series which were part of the original eligibility criteria, or case reports and case series/literature reviews, from the quality assessment. The restrictive approach to quality assessment does not appear to have been predefined and does not give a complete overview of the quality of the evidence base.

An overview of quality assessment ratings for the 18 studies[3, 20, 30-33, 36, 43, 46, 47, 52, 54, 56, 57, 60, 61, 66, 73] that were assessed is provided in CS Appendix 4, Table 6, which shows the 0 or 1 score for each of the item and the total score out of 26 (adapted in Appendix 10.1, Table 81). A graph representing the range of total scores out of 26 was also provided (Figure 5).

Figure 5. Total quality index scores for 18 cohort studies included in the effectiveness SLR (reproduced from CS Appendix 4, Figure 1)



The company cites two papers using a cut-off of 11: one defined below 11 as poor regardless of study type,[168] and the other considered a score of 12 or more to indicate an excellent quality observational studies. The Downs and Black validation paper does not define a cutoff,[167] stating only that the mean score for observational studies was 11.7. The ERG considers there to be no consensus to a reliable cut-off of 11 to indicate poor study quality, particularly as this was not predefined in the SLR inclusion criteria. Mean score for the 18 studies was 10.78, with a median of 11 and a range from 5 to 19. The company's summary of the quality of the 18 studies assessed is given in Box 1. The ERG notes that the company reported "eight studies included patients with mMCC", although as no citations were provided for these studies, the ERG was unable to ascertain the sites of the metastases. The remaining ten studies were reported to include patients with distant metastases.

Box 1. Company summary of the quality assessment of 18 cohort studies in the effectiveness SLR (CS Appendix 4, pages 9–10)

The mean total quality index score on the 26-item Downs and Black checklist of the nine included studies was 10.78 (range: 5.0 to 19). Of the 18 studies, ten studies included patients with distant metastases, while eight studies included patients with mMCC. A quality score of ≤11 was observed in 11 (61.11%) studies, indicating poor study quality.

The study question was specifically stated and well-defined, and intervention of interest was clearly defined in all included studies. A total of 50% of the studies reported adverse events (AEs) that might have been drug-related.

Patient characteristics and study findings were clearly described in all of the included studies; however, characteristics of patients lost to follow-up and estimates of random variability were described in eight of 18 studies (44%).

In terms of external validity provided in the studies, 13 of 18 studies (72% studies) recruited patients from a pool representative of the general population. In terms of internal validity to address bias, the main outcome measures were valid and reliable in all the studies, while methods of "data dredging" (if any) were clearly stated in five of 18 studies (28%). Eight of the included studies clearly stated statistical tests. Only two studies addressed the internal validity for confounding factors (Kaufman 2016; Nghiem 2016).
Abbreviations: mMCC, metastatic Merkel cell carcinoma

The ERG attempted to validate the quality assessments for the four studies (Kaufman 2016,[3] Iyer 2016,[88] Cowey 2016[33] and Becker 2016[20]) forming the basis of the indirect comparison between avelumab and chemotherapy (Section 4.4). The company's assessments are reproduced in Table 10, showing the total scores to be 19 (Kaufman 2016), 16 (Iyer 2016), 11 (Cowey 2016) and 8 (Becker 2016). The ERG notes that the Downs and Black checklist[167] includes several items that do not apply to non-comparative single-arm studies such as JAVELIN Merkel 200 or the retrospective studies used for control data,[20, 33, 88] so has limited confidence in the overall scores as a method of comparing the quality of the four studies. Instead, the ERG provides a narrative quality summary of the studies underpinning the indirect treatment comparison, based on the Downs and Black checklist[167] but accounting for their designs. While no justifications were provided by the company, the ERG broadly agrees with the assessments of items that can be considered relevant to non-comparative studies.

All four studies clearly describe their objectives (item 1), planned outcomes (item 2), population characteristics (item 3) and main findings (item 6), and measured valid and reliable outcomes (item 20). Across all four studies, the company's assessment suggested that while those asked to participate were representative of the whole population (item 11), those who participated were not (items 12). None of the studies included two groups of patients, so standard quality metrics for comparative studies such as randomisation (item 23), allocation concealment (item 24), group comparability (items 17, 21 and 22) and description and adjustment for confounding (items 5 and 25) cannot be assessed. None of the studies attempted to blind patients or those measuring outcomes (items 14 and 15), and only Kaufman 2016[3] reported exact probability values for their findings (item 10). All four studies reported multiple outcomes and subgroup analyses which were not predefined so data dredging and selective reported cannot be ruled out (item 16). The company judged that Becker 2016[20] was the only study of the four not to adequately define the intervention (item 4), report estimates of random variability for the main outcomes (item 7), or be conducted in a context representative of clinical practice (item 13). Similarly, the company judged that Becker 2016[20] and Cowey 2016,[89] publications of the main study used for the chemotherapy comparison in Section 4.4, did not adequately report adverse events (item 8), describe or account for loss to follow-up (item 9 and 26), or use appropriate statistical tests; Kaufman 2016[3] and Iyer 2016[88] were both rated 'yes' for these items.

Table 10. Company's Downs and Black[167] quality assessments of studies constituting the indirect comparison between avelumab and chemotherapy (adapted from CS appendix 4, Table 6)

Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	T
Becker 2016[20]	1	1	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	**8**
Cowey 2016[89]	1	1	1	1	0	1	1	0	0	0	1	0	1	0	0	0	0	0	1	1	0	1	0	0	0	0	**11**
Iyer 2014[43]	1	1	1	1	0	1	1	1	1	0	1	0	1	0	0	0	1	1	1	1	1	0	0	0	0	1	**16**
Kaufman 2016[3]	1	1	1	1	2	1	1	1	1	1	1	0	1	0	0	0	0	1	1	1	1	1	0	0	0	1	**19**

Abbreviations: ID, identifier; T, total score; SLR, systematic literature review; CS, company submission

1: Is the hypothesis/objective of the study clearly described?; 2: Are the main outcomes to be measured clearly described in the introduction or methods section?; 3: Are the characteristics of the patients included in the study clearly described?; 4: Are the interventions of interest clearly described?; 5: Are the distributions of principal confounders in each group of subjects to be compared clearly described? (only item to be scored 0, 1 or 2); 6: Are the main findings of the study clearly described?; 7: Does the study provide estimates of the random variability in the data for the main outcomes?; 8: Have all important adverse events that may be a consequence of the intervention been reported?; 9: Have the characteristics of patients lost to follow-up been described?; 10: Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?; 11: Were the subjects asked to participate in the study representative of the entire population from which they were recruited?; 12: Were those subjects who were prepared to participate representative of the entire population from which they were recruited?; 13: Were the staff, places and facilities where the patients were treated representative of the treatment the majority of the patients receive?; 14: Was an attempt made to blind study subjects to the intervention they received?; 15: Was an attempt made to blind those measuring the main outcomes of the intervention?; 16: If any results of the study were based on "data dredging" was this made clear?; 17: In trials and cohort studies, do the analyses adjust for different lengths of follow up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?; 18: Were the statistical tests used to assess the main outcomes appropriate?; 19: Was compliance with the interventions reliable?; 20: Were the main outcomes measures used accurate (valid and reliable)?; 21: Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case control studies) recruited from the same population?; 22: Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case control studies) recruited over the same period of time?; 23: Were study subjects randomized to intervention groups?; 24: Was the randomized intervention assignment concealed from both patients and healthcare staff until recruitment was complete and irrevocable?; 25: Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?; 26: Were losses of patients to follow-up taken into account?

Overall, the company provide quality assessments of only 18 of the 63 studies listed as included for the effectiveness SLR, including the four studies on which the indirect treatment comparison is based[3, 20, 88, 89]. The type of studies assessed was not predefined and the use of the total score may be misleading because items cannot be assumed to have equal weighting, and there appears to be no consensus for an 11/26 cut-off to indicate poor study quality. The Downs and Black checklist[167] may not be an appropriate assessment tool for the four studies underpinning the indirect comparison because they are non-comparative, but the ERG generally agrees with the judgments provided; Cowey 2016[89] and Becker 2016[20] may be considered to be lower methodological quality than Kaufman 2016[3] and Iyer 2016[88].

4.1.4.2 Safety SLR (SCLC and melanoma)

Quality assessments were not initially provided for studies included in the safety SLR. From the data extraction tables provided by the company, the ERG noted that, within the 21 melanoma studies,[137, 143-166] around half were non-randomised and were either open-label or had unknown blinding status (for randomisation: 11 randomised, 4 not applicable, 3 non-randomised, 2 single-arm, 1 non-randomised and randomised cohort; for blinding: 7 not applicable, 6 open-label, 4 double-blind, 3 not reported, and 1 open-label and double-blind depending on the comparison); within the 59 SCLC studies,[90-141] the majority were randomised and either open-label or unclassified for blinding (for randomisation: 49 randomised, 4 not reported, 4 not applicable, 2 non-randomised; for blinding: 39 not reported, 14 open-label, 4 not applicable, 2 blinded or single-blind).

Structured quality assessments were provided by the company at the clarification stage, separately for melanoma and SCLC RCTs and non-RCTs (Appendix 10.1, Table 82, Table 83, Table 84, Table 85). The number of studies assessed do not match the number of RCTs and non-RCTs for melanoma and SCLC detailed in Figure 4.

Table 82 and Table 83 (Appendix 10.1) show the quality assessment of 12 melanoma RCTs[143-145, 147, 152-154, 156-159, 163] (11 listed as included in Figure 4) and 48 SCLC RCTs[90, 92-99, 102-106, 108-121, 123-129, 132, 133, 135, 137-139, 141, 142, 164-166, 169] (49 listed as included in Figure 4), respectively from the safety SLR. The company state that the assessments were conducted according to criteria suggested by NICE, which the ERG notes broadly reflect the Cochrane Risk of Bias Tool.[170] Studies were rated as Yes (low risk of bias), No (high risk of bias) or Not Clear to 7 domains: randomisation, allocation concealment, baseline comparability, blinding, dropout between groups, more outcomes than reported and intention to treat. Across the melanoma RCTs, the most common issues were lack of blinding (5 studies), imbalanced dropout (5 studies) and selective reporting (7 studies). Across the SCLC RCTs, there was far more uncertainty and more domains rated as high risk of bias, particularly in the allocation concealment, blinding, dropout, selective reporting and intention-to-treat domains. The company did not provide

justifications for the RCT assessments. Overall, the ERG considers the body of RCTs included in the safety SLR to be of relatively low quality.

Table 84 and Table 85 (Appendix 10.1) show the quality assessment of 9 melanoma non-RCTs[146, 148-151, 155, 160-162] (10 listed as included in Figure 4) and 12 SCLC non-RCTs[91, 100, 101, 104, 107, 108, 122, 130, 131, 134, 140] (10 listed as included in Figure 4), respectively from the safety SLR. The assessments were based on a 27-item version of the Downs and Black checklist[167] used in the effectiveness SLR. Within the melanoma non-RCTs, total scores ranged from 3 to 17 out of 27; the mean score was 9.9 and the median score was 11. Within the SCLC non-RCTs, total scores ranged from 8 to 17, with a mean score of 11.7 and median of 11.

4.1.5 Evidence Synthesis

Comparative estimates of overall survival (OS) and progression-free survival (PFS) for avelumab against the comparators listed in the NICE final scope[1] were by naïve comparison. In the clinical effectiveness section of the CS, the company use its own observational study evidence for comparison with JAVELIN Merkel 200, whereas additional evidence identified in Appendix 10 (Table 9) were also used to inform clinical effectiveness in the economic model.

The company state that the naïve comparison is justified because patient characteristics were not found to be prognostic of outcome, based on a series of regression analyses; this is discussed further in Section 4.4 (CS Appendix 10). At the clarification stage, the ERG requested that a matched adjusted indirect comparison (MAIC) be conducted, which is discussed further in Section 4.4.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

As discussed in Section 4.1, the company's SLR identified one study,[3] JAVELIN Merkel 200 (EMR100070-003), an ongoing study which aims to evaluate the safety and efficacy of avelumab in adults with mMCC. JAVELIN Merkel 200 is a multicentre, international, prospective, single-group, open-label, Phase II study to evaluate the efficacy and safety of avelumab in patients with mMCC. Study sites for JAVELIN Merkel 200 are spread across sites in North America, Europe, Australia and Asia; however, the ERG notes that there are no patients recruited from UK sites.

JAVELIN Merkel 200 comprises of two independent parts: Part A which included patients with metastatic MCC who had failed at least one prior line of chemotherapy (referred to from here-in as the second-line plus [2L+] or treatment-experienced cohort) and Part B which included patients with no prior therapy (referred to from here-in as the first-line [1L] or treatment-naïve cohort). The key features of each phase of JAVELIN Merkel 200 are summarised in Table 11 and each part is discussed in more detail in the subsections of Section 4.2 below. In general, the two parts of JAVELIN Merkel 200 were

similar, both had the same intervention and similar outcomes assessed although the two parts differed in their patient populations and primary objectives.

Table 11. Summary of the key features of Part A and Part B of JAVELIN Merkel 200 (adapted from the CS page 51, Table 9)

Trial no. (acronym)	JAVELIN Merkel 200 – 2L+ cohort (Part A) (EMR100070-003)	JAVELIN Merkel 200 – 1L cohort (Part B)* (EMR100070-003)
Phase	Phase II	Phase II
Objective	The primary objective is to assess the clinical activity of avelumab as determined by the ORR according to RECIST 1.1 by an IERC in patients with metastatic MCC after failing 1L chemotherapy	The primary objective is to evaluate the clinical activity of avelumab as 1L treatment for metastatic or distally recurrent MCC as determined by the DRR according to RECIST 1.1 by an IERC
Population	Patients must have histologically proven metastatic MCC and must have received at least one line of chemotherapy in the metastatic setting.	Patients must have histologically proven metastatic MCC and must be treatment-naïve to systemic therapy in the metastatic setting.
Intervention	Avelumab 1h IV infusion, 10 mg/kg, once every 2 weeks, until therapeutic failure, unacceptable toxicity, or any criterion for withdrawal from the trial or the trial drug is fulfilled. Premedication with an antihistamine and with paracetamol is required 30-60 minutes prior to each dose of avelumab for the first four infusions and subsequently as needed.	Avelumab 1h IV infusion, 10 mg/kg, once every 2 weeks, until therapeutic failure, unacceptable toxicity, or any criterion for withdrawal from the trial or the trial drug is fulfilled. Premedication with an antihistamine and with paracetamol is required 30-60 minutes prior to each dose of avelumab for the first four infusions and subsequently as needed.
Comparator	None (single-arm study)	None (single-arm study)
References	Primary reference: (Kaufman 2016c) Secondary references: (Merck KGaA 2016h; Merck KGaA 2016e; Merck KGaA 2017b; Kaufman 2017; Kaufman 2016a)	Primary reference: (D'Angelo 2017) Secondary references: (Merck KGaA 2017c; Merck KGaA 2016c)

*Recruitment is currently ongoing
Abbreviation: 1L: First-line; 2L+: Second-line and further; DRR: Durable response rate; IERC: Independent Endpoint Review Committee; IV: Intravenous; MCC: Merkel cell carcinoma; N/A: Non-applicable; ORR: Objective response rate; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1

4.2.1 Trial conduct

4.2.1.1 JAVELIN Merkel 200 2L+ cohort (Part A)

Part A of JAVELIN Merkel 200 (2L+ cohort) commenced on 25 July 2014 and follow-up is currently ongoing, although recruitment has been completed. There are 88 patients in the 2L+ cohort and the data presented in the CS are based on the most recent data which comprises a minimum of 18 months follow-up for all patients (24 March 2017 data-cut), in addition to 6-month (conducted 6 months after the accrual of the last patient) and 12-month (conducted 12-month after the accrual of the last patient) follow-up analyses.[3, 171, 172] The company also reported in the CS that a data cut with a minimum of 24-month follow-up is planned for [redacted] and the estimated study completion date for JAVELIN Merkel 200 Part A is 30 June 2025.

The inclusion and exclusion criteria for JAVELIN Merkel 200 Part A are summarised in Table 12 and the ERG's clinical experts report that, with the exception of excluding patients with immunosuppression, they appear reasonable. The ERGs clinical experts consider that some immunosuppressed patients may be eligible for avelumab and the omission of these patients from the JAVELIN Merkel 200 trial makes it difficult to assess whether they would have any difference in efficacy or safety compared to immunocompetent patients treated with avelumab. In addition, performance status (PS) was restricted to patients with a Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, whereas the ERGs clinical experts report that some patients with an ECOG PS of 2 may be suitable for avelumab therapy. It should be noted that the key difference between the inclusion criteria for Part A and Part B of JAVELIN Merkel 200 is that Part A comprised of 2L+ patients whereas Part B was restricted to 1L patients.

The intervention in Part A of JAVELIN Merkel 200 was avelumab and this was dosed in an identical way to that in Part B and was in keeping with the anticipated marketing authorisation. The company reported that medications (other than those excluded by the clinical study protocol) that were considered necessary for the patients' welfare and would not interfere with avelumab could be given at the Investigator's discretion although no further details on the number of patients impacted by this criterion were provided, nor what concomitant drugs were taken during the study.

Treatment with avelumab was continued in the study until "significant clinical deterioration", of which reasons included:

- Therapeutic failure (patients may stay on treatment beyond observation of progressive disease provided there was no significant clinical deterioration);
- Unacceptable toxicity;
- Withdrawal of consent; and
- Other protocol-specified criteria for withdrawal from the study or study drug.

Patients in JAVELIN Merkel 200 Part A who experienced a confirmed CR according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1[173] could be treated for a maximum of 12 months and a minimum of 6 months after confirmation, at the discretion of the Investigator. However, it was reported in the CS that if the Investigator believed a patient could benefit from treatment beyond 12 months, it was permissible after discussion with the Sponsor. In addition, if a patient with a confirmed CR relapsed after stopping treatment, but prior to the end of the study, one re-initiation of treatment was allowed at the discretion of the Investigator and agreement of the Medical Monitor. No details were provided in the CS of the number of patients affected by these criteria and so the ERG is

unclear as to whether they may have impacted the results. The ERG's clinical experts reported that treatment beyond 12 months is likely to be standard clinical practice with avelumab in England in the absence of clinical trial data or guidance to suggest that it should be stopped earlier. The ERG considers that allowing patients with a CR to restart avelumab during the trial if they had a relapse may be the equivalent of using avelumab at a further line of therapy and clinical experts reported that this would possibly occur in clinical practice in England. However, the ERG is concerned that the inclusion of these data in the analyses may confound the results and subgroup analyses excluding these patients should ideally have been presented to rule out this possibility.

The primary endpoint of JAVELIN Merkel 200 Part A was confirmed best overall response (BOR) which was defined as a combination of CR or partial response (PR) according to RECIST Version 1.1, as determined by an Independent Endpoint Review Committee (IERC), that was obtained from the start of the study drug (i.e. avelumab) until documented disease progression, which was assessed every 6 weeks. The secondary and tertiary outcomes along with the exploratory outcomes and pre-planned subgroup analyses are summarised in Table 12.

Table 12. Summary of key methodological features of JAVELIN Merkel 200 Part A (2L+) (adapted from CS page's 53-58, Table 10)

	JAVELIN Merkel 200 Part A
Key eligibility criteria for participants	Enrolled patients must have received at least one line of chemotherapy for the treatment of metastatic MCC. Eligible patients were enrolled before treatment start, after verification of fulfilling all inclusion criteria and without matching any exclusion criteria. The key eligibility criteria for the study were: • Adults aged ≥18 years • Estimated life expectancy of more than 12 weeks • At least one unidimensional measurable lesion by RECIST 1.1 • Histologically proven Stage IV MCC • At least one prior line of chemotherapy and progression after the most recent line of chemotherapy • Prior adjuvant therapy allowed • Patients with HIV, immunosuppression, or haematologic malignancies, and previous solid organ transplant recipients were excluded • Naïve to therapies targeting T-cell co-regulatory proteins (i.e. immune checkpoint inhibitors), concurrent anticancer treatment, or systemic treatment with corticosteroids or other immunosuppressive drugs • No previous vaccinations for prevention of infectious disease within 4 weeks of trial drug administration or while on trial (with the exception of inactivated vaccines) • Unselected for PD-L1 expression or MCPyV status • ECOG PS 0-1 and adequate haematological, hepatic, and renal function
Primary outcomes	The primary endpoint of the trial was confirmed BOR, defined as CR or PR according to RECIST 1.1, as determined by an IERC. The confirmed BOR was defined as the best response obtained among all tumour assessment visits after the start of the study treatment until documented disease progression, excluding assessments after start of subsequent anticancer therapy, taking the following requirements for confirmation into account: • CR or PR needed to be confirmed at a subsequent tumour assessment, preferably 6 weeks after the initial observation of response and according to the

	normal 6-week assessment schedule but no sooner than 5 weeks after the initial documentation of CR or PR • PR could be confirmed at an assessment later than the next assessment after the initial documentation of PR • The minimum duration for a BOR of SD was defined as at least 6 weeks after start of study treatment.
Secondary/ tertiary outcomes	• DoR according to RECIST 1.1 (defined as the time from first documented CR or PR until documented PD or death, whichever occurred first) as determined from IERC tumour assessments • PFS time (defined as the time from the first administration of avelumab until documented PD or death, whichever occurred first), according to RECIST 1.1, as determined by an IERC • Occurrence and severity of TRAEs according to NCI-CTCAE v4.0 • OS time (from first administration of avelumab until the date of death) • Response status according to RECIST 1.1 at 6 months and 12 months after start of study treatment • Serum titers of anti-avelumab antibodies • Population PK profile (sparse sampling)
Exploratory outcomes	• BOR, duration of response, and PFS per Investigator assessment • irBOR and irPFS according to modified irRC, respectively, per Investigator assessment • TTP under last prior anticancer therapy • Tumour shrinkage in target lesions per time point from baseline • Expression of PD-L1 in tumour tissue • Expression of CD8 in tumour tissue • Expression of MCPyV in tumour tissue • Changes in soluble factors (e.g. cytokine profiles) • Changes in MCPyV-specific humoral responses • Changes in EQ-5D and FACT-M scores over the treatment period • Description of effects of avelumab treatment as perceived and reported in interviews by patients with metastatic MCC
Pre-planned subgroups*	Objective response by: • Age (Group 1: <65 years, ≥65 years; Group 2: ≤Median, >Median) • Gender (male, female) • Pooled region (North America, Europe, Rest of World) • Time from initial diagnosis to study entry (≤1 year, >1 year and ≤2 years, >2 years) • Site of primary tumour (skin, non-skin) • Visceral metastases at baseline (present, absent) • Disease burden at baseline (Baseline SLD ≤median, Baseline SLD >median) • Baseline ECOG PS (ECOG PS 0, ECOG PS 1) • Number of previous systemic treatments for metastatic disease (n=1, n≥2) • Number of previous systemic therapies for metastatic disease or locally advanced therapies (n=1, n≥2) • Tumour PD-L1 cell expression at cut-off of 1% (PD-L1 expression <1%, PD-L1 expression ≥1%) • Tumour PD-L1 cell expression at cut-off of 5% (PD-L1 expression <5%, PD-L1 expression ≥5%) • Tumour MCPyV status by IHC and by PCR (positive, negative) • Combination of PD-L1 expression (cut-off of 1%) and IHC MCPyV status (PD-L1+/MCPyV+, PD-L1+/MCPyV-, PD-L1-/MCPyV+, PD-L1-/MCPyV-)
*JAVELIN Merkel 200 was not powered for any subgroup analysis and as such all analyses were exploratory in nature. Abbreviations: AE: Adverse event; BOR: Best overall response; CR: Complete response; DoR: Duration of response; ECOG PS: Eastern Cooperative Oncology Group performance score; EQ-5D: EuroQol-5 dimensions; FACT-M: Functional Assessment of Canter Therapy – Melanoma; HIV: Human immunodeficiency virus; IERC: Independent Endpoint Review	

Committee; IHC: Immunohistochemistry; irBOR: Immune-related best overall response; irPFS: Immune-related progression-free survival; irRC: Immune-related response criteria; ITT: Intent-to-treat; IV: Intravenous; MCC: Merkel cell carcinoma; MCPyV: Merkel cell polyomavirus; N/A: Non-applicable; NCI-CTCAE: National Cancer Institute-Common Technology Criteria for Adverse Events; ORR: Objective response rate; OS: Overall survival; PCR: Polymerase chain reaction; PD: Progressive disease; PD-L1: Programmed death ligand-1; PFS: Progression-free survival; PK: Pharmacokinetics; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SD: Stable disease; SLD: Sum of the longest diameter; TRAE: Treatment-related adverse event; TTP: Time to progression.

A PRISMA flow diagram was presented in the CS to show the flow of patients through JAVELIN Merkel 200 Part A, although the ERG notes from the clinical study report (CSR) that it referred to the primary analysis that was conducted at 6 months (3 March 2016) rather than the ≥18 months follow-up (24 March 2017) analysis that was the data source used in the CS. The ERG therefore does not consider the PRISMA diagram relevant. The company also provided a table in the CS that summarised the patient flow and reasons for treatment discontinuation for the ≥18 months follow-up analyses (Table 13). In summary, 125 patients were enrolled and screened although only 88 patients went on to receive at least one dose of avelumab. The 88 patients who received avelumab were included in the intention-to-treat (ITT) and safety analyses. At ≥18 months follow-up, [redacted] of patients were continuing on active treatment and the most common reason for treatment discontinuation was disease progression (42 patients, 47.7%).

Table 13. Patient disposition in JAVELIN Merkel 200 - 2L+ cohort (Part A) – 18-month follow-up (adapted from CS page 64, Table 14)

Disposition	Avelumab N=88
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

*One patient discontinued treatment due to treatment-related Grade 1 creatinine elevation, which occurred after the treatment-emergent period and followed an event of Grade 2 treatment-related acute intestinal nephritis

The ERG notes that there were no details provided in the CS of the subsequent treatments (if any) used by patients discontinuing avelumab and considers this important as any subsequent therapies received could confound the results for overall survival.

4.2.1.2 JAVELIN Merkel 200 1L cohort (Part B)

Part B of JAVELIN Merkel 200 was added as a protocol amendment to investigate avelumab in treatment-naïve patients (1L) as it was anticipated that treating mMCC earlier in the disease would yield better response rates and a better prognosis for patients. Part B was started on 15 April 2016 and

recruitment is currently ongoing (target n=112) and the estimated study completion date is 30 June 2025. The data presented in the CS are from a pre-planned interim analysis of a data-cut from 24 March 2017 (n=39), which was used for three analyses; efficacy for patients with ≥3-month follow-up (n=29); patients with 6-month follow-up (n=14); efficacy and safety endpoints for the full 39 patients. Part B of JAVELIN Merkel 200 is being conducted only in the USA and Europe and there are no UK study centres.

Entry into JAVELIN Merkel 200 Part B was restricted to adults aged 18 years or older who were treatment-naïve to systemic therapy for metastatic MCC defined as, "No prior therapy with any antibody/drug targeting T-cell coregulatory proteins such as anti-PD-1, anti-PD-L1, or anti-Cytotoxic T-lymphocyte-associated (CTLA) protein-4 antibody", and receiving no concurrent anticancer treatments. The ERGs clinical experts reported that as for Part A of JAVELIN Merkel 200, the inclusion and exclusion criteria for JAVELIN Merkel 200 Part B were in keeping with the expected patients in England whom would potentially be eligible for avelumab, except for immunosuppressed patients and those with an ECOG PS of 2 who may also be eligible for avelumab.

Administration of avelumab in the JAVELIN Merkel 200 1L cohort was in accordance with the anticipated European marketing authorisation, although treatment for patients who experienced a complete response (CR) could be treated for a maximum of 12 months after confirmation of the CR, at the discretion of the Investigator. If the Investigator believed that a patient could benefit from treatment beyond 12 months, it was permissible after discussion with the Sponsor. The ERG's clinical experts report that patients in the UK who receive avelumab are likely to continue beyond 12 months if they remain in remission as the marketing authorisation is not expected to include any stopping rules for these patients tolerating the drug and so in clinical practice it would be an individual patient-physician level decision as to when to withdraw treatment. The ERG is unclear if patients in JAVELIN Merkel 200 had treatment withdrawn from them at 12 months (if treatment had not otherwise been discontinued for protocol-driven reasons like adverse events or progression) and, if so, whether their outcomes would differ from those patients that continued treatment beyond 12 months.

The primary endpoint in JAVELIN Merkel 200 Part B was durable response which was defined as an objective response (CR or PR) according to RECIST version 1.1, determined by IERC, with a duration of at least 6 months. The secondary endpoints of JAVELIN Merkel 200 were not explicitly reported in the CS although additional exploratory endpoints were described (Table 14). Data for the outcomes of importance to the NICE final scope[1] were however included (with the exception of HRQoL) and so the ERG assumes that they were secondary outcomes in the study. In addition, there were a large number of pre-planned subgroup analyses for JAVELIN Merkel 200 Part B for the outcome of objective response according to various patient baseline characteristics (Table 14).

Table 14. Summary of exploratory outcomes and pre-planned subgroups specific to JAVELIN Merkel 200 – 1L cohort (Part B) (adapted from CS page's 59-60, Table 11)

	JAVELIN Merkel 200 – 1L cohort (Part B)
Exploratory outcomes	• Correlate immunogenicity of avelumab with clinical results (ORR and AEs) • Tumour shrinkage in target lesions at each time point from baseline • Changes in biomarkers in relation to disease responses to avelumab • Association between tumour PD-L1 expression and BOR • Benefits of avelumab treatment as perceived by patients with metastatic MCC
Pre-planned subgroups*	Objective response by: • Age (Group 1: <65 years, ≥65 years; Group 2: ≤Median, >Median) • Gender (male, female) • Race (Caucasian/White, Asian, Black/African American, Other) • Pooled region (North America, Europe, Asia, Rest of World) • Time from initial diagnosis to study entry (≤1 year, >1 year and ≤2 years, >2 years) • Site of primary tumour (skin, non-skin) • Visceral metastases at baseline (present, absent) • Lymph node disease only at baseline (yes, no) • Baseline CD8 T-cell density (<median, ≥median) • Number of previous systemic chemotherapies (n=0, n≥1) • Tumour PD-L1 cell expression at cut-off of 1% (PD-L1 expression <1%, PD-L1 expression ≥1%) • Tumour PD-L1 cell expression at cut-off of 5% (PD-L1 expression <5%, PD-L1 expression ≥5%) • Tumour MCPyV status by IHC and by PCR (positive, negative) • Combination of PD-L1 expression (cut-off of 1%) and IHC MCPyV status (PD-L1+/MCPyV+, PD-L1+/MCPyV-, PD-L1-/MCPyV+, PD-L1-/MCPyV-)
*JAVELIN Merkel 200 was not powered for any subgroup analysis and as such all analyses were exploratory in nature. Abbreviations: AE: Adverse event; BOR: Best overall response; CR: Complete response; IERC: Independent Endpoint Review Committee; IHC: Immunohistochemistry; ITT: Intent-to-treat; MCC: Merkel cell carcinoma; MCPyV: Merkel cell polyomavirus; N/A: Not applicable; ORR: Objective response rate; PCR: Polymerase chain reaction; PD-1: Programmed death protein-1; PD-L1: Programmed death ligand-1; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1	

The patient flow in the interim analysis presented in the CS of Part B of JAVELIN Merkel 200 was described narratively and for the patients in the ≥3 months analyses further detail was provided in a table in the CS (Table 15). In summary, 52 patients were screened for participation in the 1L cohort (Part B) with only 39 patients receiving at least one dose of avelumab and included in the intent-to-treat (ITT) and safety analysis sets. Of the 13 patients who did not receive study medication the reasons were as follows: pre-defined eligibility criteria not met (n=11), adverse event (AE; n=1), and other (n=1). Out of the 39 patients in the ITT population, there were [redacted] patients [redacted] still on avelumab at ≥3 months. The reasons for treatment discontinuation in the [redacted] patients [redacted] who were no longer receiving avelumab at the time of data cut-off are reported in Table 15.

Table 15. Patient disposition in JAVELIN Merkel 200 - 1L cohort (Part B) – minimum follow up of 13 weeks (adapted from CS page's 66, Table 16)

Disposition	**Avelumab N=39 (%)**
Patients continuing in treatment period	[redacted] ([redacted]
Reason for discontinuation of treatment	

Disposition	Avelumab N=39 (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The ERG notes that there were no details provided in the CS of the subsequent treatments (if any) used by patients discontinuing avelumab and considers this important as any subsequent therapies received could confound the results for overall survival.

4.2.2 Baseline characteristics

4.2.2.1 JAVELIN Merkel 200 2L+ cohort (Part A)

The baseline characteristics of the 2L+ cohort of JAVELIN Merkel 200 are reported in Table 16. The ERG notes that the median age of the 2L+ patients of 72.5 years is reported by its clinical experts to possibly be slightly younger than expected in clinical practice in England (approximately 75 years). The ERG also notes that the median age of the 2L+ population is [redacted] (72.5 years versus [redacted] years, respectively). The ERG's clinical experts also reported that the Eastern Cooperative Oncology Group performance score (ECOG PS) of patients was slightly better than expected in clinical practice in England, with more patients expected to be ECOG 1 and some ECOG 2 at second and third line or beyond. The ERG's clinical experts also considered that patients in England rarely get active treatment beyond second line and those that do are unlikely to progress beyond third line treatment. In addition, they reported that patients at later lines of therapy generally have worse ECOG PS and are less able to tolerate the side effects of therapies and so are more likely to have worse outcomes. The ERG notes that 30.7% of patients in JAVELIN Merkel 200 Part A were at third line therapy and 4.5 % of patients were fourth line and beyond. The ERG considers that subgroups by line of therapy would be useful and that the efficacy for the whole 2L+ population may be underestimated for the equivalent 2L population in England likely to receive avelumab.

Table 16. Baseline characteristics of 2L+ patients in JAVELIN Merkel 200 (adapted from CS page 64-66, Table 15 and CQ response A8)

Baseline characteristic	***JAVELIN Merkel 200 – 2L+ cohort (Part A)***
	Avelumab (N=88)
Age <65 years, n (%) ≥65 year, n (%) Median, years (range)	 22 (25.0) 66 (75.0) 72.5 (33-88)
Gender, n (%) Male Female	 65 (73.9) 23 (26.1)

Baseline characteristic	***JAVELIN Merkel 200 – 2L+ cohort (Part A)***
	Avelumab (N=88)
ECOG PS, n (%)	
0	49 (55.7)
1	39 (44.3)
Weight (kg)	
Median (range)	82.85 (47-153)
Region, n (%)	
North America	51 (58.0)
Europe	29 (33.0)
Rest of world	8 (9.1)
Site of primary tumour, n (%)	
Skin	67 (76.1)
Lymph node	12 (13.6)
Other	2 (2.3)
Missing	7 (8.0)
Metastatic involvement at study entry, n (%)	
Yes	88 (100.0)
No	0 (0.0)
Number of prior systemic cancer therapies received, n (%)	
1	52 (59.1)
2	26 (29.5)
≥3	10 (11.4)
Number of prior systemic cancer therapies received for metastatic disease, n (%)	
1	57 (64.8)
2	27 (30.7)
≥3	4 (4.5)
Prior anticancer therapy, n (%)	
Chemotherapy for metastatic disease	88 (100.0)
Chemotherapy for non-metastatic disease	3 (3.4)
Antibody therapy	1 (1.1)
Experimental T cell co-regulator therapy	1 (1.1)
Kinase inhibitors	3 (3.4)
Other	4 (4.5)
Prior chemotherapy for metastatic disease, n (%)	
Etoposide	61 (69.3)
Carboplatin	45 (51.1)
Cisplatin	25 (28.4)
Doxorubicin	9 (10.2)
Visceral disease at study entry, n (%)	
Present	47 (53.4)
Absent	41 (46.6)
Lymph node disease only at study entry, n (%)	
Yes	19 (21.6)
No	69 (78.4)
Sum of target lesion diameters (SLD) at baseline	
Median SLD, mm (range)	79 (16-404)
Tumour PD-L1 expression, n (%)[+]	
PD-L1+	58 (65.9)
PD-L1-	16 (18.2)
Not evaluable	14 (15.9)

Baseline characteristic	*JAVELIN Merkel 200 – 2L+ cohort (Part A)*
	Avelumab (N=88)
Tumour MCPyV status, n (%) MCPyV+ MCPyV- Not evaluable	 46 (52.3) 31 (35.2) 11 (12.5)
Median tumour size	1.8cm; range: 0.6-17.0cm
*Not-evaluable included those data that were missing, of poor quality, or otherwise not available to provide results +Determined in post-hoc analysisFA Abbreviations: CQ, clarification questions; ECOG PS: Eastern Cooperative Oncology Group performance status; MCPyV: Merkel cell polyomavirus; PD-L1: Programmed death ligand-1	

4.2.2.2 JAVELIN Merkel 200 1L cohort (Part B)

The baseline characteristics of the 1L cohort of JAVELIN Merkel 200 are reported in Table 17. The median age of the 1L patients enrolled in JAVELIN Merkel 200 Part B was [redacted] years. According to the company's clinical experts this [redacted] The ERG's clinical experts reported that the gender split [redacted] and the ECOG PS was [redacted] The ERG does however consider that as the study doesn't have any UK centres, issues of generalisability are critical in terms of interpreting the appropriateness of the results to the population of England.

Table 17. Baseline characteristics of 1L patients in JAVELIN Merkel 200 (adapted from CS page 67, Table 17 and CQ response A9)

Baseline characteristic	*JAVELIN Merkel 200 – 1L cohort (Part B)*
	Avelumab (N=39)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: CQ, clarification questions; CS, company submission; ECOG PS: Eastern Cooperative Oncology Group performance status

4.2.3 Description and critique of statistical approach used

4.2.3.1 JAVELIN Merkel 200 2L+ cohort (Part A)

The primary endpoint of JAVELIN Merkel 200 Part A was BOR according to RECIST 1.1, based on independent review of tumour assessments. The overall response rate (ORR) was the proportion of patients with a confirmed BOR of PR or CR. The null hypothesis was that the ORR was less than or equal to 20% based on an exact binomial test. The planned sample size was 84 patients and 88 patients were included in the ITT analysis12-month ORR was. The sample size calculation assumed an ORR of 35% and an overall alpha of 0.025 (1-sided) for the test of the null hypothesis of an ORR ≤20%. The analysis had a power to reject the null hypothesis at the interim or the primary analysis of approximately 87%.

The same as for Part B of the study, efficacy analyses were conducted using the ITT population which was defined as all patients who received ≥1 dose of study treatment. It is reported in the CS that there was an interim analysis for futility after 20 patients had been enrolled and observed for at least 3 months, and a further interim analysis for efficacy at 6 months after 56 patients had been enrolled. The primary analysis was planned to be 6 months after the final patient was enrolled. Further exploratory analysis of secondary and additional outcomes was conducted 12 months after the enrolment of the final patient. The ERG notes that analyses reported in the CS also include 18-month follow-up and that it was reported further in the CS that further data cuts are expected in 2017 and 2018.

The Clopper-Pearson method was used to calculate the 2-sided CI for the ORR at both the interim and the primary analyses. DoR, PFS and OS were analysed with K-M methods and median values calculated with corresponding 2-sided CIs using the Brookmeyer-Crowley method.

As for Part B, Statistical Analysis Software (SAS) version 9.2 (or higher) was used for the statistical analysis, and R software package version 2.15.2 was used for the sample size calculations. In addition,

data were evaluated as observed with no imputation method for missing values, unless otherwise specified.

Tumour response was based on the IERC assessment of overall response at each time point and DoR was censored at the date of the last adequate tumour assessment. The last recorded date that a patient was known to be alive was used for censoring OS, and PFS was censored on the date of the last adequate tumour assessment in patients with no progressive disease (PD) or death. Patients who had no tumour assessments during the trial and whom did not die were censored on the date of first study treatment.

Two health-related quality of life questionnaires were utilised during JAVELIN Merkel 200, EQ-5D and FACT-M. Both the EQ-5D and FACT-M tools [redacted] In addition, optional patient interviews were undertaken to gather further HRQoL data.

Safety analyses were performed using the safety analysis set and included a review of the incidence of TEAEs, and assessments of changes in vital signs, ECGs, body weight, and laboratory values

4.2.3.2 JAVELIN Merkel 200 1L cohort (Part B)

The primary endpoint of JAVELIN Merkel 200 Part B was durable response, defined as an objective response (of CR or PR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and determined by an Independent Endpoint Review Committee (IERC), with a duration of at least 6 months. The company reported that the planned total sample size for Part B was 112 patients and the sample size calculation was based on the assumption that there was, "a DRR of 45% (the probability to observe lower bound of 95% CI above 20% would be >99% and above 30% would be 90%)". The ERG notes that only 39 patients are included in the 1L data provided in the CS and recruitment is ongoing. This value of 39 is substantially lower than the 112 required by the sample size calculation and thus the analyses reported in the CS for this 1L cohort are underpowered.

The ERG notes that for the analyses of efficacy the ITT population was used, which comprised all patients who received ≥1 dose of study treatment. There was one exploratory interim analysis and one primary analysis planned for JAVELIN Merkel 200 Part B: the interim analysis was scheduled for 3 months after the 25th patient received the first dose of avelumab; the primary analysis was planned to be 15 months after the last enrolled patient received their first dose of avelumab. The ERG notes that the primary analysis is yet to be conducted. The ERG also notes that the analyses presented in the CS utilise the patients enrolled at the data cut-off date in March 2017 (n=39) with at least 3 months' follow-up (n=29) and at least 6-months follow-up (n=14). In addition, the company reported that analyses for efficacy and safety endpoints for the full 39 patients were done using the March 2017 data set although

these are not discussed in the CS. A further data cut comprising a minimum of 50 patients with ≥3-months follow-up is planned for [redacted] with additional data cuts expected in 2018.

In terms of statistical methods, it is reported that SAS version 9.2 was used for the statistical analysis, and the R software package version 2.15.0 was used for the sample size calculations. The Clopper-Pearson method was used to calculate the 2-sided confidence interval (CI) for the DRR and ORR outcomes. OS, DoR and PFS were analysed with Kaplan-Meier (KM) methods.

All data was evaluated as observed with no imputation method for missing values outside of the censoring for each outcome described below:

- DoR was analysed using patients with a CR but neither documented disease progression nor death within 12 weeks after the last tumour assessment with censoring occurring at the date of the last tumour assessment.

- OS was defined as all patients still alive at the time of data analysis or for those who were lost to follow-up, OS was censored at the last recorded date that the patient was known to be living.

- PFS was defined as patients without a PD or death event and was censored at the date of last 'adequate tumour assessment'. The ERG is unclear as to the definition of 'adequate tumour assessment'.

- Two health-related quality of life questionnaires were utilised during JAVELIN Merkel 200, EuroQol-EQ-5D (EQ-5D) and Functional Assessment of Cancer Therapy – Melanoma (FACT-M). In addition, optional patient interviews were undertaken to gather further HRQoL data.

- Safety analyses were performed on the safety analysis set, which the ERG notes is the same as the efficacy analysis set, and included the recording of the incidence of TEAEs and changes in vital signs, ECGs, body weight, and laboratory values.

4.2.4 Summary statement

In summary, the ERG considers the company's electronic database searches for the effectiveness SLR were sufficiently broad and sensitive to identify published RCT and non-RCT evidence relevant to the decision problem, and eligibility criteria were appropriate. However, ongoing or unpublished studies may have been overlooked because trial registries were not searched. The process of selecting appropriate comparative evidence from studies included in the clinical effectiveness SLR was non-systematic, and differs from the SLR described in Appendix 10 of the CS to identify effectiveness data for the economic model. Quality assessments were not provided for all included studies but did cover the four studies ultimately used for the indirect treatment comparison in the clinical effectiveness

section of the CS. The tool used may not be appropriate for non-comparative studies but the ERG generally agrees with the judgments provided. The ERG considers both parts of JAVELIN Merkel 200 to be at a high risk of bias due to their observational nature and single-arm design. In addition, the ERG notes that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and OS.

The ERG considers that the searches for the safety SLR may have been overly restrictive by the way safety outcome terms were incorporated into the searches although no explicit eligibility criteria were provided in the CS. As with the effectiveness SLR, the process of deciding which study data contributed to the economic modelling is not fully described.

One study, JAVELIN Merkel 200 was used to provide the clinical effectiveness and safety data for avelumab in the CS. JAVELIN Merkel 200 comprised of two parts: Part A in a 2L+ mMCC population and Part B in a 1L mMCC population. The ERG considers JAVELIN Merkel 200 to address the population requested in the NICE final scope.

The ERG's clinical experts reported that the median age of the 2L+ and 1L populations in JAVELIN Merkel 200 (72.5 years versus [redacted] years, respectively) is broadly consistent with the median age expected of mMCC patients in England. However, the ERG's clinical experts reported that the ECOG PS of patients in both Part A and Part B was slightly better than expected in clinical practice in England, with more patients expected to be ECOG 1 and some ECOG 2 at second and third line or beyond. In addition, they reported that patients at later lines of therapy (i.e. 2L and beyond) generally have worse ECOG PS and are less able to tolerate the side effects of therapies and so are more likely to have worse outcomes. The ERG noted that 30.7% of patients in JAVELIN Merkel 200 Part A were at third line therapy and 4.5 % of patients were fourth line and beyond. The ERG also considers that subgroups by line of therapy would be useful and that the efficacy for the whole 2L+ population may be underestimated for the equivalent 2L population in England likely to receive avelumab.

In the final scope issued by NICE, the comparator of interest for the 2L+ population was identified as best supportive care (BSC). The ERG notes that no trial level data were presented in the CS for BSC and chemotherapy was used as a surrogate to provide the comparison of avelumab versus BSC in the economic modelling.

The outcomes reported in the CS were in line with those requested in the NICE final scope, with the exception of HRQoL in the 1L population, where no data were presented.

4.3 Clinical effectiveness results

4.3.1 Progression-free survival in JAVELIN Merkel 200

The ERG considers it important to highlight that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and so the data presented here should be interpreted with caution.[22]

The PFS results for the 1L and 2L+ cohorts of JAVELIN Merkel 200 are presented in Table 18. Median PFS for the 2L+ cohort (Part A) of JAVELIN Merkel 200 was 2.7 months (95% CI: 1.4 to 6.9) at the 18-month follow-up analysis and [redacted] had undergone a progression or death event. The ERG notes that the same proportion of patients who were progression-free at 12 months remained progression free at 18 months in the 18-month analysis ([redacted].

In the 1L cohort (Part B) of JAVELIN Merkel 200, [redacted] had a progression or death event at the ≥3-month follow-up analysis. The median PFS was 9.1 months (95% CI: 1.9 to not reached).

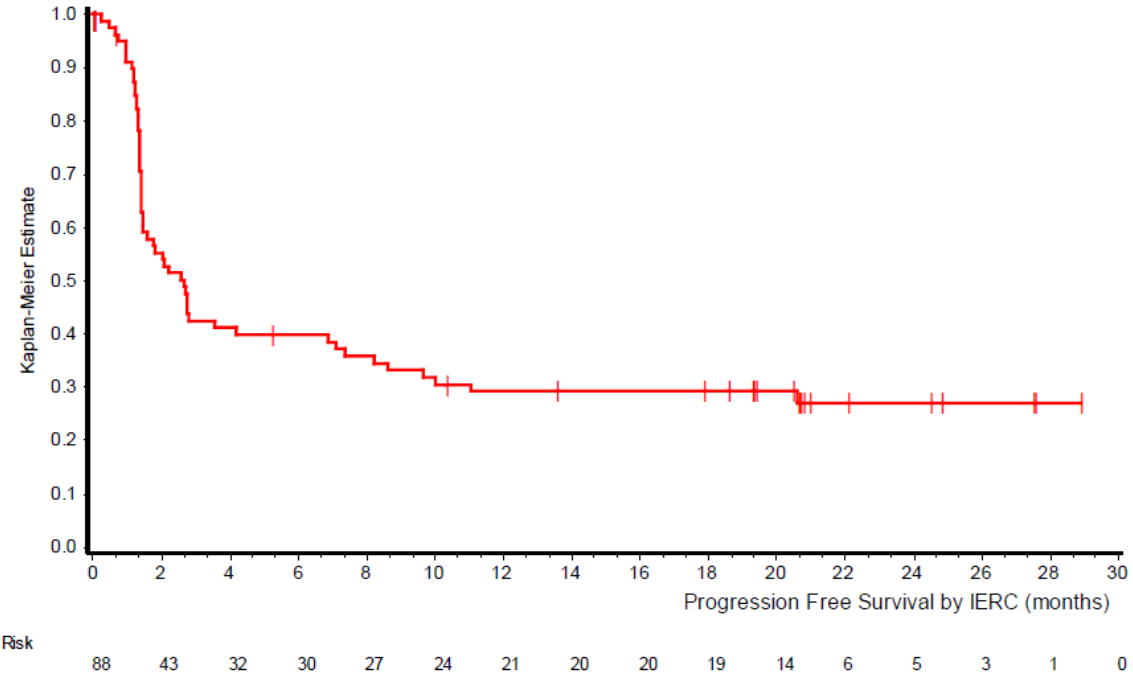
Table 18. PFS according to IERC assessment in JAVELIN Merkel 200 (adapted from CS page 75, Table 22)

n (%)	2L+ cohort (Part A) N=88 (100%)			1L cohort (Part B) N=39 (100%)
	6-month follow-up	12-month follow-up	18-month follow-up	3-month follow-up
Number of patients without event (censored)	36 (40.9)	33 (37.5)	32 (36.4)	24 (61.5)
Number of patients with an event	52 (59.1)	55 (62.5)	56 (63.6)	15 (38.5)
Progressive disease	44 (50.0)	47 (53.4)	48 (54.5)	12 (30.8)
Death	8 (9.1)	8 (9.1)	8 (9.1)	3 (7.7)
PFS time				
Median (months)	2.7	2.7	2.7	9.1
Range	0.03-18.8	0.03-24.5	0.03-28.9	0.03-11.0
95% CI	1.4-6.9	1.4-6.9	1.4-6.9	1.9-NR
PFS rates (95% CI)				
3 months	42 (31-53)	42 (31-53)	42 (31-53)	67 (48-80)
6 months	40 (29-50)	40 (29-50)	40 (29-50)	-
12 months	30 (19-41)	30 (21-41)	29 (19-39)	-
15 months	-	30 (21-41)	[redacted]	-
18 months	-	-		-

Abbreviations: CI: Confidence interval; IERC: Independent Endpoint Review Committee; ITT: Intent-to-treat; NE: Not-estimable; PFS: Progression-free survival

The KM plot for the 2L+ cohort at the ≥18-month follow-up analysis illustrates the spread of progression events with avelumab over time and the estimation of the prognosis for the 19 remaining patients (22%) at risk beyond the 18-month follow-up data available from JAVELIN Merkel 200 Part A (Figure 6).

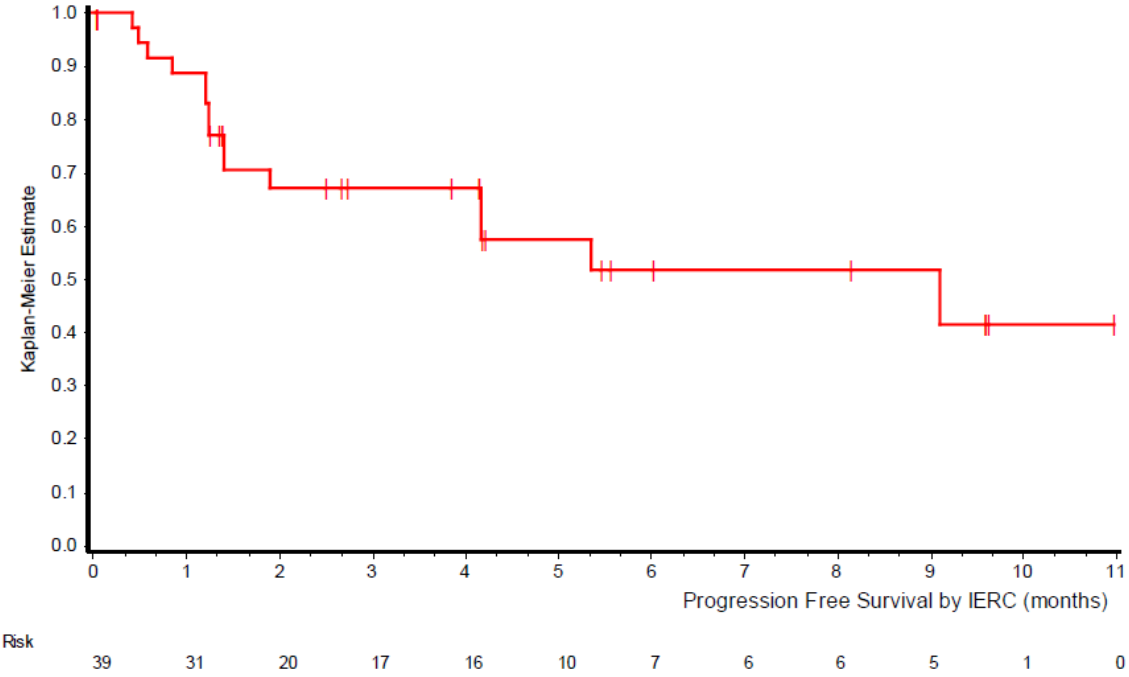
Figure 6. Kaplan-Meier estimate of PFS in the ITT population of the 2L+ cohort (Part A) of JAVELIN Merkel 200 (n=88) (reproduced from CS page 76, Figure 10)



Note: Vertical lines show censored events.
Abbreviations: IERC: Independent endpoint review committee

The KM plot for the 1L patients from the ≥3-month follow-up analysis of JAVELIN Merkel 200 Part B is presented in Figure 7. The company reported that of patients who responded to avelumab 67% (95% CI: 48 to 80) were progression-free at 3 months.

Figure 7. Kaplan-Meier estimate of PFS in full analysis set with ≥3 months follow-up in the 1L cohort (Part B) of the JAVELIN Merkel 200 trial (n=39) (reproduced from CS page 76, Figure 11)



[redacted]Vertical lines show censored events. Abbreviations: IERC: Independent endpoint review committee

4.3.2 Overall survival in JAVELIN Merkel 200

The ERG considers it important to highlight that the OS data for JAVELIN Merkel 200 are immature and particularly for the 1L cohort (Part B) are extremely limited as median OS has not yet been reached and data are restricted to 3 months' follow-up. The ERG also considers it important to highlight that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as OS and so the data presented here should be interpreted with caution.[22]

For the 2L+ population where there was a minimum of 18-months follow-up, [redacted] had died at data cut-off and median OS was reported to be [redacted]; [Table 19]). In terms of responders, it was reported in the CS that [redacted].

Table 19. OS according to IERC assessment in JAVELIN Merkel 200 (adapted from CS page 73, Table 21)

	2L+ cohort (Part A)			1L cohort (Part B)
Outcome	**6-month follow-up (N=88)**	**12-month follow-up (N=88)**	**18-month follow-up (N=88)**	**3-month follow-up (N=39)**
OS rate, % (95% CI) 3 months 6 months 12 months 15 months 18 months	 87 (78-93) 69 (58-78) 48 (35-60) - -	 87 (78-93) 70 (59-78) 52 (41-62) 44 (32-54) -	[redacted]	[redacted]
OS median, months (95% CI) Range, months	 11.3 (7.5-14.0) 0.4-18.8	 12.9 (7.5-NE) 0.4-24.7	[redacted]	[redacted]

Abbreviations: CI: Confidence interval; IERC: Independent Endpoint Review Committee; ITT: Intent-to-treat; OS: Overall survival; NE- non-evaluable

The company stated that the durable responses seen in the 2L+ cohort were represented by a possible plateau observed in the Kaplan-Meier curve for OS (Figure 8). The company also reported in the CS that as more mature 2L+ data have become available from the 88 patients in JAVELIN Merkel 200 Part A, the median OS has increased from 11.3 months at 6-months follow-up to [redacted] at 18-months follow-up.

Figure 8. Kaplan-Meier estimate of OS in the ITT population in the 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial (n=88) (reproduced from CS page 73, Figure 8)

Note: Vertical lines show censored events

There were a total of [redacted] in the 1L cohort (Part B) of JAVELIN Merkel 200 who had died at the ≥3-month follow-up analysis. The KM estimates for OS in the 1L population suggested a 3-month OS rate of [redacted];Figure 9).

Figure 9. Kaplan-Meier estimate of OS in the full analysis set with ≥3 months follow-up in the 1L cohort (Part B) of the JAVELIN Merkel 200 trial (n=39) (reproduced from CS page 74, Figure 9)

Vertical lines show censored events

4.3.3 Response rates in JAVELIN Merkel 200

The results for the analysis of BOR in JAVELIN Merkel 200 are presented in Table 20 for both the 1L and 2L+ cohorts.

The primary endpoint for the 2L+ cohort (Part A) of JAVELIN Merkel 200 was BOR, and the null hypothesis of ORR ≤20% was [redacted]. The results for BOR suggest that [redacted] and the proportion of patients with a BOR of stable disease was [redacted] (Table 20). The ORR for the 2L+ cohort at the 18-month analysis was 33.0% (95% CI: 23.3 to 43.8%).

The ERG notes that the results for the 1L cohort reflects an interim analysis conducted in only a small number of patients (minimum 3-months follow-up n=29; minimum of 6-months follow-up n=14) and so they should be interpreted with caution. However, the ERG also acknowledges that the 6-month results for ORR in the 1L cohort suggest they have [redacted].

Table 20. Summary of the best overall response in JAVELIN Merkel 200 (adapted from CS page's 68-69, Table 18)

BOR by RECIST 1.1 n (%)	2L+ cohort (Part A)			1L cohort (Part B)	
	6-month follow-up (N=88)	12-month follow-up (N=88)	18-month follow-up (N=88)	3-month follow-up (N=29)	6-month follow-up (N=14)
CR	8 (9.1)	10 (11.4)	10 (11.4)	4 (13.8)	[redacted]
PR	20 (22.7)	19 (21.6)	19 (21.6)	14 (48.3)	[redacted]
SD	9 (10.2)	9 (10.2)	9 (10.2)	3 (10.3)	[redacted]
PD	32 (36.4)	32 (36.4)	32 (36.4)	7 (24.1)	[redacted]
Non-CR/non-PD	1 (1.1)*	0	0	0	[redacted]
Non-evaluable¥	18 (20.5)	18 (20.5)	18 (20.5)	1 (3.4)	[redacted]
ORR, % (95% CI)	31.8 (21.9-43.1)	33.0 (23.3-43.8)	33.0 (23.3-43.8)	62.1 (42.3-79.3)	[redacted]

*Patient 4070003 was assessed with a CR according to IERC assessment at last visit prior to the data cut-off on Study Day 253 (22 February 2016). The data cut-off for this report was prior to the next tumour assessment for this patient, thus the CR could not be confirmed and a confirmed BOR of non-CR / non-PD was recorded.
¥Patients not assessable for a confirmed BOR had no baseline lesions identified by the independent review committee (n=4), baseline but no post-baseline assessments (n=10; four patients died within 6 weeks after the start of treatment and six additional patients discontinued study treatment in the first 6 weeks), all non-assessable post-baseline assessments (n=2), no post-baseline tumour assessment before the start of new anticancer therapy (n=1), or SD of insufficient duration (<6 weeks after start date without further tumour assessment; n=1)
Abbreviations: BOR: Best overall response; CI: Confidence interval; CR: Complete response; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; RECIST: Response evaluation criteria in solid tumours; SD: Stable disease

The company presented sensitivity analyses for BOR and ORR results based on Investigator assessment for the 1L and 2L+ cohorts. For the 2L+ cohort the 12-month ORR was identical with IERC and Investigator assessment (33.0%), whereas Investigator assessment showed better partial response (PR; 22.7% vs 21.6%), stable disease (SD; 14.8% vs 10.2%) and progressive disease (PD; 39.8% vs 36.4%) than IERC assessment, respectively.

The company reported that in the 1L cohort (Part B) of JAVELIN Merkel 200 both the 3-month and 6-month follow-up analyses, there was an increased ORR reported with IERC assessment compared with Investigator assessment (62.1%_[redacted], 3-months; and 71.4%_[redacted], 6-months). In contrast, there was increased reporting of SD with Investigator assessment compared to with IERC assessment ([redacted] 3-months; [redacted], 6-months).

Table 21. Sensitivity analyses for confirmed best overall response in JAVELIN Merkel 200 (adapted from CS page 69, Table 19)

	2L+ cohort (Part A): 18-month follow-up	2L+ cohort (Part A): 12-month follow-up		1L cohort (Part B): 3-month follow-up	
	IERC assessment N=88 (100%)	Investigator assessment N=88 (100%)	IERC assessment N=88 (100%)	Investigator assessment N=29 (100%)	IERC assessment N=29 (100%)
BOR (n (%))					
CR	10 (11.4)	9 (10.2)	10 (11.4)	3 (10.3)	4 (13.8)
PR	19 (21.6)	20 (22.7)	19 (21.6)	13 (44.8)	14 (48.3)
SD	9 (10.2)	13 (14.8)	9 (10.2)	5 (17.2)	3 (10.3)

PD	32 (36.4)	35 (39.8)	32 (36.4)	7 (24.1)	7 (24.1)
Non-CR/Non-PD	0	-	0	-	0
Not evaluable	18 (20.5)	11 (12.5)	18 (20.5)	1 (3.4)	1 (3.4)
ORR					
CR + PR (Response rate)	29 (33.0)	29 (33.0)	29 (33.0)	16 (55.2)	18 (62.1)
95% CI	23.3-43.8	23.3-43.8	23.3-43.8	35.7-73.6	42.3-79.3
Abbreviations: BOR: Best overall response; CI: Confidence interval; CR: Complete response; IERC: Independent Endpoint Review Committee; ITT: Intent-to-treat; ORR: Overall response rate; PD: Progressive disease; PP: Per protocol; PR: Partial response; SD: Stable disease					

The company also provided additional results in the CS from a sensitivity analysis for BOR using immune-related response criteria (irRC), reporting that there was [redacted] with a CR compared to using RECIST 1.1 (according to IERC) at 12-months follow-up. In addition, there were more patients assessed with immune-related SD (irSD; 15 patients, 17.0%) although there were fewer with immune-related PD (irPD; 24 patients, 27.3%) compared with the RECIST 1.1 assessments (SD = 9 patients, 10.2% and PD = 32 patients, 36.4%).

4.3.3.1 Duration of response (DoR) as determined from IERC tumour assessments

Durable response was defined as an objective response (CR or PR) according to RECIST 1.1 lasting at least 6 months. The company stated that in order to adjust for the bias resulting from censoring patients at data cut-off, the durable response rate (DRR) was estimated in a *post-hoc* analysis, using the ORR and a KM estimate of 6-month durability of response. For the 2L+ cohort, the estimate of the proportion of patients with ≥6 months duration of response (DoR) was 93% (95% CI: 75 to 98%). This fell to 71% (95% CI: 51 to 85%) with ≥12 months DoR, and [redacted] with a DoR of 18-months (Table 22). At the 18-month data cut-off, the median DoR for the 2L+ cohort was not estimable (95% CI: 18.0 months to not estimable). The 6-month DRR in the 2L+ cohort increased from 29.1% at 6-months follow-up to 30.7% at 12-months because of the inclusion of a non-evaluable patient as a CR (Table 22).

The median DoR was not reached for the 1L cohort ([redacted]) for those with either ≥3-month follow-up, or those patients with [redacted]) (Table 22). The 6-month DRR in the 1L patients with ≥6 months follow-up (n=[redacted]) was [redacted], and [redacted]) of responses had a duration of ≥6 months (Table 22). The DRR results therefore suggest that 1L patients [redacted] compared to 2L+ patients ([redacted] versus 30.7%). The ERG also notes that DRR was the primary outcome for the 1L cohort of JAVELIN Merkel 200 and although

[redacted]

Table 22. Duration of response according to IERC assessment in the JAVELIN Merkel 200 trial (adapted from CS page 72, Table 20)

	2L+ cohort (Part A)			1L cohort (Part B)	
	6-month follow-up (N=28)	**12-month follow-up (N=29)**	**18-month follow-up (N=29)**	**3-month follow-up (N=[redacted])**	**6-month follow-up (N=[redacted])**
Number of patients without event (censored), n (%)	23 (82.1)	21 (72.4)	[redacted]	15 (83.3)	[redacted]
Number of patients with an event, n (%) Progressive disease, n (%) Death, n (%)	5 (17.9) 5 (17.9) 0	8 (27.6) 8 (27.6) 0	[redacted]	3 (16.7) 2 (11.1) 1 (5.6)	[redacted]
Duration of response Median, months Range 95% CI	NR 2.8-17.5 8.3-NR	NR 2.8-23.3 18.0-NR	[redacted]	[redacted]1.2-8.3 (4.0-NR)	[redacted]
Proportion of DoR, % (95% CI) 3 months 6 months 12 months 15 months 18 months	96 (77-99) 92 (70-98) 74 (47-89) - -	97 (78-100) 93 (74-98) 74 (53-87) - -	[redacted]	[redacted]93 (61-99)[redacted]	[redacted]
6-month DRR*, %	29.1	30.7	30.7	[redacted]	[redacted]

*ORR multiplied by Kaplan-Meier estimate for 6-month proportion of DoR
+Calculated from a small patient population (n=14) as data is currently evolving
Abbreviations: CI: Confidence interval; DoR: Duration of response; DRR: Durable response rate; IERC: Independent Endpoint Review Committee; NR: Not reached; ORR: Objective response rate

The median time to response in the 2L+ cohort of JAVELIN Merkel 200 with ≥18-month follow-up was [redacted], and 76% of responders (CR or PR; 22/29) had responded by week 7 (i.e. the first post-baseline study assessment; Figure 10). In addition, the company stated that many of the 2L+ patients experienced a continued response after treatment discontinuation although no numerical data were provided in the CS to quantify this (Figure 10).

Figure 10: Time to and duration of response to avelumab in 29 patients with a confirmed response (CR or PR) in the ITT population of JAVELIN Merkel 200 – 2L+ cohort (Part A) with 18 months follow-up (reproduced from CS page 70, Figure 6)

Some patients who experienced a response stopped discontinued treatment before disease progression or the 6 month minimum recommended treatment time due to adverse events, organisational issues such as protocol non-compliance, or suspected disease progression.
Abbreviations: CR: Complete response; PR: Partial response

[redacted]In the 1L cohort of JAVELIN Merkel 200 at ≥3 months follow-up, [redacted] of responding patients had experienced a confirmed response or either a CR or PR by week 7. Ongoing responses were reported in [redacted]) of 1L responding patients at ≥3-month follow-up ([redacted]).

Figure 11: Time to and duration of response to avelumab in 18 patients with a response (CR or PR) in the full analysis set of JAVELIN Merkel 200 (Part B – 1L cohort) with ≥3 months follow-up (reproduced from CS page 71, Figure 7)

Abbreviations: CR: Complete response; PR: Partial response

4.3.4 Health-related quality of life (HRQoL)

As discussed in Section 3.2, the JAVELIN Merkel 200 trial assessed the HRQoL of enrolled patients, using the EQ-5D and FACT-M questionnaires. FACT-M is a disease specific instrument for melanoma that was selected for use due to the disease similarity with MCC. Data available for HRQoL were limited to the 2L+ population (Part A) of JAVELIN Merkel 200, and that was limited to patients on treatment, or at the latest, to the first visit on disease progression. The company reported that at least 60% of the available patients completed each questionnaire during the study, although this fell to 21/61 patients (34.4%) for each questionnaire at the End-of-Treatment (EoT) visit. In addition, the company stated that, "The limited proportion of patients (21-72 patients) with available patient-reported outcome data represent a potential source of bias, especially post week 25". There were no HRQoL data available beyond 25 weeks; the ERG notes that HRQoL data are restricted to less than 6-months study follow up in 2L+ patients.

4.3.4.1 EQ-5D

The EQ-5D-5L questionnaire was administered at baseline, Week 7, every 6 weeks thereafter, and at the EoT visit in the JAVELIN Merkel 200 study. However, as the value set for EQ-5D-5L has not been validated in the UK, the 'crosswalk' algorithm was used to convert EQ-5D-5L to EQ-5D-3L values[174] for use in the economic analyses. The company reported that at baseline, the average EQ-5D-5L utility

scored via the crosswalk to EQ-5D-3L values was [redacted] and given the median age at baseline, this utility value is high compared to the equivalent age-matched general population utility (see Section 5.4.8.2 for further detail). The company reported that this may be due to patients expecting the treatment to provide durable responses and long-term survival or by the euphoria patients feel from less visible lesions on the skin and the impact a more effective and promising medicine may have on improving a patient's depression.

The mean progression-free EQ-5D-3L utility value was 0.8269 (standard error [SE] 0.0214) and the mean post-progression utility value was 0.7415 (SE 0.0257). These utility values suggest progression-free patients on avelumab have similar values to baseline and those who experience disease progression have a worsening of HRQoL.

The EQ-5D-5L data presented in the company response to clarification (question B7) for the 2L+ population are summarised in Table 23. The ERG notes that beyond week 25 (other than EoT visit) there were only 30% (n=21) of patients with EQ-5D-5L responses compared to the number of patients with data at baseline (n=71) and so the ERG considers these data to be potentially unreliable. The results from baseline to week 25 suggest a trend of improvement in utility value over time with avelumab treatment. In addition, the EoT utility value is higher compared to the baseline value suggesting avelumab has had a beneficial effect on the HRQoL of patients (mean utility score 0.739 and 0.797, respectively).

Table 23. Mean and standard deviations of EQ-5D-5L utility scores at selected timepoints in the 2L+ cohort of JAVELIN Merkel 200 (adapted from company response to CQs page 49, Table 15)

Visit	N	Mean	SD
Baseline	71	0.739	0.224
Week 7 Day 43	52	0.774	0.167
Week 13 Day 85	39	0.789	0.146
Week 19 Day 127	30	0.755	0.128
Week 25 Day 169	28	0.796	0.130
At end of treatment	27	0.797	0.163
Key: CQs, clarification questions; NA, not applicable; SD, standard deviation.			

4.3.4.2 FACT-M

The company reported that investigations were conducted to confirm the reliability and validity of FACT-M in the MCC population and its ability to detect changes from baseline to week 7. The analysis suggested there was, "good item convergent validity (≥75%), good discriminant validity with some evidence of insufficient item discriminant validity in the melanoma subscale, very good internal consistency reliability, and encouraging ability to detect change given the small sample size (n=37)" and it was therefore an acceptable tool to use in MCC.

[redacted]

Figure 12. FACT-M Total scores from baseline to EoT in the ITT analysis set of 2L+ cohort (Part A) of JAVELIN Merkel 200 (reproduced from CS page 80, Figure 15)

[redacted]

4.3.4.2.1 Association of tumour response with HRQoL

Figure 13. Tumour size change versus FACT-M total score at week 7 (n=39) (reproduced from CS page 81, Figure 16)

Abbreviation: FACT-M: Functional Assessment of Cancer Therapy – Melanoma; HRQoL: Health-related quality of life
A higher FACT score indicates better HRQoL
n is the number of patients who had non-missing values for both tumour assessment and HRQoL assessment at the given visit. A visit window of -/+7 days was applied to map the time point between these two assessments.

4.3.4.3 Qualitative patient interviews

All 2L+ patients (n=88) with mMCC enrolled in JAVELIN Merkel 200 (except those patients in Japan, n=3) were invited to participate in the optional qualitative patient interviews, of which 33 agreed to participate. Interviews were conducted at baseline (n=33), at week 13 (n=21) and week 25 (n=17) by a trained psychologist/researcher, and analysed using a qualitative software package (ATLAS.ti Version 7).[175]

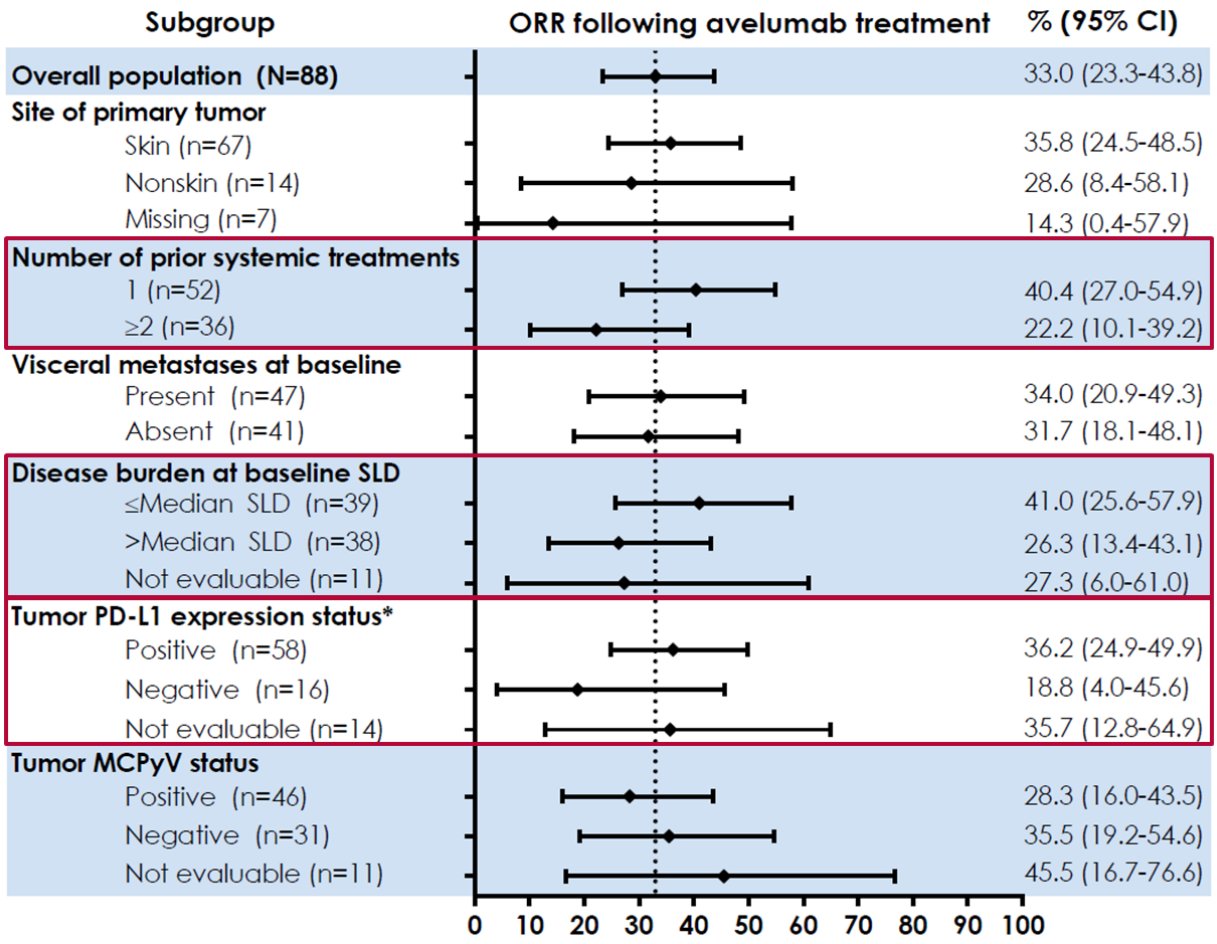
The results of the interviews (n=19) suggested that mMCC was associated with a negative psychological impact on patients, due to the challenging diagnosis, painful disease presentation at diagnosis and rapid disease progression.[175] In addition, diagnosis of mMCC had a negative psychological impact on patient's relatives and friends in providing help and support.[175]

At week 13, 62% of patients reported a benefit with avelumab treatment. The CS also reported that avelumab was associated with a visible improvement in tumour status, although no further detail on how this was assessed was provided in the CS. The benefit was also reported to be a greater improvement in physical and psychological status compared with their previous experience of treatment with chemotherapy.

4.3.5 Subgroup analyses

Subgroup analyses were reported in the CS for only the 2L+ cohort (Part A) of JAVELIN Merkel 200 (n=88) and were reported to be *post hoc* (Figure 14). The company stated that, "no significant differences in response were observed across subgroups" and, "responses to avelumab were observed across all subgroups defined by demographic and baseline characteristics". The ERG considers the subgroup data to be based on small patient numbers and notes that the subgroups were not powered to detect statistically significant differences between groups. The ERG considers the subgroup data do suggest some trends, with the most notable one being an improved ORR with only 1 prior systemic treatment compared to ≥2 prior treatments (40.4% versus 22.2%, respectively). The ERG also acknowledges that the 95% confidence intervals for the subgroups are overlapping and many are wide indicating high uncertainty in the results. The ERG notes that the company highlighted the subgroups of number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status in the forest plot. The ERG considers these highlighted subgroups suggest there may be within subgroup differences in ORR with avelumab although the ERG acknowledges the differences were not statistically significant.

Figure 14. Objective response by subgroup for select patient characteristics in the 2L+ cohort (Part A) of the JAVELIN Merkel 200 trial (reproduced from CS page 83, Figure 18)



Non assessable specimens included those that were missing, of poor quality, or otherwise not available to provide results
Abbreviation; CI: Confidence interval; MCPyV: Merkel cell polyomavirus; PD-L1: Programmed death ligand-1; SLD: sum of longest diameters

4.3.6 Adverse effects

The company reported that the safety of avelumab was initially investigated in the JAVELIN Solid Tumor study[176, 177] which was a Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics (PK), and biological and clinical activity of avelumab in patients with metastatic or locally advanced solid tumours. The methodology for the JAVELIN Solid Tumor trial was provided in Appendix 11 of the CS but no data on the AEs from the study were provided in the CS or its appendices. The ERG notes that the initial dose escalation phase of the trial enrolled 53 patients with avelumab doses ranging from 1 mg/kg to 20 mg/kg. There was also a subsequent expansion phase of the study which enrolled 1,452 patients with multiple tumour types, across 16 expansion cohorts, all of whom received at least one dose of avelumab (10 mg/kg). The company stated that the expansion cohorts did not include any patients with MCC but that it did not expect any major difference in the safety of avelumab across different types of solid tumours. In addition the company stated that, "Consequently the safety data base consisting of a total of 1,540 patients treated with the proposed dose and treatment schedule of 10 mg/kg every 2 weeks is considered of an acceptable

magnitude for identifying the safety profile of avelumab in the short-term perspective".[17] However, the reference details provided with the CS do not reflect the statement made by the company and no clinical data from the JAVELIN Solid Tumor study are presented in the CS and so the ERG is unclear of its relevance to the appraisal of avelumab in mMCC. There were safety data available on avelumab in mMCC from JAVELIN Merkel 200 and these were summarised in the CS. The ERG therefore only discusses the JAVELIN Merkel 200 avelumab safety data in this report.

The JAVELIN Merkel 200 safety analyses were conducted using the safety analysis set, which included all patients in the 2L+ cohort (Part A) and 1L cohort (Part B) who had received at least one dose of avelumab. The data cut-off for safety analyses was 18-months follow-up for the 2L+ cohort, and 3-months follow-up for the 1L cohort. The CS provided limited summary data on the AEs in JAVELIN Merkel 200 and so the ERG has supplemented the CS data with additional data from the primary publications of the 1L and 2L+ data,[3, 178] although these had earlier data cut-offs than the March 2017 analyses presented in the CS (30 December 2016 and 3 March 2016, respectively).

The median duration of therapy for the 2L+ cohort was 17 weeks (range: 2.0 to 132.0 weeks) with a median number of infusions of [redacted]. The median duration of therapy in the 1L cohort was [redacted] with a median number of infusions of [redacted]. [redacted]. The ERG notes that the company reported most patients (both 1L and 2L+) received between [redacted] of the planned dose per cycle although numerical data in support of this were not provided in the CS. In addition, it was reported in the CS that none of the patients in JAVELIN Merkel 200 received greater than [redacted] of the planned dose.

The ERG notes that as of 3 March 2016, 97.7% (86/88) of the 2L+ patients experienced an AE during JAVELIN Merkel 200 and 75.5% of the 2L+ patients (66/88) experienced an AE that was deemed to be a treatment-related AE (TRAE)[3]. In the 1L cohort, as of 30 December 2016, 71.8% (28/39) patients had experienced a TRAE. The company stated in the CS that only [redacted] of the 2L+ cohort and [redacted] of the 1L cohort experienced Grade ≥3 treatment-related adverse events (TRAEs) with avelumab, and there were [redacted]. The ERG notes from the Kaufman 2016 publication that by 3 March 2016, 61.4% of the 2L+ patients (54/88) had experienced a Grade ≥3 treatment-emergent adverse event (TEAE), although relatively few were deemed to be Grade ≥3 TRAEs (4/88 [4.5%]). Equivalent data on Grade ≥3 TEAEs were not available for the 1L population from the D'Angelo publication.

Table 24 presents the most common TEAEs reported in the JAVELIN Merkel 200 trial separately for the 2L+ cohort (Part A) and 1L cohort (Part B). The ERG notes that the most common TEAE was [redacted]

Table 24. Most common TEAEs in ≥10% of patients with avelumab treatment in JAVELIN Merkel 200 (adapted from CS page's 89-90, Table 25)

Adverse events	2L+ cohort (Part A) 18-month follow-up (N=88)		1L cohort (Part B) 3-month follow-up (N=[redacted])	
	Any grade, n (%)	Grade ≥3, n (%)	Any grade, n (%)	Grade ≥3, n (%)
Fatigue*	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral oedema+	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain¥	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Rash¤	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus**	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Decreased weight	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
DyspnoeaΦ	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]	[redacted]	[redacted]

*Fatigue is a composite term that includes fatigue and asthenia
+Peripheral oedema is a composite term that includes peripheral oedema and peripheral swelling
¥Abdominal pain is a composite term that includes abdominal pain and abdominal pain upper
¤Rash is a composite term that includes rash, maculopapular rash, erythema, and dermatitis bullous
**Pruritus is a composite term that includes pruritus and pruritus generalised
ΦDyspnoea is a composite term that includes dyspnoea and dyspnoea exertional
Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; NR: Not reported; TEAE: Treatment-emergent adverse event

4.3.6.1 Serious adverse events and deaths

In terms of serious TEAEs, [redacted] in the 2L+ cohort experienced a serious TEAE and [redacted] of the serious TEAEs were deemed to be related to treatment with avelumab based on the 18-month follow-up data set. In the 1L cohort, [redacted]) of patients experienced a serious TEAE and [redacted] of these were attributed to avelumab (3-month follow-up data set).

Deaths due to any TEAE were reported in [redacted] in the 2L+ cohort and [redacted] in the 1L cohort; [redacted].

4.3.6.2 Adverse events leading to discontinuation

TEAEs led to the permanent discontinuation of avelumab in [redacted] at 18 months and [redacted] at 3 months. The company only provided reasons for treatment discontinuation at 12 months in the 2L+ cohort and so the ERG are unsure of the reasons for the discontinuations in the data presented above. In addition, no explanation was provided in the CS for [redacted]

The AEs that resulted in avelumab treatment discontinuation at 12-months follow-up in the 2L+ cohort were: ileus, Grade 3 transaminitis, Grade 3 creatine kinase elevation, tubulointerstitial nephritis, and Grade 3 pericardial effusion. The company also reported that avelumab was temporarily discontinued in [redacted] 2L+ patients for AEs (excluding temporary dose interruption for infusion-related reactions where infusion was restarted the same day) with the most common reason being anaemia.

4.3.6.3 Immune-related adverse events

Given the mechanism of action of avelumab, the ERG considers that immune-related AEs (irAEs) are of clinical importance. The company provided data on the treatment-emergent irAEs observed in the 2L+ cohort of JAVELIN Merkel 200 in the CS at 18-months follow-up (Table 25) and a narrative summary of the data for the 1L cohort at 3-months follow-up. Treatment-emergent irAEs occurred in [redacted], with [redacted] Grade ≥3 irAEs [redacted] The most common immune-mediated reactions in the 2L+ cohort were [redacted]. The ERGs clinical experts report that [redacted]

Table 25. Summary of immune-relatedd adverse events experienced with avelumab treatment in JAVELIN Merkel 200 – 2L+ cohort (Part A) (adapted from CS page 91, Table 26)

	2L+ cohort (Part A) (N=88)	
Immune-related adverse events	**Any grade, n (%)**	**Grade ≥3, n (%)**
Patients with ≥1 treatment-emergent irAE	[redacted]	[redacted]
Immune-mediated endocrinopathies: Thyroid disorders Hypothyroidism	[redacted]	[redacted]
Immune-mediated rash	[redacted]	[redacted]

	2L+ cohort (Part A) (N=88)	
Immune-related adverse events	**Any grade, n (%)**	**Grade ≥3, n (%)**
Erythema Pruritus Rash Rash maculo-papular		
Immune-mediated colitis Diarrhoea	[redacted]	[redacted]
Immune-mediated hepatitis Transaminases increased Alanine aminotransferase increased Aspartate aminotransferase increased	[redacted]	[redacted]
Immune-mediated nephritis and renal dysfunction Tubulointerstitial nephritis	[redacted]	[redacted]
Immune-mediated endocrinopathies: Adrenal insufficiency	[redacted]	[redacted]
Immune-mediated endocrinopathies: Pituitary dysfunction	[redacted]	[redacted]
Immune-mediated endocrinopathies: Type 1 diabetes mellitus	[redacted]	[redacted]
Immune-mediated pneumonitis	[redacted]	[redacted]
Other immune-mediated adverse events Autoimmune disorder	[redacted]	[redacted]
*An infusion-related reaction in this analysis was based on a composite definition with five different MedDRA terms Abbreviation: MedDRA: Medical Dictionary for Regulatory Activities		

For the 1L cohort, treatment-emergent irAEs were reported in [redacted] and [redacted]. The percentage of irAEs was [redacted]

4.3.6.4 Infusion-related adverse events

Infusion-related AEs were reported in [redacted] and [redacted], with only [redacted] (Table 26). The ERG also notes that [redacted] experienced an infusion-related AE which lead to permanent discontinuation of avelumab compared to [redacted]

Table 26. Summary of infusion-related adverse events experienced with avelumab treatment in JAVELIN Merkel 200 – 2L+ cohort (Part A) (adapted from CS page 92, Table 27)

	2L+ cohort (Part A) (N=88)	1L cohort (Part B) (N=[redacted])
	18-month follow-up, n (%)	**3-month follow-up, n (%)**
Patients with ≥1 infusion-related reaction Grade 1 Grade 2 Grade ≥3	[redacted]	[redacted]

Number of patients with infusion-related reactions leading to permanent discontinuation of study treatment	[redacted]	[redacted]
Time relative to first onset Infusion 1 Infusion 2 Infusion ≥3	[redacted]	[redacted]

4.4 Critique of the indirect comparison

In the clinical section of the CS, the company provided a naïve comparison of avelumab versus chemotherapy in the 1L and 2L+ populations using a retrospective observational study that they conducted specifically for the comparison (Study 100070-Obs001), and Iyer 2016,[88] a study identified through the SLRs. However, as discussed is Section 4.1.3.1, there were 10 studies identified as providing potential comparator data for chemotherapy and/or BSC in mMCC patients (Table 9). Study 100070-Obs001 accounted for 3 of the 10 studies identified in the SLR[20, 89], and Iyer 2016[88] accounted for a further study. The remaining six studies identified from the clinical effectiveness and CS appendix 10 SLRs were explored for use in the economic modelling.

The company provided an appendix to the CS (CS appendix 10) detailing a series of analyses which were presented as evidence to show there are no patient characteristics that are prognostic of outcomes (including factors such as ECOG PS and stage at diagnosis in mMCC). The company conducted separate regression analyses for the 1L and 2L+ populations using the Study 100070-Obs001 chemotherapy data for the following baseline characteristic subgroups:

- stage at diagnosis,
- age,
- gender,
- immunosuppression status, and
- ECOG PS.

The univariate regression analyses were plotted alongside the KM data for the outcomes of OS and PFS. The company reported that for the 1L population, none of the patient characteristics in the univariate regression analyses were statistically significant. In multivariate regression analyses for OS and PFS, the only characteristic that was statistically significant was stage II at diagnosis, which the company considered to be potentially implausible because with worsening stage there was a trend towards survival increasing. In terms of the 2L population, only univariate regression and KM plots were reported in Appendix 10 of the CS. The 2L+ regression analyses for these patient baseline

characteristics were reported to demonstrate that no patient characteristic in isolation was a significant predictor of OS or PFS. The company used these regression analyses and visual inspections of KM plots, as the basis for their assertion that it was not necessary to adjust for prognostic factors or use treatment effect modifier techniques such as matching adjusted indirect comparison (MAIC) or simulated treatment comparison (STC). The company asserted that matching on characteristics that do not predict outcomes would likely introduce bias because, "matching would be conducted on essentially random variables, introducing a large element of variability to the results". The ERG does not agree with the approach taken by the company and considers that further analyses should have been provided to support the validity of the approach taken by the company in the CS, in particular to explore further potential prognostic factors.

The ERG considers that the results using MAIC should be similar to the results of unadjusted analyses if the company's assertion that there are no prognostic patient characteristics in mMCC is correct. The ERG also considers the small number of patients in the regression analyses presented by the company in CS appendix 10 means that there is a large amount of uncertainty around the results purely based on an initial small sample size. The ERG therefore considers that caution should be taken when drawing conclusions as the statistically non-significant results from the regression analyses could be a result of the small patient numbers rather than the absence of a subgroup effect (prognostic indicator). The ERG therefore does not consider the analyses presented by the company in appendix 10 of the CS can be used to exclude the possibility of prognostic indicators in mMCC. The ERG considers that subgroups identified in the subgroup analyses (Section 4.3.5), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, adjusted outcomes appropriately.

The ERG requested MAICs for the 1L and 2L populations during the clarification question stage and the company response is discussed in Section 4.4.5.

4.4.1 Study 100070-Obs001 - chemotherapy

Study 100070-Obs001 was a retrospective, observational study conducted by Merck KGaA/Pfizer in two parts; one in the EU (EU2L; n=34),[20] and one in the US (US2L; n=20, and US1L; n=67).[21] The company reported that Study 100070-Obs001 was designed to investigate clinical outcomes in mMCC patients with chemotherapy treatment and to provide comparator data on PFS and OS for the avelumab data from JAVELIN Merkel 200.[20, 21] Study 100070-Obs001 included adult patients with distant mMCC and was conducted in two parts: Part A was conducted in the US and included both 1L and 2L+ patients, whereas Part B was conducted in Europe and only included 2L+ patients. The company reported that Study 100070-Obs001 Part A (2L+ and 1L cohorts) and Part B (2L+ only) were designed to mimic the entry criteria of the ongoing Part A (2L+ avelumab) and Part B (1L avelumab) of JAVELIN Merkel

200 trial.[20, 21] As discussed above, the company considered that the statistical analyses they conducted suggested that patient characteristics do not appear to be predictive of outcomes in mMCC although outcomes do differ based on whether a patient has previously received chemotherapy for mMCC. The company thus considered that naïve comparisons of JAVELIN Merkel 200 avelumab data and Study 100070-Obs001 chemotherapy data for the 1L and 2L+ populations was acceptable. The ERG requested baseline characteristics of the Study 100070-Obs001 patients during the clarification stage. These are discussed in comparison to the 1L and 2L+ cohorts of JAVELIN Merkel 200 below.

4.4.1.1 Baseline characteristics of Study 100070-Obs001

The ERG notes that 30.0% of the US 2L+ patients and 14.7% of the EU 2L+ patients in Study 100070-Obs001 were immunocompromised, in contrast to 0% of the JAVELIN Merkel 200 patients. The ERG is unsure what impact this is likely to have on the results of the studies, especially given that there is no published data on avelumab use in immunosuppressed mMCC patients. The ERG, therefore, considers immunosuppression to be a potential confounder and that results of Study 100070-Obs001 that include the immunosuppressed patients should be interpreted with caution.

The baseline characteristics for the 2L+ patients from the US and EU parts of Study 100070-Obs001 are presented in Table 27 along with the immunocompetent patient subgroups from each study. The ERG notes that the patients in the US study were slightly older (median age 73.5 years versus [vs] 67.5 years; US and EU, respectively) and there was a higher proportion of males in the US study (70% vs 64.7%; US and EU, respectively).

In comparison to the avelumab patients in JAVELIN Merkel 200, the ERG notes that the patients from the EU part of Study 100070-Obs001 were younger (median age 72.5 years vs 67.5 years; JAVELIN Merkel 200 and Study 100070-Obs001 EU, respectively) and comprised a smaller proportion of males (73.9% vs 64.7%; JAVELIN Merkel 200 and Study 100070-Obs001 EU, respectively). The JAVELIN Merkel 200 and US part of Study 100070-Obs001 had similar median ages and proportions of patients who were male. Baseline ECOG performance status data were only available for the US part of Study 100070-Obs001, but this suggests that the patients in JAVELIN Merkel 200 had a better baseline ECOG status compared to the patients in Study 100070-Obs001 with more ECOG 0 patients in JAVELIN Merkel 200 (ECOG 0: 55.7% vs 5.0%; JAVELIN Merkel 200 and Study 100070-Obs001, respectively).

The ERG's clinical experts reported that the median age in JAVELIN Merkel 200 was reasonable in comparison to that expected in England, and so the ERG considers the median age in the EU part of Study 100070-Obs001 (67.5 years) to be younger than expected. In addition, the ERG considers there to be slightly fewer males than expected in England, in the EU part of Study 100070-Obs001 (64.7%). In terms of ECOG status, the ERG considers the ECOG status at baseline seen in the US part of Study 100070-Obs001to be a closer match to that expected in patients in England, although as no data were

available for the EU part, it is unclear what the discrepancy between the avelumab JAVELIN Merkel 200 data and pooled EU and US chemotherapy Study 100070-Obs001 data is (Table 27).

Table 27. Baseline characteristics for the 2L+ patients from Study 100070-Obs001 including the subgroup who were immunocompetent (adapted from CQ response, Table's 3-6)

Baseline characteristic	**100070-Obs001 part A, 2L+ All patients**	**100070-Obs001 part A, 2L+ immunocompetent patients**	**100070-Obs001 part B, 2L+ All patients**	**100070-Obs001 part B, 2L+ immunocompetent patients**
	(N=20)	**(N=14)**	**(N=34)**	**(N=29)**
Age				
<65 years, n (%)	-	7 (50.0)	12 (35.3)	11(37.9)
≥65 year, n (%)	-	7 (50.0)	22 (64.7)	18 (62.1)
<75 years, n (%)	11 (55)	-	-	-
≥75 year, n (%)	9 (45)	-	-	-
Median, years (range)	73.5 (66.0-81.1)	75.2 (63.6, 81.1)	67.5 (61.0-72.0)	67.0 (61.0-73.0)
Gender, n (%)				
Male	14 (70)	11 (78.6)	22 (64.7)	18 (62.1)
Female	6 (30)	3 (21.4)	12 (35.3)	11 (37.9)
ECOG PS, n (%)				
0	1 (5.0)	0	NA	NR
1	16 (80.0)	13 (92.9)	NA	NR
2	1 (5.0)	0	NA	NR
Unknown	2 (10.0)	1 (7.1)	34 (100)	29 (100.0)
Region, n (%)				
Midwest or Northeast	5 (25.0)	4 (20.0)	NA - Europe	NA - Europe
South or west	15 (75.0)	10 (80.0)	NA - Europe	NA - Europe
Site of primary tumour, n (%)				
Face	5 (25.0)	3 (21.4)	NA	N/A
Lower limb or trunk	7 (35.0)	7 (50.0)	NA	N/A
Scalp and neck	2 (10.0)	1 (7.1)	8 (23.5)	6 (20.7)
Upper limb	5 (25.0)	2 (14.3)	NA	N/A
Unknown primary	1 (5.0)	1 (7.1)	1 (2.9)	1 (3.5)
Arm	NA	N/A	9 (25.5)	9 (31.0)
Leg	NA	N/A	5 (14.7)	4 (13.8)
Trunk	NA	N/A	6 (17.7)	5 (17.2)
Missing	NA	N/A	5 (14.7)	4 (13.8)
Metastatic involvement at study entry, n (%)*				
Yes	NA	NA	10 (29.4)	7 (24.)
No	NA	NA	24 (70.6	22 (75.9)
Number of prior systemic cancer therapies received, n (%)				
1	NA	NA	0	0
2	NA	NA	29 (85.3)	24 (82.8)
≥3	NA	NA	5 (14.7)0	5 (17.2)
Visceral disease at study entry, n (%)				
Present	14 (70.0)	10 (71.4)	20 (58.8)	16 (55.2)
Absent	4 (20.0)	2 (14.3)	7 (20.6)	6 (20.7)
Not noted or missing	2 (10.0)	2 (14.3)	7 (20.6)	7 (24.1)

Lymph node disease only at study entry, n (%) Yes No	 4 (20.0) 16 (80.0)	 2 (14.3) 12 (85.71)	 7 (20.6) 27 (79.4)	 7 (24.1) 22 (75.9)
NA: Not available *Patients identified were diagnosed with metastatic MCC on or any time before September 2014- determined initially through structured data (i.e. mention of metastatic in line of therapy or stage IV at initial/current diagnosis) and then confirmed by radiology reports and physician notes. a: Visceral metastases and/or elevated lactate dehydrogenase according to classification of malignant melanoma. b: Distant soft tissue and lymph node metastases according to classification of malignant melanoma.				

Similar to the 2L+ cohort of Study 100070-Obs001, the 1L cohort included immunosuppressed patients. In total 23.9% of the Study 100070-Obs001 1L chemotherapy patients were immunosuppressed (n=16), whereas none of the 1L JAVELIN Merkel 200 avelumab patients were immunosuppressed. The baseline characteristics for the 1L patients in Study 100070-Obs001 and the immunocompetent subgroup were similar although there was a slightly higher proportion of males in the immunocompetent subgroup (79.1% vs 84.3%, all patients and immunocompetent, respectively). The ERG considers it important to highlight that in comparison to the 2L+ patients, the 1L patients in Study 100070-Obs001 had a higher median age (75.8 years vs 73.5 years; 1L and 2L+, respectively) and a higher proportion of males (79.1% vs 70.0%; 1L and 2L+, respectively). The ERG also notes that in comparison to the 1L patients in JAVELIN Merkel 200, the baseline characteristics for the 1L patients in Study 100070-Obs001 were broadly similar. The most notable difference was that there was a larger proportion of 1L ECOG 0 patients in JAVELIN Merkel 200 compared to in Study 100070-Obs001 (79.5% vs 20.9%; JAVELIN Merkel 200 and Study 100070-Obs001, respectively). In addition, there were no ECOG 2 patients in JAVELIN Merkel 200, compared to 9% of patients in Study 100070-Obs001.

Table 28. Baseline characteristics of the 1L patients from Study 100070-Obs001 including the subgroup who were immunocompetent (adapted from CQ response, Table's 7 and 8)

Baseline characteristic	**Study 100070-Obs001 part A, 1L+ All patients**	**Study 100070-Obs001 part A, 1L+ immunocompetent patients**
	(N=67)	(N=51)
Age <65 years, n (%) ≥65 year, n (%) Median, years (range)	 14 (20.9) 53 (79.1) 75.8 (67.1-82.3)	 10 (19.6) 41 (80.4) 78.1 (67.9-83.7)
Gender, n (%) Male Female	 53 (79.1) 14 (20.9)	 43 (84.3) 8 (15.7)
ECOG PS, n (%) 0 1 2 Unknown	 14 (20.9) 32 (47.8) 8 (9.0) 13 (19.4)	 11 (21.6) 25 (49.0) 5 (5.9) 10 (19.6)
Region, n (%) Midwest or Northwest South West	 11 (16.4) 42 (62.7) 14 (20.9)	 6 (11.8) 37 (72.5) 8 (15.7)

Site of primary tumour, n (%)		
Face	16 (23.9)	12 (23.5)
Lower limb or trunk	22 (32.8)	18 (35.3)
Unknown primary	2 (3.0)	2 (3.9)
Scalp and neck	12 (17.9)	8 (15.7)
Upper limb	15 (22.4)	11 (21.6)
Metastatic involvement at study entry, n (%)		
Yes	7 (10.4)	6 (11.8)
No	18 (71.6)	35(68.6)
Unknown	12 (17.9)	10 (19.6)
Visceral disease at study entry, n (%)		
Present [a]	46 (68.65)	34 (66.67)
Absent	14 (20.90)	10 (19.61)
Not noted or missing	7 (10.45)	7 (13.72)
Lymph node disease only at study entry, n (%)		
Yes[b]	14 (20.90)	10 (19.6)
No	53 (79.1)	41 (80.4)
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status.		

4.4.2 Iyer 2016 – chemotherapy

The company reported that they included data from Iyer 2016[88] alongside the data from Study 100070-Obs001 to "provide further context" for the comparison of avelumab with both 1L and 2L+ chemotherapy treatment. However, the ERG is unclear why the Iyer 2016[88] paper was selected from the other papers identified by the SLR. The ERG notes that Iyer 2016 was the only chemotherapy paper identified by the company SLR that reported data on 1L and 2L patients. The ERG considers that other studies may have been equally or better suited than Iyer 2016[88] for the naïve comparison of avelumab with chemotherapy in the 1L and 2L settings, and that given they are independent populations, a different study could have been used for each. Due to time constraints, the ERG was unable to evaluate the alternative studies identified by the company SLR for this purpose.

4.4.2.1 Baseline characteristics of Iyer 2016

Limited information is provided in the Iyer 2016[88] publication on the baseline characteristics for the 1L and 2L study populations making it difficult to compare them with those of patients in JAVELIN Merkel 200 or Study 100070-Obs001. The median age is provided only for the 1L population in Iyer 2016[88] and was 68.4 years, which is younger than the Study 100070-Obs001 and JAVELIN Merkel 200 (median ages of 75.8 years and 75.0 years, respectively). Similar to Study 100070-Obs001, Iyer 2016[88] included immunosuppressed patients, unlike JAVELIN Merkel 200 where all patients were immunocompetent. The proportion with immunosuppression at 1L in Iyer 2016[88] was 23%, and at 2L it was only 17%. The Iyer 2016[88] and Study 100070-Obs001 both had similar proportions of patients with immunosuppression in at 1L and 2L+.

In summary, the ERG considers the Iyer 2016[88] study population to be younger than that of the Study 100070-Obs001 and JAVELIN Merkel 200 populations. In addition, the ERG notes Iyer 2016[88] contains

immunosuppressed patients that were excluded from JAVELIN Merkel 200. The ERG is unable to comment further on the likely direction of any bias resulting from interplay of these discrepancies.

4.4.3 Avelumab versus BSC in 2L+ patients

The company reported that to address the comparison of avelumab with BSC requested in the 2L+ population in the NICE final scope[1] they have assumed that the efficacy data from chemotherapy regimens are equal to those of BSC. The company cited clinical experts' opinion stating that, "efficacy outcomes with BSC and chemotherapy are likely to be very similar due to very poor patient performance with both". Data from Part A of JAVELIN Merkel 200 (2L+ cohort) were presented in the clinical effectiveness section of the CS along with the EU and US 2L data from Study 100070-Obs001, and Iyer 2016[88] for the comparison of avelumab versus BSC in 2L+ patients (Table 29).

The results for avelumab in the 2L+ mMCC population of the JAVELIN Merkel 200 trial, relative to chemotherapy (surrogate for BSC) in Study 100070-Obs001 and Iyer 201688, indicate that avelumab is associated with a higher 6-month DRR (30.6% [JAVELIN Merkel 200] vs 0.0% [Study 100070-Obs001] and 6.7% [Iyer 2016]), longer 12-month PFS (29.0% vs 0.0%), longer 12-month OS (50.0% vs 0.0%), and a higher CR rate (11.4% vs 0.0% to 3.3%).

The ERG notes that the response rates in the US cohort of Study 100070-Obs001 (Part A; ORR: 28.6%) and the US observational study Iyer 2016[88] (ORR: 23.3%) are higher than those reported in the EU cohort of Study 100070-Obs001 (Part B; ORR: 10.3%). The company reported that they considered the EU study most likely to best reflect clinical practice in England as the US studies are likely to be associated with more aggressive treatments, resulting in improved outcomes. The ERG and its clinical experts agree that Part B of Study 100070-Obs001 is likely to be the best study of those presented by the company in terms of reflecting the outcomes of 2L patients on chemotherapy or BSC in England.

Table 29. Efficacy results from JAVELIN Merkel 200 – 2L+ cohort (Part A), Observational study 100070-Obs001 (Part A and B) and Iyer et al. 2016 in the 2L+ setting (adapted from CS page's 85-86, Table 23)

Efficacy parameter	JAVELIN Merkel 200 (Part A - 2L+ cohort) (N=88)	Study 100070-Obs001 Overall		Study 100070-Obs001 Immunocompetent[a]		Retrospective study[b] (Iyer 2016) (N=30)
		(Part A - US) (N=20)	(Part B - EU) (N=34)	(Part A - US) (N=14)	(Part B - EU) (N=29)	
BOR per RECIST 1.1						
CR, n (%)	10 (11.4)	0	0	0	0	1 (3.3)
PR, n (%)	19 (21.6)	4 (20.0)	3 (8.8)	4 (28.6)	3 (10.3)	6 (20.0)
SD, n (%)	9 (10.2)	2 (10.0)	3 (8.8)	2 (14.3)	3 (10.3)	1 (3.3)
PD, n (%)	32 (36.4)	8 (40.0)	28 (82.4)	5 (35.7)	23 (79.3)	22 (73.3)

Non-CR/Non-PD*, n (%)	0	0	0	0	0	0
Not evaluable, n (%)	18 (20.5)	6 (30.0)	0	3 (21.4)	0	0
ORR						
Response rate (CR+PR) (95% CI)	33.0 (23.3-43.8)	20.0 (5.7-43.7)	8.8 (1.9-23.7)	28.6 (8.4-58.1)	10.3 (2.2-27.4)	23.3 (9.9-42.3)
DoR						
Median, months (95% CI)	NE (18.0-NE)	1.7 (0.5-3.0)	1.9 (1.3-2.1)	1.7 (0.5-3.0)	1.9 (1.3-2.1)	3.3
6–month DRR, % (95% CI)	30.7 (20.9-40.3)[d]	0.0 (0.0-16.8)	0.0 (0.0-10.3)	0.0 (0.0-23.2)	0.0 (0.0-11.9)	6.7 (0.8-22.1)
PFS						
Median, months (95% CI)	2.7 (1.4-6.9)	2.1 (1.0-3.2)	3.0 (2.6-3.1)	2.2 (1.2-3.5)	3.0 (2.5-3.2)	2.0 (1.3-2.7)
6-month PFS rate by KM, % (95% CI)	40.0 (29.0-50.0)	0.0	2.9 (0.2-13.0)	0.0	3.4 (0.3-14.9)	13
12-month PFS rate by KM, % (95% CI)	29.0 (19.0-39.0)	0.0	0.0	0.0	0.0	NR
OS						
Median, months (95% CI)	[redacted]	4.4 (2.2-6.2)	5.3 (4.3-5.8)	4.3 (2.1–6.2)	5.3 (4.3–6.0)	5.7 (NR)
6-month OS rate by KM, % (95% CI)	[redacted]	30.2 (11.6-51.4)	26.4 (13.1-41.8)	26.8 (7.3-51.5)	27.5 (13.0-44.2)	NR
12-month OS rate by KM, % (95% CI)	[redacted]	0.0	0.0	0.0	0.0	NR

*One patient did not have measurable disease at baseline and thus a BOR of PR or SD could not be distinguished
[a]Analysis conducted on the immunocompetent patients did not show any meaningful impact on OS. As such the overall population has been used in the economic model
[b]Data from Iyer 2016 was reported after 2L chemotherapy and not-specific for immunocompetent patients (13.3% had systemic immune suppression)
[c]Based on number of patients with confirmed response (CR+PR)
[d]Based on the ORR and the KM estimate for 6-month durability
Abbreviations: BOR: Best overall response; CI: Confidence interval; CR: Complete response; DoR: Duration of response; DRR: Durable response rate; KM: Kaplan-Meier; NR: Not reported; ORR: Overall response rate; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: Stable disease

The KM plots for the JAVELIN Merkel 200 2L+ avelumab patient data and the Study 100070-Obs001 pooled EU and US 2L+ chemotherapy data for OS and PFS are shown in Figure 15 and Figure 16.

For OS, the KM plots suggest that, patients on avelumab generally had a longer OS than the chemotherapy patients (Figure 15). The KM plot suggests no patients on chemotherapy lived beyond 9 months, whereas over 50% of patients on avelumab were still alive at 9 months, and at 2 years over

30% of patients on avelumab were still alive. The results, therefore, suggest that avelumab may be more effective than chemotherapy in 2L+ patients although the results are based on a naïve comparison and there are only a small number of patients in the analyses (n= 88 with avelumab and n= 54 with chemotherapy). The ERG considers the results should be interpreted with caution as they are based on small patient numbers and therefore subject to uncertainty.

Figure 15. OS KM plot for avelumab versus chemotherapy in 2L+ patients (JAVELIN Merkel 200 and Study 100070-Obs001 [pooled EU and US data]; produced by the ERG based on CS page 133, Figure 45)

The ERG considers that the KM plots for PFS in the 2L+ population suggest that beyond approximately 3 months, avelumab is associated with a longer PFS compared to chemotherapy (Figure 16). In addition, the KM plots suggest that everyone on chemotherapy has experienced a progression or death event by approximately 6 months. In contrast, approximately 40% of patients on avelumab are still progression-free at 6 months and at 2 years there are still over 25% of patients on avelumab who are progression-free.

Figure 16. PFS KM plot for avelumab versus chemotherapy in 2L+ patients (JAVELIN Merkel 200 and Study 100070-Obs001 [pooled EU and US data]; produced by the ERG based on CS page 133, Figure 45)

4.4.3.1 Avelumab versus BSC in 2L+ patients in the economic model

The ERG notes that the company critique in the clinical effectiveness section for the 2L+ population focuses on the data from the EU and US parts of Study 100070-Obs001 and Iyer 2016.[20, 21, 88] However, the SLRs for 2L+ chemotherapy treatment in mMCC patients identified an additional study, Samlowski 2010,[54] which was also used in the economic modelling.

Iyer 2016[88] is described in Section 4.4.2 and only provides data on PFS. Samlowski 2010[54] provides data for both PFS and OS, although it comprises a mixed population of 1L patients (n=9) and 2L+ patients (n=14). The ERG does not consider it appropriate to use the data from Samlowski 2010[54] for any comparisons with avelumab in the 2L+ population due to the clinical heterogeneity within the Samlowski trial population. The company, however, considered it appropriate to combine the chemotherapy data from Study 100070-Obs001, Iyer 2016[88] and Samlowski 2010[54] in a meta-analysis as a sensitivity analysis in the economic modelling for the 2L+ population. The company reported that visual inspection of KM plots and regression analysis of the individual patient data from Study 100070-Obs001, suggested that no patient characteristics beyond line of therapy (age, gender, immunosuppression status, ECOG, or stage at diagnosis) were prognostic of outcomes, and thus there was no need to adjust for differences in patient characteristics between studies. The ERG does not agree with the company approach but presents the resulting curves for the meta-analysis of the 2L+ studies

alongside the JAVELIN Merkel 200 data for OS and PFS for completeness (Figure 17 and Figure 18, respectively).

The meta-analysis results for both OS and PFS suggest chemotherapy is associated with longer OS and PFS compared to chemotherapy in the pooled data from Study 100070-Obs001 (OS approximately 1.25 years versus approximately 0.75 years, respectively; and PFS approximately 0.75 years versus approximately 0.5 years, respectively). However, in comparison to avelumab, chemotherapy is still associated with shorter OS and PFS in the 2L+ population when the meta-analysis results for chemotherapy are used for the comparison. The ERG considers the improved PFS and OS seen with chemotherapy in this analysis is likely, at least in part, due to be the result of the inclusion of 1L patients in some of the studies included in the meta-analysis. The ERG, therefore, considers these analyses to be confounded by clinical heterogeneity and that the results should be interpreted with caution.

Figure 17. OS KM plot for avelumab versus chemotherapy in 2L+ patients (JAVELIN Merkel 200 and meta-analysed chemotherapy data; produced by the ERG based on CS page 134, Figure 47)

Figure 18. PFS KM plot for avelumab versus chemotherapy in 2L+ patients (JAVELIN Merkel 200 and meta-analysed chemotherapy data; produced by the ERG based on CS page 134, Figure 46)

4.4.4 Avelumab versus chemotherapy in 1L patients

The company presented the results of the 1L population of JAVELIN Merkel 200 (Part B) along with the results from the 1L US cohort of Study 100070-Obs001 (Part A) and the US Iyer *et al.* 1L patients for the comparison of avelumab versus chemotherapy in 1L patients (Table 30).

The ERG notes from its clinical experts that the most commonly used 1L regimens for mMCC in the UK are carboplatin plus etoposide and cisplatin plus etoposide. These regimens are included amongst other regimens in both Study 100070-Obs001 and Iyer 2016[88], and experts reported that the type of chemotherapy regimen is unlikely to have much effect on the resulting PFS and OS estimates. The clinical experts did highlight that the US studies are likely to have better outcomes due to the more aggressive treatment regimens than typically used in England. The ERG, therefore, considers that Study 100070-Obs001 and Iyer 2016[88] may potentially over-estimate the effectiveness of chemotherapy at 1L compared to that expected in England, assuming no other differences in patient characteristics in these studies have a prognostic impact in mMCC.

The results for the 1L population of the naïve comparison of avelumab from JAVELIN Merkel 200 Part B suggest avelumab is associated with improved ORR, PFS and OS outcomes compared to chemotherapy in Study 100070-Obs001 and in Iyer 2016[88] (Table 30).

Table 30. Efficacy results from JAVELIN Merkel 200 – 1L cohort (Part B), Observational study 100070-Obs001 (Part A) and Iyer 2016[88] in treatment-naïve patients (adapted from CS page's 87-88, Table 24)

Efficacy parameter	JAVELIN Merkel 200 (Part B - 1L cohort)		Study 100070-Obs001 (Part A - US) Overall (N=67)	Study 100070-Obs001 (Part A - US) Immunocompetent[a] (N=51)	Retrospective study[b] (Iyer 2016) (N=62)
	3-month follow-up (N=29)	6-month follow-up (N=14)			
CR, n (%)	4 (13.8)	4 (28.6)	10 (14.9)	7 (13.7)	8 (12.9)
PR, n (%)	14 (48.3)	6 (42.9)	11 (16.4)	8 (15.7)	26 (41.9)
SD, n (%)	3 (10.3)	1 (7.1)	1 (1.5)	1 (2.0)	4 (6.5)
PD, n (%)	7 (24.1)	2 (14.3)	31 (46.3)	21 (41.2)	24 (38.7)
Non-CR/Non-PD*, n (%)	0	0	-	-	-
Not evaluable, n (%)	1 (3.4)	1 (7.1)	-	-	-
ORR, % (95% CI)	62.1 (42.3-79.3)	71.4 (41.9-91.6)	31.3 (20.6-43.8)	29.4 (17.5-43.8)	55
Median DoR, months (95% CI)	NR (4.0-NR)	NR (4.0-NR)	5.7 (2.6-8.7)	6.7 (1.2-10.5)	3.0
DRR, % (95% CI)c	-	64.5+	14.9 (7.4-25.7)	15.7 (7.0-28.6)	2.8
	Full analysis set (N=39)				
Median PFS, months (95% CI)	9.1 (1.9-NR)		4.6 (3.0-7.0)	4.6 (2.8-7.7)	3.4
6-month PFS rate, % (95% CI)	52.0 (31.0-69.0)		44.8 (32.7-56.2)	47.1 (33.0-59.9)	-
12-month PFS rate, % (95% CI)	-		21.8 (12.7-32.4)	24.8 (13.8-37.4)	-
Median OS, months (95% CI)	[redacted]		10.2 (7.4-15.2)	10.5 (7.2-15.2)	9.5
6-month OS rate, % (95% CI)	[redacted]		70.1 (57.5-79.5)	66.7 (52.0-77.8)	-
12-month OS rate, % (95% CI)	-		44.0 (31.5-55.8)	45.3 (31.0-58.6)	-

[a]Analysis conducted on the immunocompetent patients did not show any meaningful impact on OS. As such the overall population has been used in the economic model
[b]Study included all patients regardless of immunocompetent status
[c]Based on the ORR and the KM estimate for 6-month durability
[+]Calculated from a small patient population (n=14) as data is currently evolving
Abbreviations: BOR: Best overall response; CI: Confidence interval; CR: Complete response; DoR: Duration of response; DRR: Durable response rate; KM: Kaplan-Meier; NR: Not reached; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: Stable disease

[redacted] The ERG considers it important to highlight that the OS data for avelumab are extremely limited due to the lack of long-term follow-up data for JAVELIN Merkel 200 1L patients and the small number of patients in the analysis (maximum n=29, and only 14 patients with 6 months or longer follow-up). [redacted]

Figure 19. OS KM plot for avelumab versus chemotherapy in 1L patients (JAVELIN Merkel 200 and Study 100070-Obs001 [US data]; produced by the ERG based on CS Appendix 10 pg 7, Figure 2)

[redacted]

[redacted] Figure 20. PFS KM plot for avelumab versus chemotherapy in 1L patients (JAVELIN Merkel 200 and Study 100070-Obs001 [US data]; produced by the ERG based on CS Appendix 10 pg 7, Figure 2)

[redacted]

4.4.4.1 Avelumab versus chemotherapy in 1L patients in the economic model

In total there were seven studies that the company identified from the SLRs and their own studies with OS or PFS (or both) data on chemotherapy in 1L mMCC patients (Study 100070-Obs001;[33]Iyer 2016;[88] Voog 1999;[67] Satpute 2014;[56] Santamaria-Barria 2013;[9] Fields 2011;[86] Allen 2005;[8] Table 31).

Table 31. Comparator data available for treatment-naïve metastatic MCC patients (adapted from CS page 135, Table 38)

Reference	N	PFS	OS	Patient characteristics
Cowey 2016 [Study 100070-Obs001]	67	Yes	Yes	Yes
Iyer 2016	62	Yes	Yes	Yes
Voog 1999	101		Yes	Yes
Satpute 2014	13	Yes		Yes
Santamaria-Barria 2013	15		Yes	
Fields 2011	26		Yes	
Allen 2005	14		Yes	
Abbreviations: MCC, Merkel cell carcinoma; OS, Overall survival; PFS, Progression-free survival				

The ERG notes that the company considered that, "the OS and PFS data appeared similar between the majority of studies (although studies are not perfectly aligned)" and the company also highlighted that treatment-naïve patients showed substantially better outcomes than treatment-experienced patients and a few patients also had durable survival.

The company also reported that analysis of individual patient data (IPD) for the variables of age, ECOG, gender, immunosuppression status and stage at diagnosis from Study 100070-Obs001 indicated, "no patient characteristic of prognostic importance beyond line of therapy based on both regression analysis

and visual inspection". The company considered that the additional six chemotherapy studies had similar outcomes to Study 100070-Obs001 and so they naïvely pooled the data from all the studies and fit parametric curves to inform the base-case analysis in 1L patients. The company reported that, "this results in increased patient numbers for analysis, and likely the most generalisable results". The ERG considers that the approach is likely to introduce unnecessary heterogeneity into the analysis although it is not possible to predict the likely direction of the resulting bias.

The resulting parametric curves and goodness of fit statistics are discussed further in Section 5 but the KM plots for the pooled chemotherapy study data are presented in Figure 21 and Figure 22. The ERG considers it difficult to draw any conclusions relating to OS or PFS for avelumab compared to chemotherapy in 1L mMCC because the data for avelumab are extremely limited due to the lack of long-term follow-up and small number of patients in the analysis (maximum n=29, and only 14 patients with 6 months or longer follow-up).

[redacted]

Figure 21. OS KM plot for avelumab versus chemotherapy in 1L patients (JAVELIN Merkel 200 and pooled chemotherapy study data; produced by the ERG based on CS Appendix 10 pg 27, Figure 10)

Figure 22. PFS KM plot for avelumab versus chemotherapy in 1L patients (JAVELIN Merkel 200 and pooled chemotherapy study data; produced by the ERG based on CS Appendix 10, pg 26, Figure 10)

4.4.5 Additional analyses

During the clarification stage, the ERG requested the company conduct MAIC analyses using the Study 100070-Obs001 and Iyer 2016[88] chemotherapy data and the JAVELIN Merkel 200 avelumab data. MAIC is a statistical method of adjusting results based on differences in observed patient characteristics that might be indicative of prognostic indicators and/or treatment effect modifiers. MAIC makes use of patient level data from one study compared to the aggregate data from a second study.[179] As highlighted by the company, MAIC is suitable for use in the absence of IPD for both studies. Alternative methods can be used where IPD are available for both studies, such as propensity score matching.

The company reported in their response to the clarification questions that IPD were available for both JAVELIN Merkel 200 and Study 100070-Obs001, and that they therefore did not consider MAIC to be a suitable method for adjustment. The company cited NICE TSD 17[180] in support of this decision and reported that propensity score-based methods that use IPD (such as reweighting or matching), would have be more accurate as they use patient-level data rather than only summary characteristics of aggregated data.

The company also argued that there were, "no predictive or prognostic variables for matching", and so they considered that their base-case using naïve comparisons of unmatched and unadjusted data for the OS and PFS comparisons of avelumab with chemotherapy and BSC was appropriate. The company referenced the regression analyses and KM plots in Appendix 10 of the CS where they considered the only predictive variable in MCC identified was the line of treatment. The company highlighted immunosuppression status as an example of a variable which demonstrated no statistically significant

difference on PFS despite multivariate regression suggesting that immunosuppression was a predictor of longer progression-free survival (p=0.28). In univariate regression, immunosuppression was also not statistically significant (p not reported in CQ response document), and the KM plots for immunosuppressed and immunocompetent patients overlapped several times (CQ response, Figure 5).

2L+ population

In their response to clarification, the company conducted some analyses for the 2L+ population using propensity scoring and regression adjustment (JAVELIN Merkel 200, n= 88; [redacted]). These analyses are discussed further in Section 4.4.5.1 and Section 4.4.5.2.

1L population

The company did not conduct any propensity score matching or regression analyses for the IL population using the JAVELIN Merkel 200 and Study 100070-Obs001 data as they considered the patient numbers and PFS and OS event rates in JAVELIN Merkel 200 were too small (n = 39; [redacted]). The company reported that published literature suggests that for propensity scoring, it is recommended there is a minimum of 10 events for every characteristic to be included.

[redacted]

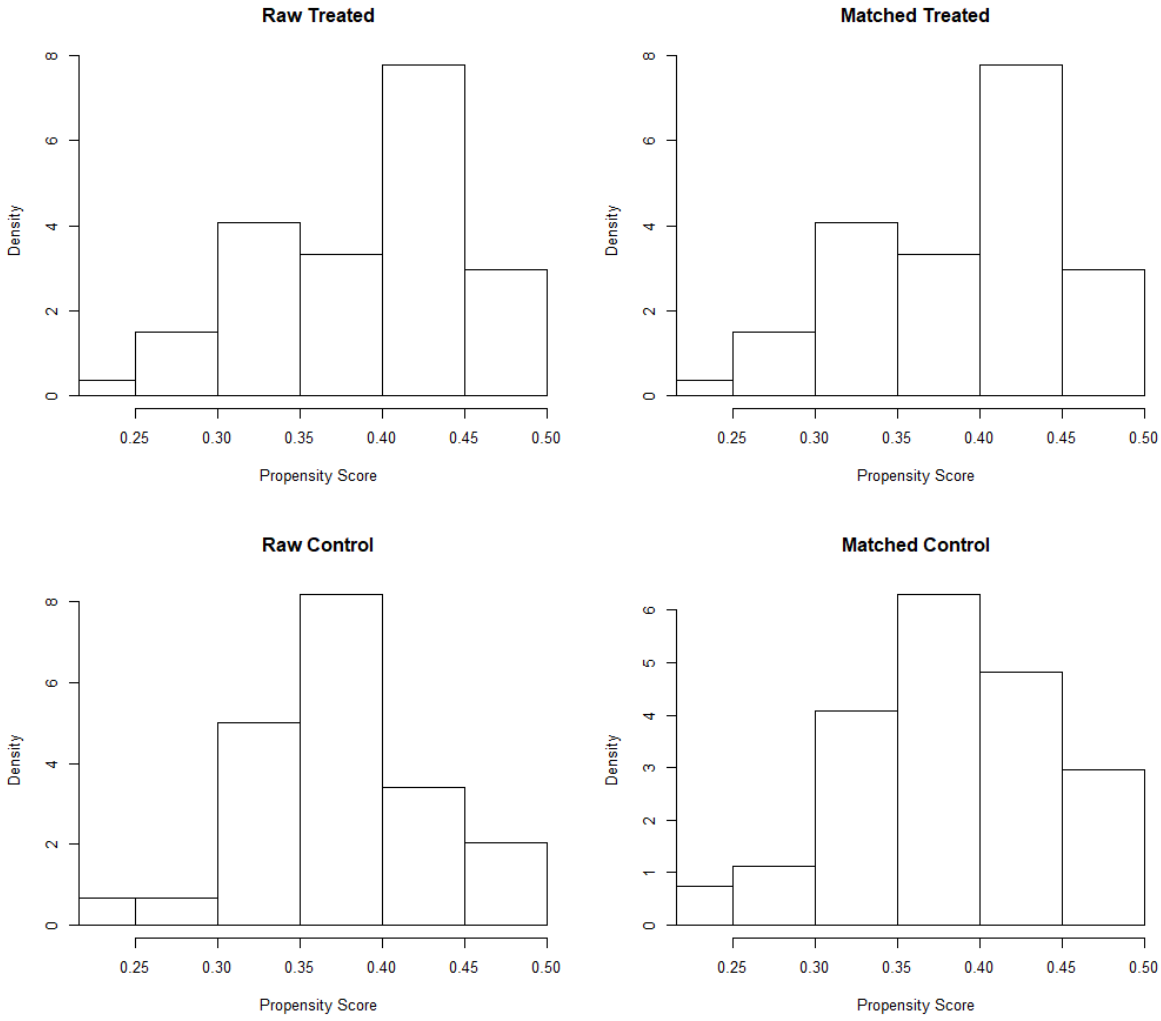
At the clarification stage, the ERG also requested the company conduct an MAIC with the JAVELIN Merkel 200 1L data (part B) and the Iyer 2016[181] 1L data. The company agreed that MAIC methodology was appropriate for this but did not conduct the analysis. The company rationale for not doing this analysis was that the only characteristic listed by the ERG that they could adjust for was age due to data availability, and they did not consider age or other factors to be relevant to OS or PFS given the earlier analyses they conducted into potential prognostics factors (CS, appendix 10). In addition, the company considered the small 1L sample size of JAVELIN Merkel 200 – Part B of only 39 patients, "unlikely to be informative". The only data presented by the company for the 1L population are from the naïve comparisons of JAVELIN Merkel 200, Study 100070-Obs001 and Iyer 2016[88] (Section 4.4.4).

4.4.5.1 Propensity score matching

The company used a propensity score matching method to match the 2L+ patients from Study 100070-Obs001 (US 2L - Part A and EU 2L - Part B; n=54) on a 1:1 basis with 2L+ patients in JAVELIN Merkel 200 (Part A; n=88). Patients were matched based on their propensity score, "using optimal matching across the whole dataset", which the company reported minimised the overall distance between matches. The only variables which the company used in the matching process to calculate the propensity score, were age and gender, [redacted] The ERG is unclear why the company did not explore using alternative variables for matching. The ERG considers that subgroups identified in the subgroup analyses (Section 4.3.5), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, included as characteristics for matching.

The company stated that, "the matched units demonstrate a loose match across both treatment arms with a good overlap between studies" (Figure 23). However, it was also highlighted in the CS that this was based on a, "limited number of variables (two) for matching". The ERG considers there to be a notable difference in the propensity scores of the unmatched and matched patients between the two studies (Figure 23).

Figure 23. Histogram of raw and matched patients (reproduced from CQ response page 5, Figure 1)



[redacted]

Figure 24. Jitter plot of matched and unmatched patients (reproduced from CQ response page 6, Figure 2)

NB: Avelumab patients are classed as 'control' patients by the software, as they are more numerous
Each circle represents an individual patient's propensity score.

The matched patients were used to generated KM curves for OS and PFS for avelumab (Figure 25). The company also included KM curves for the trial level data for the full 88 avelumab patients along with 95% confidence intervals. The ERG considers the 95% confidence interval for the matched population curves are slightly wider, which is as expected given the smaller sample size.

Figure 25: Propensity score matched Kaplan-Meier curves (reproduced from CQ response page 7, Figure 3)

Key: OS, overall survival; PFS, progression-free survival.
Note: The solid lines (——) demonstrate the full patient population, with the darker shaded areas denoting the associated 95% confidence interval. The dashed lines (- - -) demonstrate the propensity matched population, with the lighter shaded areas denoting the associated 95% confidence interval.

Figure 26 and Figure 27 show the JAVELIN Merkel 200 propensity score matched and unmatched 2L+ populations along with the Study 100070-Obs001 pooled US and EU 2L+ chemotherapy data for OS and PFS, respectively.

Figure 26. Propensity score matched OS KM plot for avelumab versus chemotherapy in 2L+ patients (JAVELIN Merkel 200 and Study 100070-Obs001 [pooled EU and US data]; produced by the ERG based on clarification responses Figure 4 and CS Figure 45)

Figure 27. Propensity score matched PFS KM plot for avelumab versus chemotherapy in 2L+ patients (JAVELIN Merkel 200 and Study 100070-Obs001 [pooled EU and US data]; produced by the ERG based on clarification responses Figure 4 and CS Figure 45)

[redacted]

4.4.5.2 Regression analysis

The company conducted regression analyses in addition to the propensity score matching for the 2L+ population comparison of avelumab versus BSC (where chemotherapy was used as a surrogate for BSC). The regression analyses were performed using the IPD from the 2L+ patients from Study 100070-Obs001 (US 2L - Part A and EU 2L - Part B) rather than the JAVELIN Merkel 200 data. The company reported that the Study 100070-Obs001 data was used in preference to the JAVELIN Merkel 200 data because there were more events observed and the data fitted standard parametric regression better. There were, however, fewer 2L+ patients in Study 100070-Obs001 compared to in JAVELIN Merkel 200.

The company stated that Weibull regression was deemed to be the best fitting distribution and predictive variables of age, gender and immunosuppression were included in the model as covariates. Regression analyses were conducted for the outcomes of PFS and OS with the results presented in Figure 28 and Figure 29.

Figure 28. Regression analysis for PFS in 2L+ patients from Study 100070-Obs001 (reproduced from CQ response page 9, Regression 1)

Estimates:

	data mean	est	L95%	U95%	se	exp(est)	L95%	U95%
shape	NA	2.16929	1.75683	2.67859	0.23341	NA	NA	NA
scale	NA	76.93740	53.84810	109.92705	14.00698	NA	NA	NA
as.numeric(Age)	14.29630	0.00968	-0.00616	0.02553	0.00808	1.00973	0.99386	1.02586
gendermale	0.66667	0.12426	-0.14892	0.39744	0.13938	1.13231	0.86163	1.48801
immunosup	0.12963	-0.01875	-0.42404	0.38654	0.20679	0.98142	0.65440	1.47188

N = 54, Events: 54, Censored: 0
Total time at risk: 4626
Log-likelihood = -275, df = 5
AIC = 561

Key: AIC, Akaike Information Criterion.

Figure 29. Regression analysis for OS in 2L+ patients from Study 100070-Obs001 (reproduced from CQ response page 9, Regression 2)

```
Estimates:
                data mean  est        L95%       U95%       se          exp(est)   L95%       U95%
shape                  NA   3.16e+00   2.53e+00   3. .95e+00   3.58e-01         NA         NA         NA
scale                  NA   1.42e+02   1.09e+02   1.86e+02   1.96e+01         NA         NA         NA
as.numeric(Age)   1.43e+01   1.00e-02  -8.93e-04   2.09e-02   5.57e-03   1.01e+00   9.99e-01   1.02e+00
gendermale        6.67e-01  -3.91e-02  -2.39e-01   1.61e-01   1.02e-01   9.62e-01   7.88e-01   1.17e+00
immunosup         1.30e-01   1.87e-01  -1.13e-01   4.88e-01   1.53e-01   1.21e+00   8.93e-01   1.63e+00

N = 54,  Events: 52,  Censored: 2
Total time at risk: 7895
Log-likelihood = -281, df = 5
AIC = 571
```

Key: AIC, Akaike Information Criterion.

The 2L+ cohort of JAVELIN Merkel 200 had a mean age of 69.7 years, were 73.9% male, and 100% immunocompetent, whereas the Study 100070-Obs001 chemotherapy patients had a mean age of 72 years, 66.7% were male and 13% had immunosuppression. The regression analysis was used to match the Study 100070-Obs001patients to the JAVELIN Merkel 200 patients baseline age, gender and immunosuppression status. OS and PFS parameters for Weibull curves were estimated for the Study 100070-Obs001 chemotherapy data matched to the data from the avelumab 2L+ patients and the resulting curves are presented in Figure 30 and Figure 31. [redacted]

Figure 30. Regression analysis curve for chemotherapy in 2L+ patients (Study 100070-Obs001 pooled EU and US data) with JAVELIN Merkel 200 2L+ KM plot for OS (produced by the ERG based on clarification responses pg 9, Regression 2)

Figure 31. Regression analysis curve for chemotherapy in 2L+ patients (Study 100070-Obs001 pooled EU and US data) with JAVELIN Merkel 200 2L+ KM plot for PFS (produced by the ERG based on clarification responses pg 9, Regression 1)

The ERG considers the regression analysis to be a more robust analysis of avelumab versus chemotherapy compared to the naïve comparison and propensity score matching because it adjusts for a greater range of likely covariates. However, the ERG would have preferred an analysis with further

potential prognostic factors adjusted for such as line of therapy 2L or third line and beyond (3L+), and PD-L1 status. The ERG considers that the inclusion of further covariates would confirm the robustness of the company's preferred option, the naïve comparison of study level data from JAVELIN Merkel 200 for avelumab with pooled data from Study 100070-Obs001 for chemotherapy if the results of both analyses were similar.

4.4.6 Safety data for chemotherapy studies

As discussed in Section 4.1, the company conducted a separate safety SLR looking for chemotherapy studies in melanoma and SCLC. The safety SLR identified a total of 80 studies suitable for inclusion (59 SCLC[88, 90-141] and 21 melanoma[137, 142-165]). The company did not discuss the safety SLR or its findings in the clinical effectiveness section of CS, and no safety data were provided for chemotherapy studies in mMCC in the CS. The company reported in the CS that, "Where evidence for the chemotherapies' use in metastatic MCC was unavailable, evidence related to their use in the treatment of small-cell lung cancer (SCLC) has been used as the best proxy for likely AE rates due to similarities in the neuroendocrine properties between the two diseases". The ERG notes that not all 80 of the chemotherapy studies were used in the economic model. The company stated that, "data were extracted from studies identified in the SLR for each treatment matching patient characteristics, such as age and ECOG performance status as closely as possible with patients from the JAVELIN Merkel 200 trial. No further detail was provided in the CS on the selection criteria used in the process to narrow down the 80 studies.

The ERG considers the two chemotherapy regimens most commonly used in England for mMCC to be of the most relevance for the comparison with avelumab: carboplatin + etoposide, and cisplatin + etoposide. The ERG notes that in Table 24 of Appendix 15 of the CS, the Grade 3 and 4 AE probabilities used for the economic model are summarised, and the company cites one study for the data used for each of these two chemotherapy regimens (carboplatin + etoposide[166] and cisplatin + etoposide[182]). The ERG therefore considers these to be the most relevant studies for its critique on the AEs associated with chemotherapy regimens compared to avelumab.

The ERG notes that the two AE studies for the chemotherapy regimens were RCTs in patients with extensive SLCL rather than mMCC. All Grade 3 and 4 AEs reported in Socinski 2009[136] and Sun 2016[132, 136] for the two chemotherapy regimens of interest are presented alongside the Grade 3 and 4 AEs occurring in at least 2 patients in JAVELIN Merkel 200 in Table 32. The ERG acknowledges that only Grade 3 and 4 AEs are discussed here and that these AEs may not be reflective of the most frequently occurring AEs seen in clinical practice (i.e. AEs of any Grade). However, given that Grade 3 and 4 are likely to have the greatest impact on a patients HRQoL, the ERG considers it appropriate to focus its critique on these.

The most frequently occurring Grade 3 or 4 AE's in the 2L+ cohort treated with avelumab were asthenia (12.5%), anaemia (10.2%) and lymphopenia (6.8%). No individual Grade 3 or 4 AE occurred in more than one patient with avelumab in the 1L cohort of JAVELIN Merkel 200. In contrast, the most frequently occurring Grade 3 or 4 AE's with carboplatin + etoposide were neutropenia (47%), thrombocytopenia (10%) and hair loss (any grade) (34%). Grade 3 and 4 AE's with cisplatin + etoposide were similar in type to those observed with the carboplatin chemotherapy regimen: neutropenia (44%), leukopenia (19.3%) and hair loss (any grade) (13.3%).

Table 32. Grade 3/4 adverse event data for JAVELIN Merkel 200 avelumab study and the comparator SCLC chemotherapy studies

	Avelumab		**Carboplatin + etoposide**	**Cisplatin + etoposide**
Data source	JAVELIN Merkel 200 Part A[136]	JAVELIN Merkel 200 Part B	Socinski 2009[3]	Sun 2016[182]
Population	Chemotherapy refractory mMCC	`Treatment naïve mMCC	Extensive SCLC	Extensive SCLC
Number of patients	88		447	150
Line of therapy	2L+	1L	1L	1L
% ECOG 0/1	100 (44% had a score of 1)	100 (20.7% had a score of 1)	88	100 (78,7% had a score of 1)
Treatment	Avelumab 1h IV infusion, 10 mg/kg, once every 2 weeks	Avelumab 1h IV infusion, 10 mg/kg, once every 2 weeks	Etoposide 100mg/m^2 on day 1–3, carboplatin AUC 5 on day 1 every 3 weeks (up to 6 cycles)	Etoposide 100mg/m^2 on day 1–3 and cisplatin 80mg/m^2 on day 1 every 3 weeks (up to 6 cycles)
Grade 3 – 4 AEs*				
Anaemia	9 (10.2%)	-	33 (7.4%)	10 (6.7%)
Dyspnoea	1 (1.1%)	-	-	-
Fatigue	2 (2.3%)	0	14 (3.1%)	0
Febrile neutropenia	-	-	20 (4.5%)	-
Low haemoglobin	-	-	-	8 (5.3%)
Hyponatremia	2 (2.3%)	-	5 (1%)	-
Leukopenia	-	-	37 (8.3%)	29 (19.3%)
Lymphopenia	6 (6.8%)	-	-	-
Nausea	0	-	1 (0.2%)	4 (2.7%)
Vomiting	0	-	3 (0.7%)	6 (4.0%)
Neutropenia	-	-	210 (47%)	66 (44%)
Thrombocytopenia	-	-	46 (10%)	11 (7.3%)
Hair loss (any grade)	-	-	152 (34%)	20 (13.3%)
Constipation	0	-	-	0
Diarrhoea	0	-	2 (0.4%)	1 (0.7%)
GI disorder	-	-	-	1 (0.7%)
Pyrexia	0	-	-	0
Anorexia	-	-	-	5 (3.3%)
Lipase increase	3 (3.4%)	0	-	-

General physical health deterioration	2 (2.3%)	-	-	-
Leukocytosis	2 (2.3%)	-	-	-
Pleural effusion	2 (2.3%)	-	-	-
GGT increased	3 (3.4%)	-	-	-
Hypotension	2 (2.3%)	-	-	-
Hypertension	5 (5.7%)	-	-	-
Asthenia	11 (12.5%)	-	-	-
Decreased appetite	2 (2.3%)	-	-	-
Abdominal pain	2 (2.3%)	-	-	-
ALT increased	2 (2.3%)	1 (3.4%)	-	-
Infusion-related reaction	-	1 (3.4%)	-	-
AST increased	1 (1.1%)	1 (3.4%)	-	-
Gait disturbance	-	1 (3.4%)	-	-
Autoimmune nephritis	-	1 (3.4%)	-	-
Cholangitis	-	1 (3.4%)	-	-
Paraneoplastic syndrome	-	1 (3.4%)	-	-

Abbreviations: RCT, randomised controlled trials; SCLC, small cell lung cancer; mMCC, metastatic Merkel cell carcinoma; CTCAE, common terminology criteria for adverse events; ECOG, Eastern Cooperative Oncology Group performance status; AE, adverse event; GI, gastrointestinal; GGT, gamma-glutamyltransferase; ALT, alanine aminotransferase

Nb. Rates of Grade 3 and 4 events for avelumab are taken from the Kaufman 2016 supplementary appendix listing treatment-emergent events (rather than treatment-related); grade 3 and 4 rates have been added together.

*Rates for 2L+ Avelumab and cisplatin are for treatment-emergent events whereas the rates for carboplatin+etoposite and 1L avelumab are described as drug/treatment-related. All studies used CTCAE criteria.

4.5 Summary of clinical effectiveness

The results of JAVELIN Merkel 200 suggest that in both the 1L and 2L+ populations, avelumab is associated with favourable efficacy outcomes in terms of response rate although it is impossible to tell how it compares to chemotherapy and BSC due to the efficacy data being only from single-arm studies. In addition, it should be remembered that avelumab was associated with a high level of TRAEs.

Median PFS for the 2L+ cohort (Part A) of JAVELIN Merkel 200 was 2.7 months (95% CI: 1.4 to 6.9) at the 18-month follow-up analysis and the same proportion of patients who were progression-free at 12 months remained progression free at 18 months ([redacted]. The ERG considers that the OS data are still relatively immature for the 2L+ cohort although at 18-months follow-up, [redacted] had died at data cut-off and median OS was reported to be [redacted]. The ORR for the 2L+ cohort at the 18-month analysis was [redacted] and the proportion of patients with a BOR of stable disease was [redacted]. The estimate of the proportion of patients with ≥6 months duration of response (DoR) was [redacted] in the 18-month analysis for the 2L+ cohort) and the 18-month DRR was 30.7%. The HRQoL data from the 2L+ cohort comprised of EQ-5D data, FACT-M questionnaire responses and qualitative patient interviews. In

general, the HRQoL data suggest a trend of improvement in HRQoL over time with avelumab treatment although there were no data reported in the CS that reached statistical significance.

The 2L+ subgroup analyses reported in the CS for the subgroups of number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status were highlighted by the company in the forest plot in the CS. The ERG considers these highlighted subgroups suggest there may be within subgroup differences in ORR with avelumab although the ERG acknowledges the differences were not statistically significant but some subgroups comprised a very low number of patients.

In the 1L cohort (Part B) of JAVELIN Merkel 200, the median PFS was 9.1 months (95% CI: 1.9 to not reached) in the ≥3-month follow-up analysis. The ERG considers the OS data from the 1L cohort should be interpreted with caution as they are immature and based on small patient numbers in an interim analysis. Median OS had not been reached at the 3-month analysis for the 1L cohort; the KM estimates for OS in the 1L population suggested a 3-month OS rate of [redacted]. The 6-month results for ORR in the 1L cohort suggest they have [redacted]. The 6-month DRR in the 1L patients with ≥6 months follow-up (n=[redacted]) was [redacted], and [redacted]) of responses had a duration of ≥6 months. No HRQoL data were reported for the 1L population in the CS.

The median duration of therapy for the 2L+ cohort was 17 weeks (range: 2.0 to 132.0 weeks) with a median number of infusions of [redacted]. The median duration of therapy in the 1L cohort was [redacted] with a median number of infusions of [redacted]. The ERG notes that as of 3 March 2016, 97.7% (86/88) of the 2L+ patients experienced an AE during JAVELIN Merkel 200 and 75% of the 2L+ patients (66/88) experienced an AE that was deemed to be a treatment-related AE (TRAE). In the 1L cohort, as of 30 December 2016, 71.8% (28/39) patients had experienced a TRAE. The ERG notes that the most common treatment-emergent adverse (TEAE) was [redacted]. In terms of serious TEAEs, [redacted] in the 2L+ cohort experienced a serious TEAE and [redacted] of the serious TEAEs were deemed to be related to treatment with avelumab based on the 18-month follow-up data set. In the 1L cohort, [redacted]) of patients experienced a serious TEAE and [redacted] of these were attributed to avelumab (3-month follow-up data set). Deaths due to any TEAE were reported in [redacted] in the 2L+ cohort and [redacted] in the 1L cohort; [redacted]. Given the mechanism of action of avelumab, the ERG considers that immune-related AEs (irAEs) are of clinical importance. Data were provided on irAEs for only the 2L+ cohort; the most common immune-mediated reactions in the 2L+ cohort were [redacted].

In the clinical section of the CS, the company provided a naïve comparison of avelumab versus chemotherapy in the 1L and 2L+ populations using a retrospective observational study that they conducted specifically for the comparison (Study 100070-Obs001), and Iyer 2016, a study identified through the company's systematic literature reviews (SLRs). In addition, a further six studies were explored for use in the economic modelling.

The company provided an appendix to the CS (CS appendix 10) detailing a series of analyses which were presented as evidence to show there are no patient characteristics that are prognostic of outcomes (including factors such as ECOG PS and stage at diagnosis in mMCC). The company conducted separate regression analyses for the 1L and 2L+ populations using the Study 100070-Obs001 chemotherapy data for the following baseline characteristic subgroups:

- stage at diagnosis,
- age,
- gender,
- immunosuppression status, and
- ECOG PS.

The company used these regression analyses and visual inspections of KM plots, as the basis for their assertion that it was not necessary to adjust for prognostic factors or use treatment effect modifier techniques such as matching adjusted indirect comparison (MAIC) or simulated treatment comparison (STC). The ERG considers the small number of patients in the regression analyses presented by the company in CS appendix 10 means that there is a large amount of uncertainty around the results purely based on an initial small sample size. The ERG, therefore, considers that caution should be taken when drawing conclusions from the statistically non-significant results from the regression analyses, as they could be a result of the small patient numbers rather than the absence of a subgroup effect (prognostic indicator). The ERG considers that subgroups identified in the subgroup analyses (CS page 83, Figure 18), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, the company should have adjusted outcomes appropriately.

Study 100070-Obs001 was a retrospective, observational study conducted by Merck KGaA/Pfizer in two parts; one in the EU (EU2L; n=34), and one in the US (US2L; n=20, and US1L; n=67). The company reported that Study 100070-Obs001 was designed to investigate clinical outcomes in mMCC patients with chemotherapy treatment and to provide comparator data on PFS and OS for the avelumab

data from JAVELIN Merkel 200. Study 100070-Obs001 included adult patients with distant mMCC and was conducted in two parts: Part A was conducted in the US and included both 1L and 2L+ patients, whereas Part B was conducted in Europe and only included 2L+ patients. The pooled data from the US and EU 2L+ cohorts were used in the economic analyses and therefore the ERG critique will focus on the pooled dataset. However, the ERG and the company considered the EU study most likely to best reflect clinical practice in England as the US studies are likely to be associated with more aggressive treatments, resulting in improved outcomes.

In terms of baseline characteristics for the 2L+ populations, the ERG notes that 30.0% of the US 2L+ patients and 14.7% of the EU 2L+ patients in Study 100070-Obs001 were immunocompromised, in contrast to 0% of the JAVELIN Merkel 200 patients. The ERG considers immunosuppression to be a potential confounder and that results of Study 100070-Obs001 that include the immunosuppressed patients should be interpreted with caution. The median age in the EU 2L+ cohort of Study 100070-Obs001 was substantially younger compared to the US cohort and the JAVELIN Merkel 200 2L+ patients (67.5 years, 72.5 years and 73.5 years, respectively). Baseline ECOG performance status data were only available for the US part of Study 100070-Obs001, but this suggests that the patients in JAVELIN Merkel 200 had a better baseline ECOG status compared to the patients in Study 100070-Obs001 with more ECOG 0 patients in JAVELIN Merkel 200 (ECOG 0: 55.7% vs 5.0%; JAVELIN Merkel 200 and Study 100070-Obs001, respectively).

Similar to the 2L+ cohort of Study 100070-Obs001, the 1L cohort included immunosuppressed patients (23.9%), whereas none of the 1L JAVELIN Merkel 200 avelumab patients were immunosuppressed. The ERG considers that 1L patients had a better baseline ECOG status in JAVELIN Merkel 200 compared to in Study 100070-Obs001 (79.5% vs 20.9%; JAVELIN Merkel 200 and Study 100070-Obs001, respectively). In addition, there were no ECOG 2 patients in JAVELIN Merkel 200, compared to 9% of patients in Study 100070-Obs001.

The ERG is unclear why the Iyer 2016 paper was selected from the other chemotherapy papers identified by the SLR. The ERG considers the Iyer 2016 study population to be younger than that of the Study 100070-Obs001 and JAVELIN Merkel 200 populations. In addition, the ERG notes Iyer 2016, similar to Study 100070-Obs001, contains immunosuppressed patients that were excluded from JAVELIN Merkel 200.

The results for avelumab in the 2L+ mMCC population of the JAVELIN Merkel 200 trial, relative to chemotherapy (surrogate for BSC) in Study 100070-Obs001 and Iyer 2016, indicate that avelumab is associated with a higher 6-month DRR (30.6% [JAVELIN Merkel 200] vs 0.0% [Study 100070-Obs001] and 6.7% [Iyer 2016]), longer 12-month PFS (29.0% vs 0.0%), longer 12-month OS (50.0% vs 0.0%), and a higher CR rate (11.4% vs 0.0% to 3.3%).

The company considered it appropriate to combine the chemotherapy data from Study 100070-Obs001, Iyer 2016 and Samlowski 2010 (a study identified in the SLRs) in a meta-analysis in the economic modelling for the 2L+ population. The meta-analysis results for both OS and PFS suggest chemotherapy is associated with longer OS and PFS compared to chemotherapy in the pooled data from Study 100070-Obs001 (OS approximately 1.25 years versus approximately 0.75 years, respectively; and PFS approximately 0.75 years versus approximately 0.5 years, respectively). However, the ERG is concerned that the inclusion of Samlowski 2010 introduces clinical heterogeneity as the Samlowski trial population comprises a mix of 1L (n=9) and 2L+ (n=14) patients.

The results for the 1L population of the naïve comparison of avelumab from JAVELIN Merkel 200 Part B with chemotherapy suggest avelumab is associated with improved ORR, PFS and OS outcomes compared to chemotherapy in Study 100070-Obs001 and in Iyer 2016. However, as discussed previously, this comparison is based on small patient numbers for avelumab, and long term follow-up data for avelumab is lacking. The ERG, therefore, considers that the 1L results should be interpreted with caution.

In total, there were seven studies that the company identified from the SLRs and their own observational studies with OS or PFS (or both) data on chemotherapy in 1L mMCC patients (Study 100070-Obs001; Iyer 2016; Voog 1999; Satpute 2014; Santamaria-Barria 2013; Fields 2011; Allen 2005) that were used in a naïve pooling in the economic modelling. The company reported that, "this results in increased patient numbers for analysis, and likely the most generalisable results". The ERG considers that the approach is likely to introduce unnecessary heterogeneity into the analysis although it is not possible to predict the likely direction of the resulting bias. The ERG considers it difficult to draw any conclusions relating to OS or PFS for avelumab compared to chemotherapy in 1L mMCC because the data for avelumab are extremely limited due to the lack of long-term follow-up and small number of patients in the analysis (maximum n=29, and only 14 patients with 6 months or longer follow-up). [redacted] In response to clarification questions, the company conducted a propensity score matching analysis and a regression analysis for PFS and OS for the 2L+ population. In the propensity score matching analysis, the 2L+ patients from Study 100070-Obs001 (US 2L - Part A and EU 2L - Part B; n=54) were matched on a 1:1 basis with 2L+ patients in JAVELIN Merkel 200 (Part A; n=88). The only variables which the company used in the matching process to calculate the propensity score, were age and sex, [redacted] The ERG is unclear why the company did not explore using alternative variables for matching. The ERG considers that subgroups identified in the subgroup analyses (CS page 83, Figure 18), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and

if possible, included as characteristics for matching. The ERG considers there to be a notable difference in the propensity scores of the unmatched and matched patients between the two studies (Study 100070-Obs001 and JAVELIN Merkel 200). However, the [redacted]

The regression analysis was used to match the Study 100070-Obs0012L+ patients to the JAVELIN Merkel 200 2L+ patients baseline age, gender and immunosuppression status. [redacted]. The ERG considers the regression analysis to be a more robust analysis of avelumab versus chemotherapy compared to the naïve comparison and propensity score matching because it adjusts for a greater range of likely covariates. However, the ERG would have preferred an analysis with further potential prognostic factors adjusted for such as line of therapy 2L or third line and beyond (3L+), and PD-L1 status. The ERG considers that the inclusion of further covariates would confirm the robustness of the company's preferred option, the naïve comparison of study level data from JAVELIN Merkel 200 for avelumab with pooled data from Study 100070-Obs001 for chemotherapy if the results of both analyses were similar.

The company did not conduct any propensity score matching or regression analyses for the IL population using the JAVELIN Merkel 200 and Study 100070-Obs001 data as they considered the patient numbers and PFS and OS event rates in JAVELIN Merkel 200 were too small (n = 39; [redacted]). The later data cut that the company anticipates taking place in [redacted], is likely to have an increase in patient number and an increase in the events of interest. The ERG considers this later dataset is likely to provide the basis for a more robust assessment of avelumab versus chemotherapy in 1L patients. However, the ERG also considers that any analysis should be adjusted for potential observed treatment-effect modifiers with justification provided for the variables used.

No safety data were provided for chemotherapy studies in mMCC in the CS; surrogate data from studies in melanoma and small cell lung cancer were used to inform inputs in the economic model.

The ERG considers it important to highlight that the results of JAVELIN Merkel 200 and the naïve comparisons, propensity score matching analyses and regression analyses, all comprise evidence on avelumab from single arm studies that are at high risk of bias and thus should be interpreted with caution. In addition, the results for the 1L subgroup are based on low patient numbers and so are subject to large amounts of uncertainty.

4.6 Conclusions of the clinical effectiveness section

- Avelumab (BAVENCIO®) received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 21 July 2017 for use as a monotherapy for the treatment of adult patients with mMCC.

- The key study providing the evidence of the clinical effectiveness of avelumab is JAVELIN Merkel 200, which comprised of two single-arm studies of avelumab in adults with mMCC; Part A in 2L+ patients and Part B in 1L patients.

- Efficacy results for the 2L+ population of JAVELIN Merkel 200: Median PFS was 2.7 months (95% CI: 1.4 to 6.9) at the 18-month follow-up analysis and the same proportion of patients who were progression-free at 12 months remained progression free at 18 months (29%; 95% CI: 19 to 39%). The ERG considers that the OS data are still relatively immature for the 2L+ cohort although at 18-months follow-up, 54 of 88 patients (61.4%) had died at data cut-off and median OS was reported to be [redacted]. The ORR for the 2L+ cohort at the 18-month analysis was [redacted] and the proportion of patients with a BOR of stable disease was [redacted]. The estimate of the proportion of patients with ≥6 months DoR was [redacted] in the 18-month analysis for the 2L+ cohort) and the 18-month DRR was 30.7%. The HRQoL data from the 2L+ cohort comprised of EQ-5D data, FACT-M questionnaire responses and qualitative patient interviews. In general, the HRQoL data suggest a trend of improvement in HRQoL over time with avelumab treatment although there were no data reported in the CS that reached statistical significance.

- Efficacy results for the 1L population of JAVELIN Merkel 200: median PFS was 9.1 months (95% CI: 1.9 to not reached) in the ≥3-month follow-up analysis. The ERG considers the OS data from the 1L cohort should be interpreted with caution as they are immature and based on small patient numbers in an interim analysis. Median OS had not been reached at the 3-month analysis for the 1L cohort; the KM estimates for OS in the 1L population suggested a 3-month OS rate of [redacted]. The 6-month results for ORR in the 1L cohort suggest they have [redacted]. The 6-month DRR in the 1L patients with ≥6 months follow-up (n=[redacted]) was [redacted], and [redacted]) of responses had a duration of ≥6 months. No HRQoL data were reported for the 1L population in the CS.

- The 2L+ subgroup analyses reported in the CS for the subgroups of number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status were highlighted by the company in the forest plot in the CS. The ERG considers these highlighted subgroups suggest there may be within subgroup differences in ORR with avelumab although the ERG acknowledges the differences were not statistically significant but some subgroups comprised a very low number of patients.

- The ERG notes that as of 3 March 2016, 97.7% of the 2L+ patients experienced an AE during JAVELIN Merkel 200 and 75.0% of the 2L+ patients experienced a TRAE. In the 1L cohort, as of 30 December 2016, 71.8% patients had experienced a TRAE. The ERG notes that the most common TEAE was [redacted]. In terms of serious TEAEs, [redacted] in the 2L+ cohort experienced a serious TEAE and [redacted] of the serious TEAEs were deemed to be related to treatment with avelumab based on the 18-month follow-up data set. In the 1L cohort, [redacted]) of patients experienced a serious TEAE and [redacted] of these were attributed to avelumab (3-month follow-up data set).

- The results for avelumab in the 2L+ mMCC population of the JAVELIN Merkel 200 trial, relative to chemotherapy (surrogate for BSC) in Study 100070-Obs001 and Iyer 2016, indicate that avelumab is associated with a higher 6-month DRR (30.6% [JAVELIN Merkel 200] vs 0.0% [Study 100070-Obs001] and 6.7% [Iyer 2016]), [redacted].

- The results for the 1L population of the naïve comparison of avelumab from JAVELIN Merkel 200 Part B with chemotherapy suggest avelumab is associated with improved ORR, PFS and OS outcomes compared to chemotherapy in Study 100070-Obs001 and in Iyer 2016. [redacted]The company conducted a regression analysis to match the Study 100070-Obs0012L+ patients to the JAVELIN Merkel 200 2L+ patients baseline age, gender and immunosuppression status. [redacted]. The ERG considers the regression analysis to be a more robust analysis of avelumab versus chemotherapy compared to the naïve comparison and

propensity score matching because it adjusts for a greater range of likely covariates. However, the ERG would have preferred an analysis with further potential prognostic factors adjusted for such as line of therapy 2L or third line and beyond (3L+), and PD-L1 status. The ERG considers that the inclusion of further covariates would confirm the robustness of the company's preferred option, the naïve comparison of study level data from JAVELIN Merkel 200 for avelumab with pooled data from Study 100070-Obs001 for chemotherapy if the results of both analyses were similar.

4.6.1 Clinical issues

- Evidence on clinical effectiveness of avelumab is derived from two single-arm studies (JAVELIN Merkel 200 part A and part B), and thus is based on observational data and is at a high risk of bias.

- Single-arm studies are not considered by the FDA to be an appropriate design to capture time to event outcomes such as PFS and OS.

- There were no estimates of the clinical effectiveness of avelumab from head-to-head studies and no clinical data provided on BSC in the 2L+ population, instead chemotherapy data were used as a surrogate.

- The ERG has concerns around the generalisability of JAVELIN Merkel 200 Part A and Part B to clinical practice in England as there were no patients enrolled from study sites in England. In addition, it is considered that the ECOG PS of patients in both studies was better than expected for mMCC patients in England who are likely to be eligible for avelumab.

- OS data are likely confounded by the use of subsequent treatment although no data on subsequent treatments were recorded as part of JAVELIN Merkel 200.

- There were high levels of TRAEs in both the 1L and 2L+ cohorts of JAVELIN Merkel 200 (78.1% and 75.0% of patients, respectively).

- The ERG is concerned that Study 100070-Obs001 included immunosuppressed patients, whereas none of the JAVELIN Merkel 200 avelumab patients were immunosuppressed. In addition, the ERG considers that 1L and 2L+ patients had a better baseline ECOG status in JAVELIN Merkel 200 compared to in Study 100070-Obs001.

- The ERG considers the small number of patients in the regression analyses presented by the company in CS appendix 10 means that there is a large amount of uncertainty around the results purely based on an initial small sample size. The ERG, therefore, considers that caution should

be taken when drawing conclusions from the statistically non-significant results from the regression analyses, as they could be a result of the small patient numbers rather than the absence of a subgroup effect (prognostic indicator).

- The ERG considers that subgroups identified in the subgroup analyses (Section 4.3.5), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, the company should have adjusted outcomes appropriately.

- The ERG considers that results of the company's naïve comparisons should be interpreted with caution because they are based on non-randomised data and are at a high risk of bias. In addition, conclusions around comparative effectiveness of interventions should not be made from results from single-arm studies and the results for mMCC are based on small patient numbers (<100 patients) thus the evidence base is extremely limited for drawing any conclusions relating to avelumab in 1L or 2L+ mMCC.

- There is no data on the long-term safety and efficacy of avelumab and data on OS in mMCC from JAVELIN Merkel 200 are immature, [redacted]

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© EXCEL based economic model. Table 33 summarises the location of the key economic information within the company's submission (CS).

Table 33. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	5.1
Model structure	5.2.2
Technology	5.2.3
Clinical parameters and variables	5.3
Measurement and valuation of health effects and adverse events	5.4
Resource identification, valuation and measurement	5.5
Summary of base case inputs and assumptions	5.6
Results	5.7
Sensitivity analyses	5.8
Subgroup analysis	5.9
Validation	5.10
Interpretation and conclusions	5.11
Abbreviations used in table: CS, company submission.	

5.2 Summary of the company's key results

The company's base case results for the treatment experienced population are given in Table 34 and for the treatment-naïve population in Table 35. A fully incremental analysis for the treatment-naïve population is also presented in Table 36, given the multiple comparators.

Table 34. Results of company's base case analysis for treatment-experienced patients (produced from company's model after clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,752	3.53	2.22	-	-	-	-
BSC	£7,465	0.41	0.31	£71,287	3.11	1.91	£37,350
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; IFN: Interferon; QALY, Quality-adjusted life year.							

Table 35. Results of company's case analysis for treatment-naïve patients (produced from company's model after clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,588	4.78	2.93	-	-	-	-
Chemotherapy	£10,608	2.02	1.37	£67,979	2.76	1.56	£43,553
BSC	£7,217	2.02	1.38	£71,371	2.76	1.55	£46,148
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; IFN: Interferon; QALY, Quality-adjusted life year.							

Table 36. Results of company's fully incremental base case analysis for treatment-naive patients (produced from company's model after clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£7,217	2.02	1.38				
Chemotherapy	£10,608	2.02	1.37	£3,392	0.00	-0.01	Dominated
Avelumab	£78,588	4.78	2.93	£71,371	2.76	1.55	£46,148
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic review (SLR) to identify published cost-effectiveness studies assessing pharmacological treatments for adults with metastatic Merkel cell carcinoma (mMCC). The search was originally carried out on 28 July 2016, and updated on 16 May 2017.

The company provided the search terms and strategies that were applied in the systematic search in Appendix 7 of the company's submission (CS). The company searched the following electronic databases on Ovid (Medline, Medline in Process, EMBASE), in addition to the Cochrane Library and the Centre for Reviews and Dissemination (CRD) databases (DARE [Database of Abstracts of Reviews of Effects], HTA [Health Technology Assessment] and NHS-EED [NHS-Economic Evaluation Database]). Additionally, the company searched the publications of the following annual conferences held between August 2016 and May 2017 for abstracts reporting cost-effectiveness studies in mMCC:

- American Society of Clinical Oncology (ASCO);
- European Society of Medical Oncology (ESMO);
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

The search used a combination of disease and outcome terms to identify relevant cost-effectiveness studies. The inclusion and exclusion criteria applied in the search are presented in Table 37, and the

ERG considers them appropriate to identify all relevant publications. No limits were placed on the search in terms of language or date.

Table 37. Inclusion and exclusion criterian applied in the systematic literature review of cost-effectiveness studies (CS, pg 101, Table 29)

Inclusion criteria		**Rationale**
Population	Age: adults aged ≥18 years Gender: any Ethnicity: any Disease: metastatic MCC	Consistent with evidence base and anticipated marketing authorisation.
Interventions/Comparators	Any pharmacological treatment	This allows all relevant evidence to be identified
Outcomes	Cost- effectiveness, direct/indirect costs, resource use, BSC costs, costs, life years, QALYs, ICERs	The aim of the review was to identify relevant economic evaluations, which reported costs.
Study design	Cost-effectiveness analyses, cost-minimisation analyses, cost-utility analyses, cost/burden of illness, costing studies	The aim of the review was to identify relevant economic evaluations
Limits	No language restrictions	With limited data in MCC, all languages were included to identify all published literature
Exclusion criteria		**Rationale**
Intervention/Comparators	Studies exclusively focusing on the role of radiotherapy, chemo-radiotherapy, hormonal therapy, diagnostics, screening or surgery Studies investigating the role of maintenance/consolidation therapy after surgery Adjuvant or neo-adjuvant therapy Does not include chemotherapy regimens that are listed as comparators	In line with the anticipated NICE scope, studies were restricted to those evaluating the efficacy of comparators. Comparators were restricted to chemotherapies and BSC.
Population	Studies that included children and adults and did not provide subgroup analysis for the adult populations	Consistent with the evidence base for avelumab
Outcomes	No relevant costs or resource use	Aim of the review was to identify relevant economic evaluations reporting costs or resource use
Study design	Systematic literature reviews and meta-analyses	Studies from systematic literature reviews and meta-analyses were cross checked to ensure all relevant publications were identified
Country	None	Review was kept broad considering the limited data
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; MCC, Merkel Cell Carcinoma; QALY, quality-adjusted life year;		

The company did not identify any studies in the search. Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts.

The ERG considers the search carried out by the company to be appropriate, and sufficient to identify any published cost-effectiveness studies for treatments of mMCC.

5.4 Overview and critique of company's economic evaluation

The company submitted a *de novo* economic model to assess the cost-effectiveness of avelumab compared to chemotherapy or best supportive care (BSC) in treatment-naïve patients with mMCC, and compared to BSC in treatment-experienced patients with mMCC.

The evidence for the effectiveness of avelumab is based on the single arm JAVELIN Merkel 200 trial,[136] with comparator evidence for chemotherapy estimated from observational studies, some of which were conducted by the company given a lack of published evidence identified through the SR. No head-to-head trials were available so a naïve comparison of these data sources was used to inform the company's base case analysis.

The remainder of this section provides a detailed description of the company's methods and data sources used to model the cost-effectiveness of aveluamb in mMCC patients, as well as the ERG's critique of those methods and data sources.

5.4.1 NICE reference case checklist

Table 38 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope outlined in Section 3.

Table 38. NICE reference case checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-utility analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes. The time horizon was set at 40 years, which was deemed sufficient to capture the lifetime of patients on with mMCC.
Synthesis of evidence on outcomes	Systematic review	Yes. A systematic review was conducted to identify data sources for outcome measures including disease progression, mortality and quality of life.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes. Utility values were based on EQ-5D-5L scores elicited from patients with mMCC in the JAVELIN Merkel 200 trial, which were then mapped to EQ-5D-3L using the mapping study by Van Hout et al 2012.[3]
Benefit valuation	Time-trade off or standard gamble	Yes. Time-trade of valuation of the EQ-5D.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes. EQ-5D UK tariff.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

Abbreviations used in the table: EQ-5D, EuroQol-five dimensions questionnaire; HRQoL, health-related quality of life; mMCC, metastatic merkel cell carcinoma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.

5.4.2 Population

The company's economic model is based on the population of the JAVELIN Merkel 200 trial, i.e. people with mMCC, and considers patients who have been previously treated with chemotherapy and those who have not. The ERG considers the population in the company's model to be reflective of the NICE scope.[174]

5.4.3 Interventions and comparators

The economic analysis compared avelumab with both chemotherapy and best supportive care (BSC). Avelumab administration was applied in the model in the same way as it was administered in the JAVELIN Merkel 200 trial, and the ERG's clinical experts consider this to be reflective of clinical practice in the UK. Avelumab was administered at a dose 10 mg/kg and was treated beyond progression with a median time on treatment of 113 days, compared to median progression-free survival (PFS) of 82 days.

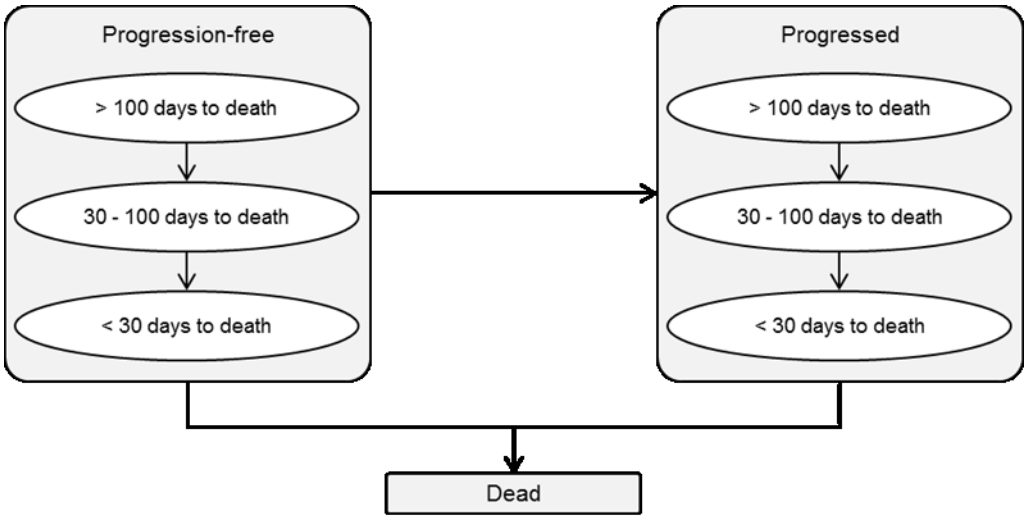
Chemotherapy was considered to be either carboplatin+etoposide or cisplatin+etoposide, and was applied as an even split in the model. This was considered to be a reasonable assumption by the ERG's clinical experts. Although the evidence for treatment effectiveness was based on a large range of chemotherapy regimens, including the two aforementioned, the ERG's clinical experts considered the effectiveness of these regimens to be similar. The duration of treatment for chemotherapy was fixed at six cycles of treatment. This was considered reasonable by the ERG's clinical experts.

The company state that chemotherapy is unlikely to be given beyond first line so BSC is the primary comparator at for the treatment-experienced population. This is in line with the NICE scope.[1] However, the company state that a small proportion of patients may be expected to receive chemotherapy at second line, so a sensitivity analysis was conducted with chemotherapy costs applied to all patients at second line.

5.4.4 Modelling approach and model structure

The company developed a *de novo* economic model in Microsoft® Excel to assess the cost-effectiveness for avelumab in both a first- and second-line setting. The company used a partitioned survival or "area under the curve" (AUC) structure, with three overarching health states: progression-free (PF) disease; progressed disease (PD); and, death. Within the PF and PD health states, the structure incorporates time until death in order to apply a deterioration in health-related quality of life as a patient approaches death. This was included as three separate sub-states: greater than 100 days to death; 30-100 days until death; and, less than 30 days until death. These intervals were chosen based on a statistical analysis indicating that there were key differences in utilities for these intervals. This is discussed in more detail in Section 5.4.8. The model structure is presented graphically in Figure 32.

Figure 32. Model Structure (CS, page 103, Figure 20)



The model estimates the proportion of patients in each of the overarching health states at weekly cycles up to a time horizon of 40 years. The proportion of patients in each state is determined by parametric survival curves fitted to PFS and OS data from the JAVELIN Merkel 200 trial and various observational studies, for avelumab and chemotherapy, respectively. The survival analysis and the data sources used are discussed further in Section 5.4.5.

5.4.4.1 ERG critique

The ERG considers the company's model structure to be reasonable as it includes all relevant health states and appropriately uses the survival data to apply relevant costs and health state utility values (HSUVs) to all patients at the appropriate stage of their disease throughout the disease pathway.

A partitioned survival structure is one commonly used for cancer models, however, the application of HSUVs using a time to death approach is not necessarily so. The ERG considers this a reasonable approach that can capture the changes in quality of life (QoL) that patients experience over their lifetime, in addition to the changes experienced after progression of the disease.

The cycle length of one week is short enough to capture the key changes in the disease pathway and the treatment pathway to apply the costs and HSUVs with sufficient accuracy. The time horizon of 40 years is long enough for approximately all patients to have reached death and, therefore, represents the lifetime of patients sufficiently.

5.4.5 Treatment effectiveness

The key measures of treatment effectiveness for the company's model are PFS and OS. This data informs both the expected survival as well as the expected progression profile for patients receiving each of the treatments being assessed – two key factors influencing the expected number of quality-adjusted life-years (QALYs) accrued by patients on each treatment. In the absence of comparative trial data, treatment effects were measured using separate sources of data. These are discussed separately for the first- and second-line settings. The company based the modelling for the treatment-naïve population in relative terms to that of the treatment-experienced population, and, hence, the treatment-experienced, or second-line population is discussed first.

5.4.5.1 Treatment experienced (second-line)

5.4.5.1.1 Avelumab effectiveness

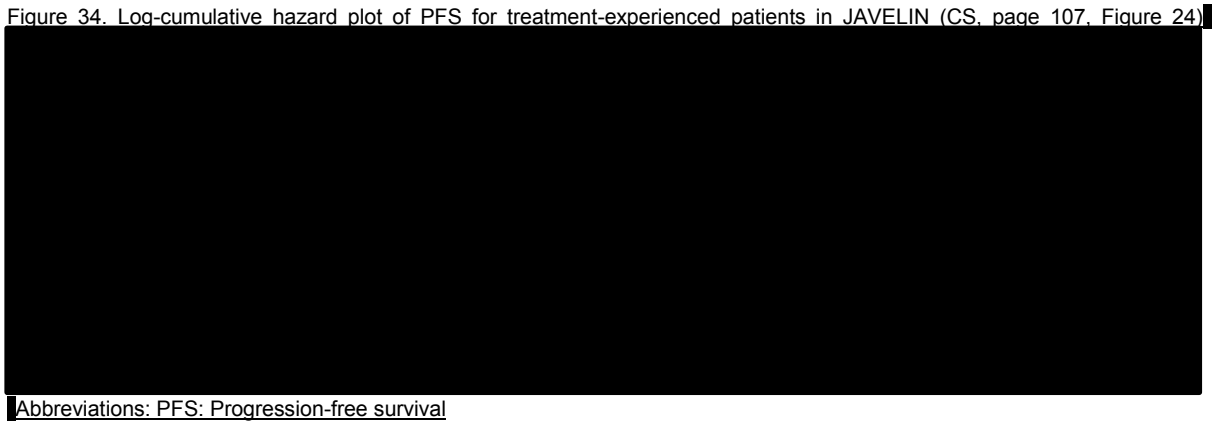
The JAVELIN Merkel 200 trial was the source of PFS and OS data for patients receiving avelumab following previous treatment with chemotherapy. This data showed a median PFS of 2.7 months and a median OS of [redacted] The Kaplan-Meier plots for both PFS and OS in the treatment-experienced population of the JAVELIN Merkel 200 trial are shown in Figure 33.[1]

Figure 33. Kaplan-Meier plots of PFS and OS for treatment-experienced patients in JAVELIN (CS, page 107, Figure 23)

Note: Shaded area demonstrates the 95% CI around the Kaplan-Meier function
Abbreviations: CI: Confidence interval; OS: Overall survival; PFS: Progression-free survival

Given the immaturity of the data, the company fitted a range of survival curves to provide an extrapolation beyond the trial period. To do this, the company firstly produced and assessed plots of log-cumulative hazard against log time (log-log plots), for both PFS and OS, to determine the monotonicity of the observed hazards, and, therefore, the extent to which a more flexible survival modelling approach using splines may be required. These plots are given in Figure 34 and Figure 35 for PFS and OS, respectively.

Figure 34. Log-cumulative hazard plot of PFS for treatment-experienced patients in JAVELIN (CS, page 107, Figure 24)



Abbreviations: PFS: Progression-free survival

Figure 35. Log-cumulative hazard plot of OS for treatment-experienced patients in JAVELIN (CS, page 108, Figure 25)

Abbreviations: OS: Overall survival

The log-log plot for PFS clearly demonstrates a non-monotonic hazard function, which, the company state, is an indication that standard parametric survival models would be unsuitable. The company, therefore, chose to fit a variety of flexible spline-based survival models rather than the less flexible, standard parametric curves. These included hazard-, odds- and normal-based spline models, using up to 3 knots. The company considered more than 3 knots to be unnecessary as it could result in overfitting.

Given the long tail observed in the KM plot for PFS, the company chose to censor all patients at 18 months to avoid the spline function being overly influenced by this uncertain and potentially optimistic plateau. The company also fitted the same spline curves to the data without censoring at 18-months, and the curves showed very little difference. The company opted for the 18-month censored data curves for the base case as these produced a slightly more conservative extrapolation. These are shown in Figure 36.

For OS, monotonicity in the hazard function is less apparent. However, for completeness, the company fitted standard parametric curves as well as spline-based curves for OS, but the company indicated a preference for the more flexible spline-based curves because they potentially provide more realistic long-term estimates by not imposing a monotonic hazard function. The spline-based curves and standard parametric curves for OS are given in Figure 37 and Figure 38, respectively.

Figure 36. Spline curve fits for PFS for treatment experienced patients (18-month censoring) (CS, page 111, Figure 27)

Note: The projections shown here are adjusted within the economic model to avoid over-estimation versus the predicted OS for avelumab patients.
Abbreviations: KM: Kaplan–Meier; PFS: Progression-free survival

Figure 37. Spline curve fits for OS for treatment experienced patients (CS, page 113, Figure 28)

Abbreviations: KM: Kaplan–Meier; OS: Overall survival

Figure 38. Parametric curve fits for OS for treatment-experienced patients (CS, page 114, Figure 29)

Abbreviations: KM: Kaplan–Meier; OS: Overall survival

To assess the best fitting curves for both OS and PFS, the company used the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) as measures of the statistical goodness-of-fit, as well as considering the plausibility of the resulting extrapolation by visual inspection.

For PFS, the company's chosen curve for the base case analysis was the 3-knot odds spline, and for OS, the chosen curve was the 1-knot odds spline. These curves had the least AIC and BIC, and hence, the best statistical fit. The alternative spline models, i.e., the hazard- and normal-based splines, with an equal number of knots, i.e., 1 knot and 3 knots for OS and PFS, respectively, showed almost equivalent goodness-of-fit.

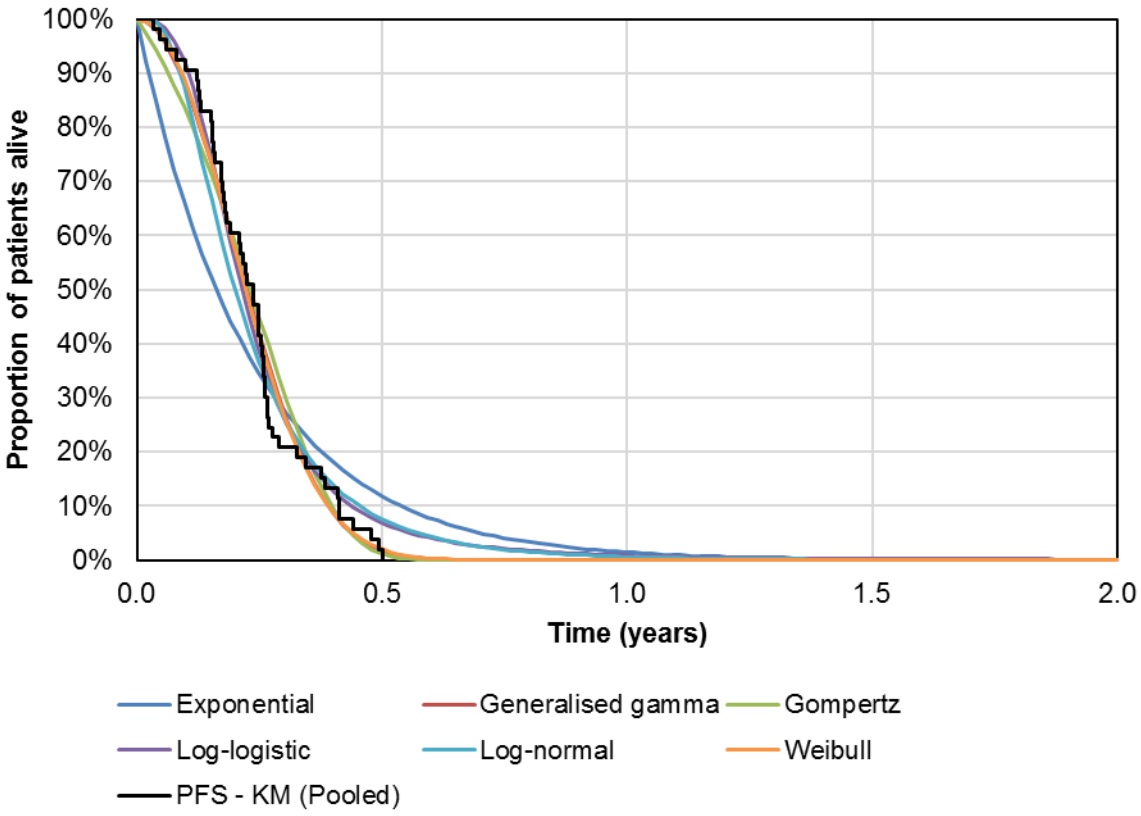
5.4.5.1.2 Comparator effectiveness

Although chemotherapy was not considered a primary comparator in the base case analysis for treatment-experienced patients, the effectiveness of BSC was assumed to be equivalent to chemotherapy. This was considered reasonable by the company's clinical experts given that chemotherapy would potentially be more effective, therefore, making the comparison relative to avelumab, conservative. To estimate the effectiveness of chemotherapy in treatment-experienced patients, and also the assumed effectiveness of BSC, the company used pooled patient level data from both the EU and US observational studies conducted by Merck KGaA/Pfizer,[3, 89] to estimate both PFS and OS for chemotherapy. These data were considered the most suitable to form the basis of a

comparison with the JAVELIN Merkel 200 trial as opposed to the studies identified in the SLR described in 4.1. The inclusion/exclusion criteria were similar in the observational studies conducted by Merck KGaA/Pfizer to the JAVELIN Merkel 200 trial and, therefore, the patient populations were considered more likely to match those in the JAVELIN Merkel 200 trial. The company fitted standard parametric survival curves to the pooled data, which are given in

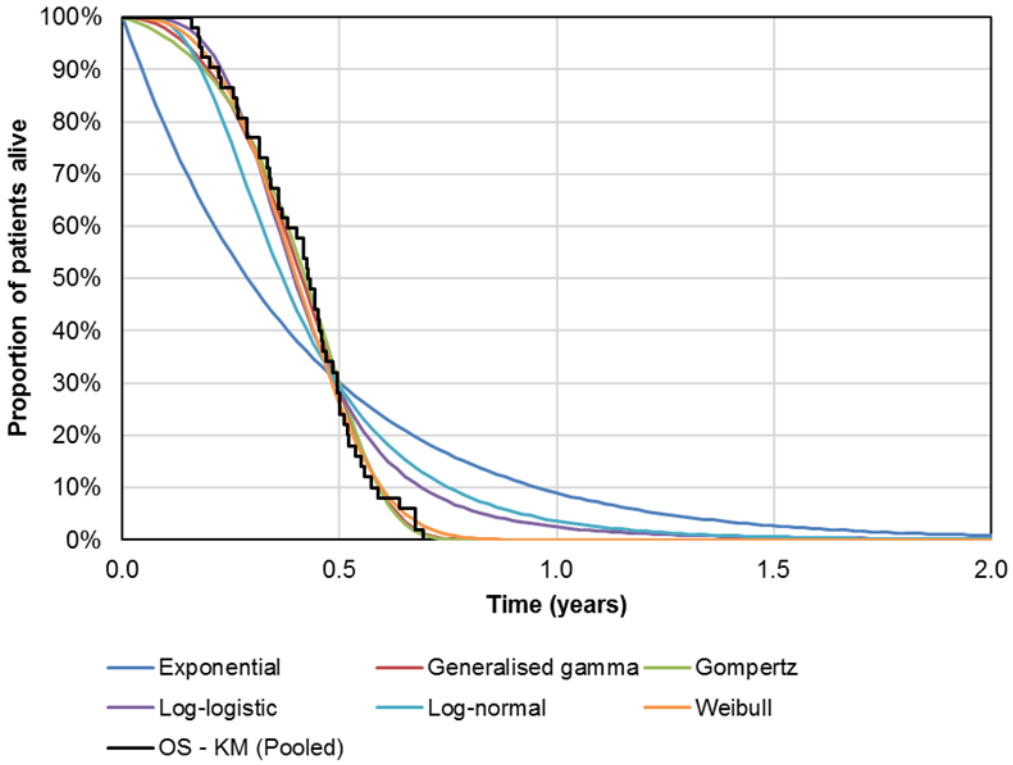
Figure 39 and Figure 40 for PFS and OS, respectively. The company chose the Gompertz curve for OS and the Weibull curve for PFS, which both had the least AIC and BIC statistics and were considered to have a good visual fit. These base case curves are shown in Figure 41.

Figure 39. Kaplan-Meier plot and fitted curves to pooled EU and US PFS data. (CS, page 131, Figure 43)



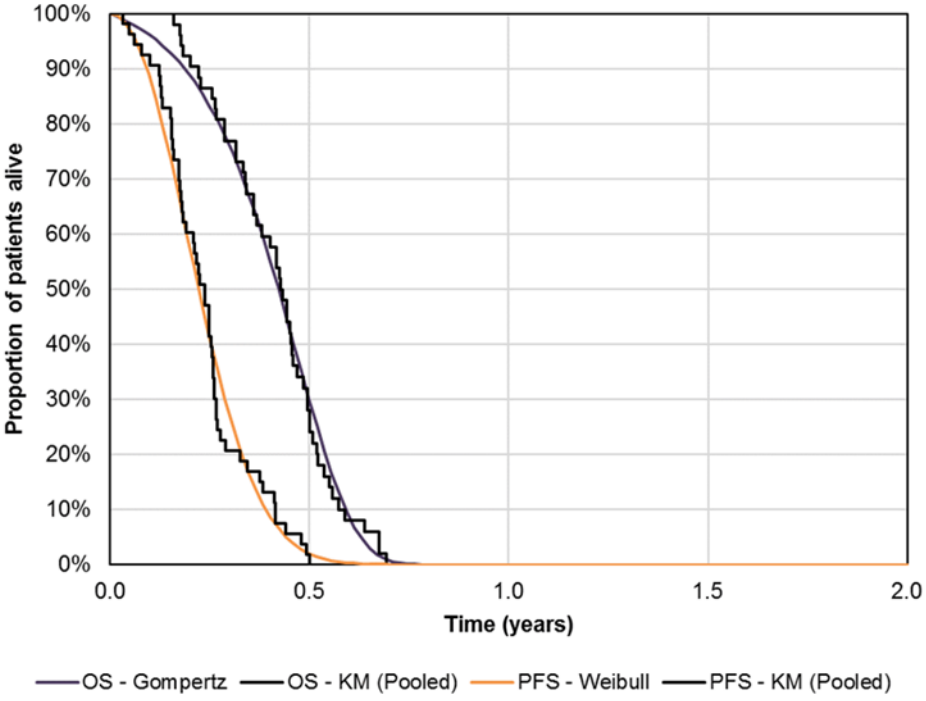
Abbreviations: EU: Europe; KM: Kaplan-Meier; PFS: Progression-free survival; US: United States

Figure 40. Kaplan-Meier plot and fitted curves to pooled EU and US OS data. (CS, page 132, Figure 44)



Abbreviations: EU: Europe; KM: Kaplan-Meier; OS: Overall survival; US: United States

Figure 41. Base case fitted PFS and OS comparator curves with KM plots for treatment-experienced patients. (CS, page 133, Figure 45)



Abbreviations: KM: Kaplan-Meier; MCC: Merkel cell carcinoma; OS: Overall survival; PFS: Progression-free survival

5.4.5.2 Treatment naïve (first-line)

5.4.5.2.1 Avelumab effectiveness

For the treatment-naïve population, data on PFS and OS were limited, with only 39 patients and a maximum follow up of 11 months. KM plots for both PFS and OS are given in Figure 42. This immature data was not considered appropriate to use directly in the model, so the company instead chose to estimate a relative effect on the hazard rate between this group and the treatment-experienced group.

Figure 42. Kaplan-Meier plots of PFS and OS for treatment-naïve patients in JAVELIN (CS, page 119, Figure 32)

Note: Shaded area demonstrates the 95% CI around the Kaplan-Meier function
Abbreviations: CI: Confidence interval; OS: Overall survival; PFS: Progression-free survival

This hazard ratio (HR) was estimated by fitting Cox proportional hazards (PH) models to the two sub-populations in the JAVELIN Merkel 200 trial for both the PFS and OS. The resulting HRs were 0.695 and 0.587 for PFS and OS, respectively. Given the immaturity of the data, the company did not consider

the results to be reliable enough to use directly in the model, instead choosing to elicit a hypothetical HR from clinicians who were experienced in using immune-oncology drugs for patients with metastatic melanoma, renal cell carcinoma and non-small cell lung cancer.

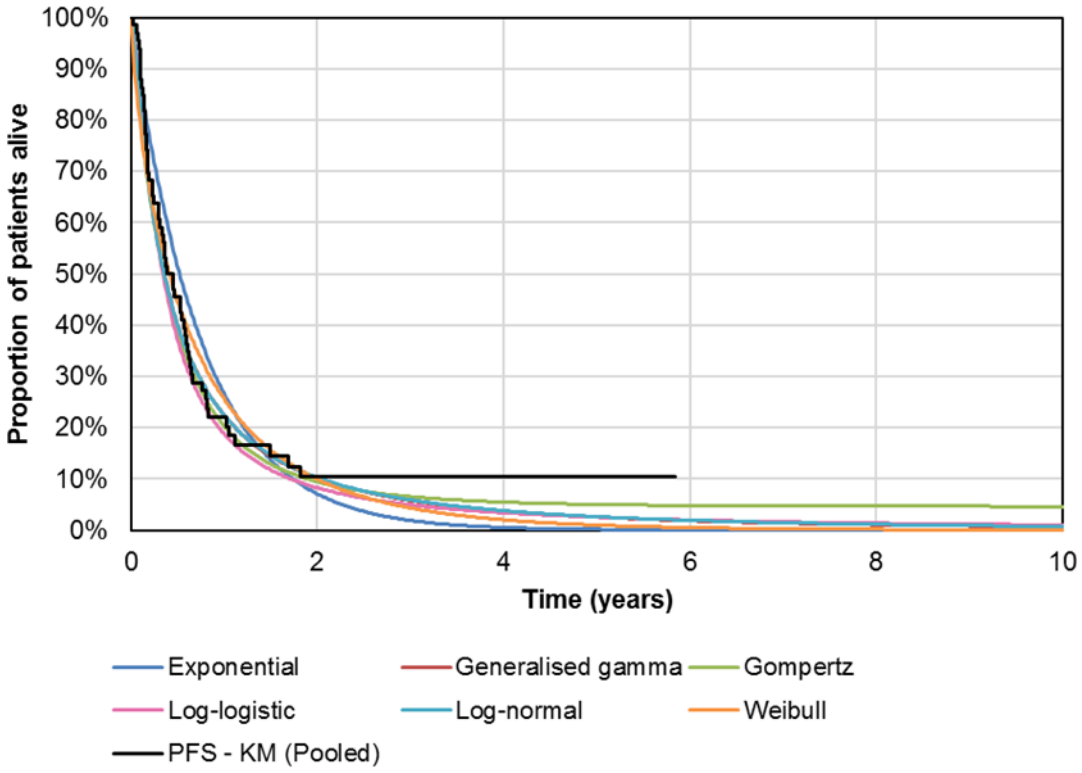
The OS HR elicited for patients receiving avelumab was 0.8, and this was applied to the treatment-experienced avelumab OS curve to estimate OS for treatment-naïve patients also receiving avelumab. For PFS, the clinicians were not able to provide an estimate of what the HR might be, so a value of 1 was assumed in the model, i.e. no difference in effectiveness between lines of treatment. These values were both higher than those derived from the Cox model and were, therefore, considered to be conservative.

5.4.5.2.2 Comparator effectiveness

A lack of evidence for BSC in treatment-naïve patients meant that the company followed the same approach as for the treatment-experienced population in assuming equal effectiveness as chemotherapy based on clinical expert opinion. However, the company state that, in this population, it provides a more conservative analysis in favour of BSC because chemotherapy is expected to have a greater effect in this population than the treatment-experienced population, and, therefore, the effectiveness of BSC is likely to be overestimated.

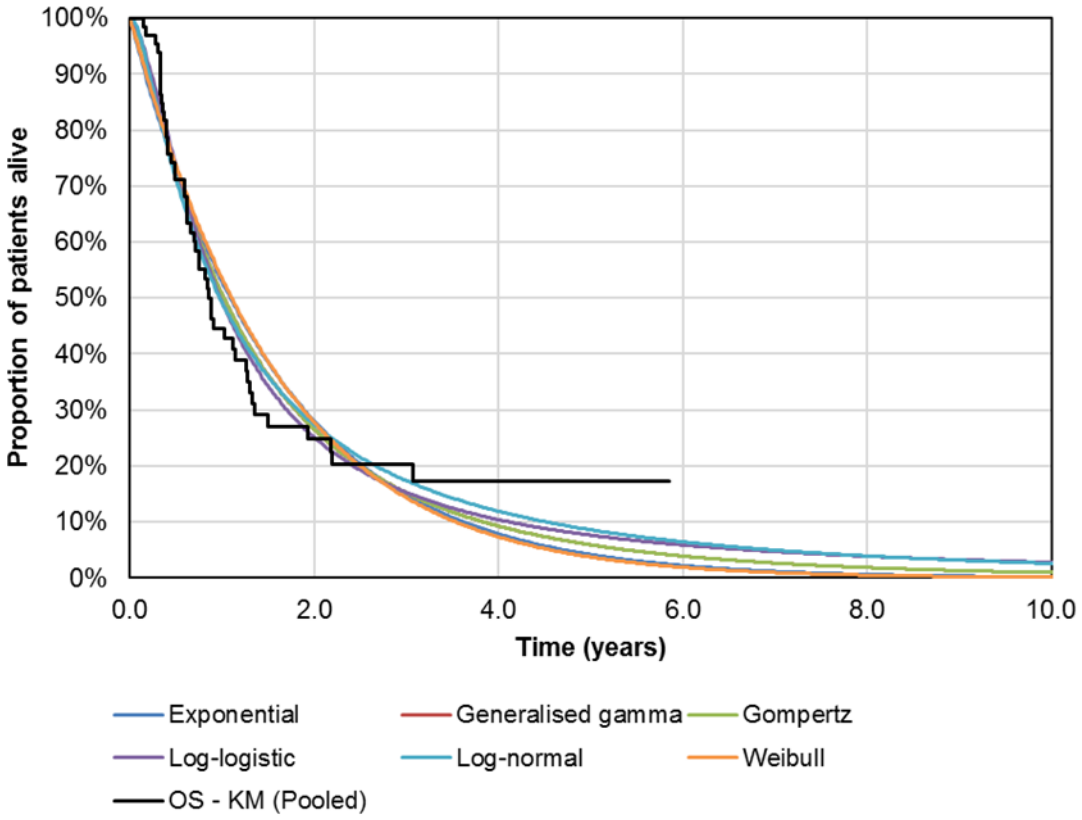
To estimate PFS and OS for treatment-naïve patients receiving chemotherapy, the company used data from another US observational study conducted by Merck KGaA/Pfizer.[20] In the same way as the treatment-experienced population observational study, discussed in Section 5.4.5.1.2, this study was considered to have similar inclusion/exclusion criteria to the JAVELIN Merkel 200 trial. The company identified six additional studies from the SLR, which contained PFS, OS or both, and were considered to have similar outcomes. Therefore, the company pooled the data and fitted standard parametric survival curves. These curves are given in Figure 43 and Figure 44 for PFS and OS, respectively. The chosen curves for the base case analysis are shown in Figure 45.

Figure 43. Kaplan-Meier plot and fitted curves to pooled PFS data. (CS, page 138, Figure 50)



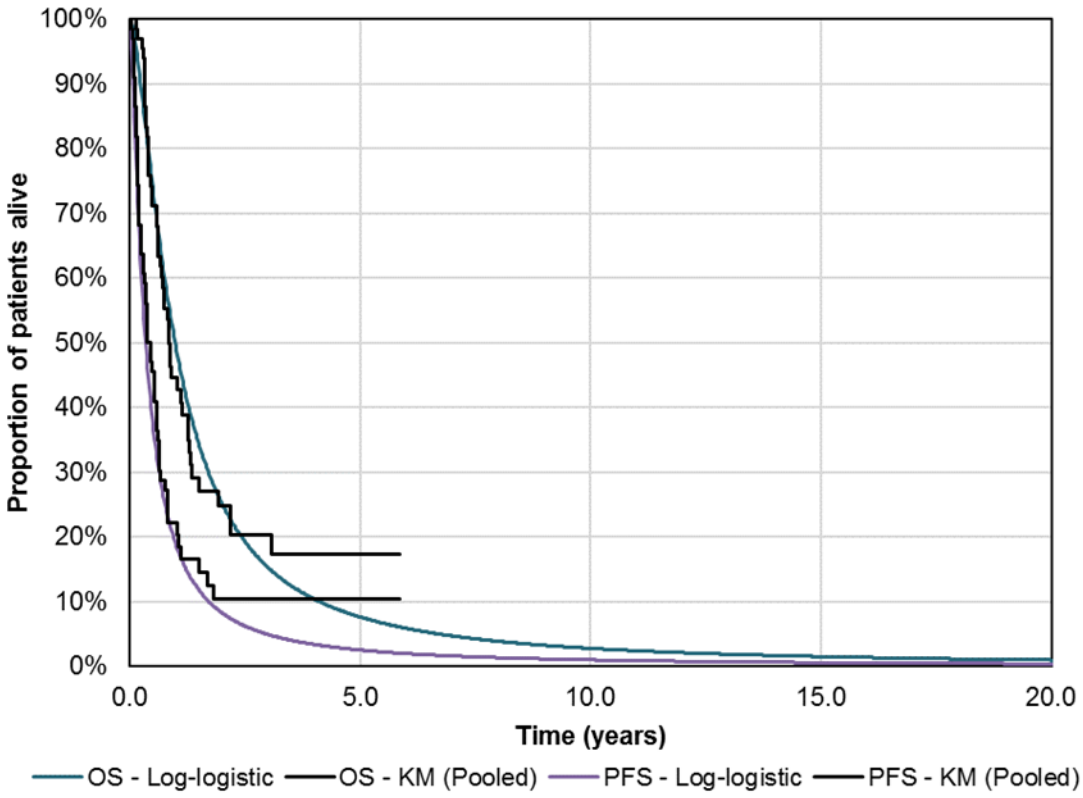
Abbreviations: KM: Kaplan-Meier; PFS: Progression-free survival

Figure 44. Kaplan-Meier plot and fitted curves to pooled OS data. (CS, page 139, Figure 51)



Abbreviations: KM: Kaplan-Meier; OS: Overall survival.

Figure 45. Base case fitted PFS and OS comparator curves with KM plots for treatment-naïve patients. (CS, page 140, Figure 52)



Abbreviations: KM: Kaplan-Meier; MCC: Merkel cell carcinoma; OS: Overall survival; PFS: Progression-free survival

5.4.5.3 Alternative modelling approaches

The company also conducted two alternative modelling approaches to extrapolate OS data. The first approach was a mixture cure model, where the survival function is split between a proportion of patients being cured and following a general population survival and a proportion being uncured and following a disease related survival curve. The second approach was a general population mortality extrapolation approach, which is similar but where a proportion of 'cured' patients is pre-specified after a given amount of time without progressed disease.

An alternative modelling approach for PFS was also considered, referred to by the company as a "custom spline". This uses spline-based survival models for PFS and OS but assumes that the PFS curve gradually follows the hazard from the fitted OS curve between two arbitrary time points: 18 months and 30 months, relating to the 18-month cut-off and the end of the KM data available at 30 months.

Further detail on these approaches can be found in Section 5.3.1 of the CS.

5.4.5.4 ERG critique

The key concerns that the ERG have regarding the estimation of treatment effectiveness largely result from the limitations caused by the small amount of underlying data available, as well as the difficulty in forming a reliable comparison of effectiveness given the lack of direct head-to-head evidence.

Although the latter issue can be addressed to some extent by adjusting for imbalances in effect-modifying variables, the reliability of the results will always be hindered by the small sample sizes in both the JAVELIN Merkel 200 trial and the observational comparator studies, as well as any unmeasured effect modifiers or prognostic indicators.[33] This can cause potentially serious uncertainty in the results of any analysis performed, and, therefore, in the results of any cost-effectiveness analyses based on these results. Given that the treatment effectiveness is likely to be one of the most influential factors on the economic model results, this uncertainty should be a key consideration when interpreting the decision analysis.

The ERG considers the company's naïve comparison of the JAVELIN Merkel 200 trial data and the observational study data, for both the treatment-naïve and treatment experienced populations to be unreliable because of the imbalances in the patient characteristics between the different studies, the small number of patients in the studies, and the uncertainty caused by unmeasured variables that may be effect modifiers or prognostic indicators. The company justified the naïve approach by performing a regression analysis, outlined in Appendix 10 of the CS, and determined that only line of treatment was a prognostic indicator of time to progression and time to death. However, the ERG considers the lack of statistical significance to potentially be a result of the lack of data to inform the regression, and may not necessarily indicate a lack of an effect on prognosis. Although not necessarily significant, the results of the regressions do show point estimates with an effect on the outcomes, which would alter the results if an adjusted analysis was used. The ERG is, therefore, concerned by the company's naïve comparison of treatment effectiveness, which may cause the cost effectiveness results to be unreliable.

In response to clarification questions (CQs), the company submitted a range of adjusted analyses, including a propensity score matched analysis and a Weibull regression for the treatment-experienced population in the JAVELIN Merkel 200 trial and the Merck KGaA/Pfizer observational studies.[3, 89] However, the propensity matched analysis only included age and gender in the matching and, therefore, fails to balance the populations for all characteristics for which data are measured, which will introduce bias in addition to that resulting from potentially unmeasured variables, if these excluded measured variables are effect modifiers or prognostic indicators. The logistic regression required to generate the propensity scores should ideally include all available covariates to appropriately match patients. However, the company state that no patients could be matched when immunosuppression was included because of a lack of overlap in propensity scores. The ERG acknowledges that the lack of data makes

it difficult for this analysis to produce useful results but considers the analysis conducted to be potentially unreliable without all covariates included. As an alternative, the ERG considers the regression used to generate adjusted parameters of a Weibull survival function for the Merck KGaA/Pfizer sponsored observational studies of treatment-experienced patients to be more reliable than the propensity score matched analysis, as the company included immunosuppression as well as age and gender for the adjustment.[20, 89] However, the ERG still has concerns about the use of the results of this analysis, as it still fails to adjust for many other factors, such as Eastern Cooperative Oncology Group performance score (ECOG PS) and stage of disease at diagnosis, that may have an important prognostic impact on the outcomes. This analysis is difficult to fully critique given that only the Weibull model was used for the regression as this was the best fit to the comparator data. However, the Weibull was not the best fit for the avelumab group. The ERG considers a better approach may have been to fit a range of dependent regression models using the JAVELIN Merkel 200 trial data as well as the comparator data, which may have shown that an alternative more flexible model such as the generalised gamma may have provided a good fit for both treatment groups.

For the treatment-naïve population, the ERG has concerns about the company's approach of assuming an OS HR of 0.8 relative to the treatment-experienced population. This was elicited from clinical experts and considered to be conservative in comparison to the HR that was estimated using a Cox model. However, given the lack of data, the Cox model estimate is extremely unreliable and an assumption of PH may also be inappropriate, especially given that hazards were shown to be non-monotonic. The company's approach may be more conservative than using the results of the Cox model directly, but the high degree of uncertainty means that the results are only more conservative in relation to a very uncertain analysis. Using the independently fitted curves provided by the company in response to CQs also indicated that the PH assumption may not be plausible. The cost-effectiveness analysis, therefore, should be considered with caution, as these results will be at least as unreliable as the effectiveness estimates upon which they are based. To account for some of the ERG's concerns, the company fitted survival functions to the treatment-naïve population curves for both PFS and OS in response to CQs. The ERG considers this approach to be preferable, but this does not solve the issue of the uncertainty in the estimates caused by the lack of data. This should, therefore, be the key consideration when assessing the applicability of this analysis. In addition to this, the ERG considers the Merck KGaA/Pfizer observational study for the treatment-naïve population to provide the most appropriate comparator data as opposed to the pooled data including an additional six studies.[9, 20, 56, 67, 86, 88, 89] The company's model does not allow for an analysis using this study alone, so the ERG's preferred base case uses the best fitting curve fitted to the pooled data. The ERG notes that in Figure 50 and Figure 51 of the CS, the plots are labelled as showing pooled KM data. However, the data appear to be from just the single observational study conducted by Merck KGaA/Pfizer.[8] However, the fitted curves appear to be correct and are those fitted to the pooled data. The difference between the KM plots can be seen in

Figure 46 and Figure 47, for OS and PFS, respectively. These plots show that PFS is largely similar but that there is a potentially important difference for OS. The impact of using the Merck KGaA/Pfizer observational study alone, as would be preferred by the ERG, would result in a reduced relative effect on OS between avelumab and chemotherapy, and hence, an increased ICER.

[redacted]

[redacted]

In terms of extrapolating these outcomes beyond the period for which data are available, the ERG considers the company's approach to be reasonably thorough, clearly described and generally sound.

The company considered a range of different survival curves and assessed the hazard functions of the data using log-log plots to choose appropriately fitting curves. The ERG considers the company's justification that splines are required when hazards are shown to be monotonic to be incorrect, as there are flexible standard parametric models that can produce non-monotonic functions, such as the log-logistic, lognormal or the generalised gamma. However, given the flexibility of spline-based survival models, and the range of different splines that were considered by the company, the ERG considers it unlikely that a better fitting model to the data could have been found. However, a more plausible extrapolation may have been possible and the ERG considers it more appropriate to assess all available survival functions. In general, however, the ERG considered the company's chosen curves for PFS and OS for the treatment-experienced population to have generally good fits with plausible extrapolations.

Another issue the ERG notes, is that the company's base case analysis uses different survival functions for the avelumab and comparator groups for both OS and PFS. This is highlighted in NICE technical support document 14 as requiring substantial justification, as different functions can produce very different shaped curves, which may be implausible. However, given the mode of action of avelumab causes an immune response, this may suitably justify the use of a different distribution. Further to this, given that the comparator data are complete and do not need extrapolation, the uncertainty in the shape of the curves is limited to only the avelumab curves. The ERG, therefore, considers this approach to be reasonable.

5.4.6 Treatment discontinuation

To accurately calculate treatment costs, the time for which patients receive the treatment needs to be considered. Patients can discontinue for numerous reasons, including disease progression, intolerable toxicity or death. Therefore, time on treatment (ToT) data are required to estimate the proportion of patients receiving treatment at each model cycle in order to accurately apply the costs of treatment. The company's approach is described for each comparator at each line of treatment in the following sub-sections. The treatment duration for chemotherapy is discussed in Section 5.4.9.2.

5.4.6.1 Treatment-experienced (second line)

5.4.6.1.1 Avelumab time on treatment

The proportion of patients remaining on treatment for patients receiving avelumab was modelled in the same way as PFS and OS, by fitting survival curves to the ToT KM data shown in Figure 48.

Figure 48. Kaplan-Meier plots of ToT for treatment-experienced patients in JAVELIN (CS, page 122, Figure 34)

The company fitted a range of standard parametric and spline curves, shown in Figure 49 and Figure 50, respectively, and used AIC and BIC statistics to find the best fitting. These were the log-logistic and the 2-knot normal spline, which produced very similar curves, as shown in Figure 51.

Figure 49. Parametric curves for ToT for treatment-experienced patients (CS, page 124, Figure 36)

Abbreviations: KM: Kaplan–Meier; ToT: Time on treatment.

Figure 50. Spline curves for ToT for treatment-experienced patients (CS, page 125, Figure 37)

Abbreviations: KM: Kaplan–Meier; ToT: Time on treatment.

Figure 51. Curve fits for ToT for treatment-experienced patients (CS, page 126, Figure 38)

Abbreviations: KM: Kaplan–Meier; ToT: Time on treatment.

The log-logistic curve was used in the base case analysis because it had superior goodness-of-fit. However, the company considered the extrapolation to be implausible and, based on clinical expert opinion, made an assumption that after two years of treatment, two thirds of patients remaining on treatment would immediately discontinue. The remaining patients stay on treatment and discontinue at a rate determined by the fitted log-logistic curve until 5 years of treatment, at which point all patients immediately discontinue. This is illustrated in Figure 52.

Figure 52. Base case model ToT curve for treatment-experienced patients (CS, page 127, Figure 39)

Abbreviations: KM: Kaplan–Meier; ToT: Time on treatment.

5.4.6.2 Treatment-naïve (first line)

5.4.6.2.1 Avelumab treatment discontinuation

Given the lack of mature data in the treatment-naïve population of the JAVELIN Merkel 200 trial the company used the same approach as they did for PFS and OS in fitting a Cox PH model to estimate a HR between the two populations.[89] The resulting HR was [redacted]. The company considered this analysis to be uncertain because of the small sample size and instead chose to assume that treatment discontinuation was equivalent to that of the treatment-experienced population.

5.4.6.3 ERG critique

The ERG considers the company's approach to estimating treatment duration in both populations to be flawed. The assumption that two thirds of patients currently on treatment at two years immediately discontinue is a very strong assumption and is likely to have a great impact on the results of the cost-effectiveness results. The ERG's clinical experts stated that there is no evidence to suggest that treatment should be discontinued after two years and considered it to be a morally difficult decision to withdraw treatment from patients who are receiving a benefit from it. The ERG considers a preferable approach in the case of an implausible tail is to choose an alternative survival curve that may have a slightly lesser goodness-of-fit but with a more plausible extrapolation. An alternative curve that has a similar goodness-of-fit but with a more plausible curve that has almost all patients discontinued by 5

years is the Weibull. The ERG includes this, without any truncation to the curve, in the ERG's preferred base case analysis described in Section 6.3.

For the treatment-naïve population, the ERG considers the company's assumption that the treatment discontinuation to be potentially underestimating treatment costs, and this is evident in the difference in the KM plots of ToT for the two populations. Following clarification questions, the company submitted an updated model with fitted survival curves for ToT in the treatment-naïve population and found the Weibull curve to be the most plausible curve with similar AIC and BIC to the statistically best fitting log-normal. The ERG has included this in the ERG's preferred base case described in Section 6.3.

5.4.7 Adverse events

The company's economic model included treatment costs and disutilities associated with Grade 3 or 4 treatment-related adverse events (TRAEs) that occurred in 5% or more of patients receiving avelumab or chemotherapy combination therapy. Febrile neutropenia and lymphopenia were included even though they occurred in less than 5% of patients to reflect the high cost of managing them, and the impact they have on patients' quality of life. Similarly, hair loss of any grade was included since it is considered to have a great impact on patients' quality of life, especially females. The complete list of adverse events included in the model is given in Table 39.

The rates of adverse events assumed for the avelumab arm in the model are based on those observed in the JAVELIN Merkel 200 trial.[3] The company reported that there was a paucity of safety data on chemotherapy used to treat mMCC, and in the absence of such data, safety data was obtained from studies assessing the same treatment regimens in small-cell lung cancer (SCLC), and from melanoma trials when data was not available. Consequently, the proportions of adverse events assumed in the model for both cisplatin+etopisode, and carboplatin+etopisode, are based on adverse events observed in SCLC clinical trials that were identified in the SLR of studies reporting safety data for chemotherapy, described in Section 4.1.[3, 182] The proportions of patients experiencing adverse events used in the model are presented in Table 39.

Table 39. Probabilities of adverse events used in the model (CS, Appendix 15, Table 23)

	Avelumab (JAVELIN)[136]	Carboplatin + etoposide (Sun et al 2016)[3]	Cisplatin + etoposide (Socinski et al 2009)[182]
Anaemia	0	7.38%	6.67%
Fatigue	0	3.13%	0
Febrile neutropenia	0	4.47%	0
Low haemoglobin	0	0	5.33%
Hyponatremia	0	1.12%	0
Leukopenia	0	8.28%	19.33%

Lymphopenia	2.27%	0	0
Nausea/vomiting	0	0.90%	6.70%
Neutropenia	0	46.98%	44.00%
Thrombocytopenia	0	10.29%	7.33%
Hair loss (Any grade)	0	34.00%	13.33%

The company reports carrying out a targeted search of previous NICE submissions to identify data on the duration of treatment with chemotherapy to estimate the duration of adverse events. The duration of adverse events assumed in the model are summarised in Table 40. The company validated all the assumptions surrounding adverse events with the clinical experts in its advisory board.

Table 40. Duration of adverse events assumed in the model (CS, Appendix 15, Table 26)

Adverse event	Duration (days)	Reference/justification
Anaemia	21.00	NICE TA 403 - Manufacturer Submission[136]
Fatigue	21.00	NICE TA 403 - Manufacturer Submission[183]
Febrile neutropenia	4.00	NICE TA 403 - Manufacturer Submission[183]
Low haemoglobin	21.00	Assumed the same as anaemia
Hyponatremia	1.90	Assumed to be the same as Neutropenia in NICE TA 391 - Manufacturer Submission[183]
Leukopenia	1.90	Assumed to be the same as Neutropenia in NICE TA 391 - Manufacturer Submission[184]
Lymphopenia	1.90	Assumed to be the same as Neutropenia in NICE TA 391 - Manufacturer Submission[184]
Nausea/vomiting	3.00	NICE TA 403 - Manufacturer Submission[184]
Neutropenia	1.90	NICE TA 391 - Manufacturer Submission
Thrombocytopenia	23.80	NICE TA 391 - Manufacturer Submission
Hair loss (Any grade)	21.00	NICE TA 403 - Manufacturer Submission[183]
Abbreviations in table: NICE, National Institute of Health and Care Excellence; TA, technology appraisal.		

The company's approach of incorporating the impact of adverse events on quality of life and costs is discussed in Sections 5.4.8 and 5.4.9, respectively.

5.4.7.1 ERG critique

The ERG acknowledges that considering the lack of sufficient data surrounding adverse events of chemotherapy when used to manage mMCC, the company's approach while not ideal is reasonable. The ERG's clinical experts supported the company's view that SCLC and melanoma can be used as a proxy for mMCC in terms of chemotherapy regimens received, and given that the same regimens are administered the rates of TRAEs would be expected to be similar. The ERG's clinical experts confirmed that all relevant adverse events have been included and that the assumptions made are in line with what is encountered in clinical practice.

5.4.8 Health-related quality of life

5.4.8.1 Systematic literature review

The company carried out an initial SLR to identify studies reporting health-related quality of life (HRQoL) data from patients with mMCC. The search was subsequently broadened to include studies reporting HRQoL data from patients with SCLC or melanoma, because of a lack of published literature on HRQoL of MCC patients. The search strategies were provided in Appendix 12 of the CS, but no details were given on the inclusion and exclusion criteria applied in the search.

No HRQoL studies of patients with mMCC were identified, while a total of 24 studies were identified for SCLC and melanoma.[120, 129, 183, 185-205] The studies are summarised and presented in Appendix 13 of the CS. The company suggests that because of differences across the three disease areas in terms of patient demographics and type of disease, the quality of life data reported in the included studies may not be directly transferable to patients with mMCC. The company highlighted that melanoma patients are a younger population compared to mMCC patients, which is supported by the mean ages of patients in the HRQoL studies included with most of the studies reporting a mean/median age between 45 years to 55 years.

Of the 12 HRQoL studies in melanoma,[185-191, 193, 196-198, 206] five studies collected data from patients with melanoma,[185, 186, 191, 193, 204] while the remaining studies were either carried out in the general population or were registry based.[187-190, 196, 197, 204] EQ-5D data were used to estimate health state utility values (HSUVs) in two of the melanoma studies (Askew *et al.* 2011 and Tromme *et al.* 2014),[185, 198] in which data were collected from patients attending melanoma clinics. However, neither study used the UK general population valuation set, with Askew *et al.* using the US valuation set and Tromme *et al.* using a social preference EQ-5D valuation set based on data from a random sample of the Belgian general population.[185, 204] Askew *et al.* reports a mean HSUV of 0.88 (SD 0.13) inpatients from an outpatient melanoma clinic in the US, while Tromme *et al.* reports a mean HSUV of 0.719 (SD 0.21) in patients recruited in a melanoma clinic in Belgium.[185, 204]

Twelve studies reporting HRQoL outcomes in patients with SCLC were identified.[120, 129, 192, 194, 195, 199-205] Of those studies, nine were primary sources of quality of life data,[120, 129, 192, 195, 199, 201-203, 206] while three were secondary sources utilising data reported in published studies.[194, 200, 206] Of the nine primary studies, eight reported data collected data from patients with SCLC enrolled in trials or attending oncological centres,[120, 129, 192, 195, 199, 201, 202, 205] and one was a registry based study.[203] EQ-5D was used to measure quality of life in four of the studies, two of which reported HSUVs based on EQ-5D (Chen *et al.* 2007 and Schwartzberg *et al.* 2016), [192, 206] while the other two reported changes in quality of life .[120, 202]

The HSUVs reported in *Chen et al.* at baseline for patients in the topotecan + BSC group and in the BSC group of a multicentre randomised open-label clinical trial were 0.72 and 0.68, respectively. The mean on-treatment HSUVs across measurements at four timepoints were 0.69 and 0.56 for topotecan + BSC and BSC, respectively. The difference across the two treatment groups was statistically significant at a 5% significance level.[129] The paper by Schwartzberg *et al.* reports HSUVs measured in patients enrolled in a longitudinal multi-centre observational study in the US at different stages of their disease prior to receiving first-line treatment. Patients who improved clinically after receiving treatment had an HSUV of 0.55 at baseline, while the baseline values for stable patients and patients who declined clinically after receiving treatment were 0.82 and 0.79, respectively.[192] No details were provided in both publications on what dataset was used for valuation.[192, 202]

5.4.8.2 HRQoL in model

HRQoL in the model is based on EQ-5D-5L data collected in part A of the JAVELIN Merkel 200 trial, and has the same values applied regardless of treatment group or whether patients are treatment-experienced or treatment-naïve. HRQoL in the JAVELIN Merkel 200 trial was assessed for patients at baseline, week 7, every 6 weeks thereafter, and at the end-of-treatment. A total 362 observations were collected from 71 patients while receiving treatment, resulting in limited data being collected after patients have progressed, as most patients discontinue treatment upon progression.

The EQ-5D-5L responses from the JAVELIN Merkel 200 trial were mapped to UK EQ-5D-3L values using the 'crosswalk' algorithm published by van Hout *et al.* 2012 to be used in the model.[202] The company provided the ERG with the descriptive statistics of the EQ-5D-5L crosswalk values at different timepoints in the trial, during the clarification stage. At baseline the mapped mean EQ-5D-3L value was [redacted]. The EQ-5D-5L data from the JAVELIN Merkel 200 trial was analysed using a generalised estimating equation (GEE) regression which accounts for multiple observations per patient.

The company adopted a time-to-death approach for the base case analysis with utility values varying across three time periods relative to time of death. The company reports that it was unclear at the beginning of the analysis which time-points (periods) would be best to predict drops in patients' utility values. Therefore, the "optim" function in the statistical software, R,[174] was used to identify the number of days before death observations that would minimise the mean absolute error of the predicted utility. The result of this analysis was groups of 30 days before death, and 30-100 days before death. Observations that were taken in the last 100 days before censoring were assumed to fall in the group furthest from death (i.e. >100 days to death). The results of the regression analysis are presented in Table 41, and show that of the three coefficient estimates only the value for 30-100 days from death is not statistically significant at a 5% significance level. The HSUVs estimated and applied to patients in the model are presented in Table 42.

Table 41. Results of regression analysis of utility by time-to-death (CS, pg 149)

Coefficients	Estimate	Standard error	Wald	Pr(>|W|)
Intercept	0.7744	0.0201	1447.87	<2e-16***
30-100	-0.0204	0.0304	0.45	0.502
<30	-0.0662	0.0307	4.66	0.031*
Abbreviations in table: Pr, probability. Significance codes: 0, '***'; 0.001, '**'; 0.01, '*' .				

Table 42. Health state utility values assumed in the model

Health state	Utility value
>100 days to death (intercept)	0.7744
30-100 days to death	0.7540
<30 days to death	0.7082

The company ran a scenario analysis, varying HSUVs according to progression status while applying utility decrements to account for the impact of adverse events on patients' quality of life, the results of which are reported in Section 5.5.2.1.

5.4.8.3 ERG critique

HRQoL in the model is based on EQ-5D data collected in part A of the JAVELIN Merkel 200 trial. As was previously discussed in Section 4, the ERG's clinical experts consider the baseline characteristics of part A of the trial to be broadly similar to patients encountered in UK clinical practice. However, one clinician stated that the performance status of patients in the trial is better than the average mMCC patient. Although this is common in a trial setting, this may lead to overestimation of quality of life estimates relative to UK patients, the magnitude of which is unknown.

The company mapped the EQ-5D-5L data collected in the JAVELIN Merkel 200 trial to EQ-5D-3L values using the mapping function developed by van Hout *et al.* 2012 in line with NICE's latest recommendations for using EQ-5D-5L data in submissions for technology appraisals.[207, 208] EQ-5D data were analysed using a GEE regression which the ERG considers to be appropriate as it allows for multiple observations per patient and hence, preserves correlation. The company explored more than one approach to incorporating quality of life in the model, and the model is flexible in allowing the use of the alternative progression-based approaches.

The ERG's clinical experts thought that the reported baseline HSUV of [redacted] in the CS for patients recruited in the JAVELIN Merkel 200 trial to be higher than what would be expected in this patient population. This is especially true since the age-matched UK population norm EQ-5D values is 0.78 reported in the publication by Kind *et al*. 1999.[174] Therefore, this suggests that the trial patients experienced a superior quality of life compared to the general population prior to receiving treatment

for their condition. However, the HSUVs applied to patients in the model were around 0.71 and 0.77, in the groups closest to death and further from death, respectively. One of the ERG's clinical experts stated that he would expect patients to have the same HSUV as the general population, making the 0.77 assumed in patients with more than 100 days to die, seem plausible. Furthermore, while the HSUVs applied in the model may be high, the company applies the same values regardless of treatment group, so the difference in HSUVs between health states is the key issue rather than the baseline magnitude, and this difference is plausible.

During the clarification stage the ERG asked the company to clarify whether the impact of adverse events on quality of life is incorporated in the base case analysis. The company explained that the time-to-death approach used does not differentiate whether patients are on or off treatment. However, the ERG notes that this indicates that the resultant HSUVs implicitly include the effect of TRAEs on quality of life as the EQ-5D data collected in the trial are from patients regardless of whether they were experiencing TRAEs or not. Furthermore, the company clarified that the scenario in the model in which HSUVs are based on progression status of patients QALY decrements attributed to TRAEs are incorporated in the PF-on treatment state. In this scenario, TRAEs have zero impact on the QALYs estimated for avelumab and cause a 0.01 decrement in QALYs for treatment-naive patients receiving chemotherapy.

The ERG acknowledges that the EQ-5D data from the JAVELIN Merkel 200 trial is the best available source of HRQoL data to inform this analysis, and that the patient demographics in SCLC and melanoma may be different from mMCC. However, the company did not attempt to compare the HSUVs used in the model to those reported in the publications identified in the SLR carried out for HRQoL which would have been a useful validation exercise, given that the company in more than one instance reports that these patient populations are considered to be a proxy to mMCC.

5.4.9 Resources and costs

5.4.9.1 Systematic literature review

The company carried out an SLR to identify studies reporting resource use and costs in mMCC alongside the SLR for cost-effectiveness studies described and critiqued in Section 5.3. The company broadened the search further to capture studies reporting resource use and costs for management of SCLC and melanoma, as no studies were identified that reported resource use and costs for mMCC. This approach was take based on input by the company's clinical experts, who stated that SCLC and mMCC are disease analogues. The company reports using data from SCLC studies where available, and only using data from melanoma studies when no SCLC sources were identified.

Table 43. Inclusion and exclusion criteria applied in systematic literature review for resource use and costs studies in MCC (CS, pg 152, Table 46)

Inclusion criteria		**Rationale**
Population	Age: adults aged ≥18 years Gender: any Ethnicity: any Disease: metastatic MCC	Consistent with evidence base and anticipated marketing authorisation.
Interventions/Comparators	Any pharmacological treatment	This allows all relevant evidence to be identified
Outcomes	Cost- effectiveness, direct/indirect costs, resource use, BSC costs, costs, life years, QALYs, ICERs	The aim of the review was to identify relevant costs and data on resource use
Study design	Cost-effectiveness analyses, cost-minimisation analyses, cost-utility analyses, cost/burden of illness, costing studies	The aim of the review was to identify relevant costs and use of resources
Limits	No language restrictions	With limited data in MCC, all languages were included to identify all published literature
Exclusion criteria		**Rationale**
Intervention/Comparators	Studies exclusively focusing on the role of radiotherapy, chemo-radiotherapy, hormonal therapy, diagnostics, screening or surgery Studies investigating the role of maintenance/consolidation therapy after surgery Adjuvant or neo-adjuvant therapy Does not include chemotherapy regimens that are listed as comparators	In line with the anticipated NICE scope, studies were restricted to those evaluating the efficacy of comparators. Comparators were restricted to chemotherapies and BSC.
Population	Studies that included children and adults and did not provide subgroup analysis for the adult populations	Consistent with the avelumab evidence base
Outcomes	No relevant costs or resource use	Not part of the aims of the literature search
Study design	Systematic literature reviews and meta-analyses	Studies from systematic literature reviews and meta-analyses were cross checked to ensure all relevant publications were identified
Country	None	Review was kept broad considering the limited data
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; MCC, Merkel Cell Carcinoma; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year;		

Table 44. Inclusion and exclusion criteria applied in systematic literature review for resource use and costs studies in SCLC (CS, pg 153, Table 47)

Inclusion criteria		**Rationale**
Population	Age: adults aged ≥18 years Gender: any Ethnicity: any Disease: SCLC with an ECOG status of 0-1	Consistent with the evidence base for avelumab and the anticipated marketing authorisation

Interventions/Comparators	topotecan cyclophosphamide + doxorubicin + vincristine carboplatin + etoposide cisplatin + etoposide carboplatin alone carboplatin + paclitaxel cisplatin + paclitaxel doxorubicin liposomal doxorubicin paclitaxel pembrolizumab	Interventions were identified from an observational study as likely treatment options for patients with metastatic MCC.
Outcomes	Cost-effectiveness, direct/indirect costs, resource use, BSC costs, costs, life years, QALYs, ICERs	The aim of the review was to identify relevant costs and data on resource use
Study design	Cost-effectiveness analyses, cost-minimisation analyses, cost-utility analyses, cost/burden of illness, costing studies	The aim of the review was to identify relevant costs and use of resources
Limits	English language studies only	Time and resource required for translation and relevance for UK setting
Exclusion criteria		**Rationale**
Intervention/Comparators	Studies exclusively focusing on the role of radiotherapy, chemo-radiotherapy, hormonal therapy, diagnostics, screening or surgery Studies investigating the role of maintenance/consolidation therapy after surgery Adjuvant or neo-adjuvant therapy Does not include chemotherapy regimens that are listed as comparators	In line with the anticipated NICE scope, studies were restricted to those evaluating the efficacy of comparators. Comparators were restricted to chemotherapies and BSC.
Population	Studies that included children and adults and did not provide subgroup analysis for the adult populations	Consistent with the avelumab evidence base
Outcomes	No relevant costs or resource use	Not part of the aims of the literature search
Study design	Systematic literature reviews and meta-analyses	Studies from systematic literature reviews and meta-analyses were cross checked to ensure all relevant publications were identified
Country	No country restriction	Review was kept broad considering the limited data
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; MCC, metastatic Merkel Cell Carcinoma; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.		

Table 45. Inclusion and exclusion criteria applied in systematic literature review for resource use and costs studies in Melanoma (CS, pg 154-155, Table 48)

Inclusion criteria		**Rationale**
Population	Age: adults aged ≥18 years Gender: any	Consistent with the evidence base for avelumab and the anticipated marketing authorisation

	Ethnicity: any Disease: melanoma	
Interventions/Comparators	topotecan cyclophosphamide + doxorubicin + vincristine carboplatin + etoposide cisplatin + etoposide carboplatin alone carboplatin + paclitaxel cisplatin + paclitaxel doxorubicin liposomal doxorubicin paclitaxel pembrolizumab	Interventions were identified from an observational study as likely treatment options for patients with metastatic MCC.
Outcomes	Cost-effectiveness, direct/indirect costs, resource use, BSC costs, costs, life years, QALYs, ICERs	The aim of the review was to identify relevant costs and data on resource use
Study design	Cost-effectiveness analyses, cost-minimization analyses, cost-utility analyses, cost/burden of illness, costing studies	The aim of the review was to identify relevant costs and use of resource
Limits	English language studies only	Time and resource required for translation and relevance for UK setting
Exclusion criteria		**Rationale**
Intervention/Comparators	Studies exclusively focusing on the role of radiotherapy, chemo-radiotherapy, hormonal therapy, diagnostics, screening or surgery Studies investigating the role of maintenance/consolidation therapy after surgery Adjuvant or neo-adjuvant therapy Does not include chemotherapy regimens that are listed as comparators	In line with the anticipated NICE scope, studies were restricted to those evaluating the efficacy of comparators. Comparators were restricted to chemotherapies and BSC
Population	Studies that included children and adults and did not provide subgroup analysis for the adult populations Studies focusing on patients with uveal or ocular melanoma	Consistent with the avelumab evidence base
Outcomes	No relevant costs or resource use	Not part of the aims of the literature search
Study design	Systematic literature reviews and meta-analyses	Studies from systematic literature reviews and meta-analyses were cross checked to ensure all relevant publications were identified
Country	None	Review was kept broad considering the limited data
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; MCC, metastatic Merkel Cell Carcinoma; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.		

Three studies reporting resource use were identified across the searches and were included for data extraction. One reported resource use in patients with SCLC,[209] and the other two reported resource use in melanoma.[210, 211] These studies are summarised in Table 46. In terms of studies reporting cost data, a total of five studies were identified by the company. Of these, two studies reported costs of management of patients with SCLC,[212, 213] and three studies reported costs of manging melanoma patients. These studies are summarised in Table 47.[210, 214, 215] All the studies were either primarily UK studies,[211, 213, 215, 216] or studies that included data collected from UK patients.[210, 212, 214]

Table 46. Resource use studies identified in company's systematic literature review (CS, Appendix 7, Table 8 and Table 10)

Author, Year, Country	Study type	Perspective	Time horizon	Treatment regimen	Resource Use
Small Cell Lung Carcinoma					
Wolstenholme, 1999, UK[216]	Retrospective analysis of treatment records	Health care provider	4 years	NR	Treatment-related resource use: Number of patients: • Inpatient palliative care: 10 (38.5%) •Palliative radiotherapy: 13 (50%) •Radical radiotherapy: 2 (7.7%) •Chemotherapy: 15 (57.7%) Monitoring resource use: •Mean length of inpatient stays (in days, over 4-year period) •Diagnosis: 11.2 (SD: 8.6) •Chemotherapy: 15.4 (SD: 9.2) •Inpatient palliative care: 13.7 (SD: 11.3) •Further investigations: 6.3 (SD: 5.6)
Melanoma					
McKendrick, 2016 Multiple[210]	Literature review, Delphi panel	Health care provider	NR	NR	Health care resource use during active treatment phase per 3 months across all countries: •physician consultations: 1.16 •CT imaging scans: 1.23 •day-hospital visits: 1.35 Health care resource use during disease progression phase: •inpatient admissions: 0.47 •radiotherapy fractions: 1.23

Lorigan 2014, UK[212]	Multinational, observational, retrospective, longitudinal survey	NR	1 year	Chemotherapy (n=115) BSC (n=68)	Number of chemotherapy patients (%) with: •any hospitalisation: 14 (12.2) •any hospice care: 13 (11.3) •any outpatient care: 80 (69.6) •requirement of hospitalization: 15 •medical management of treatment-related adverse events: 29 Reason for hospitalisation •Drug administration: 1 (7) •Disease progression: 1 (7) •Toxicity: 3 (20) • Other: 10 (67) Number of patients (%) with: •any hospitalisation: 31 (46) • any hospice care: 25 (37) •any outpatient care: 46 (68) •requirement of hospitalization: 31 •medical management of treatment-related adverse events: NA Reason for hospitalisation •Drug administration: 1 (3) •Disease progression: 15 (48) •Toxicity: 0 •Other: 18 (58)
Abbreviations in table: BSC, best supportive care; CT, computerised tomography; NR, not reported; SD, standard deviation.					

Table 47. Costs studies identified in company's systematic literature review (CS, Appendix 7, Table 9 and Table 11)

Author, Year, Country	Study type	Perspective	Time horizon	Treatment regimen	Cost year, currency	Costs
Small Lung Cell Carcinoma						
Oliver, 2001, UK[211]	Retrospective analysis of patient charts	Health care provider	4 years	First line: carboplatin + etoposide alternative for partial responders: Mediastinal radiotherapy Second line: cyclophosphamide, doxorubicin, vincristine	1998, GBP	Treatment acquisition costs: Overall disease costs by resource type: •Chemotherapy: £163,113 •Surgery: £22,896 •Radiotherapy: £30,329 •Other medication: £17,690 •Blood transfusion: £16,144 Monitoring costs: •Hospitalisation with overnight stay: £607,416 •Hospitalisation without overnight stay: £37,392 •Outpatient visits: £183,006 •Test and procedures: £141,032 Adverse event costs: •side effect management: £40,739
Wolstenholme, 1999, UK[213]	Retrospective analysis of treatment records	Health care provider	4 years	NR	1993, GBP	Mean 4-year diagnosis and management costs: •Total: £5,668 •Diagnosis: £2,746 •Radical radiotherapy: £531 Chemotherapy: £1,558 •Palliative radiotherapy: £317 •Inpatient palliative care: £2,649 •Further investigations: £2,264 •Follow-up: £414
Melanoma						

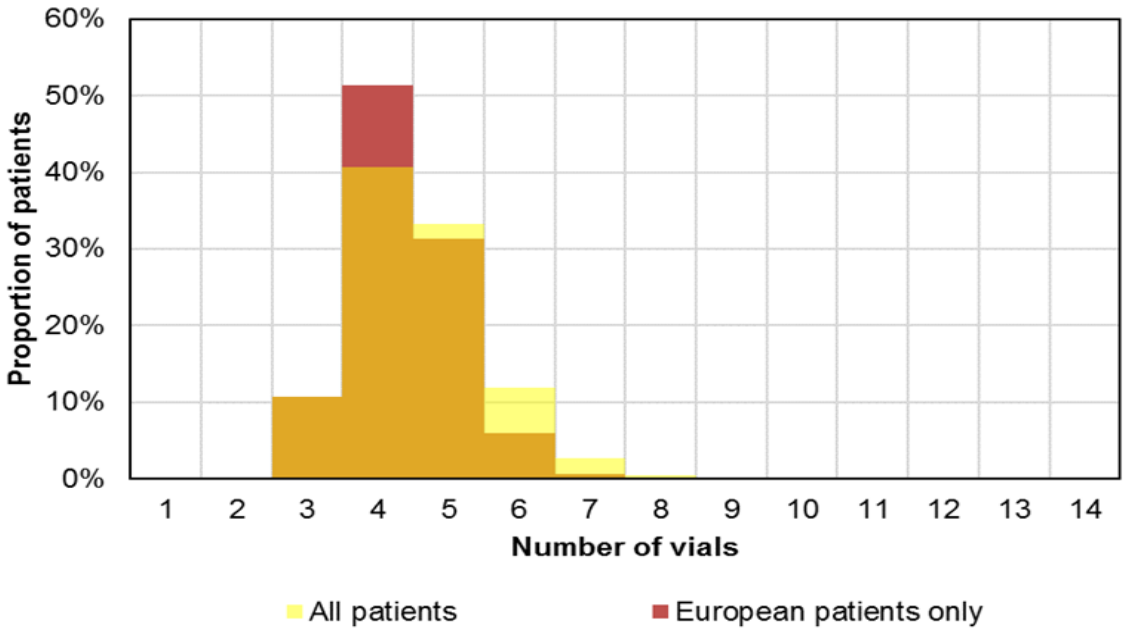
Kontoudis, 2014, Multiple[210]	Retrospective observational study	Health care provider	3 years	NR	2013, GBP	Treatment acquisition costs: •Mean total direct cost per patient: £31,123 •Melanoma treatment per patient: £24,385 •Preliminary estimates for annual national direct cost: £22.8 million Monitoring costs •Mean cost hospitalisation/emergency treatment per patient: £2,827 •Indirect costs: Total mean costs per patient: £1,427
Vouk, 2014, UK[214]	Literature review, Delphi panel	Health care provider (UK NHS)	NR	Chemotherapy	2009-2011, GBP	Adverse event costs (cost per event per patient): •Neuropathy: £432 •Thrombocytopenia: £277
Vouk, 2016, Multiple[215]	Literature review, Delphi panel	Statutory health insurance	NR	Chemotherapy	2014, GBP	Adverse event costs (cost per event per patient): •Anaphylaxis: £197.97 •Neutropenia/ Leukopenia: £272.47 Peripheral neuropathy: £432.08 •Thrombocytopenia: £276.78
Abbreviations in table: NHS, National Health Service; NR, not reported.						

5.4.9.2 *Pharmacological costs*

The company included drug acquisition costs as well as drug administration costs in the model. Treatment-related costs used for avelumab were applied in the same manner for the cost-effectiveness analyses of the treatment-naïve and the treatment-experienced populations.

Avelumab was administered as an intravenous infusion every two weeks at a target dose of 10 mg/kg in the JAVELIN Merkel 200 trial, and the same dosage is assumed in the model.[216] Time on treatment observed in the JAVELIN Merkel 200 trial was used to estimate the proportion of patients receiving avelumab in each model cycle to accurately calculate costs.[3] The mean dose of avelumab per administration assumed in the model is based on the number of vials received by patients in the JAVELIN Merkel 200 trial, as estimated using the method of moments based on the weight, and number of doses received by the European subgroup of patients.[3] A lognormal distribution was fitted to the weight data of patients, which the company reports to be the distribution that most accurately reflects the weight of patients seen in clinical practice. The lognormal distribution was then used to calculate the proportion of patients requiring a certain number of vials ranging from 1 to 14 vials, as illustrated in Figure 53. A weighted average of all possible quantities of vials and the proportion of patients receiving them was subsequently used to estimate the number of vials per administration.

Figure 53. Distribution of patients by number of vials received (CS, pg 158, Figure 55)



The relative dose intensity (RDI) of avelumab in the JAVELIN Merkel 200 trial was 95.43%, which the company defines as the proportion of doses received relative to the intended dose of 10 mg/kg. Therefore, the company adjusted the intended dose in the model to 9.543 mg/kg instead of 10 mg/kg when calculating the mean number of vials per patient. The summary statistics of the method of moments calculations are presented in Table 9, which shows the resultant mean number of vials per administration for the European subpopulation to be 4.25 vials. This is the mean number of vials assumed for avelumab in the company's base case analysis. The dose and costs of avelumab are summarised in Table 10.

Table 48. Summary statistics of methods of moments calculation for avelumab (CS, pg 158, Table 49)

Statistic	All patients	European patients
N	88	29
Mean weight (kg)	83.09	78.50
SD	19.15	14.99
SE	2.04	2.78
Average vials	4.46	4.25
Abbreviations in table: : N, number of patients; SD, standard deviation; SE, standard error		

Table 49. Dosing information for avelumab (CS, pg 159, Table 50)

Dose	10 mg/kg
Vial size	200 mg
Cost per vial	£768.00 (Merck)
Cost per mg	£3.84
Average dose per treatment	869 mg*
RDI	95.43%
Average cost per treatment	£3,261.04
Administration information	IV infusion once every 2 weeks[3]
Abbreviations in table: IV, intravenous; kg, kilogram; mg, milligram; RDI, relative dose intensity. * The average dose for avelumab is calculated via the method of moments and incorporates vial wastage.	

There are currently no approved treatments for mMCC, and therefore, the company relied on clinical expert opinion on chemotherapy regimens used to treat SCLC in England, which are also used off-label to treat mMCC. Chemotherapy dosage in the model is based on published literature identified in the SLR (CS, page 164, Table 54), complemented by clinical expert opinion. Treatment-naïve patients in the chemotherapy arm of the model in the base case analysis are assumed to be equally split between two regimens; carboplatin + etoposide and cisplatin + etoposide. Additional chemotherapy regimens are included in the model, to allow the flexibility of selecting alternative regimens if desired.

Chemotherapy dosage is calculated based on body surface area (BSA) for cisplatin and etoposide. The BSA of patients in the model is assumed to be the same as the average BSA of patients in the JAVELIN

Merkel 200 trial,[3] calculated using the DuBois approximation[3] to be 1.94 m^2. As for carboplatin, AUC dosing is used with an estimated serum creatinine level of 0.9, and assuming the average glomerular filtration rate of patients in the JAVELIN Merkel 200 trial which was 87.94 mL/min resulting in an average dose of 564.7 mg on the first day of each three-weekly cycle. The dosage assumptions and drug costs of chemotherapy in the model are summarised in Table 50 and Table 51, respectively. Chemotherapy is assumed to be administered for a maximum of 6 cycles.

Table 50. Chemotherapy dosage assumptions in base case analysis (CS, pg 161, Table 53)

Drug Regimen	Dose	Administration information	Reference
Carboplatin (IV) + Etoposide (IV) + Etoposide (oral)	Carboplatin 5 AUC	IV infusion on Day 1 of 3-week cycle	Clinical validation
	Etoposide IV 100 mg/m²	IV infusion on Day 1 of 3-week cycle	
	Etoposide oral 200 mg/m²	Oral tablets on Days 2, 3 for 3-week cycle	
Cisplatin + Etoposide (IV)	Cisplatin 80 mg/m²	IV infusion, once every 3 weeks	Sun 2016[217]
	Etoposide IV 100 mg/m²	IV infusion, three times every 3 weeks	
Abbreviations in table: AUC, are under the curve; IV, intravenous; m, metre; mg, milligram.			

Table 51. Chemotherapy costs (CS, pg 161, Table 53)

Drug Regimen	Treatments per week	Pack size assumed (number of vials/tabs)	Cost per pack[136]	Cost per cycle
Carboplatin (IV) + Etoposide (IV) + Etoposide (oral)	0.33	Carboplatin 600 mg/60 ml solution for infusion vials (1)	£25.25	£8.04
	0.33	Etoposide 500 mg/125 ml solution for injection vials (10)	£24.96	
	0.67	Etoposide 100 mg, (10)	£87.23	
Cisplatin + Etoposide (IV)	0.33	Cisplatin 100 mg/100 ml solution for infusion vials (1)	£10.56	£0.08
	1.00	Etoposide 500 mg/125 ml solution for injection vials (10)	£24.96	
Abbreviations in table: AUC, are under the curve; IV, intravenous; m, metre; mg, milligram.				

An administration cost of £199 (HRG code SB12Z, in an outpatient setting) is included for avelumab, carboplatin, cisplatin and IV etoposide in the model. No administration cost was assumed for oral etoposide. In instances when more than one drug was administered in the same day, a single administration cost is applied.

The treatment-related costs for avelumab are applied in the model every two weeks to reflect the dosing regimen of avelumab. As for chemotherapy, due to different dosing schedules across the regimens, a weekly (per model cycle) cost was estimated and applied.

5.4.9.3 Health state costs

Resource use in the model is based on studies of patients with SCLC, and clinical expert opinion. The same resource use and monitoring costs are assumed for patients regardless of whether they are treatment-naïve or treatment-experienced. Prior to progression patients receiving avelumab are assumed to have GP visits every two treatment cycles (i.e. every 4 weeks), CT scans every 3 months and blood tests every treatment cycle. Patients receiving chemotherapy are assumed to have GP visits and blood tests every treatment cycle, in addition to a CT scan every 2 months. Resource use prior to progression is summarised in Table 52. Once patients progress in either the avelumab or chemotherapy treatment arms they are assumed to receive BSC, which is assumed to consist of a GP visit every two months.

Table 52. Resource use for progression-free patients (CS, pg 172, Table 64)

Resource	Avelumab	Chemotherapy
GP visit	Every two treatment cycles	Every treatment cycle
CT scan	Every 3 months	Every 2 months
Full blood count	Every treatment cycle	Every treatment cycle
Liver function test	Every treatment cycle	Every treatment cycle
Renal function test	Every treatment cycle	Every treatment cycle
Thyroid function test	Every treatment cycle	None

According the company's clinical experts, 75% of patients with MCC receive a palliative radiotherapy regimen of 1-5 fractions, administered 1-2 times in total, which was estimated to be 3.75 days. Therefore, it is assumed that 75% of patients alive in the model, regardless of treatment arm receive radiotherapy for up to 1 year. In order to calculate the proportion of patients per model cycle receiving radiotherapy, 75% was divided by the average number of model cycles patients are alive on chemotherapy which is 21.65 cycles (for treatment-experienced patients), and 105.44 (for treatment-naïve patients) and is equal to 0.03, and 0.01 of patients, respectively. Resource use assumed for radiotherapy is summarised in Table 53. The unit costs used in the model are all either costs from the NHS Schedule of Reference Costs 2015-2016,[218] or the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2016[219] and are presented in Table 54.

Table 53. Resource use assumptions for radiotherapy (Adapted from CS, pg 173, Table 66)

Resource component	Estimate
Duration of radiotherapy treatment (days)	3.75
Assuming average survival as per chemotherapy patients, number of cycles alive	87.74
Radiotherapy applied until (all patients)	1 year

Table 54. Unit costs of resource use components (CS, pg 169, Table 60 and Table 61)

Unit description	Cost	Description	Reference
GP visit	£36.00	Surgery consultation lasting 9.22 minutes	PSSRU - Unit Costs of Health and Social Care 2016[220]
CT scan	£120.99	Total HRGs - RD26Z - CT scan of 3 areas with contrast	National Schedule of Reference Costs - 2015-16[220]
Full blood count	£3.00	Haematology - DAPS05	National Schedule of Reference Costs - 2015-16[219]
Liver function test	£1.00	DAPS04 - Clinical Biochemistry	National Schedule of Reference Costs - 2015-16[219]
Renal function test	£1.00	DAPS04 - Clinical Biochemistry	National Schedule of Reference Costs - 2015-16[219]
Thyroid function test	£1.00	DAPS04 - Clinical Biochemistry	National Schedule of Reference Costs - 2015-16[219]
Radiotherapy	£126.60	Outpatient Attendance - 800 - Clinical Oncology	National Schedule of Reference Costs - 2015-16[219]

Abbreviations in table: CT, computerised tomography; GP, general practitioner; PSSRU, Personal and Social Services Research Unit.

5.4.9.4 Adverse event costs

The company included the costs of managing TRAEs, based on the rates and durations previously described in Section 5.4.7. The costs assumed by the company for managing adverse events were obtained from studies reporting the costs associated with managing the adverse events experienced by patients receiving treatment for metastatic melanoma.[216, 219] The costs were inflated to 2016 prices using the Hospital and Community Health Services (HCHS) inflation index published by the PSSRU, and are summarised in Table 55. The costs associated with adverse events for patients receiving chemotherapy were also estimated based on the assumption that 50% of patients receive cisplatin + etoposide, and 50% receive carboplatin + etoposide. The adverse event costs per model cycle for each of the treatment regimens are presented in Table 56.

Table 55. Costs of managing adverse events (CS, pg 174, Table 67)

Adverse event	Source cost	Cost year	Inflated cost	Source
Anaemia*	£728.62 for ipilimumab patients, £792.10 for vemurafenib or BSC patients	2012	£799.39	NICE TA319. Oxford Outcomes: Anaemia. Average across both treatment arms assumed to apply.[221]
Dyspnoea	£251.00	2014	£256.62	Outpatient dyspnoea (Wehler 2017)[222]
Fatigue	£64.28	2013	£66.45	Assumed to be the same as Grade 1 or 2 anaemia (Vouk 2016)[221]
Febrile neutropenia	£4,444.00	2014	£4,543.44	Inpatient febrile neutropenia (Wehler 2017)[216]

Low haemoglobin	£64.28	2013	£66.45	Assumed to be the same as Grade 1 or 2 anaemia (Vouk 2016)[221]
Hyponatremia	£64.28	2013	£66.45	Assumed to be the same as Grade 1 or 2 anaemia (Vouk 2016)[216]
Infections	£251.00	2014	£256.62	Outpatient infection (Wehler 2017)[216]
Leukopenia	£272.47	2013	£281.67	Assumed to be the same as neutropenia / leukopenia (Vouk 2016)[221]
Lymphopenia	£272.47	2013	£281.67	Assumed to be the same as neutropenia / leukopenia (Vouk 2016)[216]
Muscle pain*	£146.00	2012	£153.49	NICE TA319. HRG service code: 191, Pain management, multi-professional non-admitted face-to-face.[216]
Nausea/vomiting*	£213.49	2014	£218.27	NICE TA357. Assumed the same as diarrhoea from NICE TA319 (Oxford Outcomes: Diarrhoea).[222]
Neutropenia	£272.47	2013	£281.67	Neutropenia / leukopenia (Vouk 2016)[223]
Low platelets	£272.47	2013	£281.67	Assumed to be the same as neutropenia / leukopenia (Vouk 2016)[216]
Sensory neuropathy	£432.00	2013	£446.59	Assumed to be the same as peripheral neuropathy (Vouk 2016)[216]
Thrombocytopenia	£276.78	2013	£286.12	Thrombocytopenia (Vouk 2016)[216]

Abbreviations in table: HRG, Health Resources Grouper; TA, Technology Appraisal.
* These costs were updated during clarification stage.

Table 56. Costs of managing adverse event per model cycle (CS, pg 176, Table 69)

Treatment regimen	Cost per model cycle
Avelumab	£0.38
Chemotherapy	£98.38
Best Supportive care	£0.00

5.4.9.5 End of life costs

The company did not identify data on resource use for terminal care of patients with mMCC, and therefore used published mean estimates from a study assessing costs of end of life care across four types of cancer in the UK. The cancers considered in the study are breast, colorectal, prostate and lung cancer.[216] The mean cost estimates across the four cancers are used in the base case analysis and are presented in Table 57, while the impact of using the separate estimates for each type of cancer is explored in scenario analyses. End of life costs are applied to the proportion of patients who die in each model cycle.

Table 57. End of life costs (CS, pg 176, Table 70)

Category	Source cost[224]	Inflated cost*[224]
Health care	£4,761.00	£4,867.53
Social care	£2,104.50	£2,151.59
Total	£6,865.50	£7,019.12

*These costs were not inflated from 2013-2014 costs to 2015-2016 costs in the CS, but were updated during clarification stage. An inflation factor of approximately 1.02 was applied based on the PSSRU inflation indices.[220]

5.4.9.6 ERG critique

The ERG considers that the company took a very rigorous approach to identify sources of data to inform resource use and costs in the model, given the lack of such data for patients with mMCC. The ERG's clinical experts confirmed that the dosage assumptions to estimate treatment related costs for both avelumab and chemotherapy in the model are in line with what would be expected in UK clinical practice.

The company reported that resource use in the model is based on studies of patients with SCLC in addition to clinical expert opinion. The ERG's clinical experts agreed that treatment and resource use for SCLC is similar to mMCC and, therefore, can be used as a proxy. They considered all of the resource use assumptions made by the company to be reasonable with the exception of including GP visits for patients prior to progression instead of outpatient oncology visits. The ERG explores the impact of substituting GP visits for outpatient oncology visits for patients prior to progression, on the cost-effectiveness results. The ERG also identified an error in the way monthly resource use was converted to weekly (per model cycle) to be applied in the model in some of the calculations. This error was the result of a month assumed to have 4 weeks instead of 4.35 weeks, and was corrected by the company during clarification stage by assuming a month is made up of 30.44 days and not 28 days.

Resource use assumptions in the model for the management of adverse events are based on two publications reporting costs of adverse events associated with chemotherapy in melanoma patients.[216, 220] The ERG considers using the adverse event costs from melanoma patients to be reasonable in light of the lack of data for mMCC patients, especially since only TRAEs are being considered in the analysis. However, the ERG has several issues with the estimates used in the model which mostly affect the overall costs of chemotherapy as patients in the chemotherapy arm experience more adverse patients receiving avelumab:

- The company states in Section 5.4.3 of the CS that melanoma patients tend to be much younger than mMCC patients. Therefore, the ERG is concerned that due to this difference in patient demographic, patients who have mMCC may require more resource use for managing adverse events due to generally being less fit than melanoma patients as a result of advanced age rendering these costs not reflective of actual care required;

- All the adverse events in the model with the exception of hair loss are Grade 3 or higher adverse events, while many of the costs assumed in the model are costs of managing Grade 1 or 2 events reflecting the grade of adverse events experienced by UK patients in the publication by Vouk *et al*.[216, 221] Therefore, there is a lack of consistency across the events experienced and the resource use assumed, with costs being potentially underestimated. The company updated the

costs for anaemia, nausea and vomiting, and muscle pain to reflect costs of managing Grade 3 or higher adverse events during the clarification stage.

- A cost of £446.59 is assumed for managing sensory neuropathy which, according to the ERG's clinical experts, has no treatment, and therefore it is unclear what this cost would entail. The ERG explored the impact of removing the cost of sensory neuropathy from the model in a scenario analysis, which had negligible impact on the results and, therefore, the ERG did not consider it necessary to present the results in full.

End of life costs applied in the model are based on estimates reported in the modelling study by Round *et al.* that utilised data from four robust studies reporting the costs of terminal care in the UK.[221, 224-227] The company directly uses the estimates from the paper in the model without inflating them to 2015-2016 costs in line with other costs in the model, despite them being based on 2013 costs .The company corrected this error during the clarification stage.

5.5 Results included in company's submission

5.5.1 Base case results

The results of the company's base case analysis for treatment-experienced patients is presented in Table 58, and for the treatment-naïve population in Table 59 and Table 60 for the pairwise and incremental analysis, respectively. According to the company's analysis, avelumab is expected to extend treatment-experienced patients' lives by around 37 months compared to BSC, and the lives of treatment-naïve patients by 33 months compared to chemotherapy and BSC, respectively. This translates to an incremental average quality-adjusted life year (QALY) gain for avelumab of 1.91 QALYs in treatment-experienced patients compared to BSC, and an average QALY gain of 1.37 and 1.38 QALYs for treatment-naïve patients compared to chemotherapy and BSC, respectively.

The incremental cost-effectiveness ratio (ICER) for avelumab compared to BSC is £37,350 per QALY in treatment-experienced patients. The pairwise analysis of avelumab compared to chemotherapy and BSC for treatment-naïve patients results in an ICER of £43,553 and £46,148 per QALY, respectively. The fully incremental analysis carried out for treatment-naïve patients shows BSC to be the least costly treatment option, and chemotherapy to be dominated by BSC (more costly, with no QALY gain), and the ICER for avelumab compared to BSC to be £46,148 per QALY.

Table 58. Results of company's base case analysis for treatment-experienced patients (produced from company's model after clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,752	3.53	2.22	-	-	-	-
BSC	£7,465	0.41	0.31	£71,287	3.11	1.91	£37,350
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; IFN: Interferon; QALY, Quality-adjusted life year.							

Table 59. Results of company's base case analysis for treatment-naïve patients (produced from company's model after clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,588	4.78	2.93	-	-	-	-
Chemotherapy	£10,608	2.02	1.37	£67,979	2.76	1.56	£43,553
BSC	£7,217	2.02	1.38	£71,371	2.76	1.55	£46,148
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; IFN: Interferon; QALY, Quality-adjusted life year.							

Table 60. Results of company's fully incremental base case analysis for treatment-naive patients (produced from company's model after clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£7,217	2.02	1.38				

Chemotherapy	£10,608	2.02	1.37	£3,392	0.00	-0.01	Dominated
Avelumab	£78,588	4.78	2.93	£71,371	2.76	1.55	£46,148
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

The QALY gain by health state in treatment-experienced and treatment-naïve patients is summarised in Table 61 and Table 62, respectively. The maximum QALY gain for avelumab compared to comparators in both the treatment-experienced and treatment-naïve populations is within the state of ">100 days from death". The LY gain by health state in treatment-experienced and treatment-naïve patients is summarised in Table 63 and Table 64, respectively. The greatest LY gain for avelumab compared to comparators in both the treatment-experienced and treatment-naïve populations is within the PF off-treatment health state.

Table 61. Summary of QALY gain by health state in treatment-experienced patients (CS, page 186, Table 81)

QALYs	Avelumab	BSC
AE disutility	0.00	0.00
>100 days to death	2.05	0.13
30-100 days to death	0.12	0.13
<30 days to death	0.05	0.05
Total	2.22	0.31
Abbreviations in table: BSC, best supportive care; QALY, quality-adjusted life year.		

Table 62. Summary of QALY gain by health state in treatment-naïve patients (CS, page 187, Table 85)

QALYs	Avelumab	Chemotherapy	BSC
AE disutility	0.00	-0.01	0.00
>100 days to death	2.77	1.20	1.20
30-100 days to death	0.12	0.13	0.13
<30 days to death	0.05	0.05	0.05
Total	2.93	1.37	1.38
Abbreviations in table: BSC, best supportive care; QALY, quality-adjusted life year.			

Table 63. Summary of life years gain by health state in treatment-experienced patients (CS, page 187, Table 83)

Life years	Avelumab	BSC
PF On Treatment	0.75	0.00
PF Off Treatment	2.24	0.24
PP On Treatment	0.03	0.00
PP Off Treatment	0.51	0.17
Total	**3.53**	**0.41**
Abbreviations in table: BSC, best supportive care; PF, progression-free; PP, post-progression.		

Table 64. Summary of life years gain by health state in treatment-experienced patients (CS, page 188, Table 87)

Life years	Avelumab	Chemotherapy	BSC
PF On Treatment	0.75	0.27	0.00
PF Off Treatment	2.86	0.64	0.90
PP On Treatment	0.03	0.00	0.00
PP Off Treatment	1.13	1.12	1.12
Total	**4.78**	**2.02**	**2.02**

Abbreviations in table: BSC, best supportive care; PF, progression-free; PP, post-progression.

A breakdown of resource use by cost category is presented in Table 65 and Table 66 for treatment-experienced and treatment-naïve patients, respectively.

Table 65. Summary of resource use by cost category for treatment-experienced patients (adapted from CS, page 187, Table 84)

Costs	Avelumab	BSC
Drug costs	£65,086	£0
Treatment administration	£3,972	£0
Resource use	£3,355	£446
Adverse events	£15	£0
End of life	£6,324	£7,019
Total	**£78,752**	**£7,465**

Abbreviations in table: BSC, best supportive care.

Table 66. Summary of resource use by cost category for treatment-naïve patients (adapted from CS, page 188, Table 87)

Costs	Avelumab	Chemotherapy	BSC
Drug costs	£65,086	£173	£0
Treatment administration	£3,972	£1,849	£0
Resource use	£3,411	£1,528	£523
Adverse events	£15	£364	£0
End of life	£6,103	£6,694	£6,694
Total	**£78,588**	**£10,608**	**£7,217**

Abbreviations in table: BSC, best supportive care.

5.5.2 Sensitivity analysis

5.5.2.1 Scenario analysis

The company carried out a range of scenario analyses exploring the impact of changing assumptions surrounding the following parameters:

- Time horizon;

- Discounting;
- Clinical inputs;
    - Patient population used to derive weight;
    - Parametric distributions for: ToT, PFS, and OS;
    - Assumed time point by which most patients discontinue treatment;
    - Proportion of patients receiving avelumab after 2 years;
    - Maximum treatment duration with avelumab.
- Health state utilities;
- Costs and resource use.

The results of the company's scenario analysis for treatment-experienced and treatment-naïve patients are presented in Table 67 and Table 68, respectively.

Table 67. Results of scenario analysis for treatment-experienced patients (produced from company's model after clarification responses)

Base case input	Scenario	ICER
Time horizon 40 years	Time horizon of 5 years	£65,176
	Time horizon of 10 years	£47,119
	Time horizon of 20 years	£38,406
	Time horizon of 30 years	£37,359
Discounting: All 3.5%	Discounting: All 0%	£31,209
	Discounting: All 1.5%	£33,877
	Discounting: All 6%	£41,521
European patients (for derivation of average patient weight)	All patients	£39,215
OS: Extrapolation options – avelumab Spline – 1 knot - odds	Parametric - exponential	£74,599
	Parametric - generalised gamma	£38,885
	Parametric - Gompertz	£30,035
	Parametric - log-logistic	£48,527
	Parametric - log-normal	£49,180
	Parametric - Weibull	£70,652
	Spline - 1 knot - hazard	£45,843
	Spline - 1 knot - normal	£41,958
	Spline - 2 knots - hazard	£44,393
	Spline - 2 knots - odds	£36,781
	Spline - 2 knots - normal	£38,244
	Spline - 3 knots - hazard	£42,785
	Spline - 3 knots - odds	£36,538
	Spline - 3 knots - normal	£38,390
	Mixture cure - exponential	£41,039
	Mixture cure - Weibull	£41,466
	Mixture cure - log-normal	£44,891

	Mixture cure - log-logistic	£28,948
	General population survival extrapolation	£31,531
OS: Extrapolation options - comparator Parametric - Gompertz	Parametric - exponential	£37,532
	Parametric - generalised gamma	£37,330
	Parametric - log-logistic	£37,864
	Parametric - log-normal	£37,722
	Parametric - Weibull	£37,342
	Inverse variance (weibull - 2L only)	£37,521
	Bivariate normal (weibull - 2L only)	£37,921
PFS: Extrapolation options - avelumab Spline - 3 knots - hazard	Spline - 1 knot - hazard	£37,363
	Spline - 1 knot - odds	£37,350
	Spline - 1 knot - normal	£37,370
	Spline - 2 knots - hazard	£37,376
	Spline - 2 knots - odds	£37,379
	Spline - 2 knots - normal	£37,371
	Spline - 3 knots - odds	£37,350
	Spline - 3 knots - normal	£37,281
	Spline - custom	£37,188
PFS: Extrapolation options - comparator Parametric - Weibull	Parametric - exponential	£37,350
	Parametric - generalised gamma	£37,350
	Parametric - Gompertz	£37,350
	Parametric - log-logistic	£37,350
	Parametric - log-normal	£37,350
	Inverse variance (weibull - 2L only)	£37,350
	Bivariate normal (weibull - 2L only)	£37,350
ToT: Extrapolation options - avelumab Parametric – Log-logistic	Parametric - exponential	£35,752
	Parametric - generalised gamma	£36,674
	Parametric - Gompertz	£38,020
	Parametric - log-normal	£38,331
	Parametric - Weibull	£36,135
	Spline - 1 knot - hazard	£36,576
	Spline - 1 knot - odds	£36,171
	Spline - 1 knot - normal	£36,327
	Spline - 2 knots - hazard	£36,695
	Spline - 2 knots - odds	£36,984
	Spline - 2 knots - normal	£36,933
	Spline - 3 knots - hazard	£36,695
	Spline - 3 knots - odds	£37,137
	Spline - 3 knots - normal	£38,085
ToT: Estimated discontinuation time for the majority of patients: 2 year(s)	1 year(s)	£31,275
	1.5 year(s)	£34,697
	2.5 year(s)	£39,516
	3 year(s)	£41,343
ToT: Proportion of patients expected to remain on treatment after 2 years of treatment: 33%	5%	£33,400
	10%	£34,097
	15%	£34,794

	20%	£35,491
	25%	£36,189
	30%	£36,886
	35%	£37,583
	40%	£38,280
	45%	£38,977
	50%	£39,674
	55%	£40,371
	60%	£41,068
	65%	£41,765
	70%	£42,462
	75%	£43,159
	80%	£43,856
	85%	£44,553
	90%	£45,250
	95%	£45,947
	100%	£46,645
ToT: Maximum expected treatment duration: 5 years	3 year(s)	£34,700
	4 year(s)	£36,181
	6 year(s)	£38,310
	7 year(s)	£39,117
Utilities: Time to death (GEE)	Progression status	£37,350
	Time to death (decrement for final 30 days)	£35,512
Costs: Average end of life care costs across different cancers	Cancer type Lung	£35,408
	Cancer type Breast	£37,475
	Cancer type Colorectal	£37,333
	Cancer type Prostate	£37,378
Comparator: BSC	Chemotherapy	£35,873
Abbreviations in table: BSC, best supportive care; GEE, Generalised Estimating Equation; OS, overall survival; PFS, progression-free survival; ToT, time-on-treatment.		

Table 68. Results of scenario analysis for treatment-naïve patients (produced from company's model after clarification responses)

Base case input	**Scenario**	**ICER (avelumab versus)**	
		Chemotherapy	**BSC**
Time horizon 40 years	Time horizon of 5 years	£127,333	£137,427
	Time horizon of 10 years	£66,102	£70,397
	Time horizon of 20 years	£45,058	£47,755
	Time horizon of 30 years	£43,300	£45,873
Discounting: All 3.5%	Discounting: All 0%	£33,488	£35,348
	Discounting: All 1.5%	£37,610	£39,761
	Discounting: All 6%	£51,654	£54,903
European patients (for derivation of average patient weight)	All patients	£45,991	£48,627
OS: Extrapolation options – avelumab Spline – 1 knot - odds	Parametric - exponential	£374,713	£428,073
	Parametric - generalised gamma	£46,294	£49,083

	Parametric - Gompertz	£32,894	£34,773
	Parametric - log-logistic	£67,467	£71,874
	Parametric - log-normal	£70,057	£74,680
	Parametric - Weibull	£252,039	£279,901
	Spline - 1 knot - hazard	£61,576	£65,516
	Spline - 1 knot - normal	£52,285	£55,511
	Spline - 2 knots - hazard	£57,930	£61,586
	Spline - 2 knots - odds	£42,575	£45,103
	Spline - 2 knots - normal	£45,091	£47,796
	Spline - 3 knots - hazard	£54,193	£57,564
	Spline - 3 knots - odds	£42,160	£44,659
	Spline - 3 knots - normal	£45,353	£48,076
	Mixture cure - exponential	£50,270	£53,342
	Mixture cure - Weibull	£51,356	£54,506
	Mixture cure - log-normal	£57,387	£60,985
	Mixture cure - log-logistic	£30,305	£32,019
	General population survival extrapolation	£34,149	£36,110
OS: Extrapolation options - comparator Parametric - Gompertz	Parametric - exponential	£38,414	£40,605
	Parametric - generalised gamma	£39,638	£41,939
	Parametric - log-logistic	£43,553	£46,148
	Parametric - log-normal	£43,813	£46,425
	Parametric - Weibull	£38,194	£40,367
PFS: Extrapolation options - avelumab Spline - 3 knots - hazard	Spline - 1 knot - hazard	£43,672	£46,269
	Spline - 1 knot - odds	£43,642	£46,239
	Spline - 1 knot - normal	£43,668	£46,265
	Spline - 2 knots - hazard	£43,639	£46,235
	Spline - 2 knots - odds	£43,673	£46,270
	Spline - 2 knots - normal	£43,668	£46,264
	Spline - 3 knots - odds	£43,553	£46,148
	Spline - 3 knots - normal	£43,330	£45,923
	Spline - custom	£43,250	£45,843
PFS: Extrapolation options - comparator Parametric - Weibull	Parametric - exponential	£43,419	£46,148
	Parametric - generalised gamma	£43,548	£46,148
	Parametric - Gompertz	£43,399	£46,148
	Parametric - log-logistic	£43,553	£46,148
	Parametric - log-normal	£43,543	£46,148
ToT: Extrapolation options - avelumab Parametric – Log-logistic	Parametric - exponential	£41,598	£44,176
	Parametric - generalised gamma	£42,725	£45,313
	Parametric - Gompertz	£44,372	£46,975
	Parametric - log-normal	£44,751	£47,358
	Parametric - Weibull	£42,067	£44,648
	Spline - 1 knot - hazard	£42,606	£45,193
	Spline - 1 knot - odds	£42,111	£44,693
	Spline - 1 knot - normal	£42,302	£44,886
	Spline - 2 knots - hazard	£42,751	£45,339
	Spline - 2 knots - odds	£43,105	£45,696

	Spline - 2 knots - normal	£43,043	£45,634
	Spline - 3 knots - hazard	£42,752	£45,340
	Spline - 3 knots - odds	£43,292	£45,885
	Spline - 3 knots - normal	£44,451	£47,055
ToT: Estimated discontinuation time for the majority of patients: 2 year(s)	1 year(s)	£36,123	£38,650
	1.5 year(s)	£40,309	£42,874
	2.5 year(s)	£46,201	£48,821
	3 year(s)	£48,435	£51,076
ToT: Proportion of patients expected to remain on treatment after 2 years of treatment: 33%	5%	£38,723	£41,273
	10%	£39,575	£42,134
	15%	£40,427	£42,994
	20%	£41,280	£43,854
	25%	£42,132	£44,714
	30%	£42,984	£45,575
	35%	£43,837	£46,435
	40%	£44,689	£47,295
	45%	£45,541	£48,155
	50%	£46,394	£49,016
	55%	£47,246	£49,876
	60%	£48,099	£50,736
	65%	£48,951	£51,596
	70%	£49,803	£52,457
	75%	£50,656	£53,317
	80%	£51,508	£54,177
	85%	£52,361	£55,038
	90%	£53,213	£55,898
	95%	£54,065	£56,758
	100%	£54,918	£57,618
ToT: Maximum expected treatment duration: 5 years	3 year(s)	£40,311	£42,877
	4 year(s)	£42,123	£44,705
	6 year(s)	£44,726	£47,332
	7 year(s)	£45,713	£48,329
Utilities: Time to death (GEE)	Progression status	£43,553	£46,148
	Time to death (decrement for final 30 days)	£40,989	£43,408
Costs: Average end of life care costs across different cancers	Cancer type Lung	£40,861	£43,271
	Cancer type Breast	£43,682	£46,279
	Cancer type Colorectal	£43,535	£46,130
	Cancer type Prostate	£43,581	£46,177

Abbreviations in table: GEE, Generalised Estimating Equation; OS, overall survival; PFS, progression-free survival; ToT, time-on-treatment.

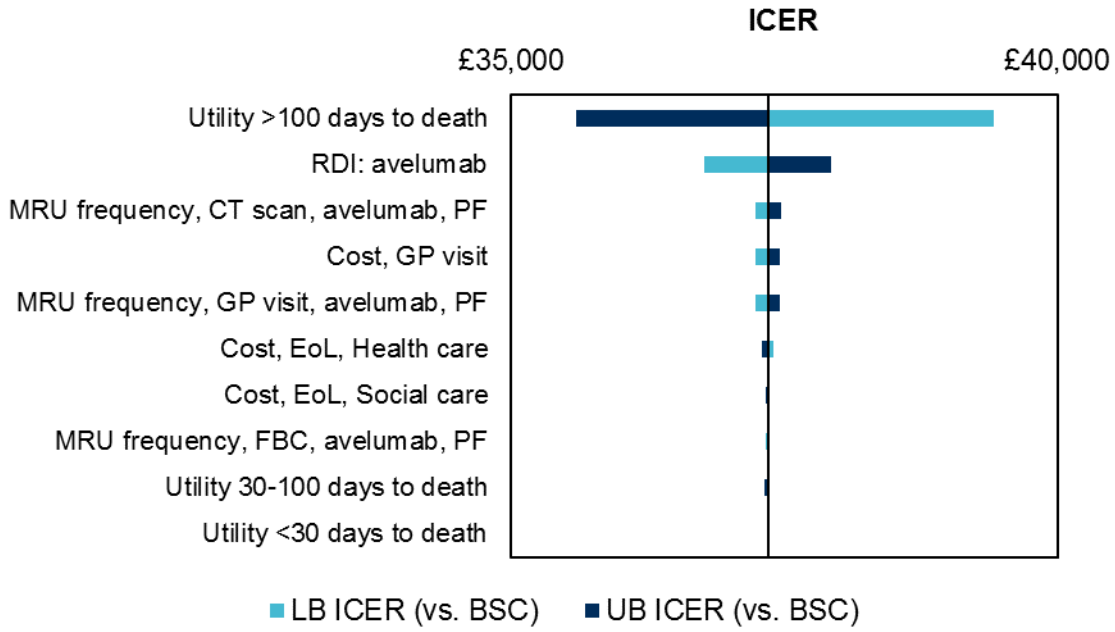
5.5.2.2 One-way sensitivity analysis

The company assessed the impact of varying parameters across their upper and lower bounds on the base case results by carrying out a one-way sensitivity analysis (OWSA). The results of the OWSA are presented in Figure 54 for avelumab compared to BSC in treatment-experienced patients which shows

the base case ICER to be relatively stable with the highest absolute mean change in ICER of £3,817 per QALY. The main model driver is the HSUV of patients with more than 100 days to live.

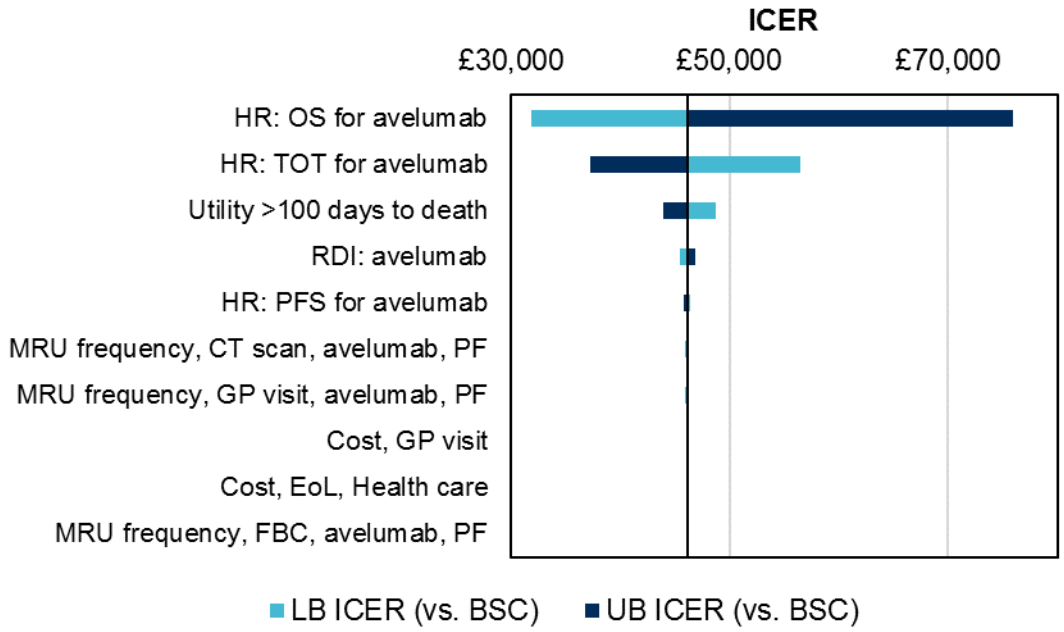
The OWSAs for the pair-wise analyses of avelumab compared to BSC and chemotherapy in treatment-naïve patients are presented in Figure 55 and Figure 56, respectively. The main model driver for treatment-naïve patients is the HR applied for OS causing an absolute mean change of ICER of around £44,000 per QALY in both comparisons. Varying the HR for ToT also impacts the results greatly but to a lesser extent with an absolute mean change in ICER of around £19,000 in both comparisons.

Figure 54. OWSA results for treatment-experienced patients (produced from company's model following clarification response corrections)



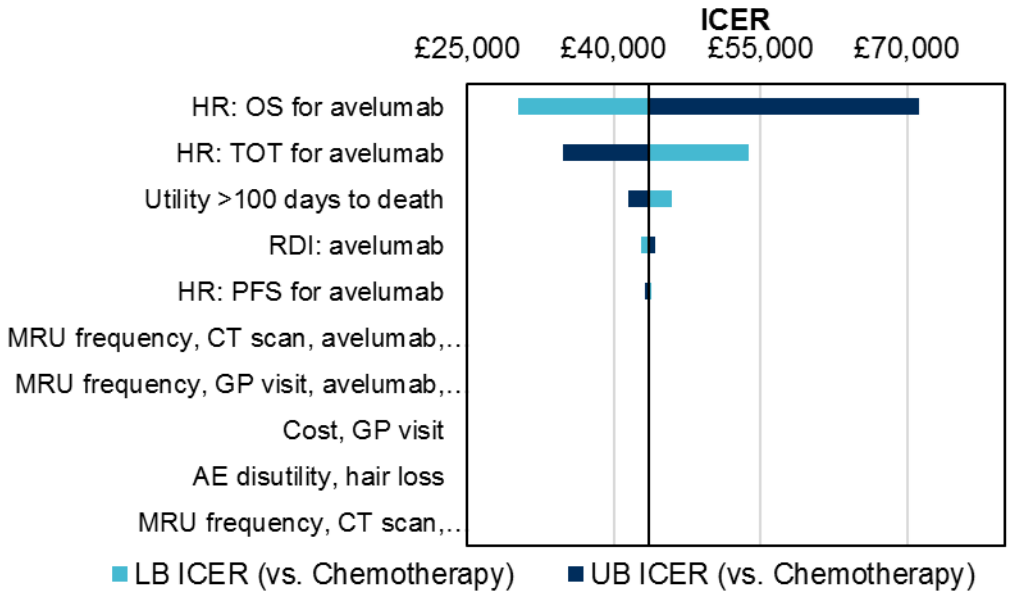
Abbreviations: BSC. Best supportive care; CT, computed tomography; EoL, end of life; GP, general practitioner; ICER, incremental cost effectiveness ratio; MRU, medical resource use; OWSA, One-way sensitivity analysis; PF, progression-free; RDI, relative dose intensity.

Figure 55. OWSA results for treatment-naïve patients, compared to BSC (produced from company's model following clarification response corrections)



Abbreviations: BSC. Best supportive care; CT, computed tomography; EoL, end of life; FBC, full blood count; GP, general practitioner; HR, hazard ratio; ICER, incremental cost effectiveness ratio; MRU, medical resource use; OWSA, One-way sensitivity analysis; PF, progression-free; PFS, progression-free survival; RDI, relative dose intensity; ToT, time on treatment.

Figure 56. OWSA results for treatment-naïve patients, compared to chemotherapy (produced from company's model following clarification response corrections)



Abbreviations: BSC. Best supportive care; CT, computed tomography; GP, general practitioner; HR, hazard ratio; ICER, incremental cost effectiveness ratio; MRU, medical resource use; OWSA, One-way sensitivity analysis; PFS, progression-free survival; RDI, relative dose intensity; ToT, time on treatment.

5.5.2.3 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. The results across 1,000 iterations are presented in Table 69 and Table 70, respectively. The PSA results produced a mean ICER of 36,310 per QALY gained for avelumab compared to BSC in treatment-experienced patients, which is £1,040 lower than the deterministic ICER. As for the treatment-naïve population the mean probabilistic ICER for avelumab compared to BSC is £44,186 which is £1,962 lower than the deterministic base case ICER.

The scatterplot and cost-effectiveness acceptability curve (CEAC) for the treatment-experienced patients are presented in Figure 57 and Figure 58, respectively. The probability of avelumab being cost-effective compared to BSC in treatment-experienced patients at willingness-to-pay (WTP) thresholds of £30,000 and £50,000 per QALY is 22% and 86%, respectively. The scatterplots and CEACs for the treatment-naive patients are presented in Figure 59 and Figure 60, respectively. The probability of avelumab being cost-effective relative to chemotherapy at WTP thresholds of £30,000 and £50,000 per QALY is 21%, and 62%, respectively. The probability of avelumab being cost-effective relative to BSC at WTP thresholds of £30,000 and £50,000 per QALY is 17% and 57%, respectively.

Table 69. Results of company's probabilistic sensitivity analysis for treatment-experienced patients (produced from company's model after clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,686	3.53	2.22	-	-	-	-
BSC	£7,448	0.41	0.31	£71,238	3.24	1.98	£36,310
Abbreviations in table: BSC. best supportive care; LY, life years; QALYs, quality-adjusted life years.							

Table 70. Fully incremental results of company's probabilistic sensitivity analysis for treatment-naïve patients (produced from company's model after clarification responses)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
BSC	£7,210	2.04	1.39	-	-	-	-
Chemotherapy	£10,611	2.04	1.38	£3,401	0.00	-0.01	Dominated
Avelumab	£79,172	4.95	3.02	£71,962	2.91	1.64	£44,186
Abbreviations in table: BSC. best supportive care; LY, life years; QALYs, quality-adjusted life years.							

Figure 57. Scatterplots for avelumab compared to BSC and chemotherapy in treatment-experienced patients (produced from company's model following clarification response corrections)

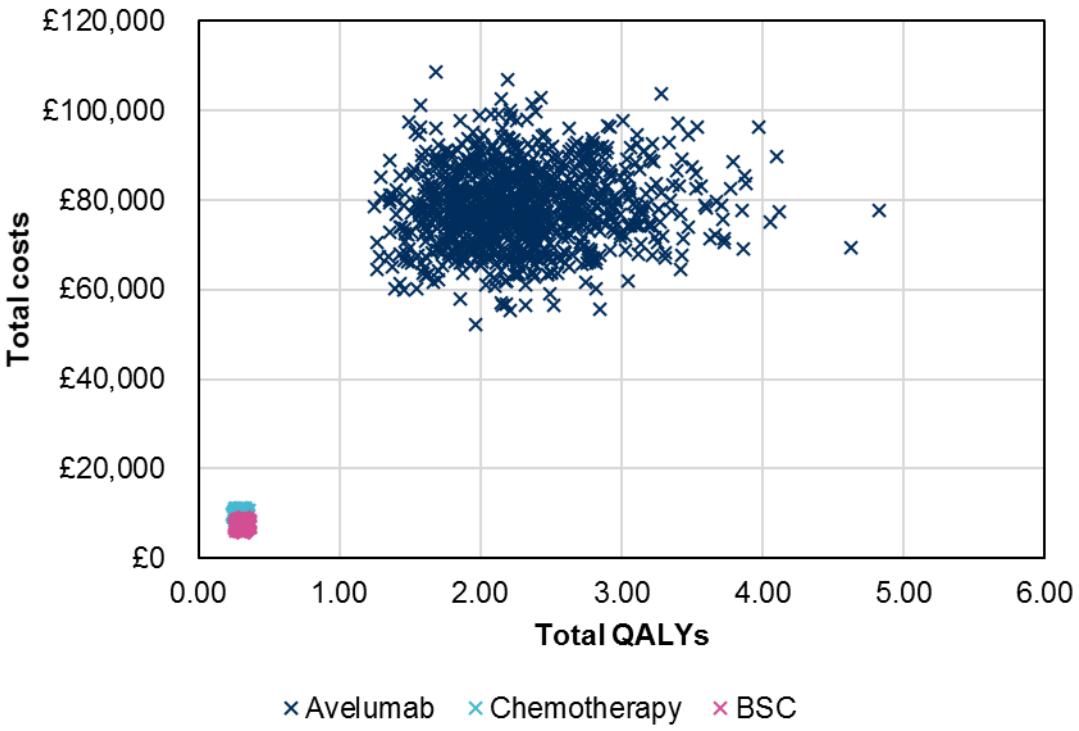


Figure 58. CEACs for avelumab in treatment-experienced patients (produced from company's model following clarification response corrections)

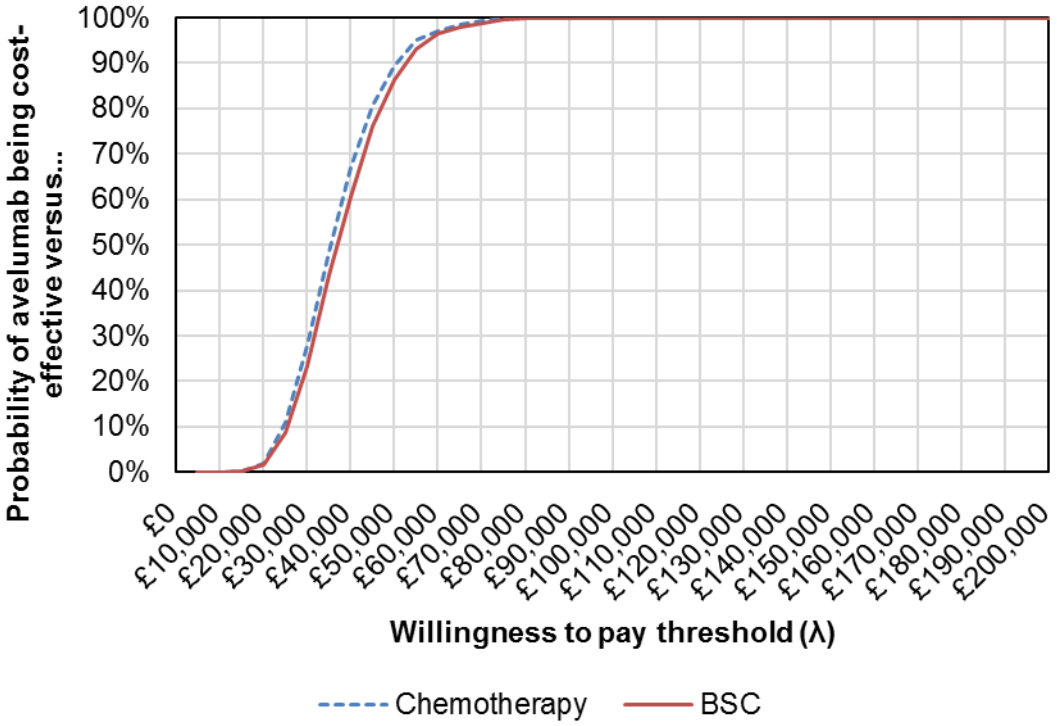


Figure 59. Scatterplots for avelumab compared to BSC in treatment-naive patients (produced from company's model following clarification response corrections)

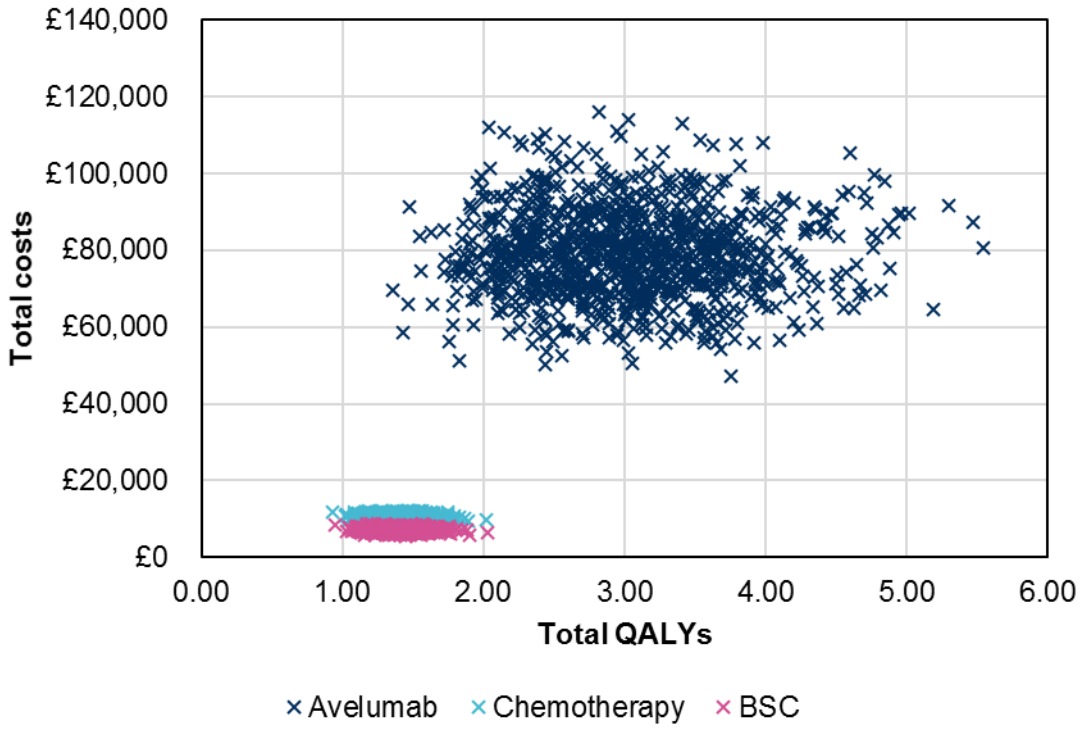
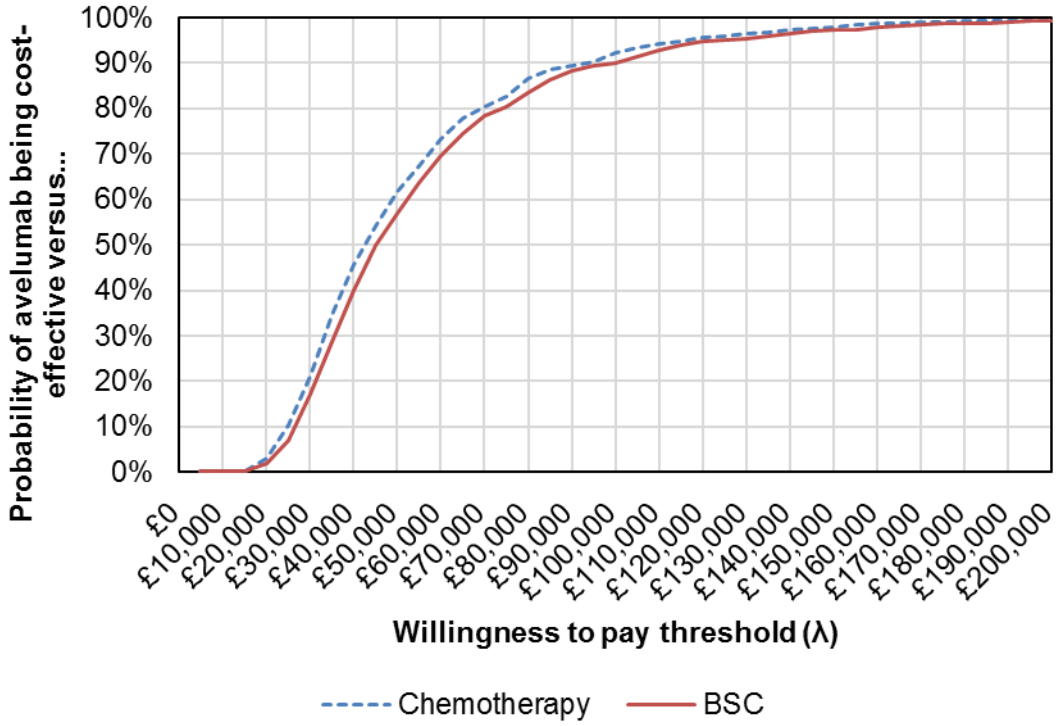


Figure 60. The CEACs for avelumab in treatment-naïve patients (produced from company's model following clarification response corrections)



5.5.3 Model validation

The company conducted a thorough validation process, which included an internal validation to compare model outputs with trial results as well as an elicitation exercise whereby clinical expert opinion was sought to validate long term extrapolations of survival as well as model assumptions.

The economic model was assessed by other health economists, who were not involved directly in the development of the model, to validate the functionality of the model. The ERG considers the company's validation approach to be thorough but also undertook their own model validation to assess the quality of the model and the likelihood that the model results are reliable. The ERG identified no errors and consider the quality of the model to be sufficient for the analysis.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The ERG did not identify any further errors following the company's response to clarification questions, hence, the company's base case around which the ERG's analyses are based is that presented in Section 5.5.

6.2 ERG scenario analysis

The ERG conducted a number of scenario analyses around the company's base cases for both the treatment-naïve and treatment-experienced populations. These are presented in Section 6.2.1 and 6.2.2, respectively.

6.2.1 Treatment-naïve (First line)

6.2.1.1 Scenario 1: Weibull treatment duration curve (without truncation)

This scenario uses the company's best fitting Weibull treatment duration curve to the treatment-naïve population data from the JAVELIN Merkel 200 trial. The ERG considers this to be preferable and a more conservative approach than assuming that the treatment duration would be equivalent to treatment-experienced patients. The results of this analysis are given in Table 71.

Table 71. Results of scenario 1 (Treatment-naïve)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£92,392	4.78	2.93	-	-	-	-
BSC	£7,217	2.02	1.38	£85,176	2.76	1.55	£55,075
Abbreviations in table: BSC. best supportive care; LY, life years; QALYs, quality-adjusted life years.							

6.2.1.2 Scenario 2: Parametric curves for PFS and OS

The company's best fitting parametric curves were used for PFS and OS instead of the company's base case approach of applying HRs. The best fitting curve was the 1-knot normal spline for both PFS and OS. The results are presented in Table 72.

Table 72. Results of scenario 2 (Treatment-naïve)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£102,690	4.16	2.65	-	-	-	-
BSC	£7,217	2.02	1.38	£95,473	2.14	1.27	£75,430
Abbreviations in table: BSC. best supportive care; LY, life years; QALYs, quality-adjusted life years.							

6.2.1.3 Scenario 3: Addition of premedication costs for avelumab treatment

Premedication treatment with 1 mg of oral paracetamol and 10 mg of IV chlorpheniramine for patients treated with avelumab. This was informed by clinical expert opinion. The results are presented in Table 73.

Table 73. Results of scenario 3 (Treatment-naïve)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,678	4.78	2.93	-	-	-	-
BSC	£7,217	2.02	1.38	£71,461	2.76	1.55	£46,206
Abbreviations in table: BSC. best supportive care; LY, life-year; QALYs, quality-adjusted life years.							

6.2.2 Treatment-experienced (Second line)

6.2.2.1 Scenario 1: Weibull treatment duration curve (without truncation)

This scenario uses the company's best fitting Weibull treatment duration curve to the treatment-experienced population data from the JAVELIN Merkel 200 trial. The ERG considers this to provide a more plausible extrapolation than the log-logistic curve used in the company's base case. The results of this analysis are given in Table 74.

Table 74. Results of scenario 1 (Treatment-experienced)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£92,557	3.53	2.22	-	-	-	-
Chemotherapy	£9,838	0.41	0.30	£82,718	3.11	1.92	£43,060
BSC	£7,465	0.41	0.31	£85,091	3.11	1.91	£44,584
Abbreviations in table: BSC. best supportive care; LY, life-year; QALYs, quality-adjusted life years.							

6.2.2.2 Scenario 2: Weibull regression for comparator PFS and OS

The adjusted Weibull regression models were used for PFS and OS for the comparator groups in this scenario. The results of this analysis are given in Table 75.

Table 75. Results of scenario 2 (Treatment-experienced)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,732	3.53	2.22	-	-	-	-
Chemotherapy	£9,630	0.43	0.31	£69,101	3.10	1.91	£36,199
BSC	£7,413	0.43	0.32	£71,319	3.10	1.90	£37,582
Abbreviations in table: BSC. best supportive care; LY, life-year; QALYs, quality-adjusted life years.							

6.2.2.3 Scenario 3: Addition of premedication costs for avelumab treatment

Premedication treatment with 1 mg of oral paracetamol and 10 mg of IV chlorpheniramine for patients treated with avelumab. This was informed by clinical expert opinion. The results are presented in Table 76.

Table 76. Results of scenario 3 (Treatment-experienced)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,842	3.53	2.22	-	-	-	-
Chemotherapy	£9,838	0.41	0.30	£69,003	3.11	1.92	£35,920
BSC	£7,465	0.41	0.31	£71,377	3.11	1.91	£37,397
Abbreviations in table: BSC. best supportive care; LY, life-year; QALYs, quality-adjusted life years.							

6.3 ERG base case ICER

6.3.1 Treatment-naïve (First line)

The key changes the ERG has made to the company's model to form the preferred base case are to remove the company's assumption that time on treatment for the treatment-naïve population is equivalent to the time on treatment for the treatment-experienced population, which uses a log-logistic curve but also assumes that two thirds of patients discontinue immediately at two years and then all patients remaining on treatment at 5 years will also immediately discontinue. These assumptions were applied due to the implausible extrapolation produced by the log-logistic distribution. The ERG preferred to use an alternative curve, the Weibull, which has a similar statistical fit but a more plausible extrapolation.

The ERG's preferred base case also applies the curves for PFS and OS that the company fitted in response to CQs, as the ERG considered the company's assumption of PH between the two populations was potentially flawed. The ERG acknowledges that, given the lack of data, this analysis is still very uncertain. In addition to this, premedication costs for avelumab were included as 10mg of IV chlorpheniramine and 1mg of oral paracetamol.

The ERG's base case ICER is presented with each change incrementally in Table 77.

Table 77. ERG base case ICER (Treament-naïve)

	Avelumab	BSC	Incremental value
Company's base case			
Total costs (£)	£78,588	£7,217	£71,371
QALYs	2.93	1.38	1.55
LYs	4.78	2.02	2.76

ICER			£46,148
Weibull time on treatment curve (without truncation)			
Total costs (£)	£92,392	£7,217	£85,176
QALYs	2.93	1.38	1.55
LYs	4.78	2.02	2.76
ICER			£55,075
Parametric curves for PFS and OS			
Total costs (£)	£159,375	£7,217	£152,158
QALYs	2.65	1.38	1.27
LYs	4.16	2.02	2.14
ICER (compared with base case)			£75,430
ICER with all changes incorporated			£120,228
Addition of pre-medication costs			
Total costs (£)	£159,570	£7,217	£152,353
QALYs	2.65	1.38	1.27
LYs	4.16	2.02	2.14
ICER (compared with base case)			£46,206
ICER with all changes incorporated			£120,383
ERG's alternative base case ICER			
ICER with all changes incorporated			**£120,383**

Abbreviation used in the table: BSC, best supportive care; ERG, evidence review group; ICER, incremental cost effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

6.3.2 Scenario analyses for the treatment-naïve population

One scenario analysis was performed around the ERG's preferred base case for the treatment-naïve population, which was the exclusion of GP visit costs. This was informed by clinical expert opinion, which suggested that these are not required as a regular follow up as patients are seen by the consultant. However, patients may have increased GP attendances themselves as a result of symptoms caused by their disease, and hence this has not been incorporated as part of the ERG's preferred base case. The results of this analysis are given in Table 78.

Table 78. Exclusion of GP costs (Treatment-naïve)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£158,529	4.16	2.65	-	-	-	-
BSC	£7,217	2.02	1.38	£151,312	2.14	1.27	£119,560

Abbreviations in table: BSC. best supportive care; LY, life-year; QALYs, quality-adjusted life years.

6.3.3 Treatment-experienced (Second line)

For the treatment-experienced population, the changes that the ERG made were similar in that time on treatment truncation was removed and the Weibull curve with a more plausible extrapolation was used instead of the log-logistic curve. For PFS and OS in the comparator group, the Weibull regression models were used, and again, premedication costs were applied as per the treatment-naïve population.

The ERG's base case ICER is presented with each change incrementally in Table 79.

Table 79. ERG base case ICER (Treatment experienced)

	Avelumab (1)	Chemotherapy (2)	BSC (3)	Incremental value (1-2)	Incremental value (1-3)
Company's base case					
Total costs (£)	£78,752	£9,838	£7,465	£68,914	£71,287
QALYs	2.22	0.30	0.31	1.92	1.91
LYs	3.53	0.41	0.41	3.11	3.11
ICER				£35,873	£37,350
Weibull time on treatment curve (without truncation)					
Total costs (£)	£92,557	£9,838	£7,465	£82,718	£85,091
QALYs	2.22	0.30	0.31	1.92	1.91
LYs	3.53	0.41	0.41	3.11	3.11
ICER				£43,060	£44,584
Weibull regression models for PFS and OS					
Total costs (£)	£92,537	£9,630	£7,413	£82,906	£85,124
QALYs	2.22	0.31	0.32	1.91	1.90
LYs	3.53	0.43	0.43	3.10	3.10
ICER (compared with base case)				£36,199	£37,582
ICER with all changes incorporated				£43,432	£44,857
Addition of pre-medication costs					
Total costs (£)	£92,644	£9,630	£7,413	£83,014	£85,232
QALYs	2.22	0.31	0.32	1.91	1.90
LYs	3.53	0.43	0.43	3.10	3.10
ICER (compared with base case)				£35,920	£37,397
ICER with all changes incorporated				£43,488	£44,914
ERG's alternative base case ICER					
ICER with all changes incorporated				**£43,488**	**£44,914**

Abbreviation used in the table: BSC, best supportive care; ICER, incremental cost effectiveness ratio; LY, life-year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

6.3.4 Scenario analyses for the treatment-experienced population

This is equivalent to the scenario analysis for the treatment-naïve population where GP costs are removed. The results of this scenario are given in Table 80.

Table 80. Exclusion of GP visit cost (Treatment-experienced)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£91,537	3.53	2.22	-	-	-	-
Chemotherapy	£9,630	0.43	0.31	£81,906	3.10	1.91	£42,908
BSC	£7,413	0.43	0.32	£84,124	3.10	1.90	£44,330
Abbreviations in table: BSC. best supportive care; ICER, incremental cost effectiveness ratio; LY, life-year; QALYs, quality-adjusted life years.							

7 END OF LIFE

The company put forward a case stating that the NICE end of life criteria are met for patients receiving avelumab for mMCC, regardless of the line of therapy. This is justified by the company based on a median life expectancy of around 4 months for patients on chemotherapy and an extension of life, as determined by the economic model, of greater than 3 months.

The ERG notes that a recent study published by Harms et al. 2016 reported median survival of patients with distant mMCC was 12 months, whereas over 70% of the patients with local or nodal mMCC survived longer than 12 months from diagnosis.[2] Harms et al.[2] reported that estimated 5-year overall survival was 51%, 35%, and 14%, respectively for local, nodal, and distant mMCC. The ERG notes that 53.4% of the 2L+ patients in JAVELIN Merkel 200 had visceral metastases at baseline, and 21.6% had lymph node only disease at baseline. The 2L+ patients in the chemotherapy comparator Study 100070-Obs001 had similar proportions of patients with visceral and lymph node disease at baseline to JAVELIN Merkel 200. The ERG considers the 2L+ population of JAVELIN Merkel 200 and Study 100070-Obs001 were likely to be the equivalent of the poorer prognosis patients in the Harms et al. study (i.e. patients with distant metastases). Details on the sites of metastases at baseline were not reported in the CS for the 1L cohort of JAVELIN Merkel 200.

The ERG notes that there is great uncertainty in the results of the economic model as a result of the uncertainty in the treatment effectiveness estimates. However, the life expectancy shown in the comparator data used in the model for either line of treatment is well within NICE's 24-month threshold considered to be a short life expectancy although the ERG considers the 2L+ population of JAVELIN Merkel 200 and Study 100070-Obs001 reflect more closely the distant mMCC subgroup of mMCC patients than local mMCC. However, avelumab appears to have a large benefit in terms of OS, which shows a greatly increased life expectancy; much more than the required 3 months. Therefore, the ERG considers the company's proposal that the end of life criteria are met, to be reasonable for the distant mMCC subgroup. The ERG is unsure whether the end of life criteria would also be met for local and nodal mMCC patients.

8 OVERALL CONCLUSIONS

The CS contained a systematic review that addressed the population specified in the decision problem outlined in the final scope issued by NICE. The ERG considers that a key limitation of the submission is the lack of direct randomised evidence comparing avelumab versus chemotherapy and the total absence of trial-level data for avelumab versus BSC. In addition, the ERG considers that the process of selecting appropriate comparative evidence from studies included in the clinical effectiveness SLR was non-systematic, and differs from the SLR described in Appendix 10 of the CS to identify effectiveness data for the economic model. The ERG is not qualified to comment on the feasibility of an RCT of avelumab in the population of interest in this decision problem, although the ERG does consider a comparative randomised study design to be preferable in accounting for observed and unobserved differences in patient populations.

Overall, the ERG considers that the available evidence on the clinical efficacy of avelumab for the treatment of 2L+ and 1L mMCC is of limited quantity and quality due to the single-arm non-randomised study design of JAVELIN Merkel 200 Part A and Part B. Based on guidance from the FDA, the ERG is concerned that single-arm studies shouldn't be used for capturing time-to-event data such as OS and PFS. In addition, the ERG considers that OS data in JAVELIN Merkel 200 are likely confounded by the use of subsequent treatment, although no data on subsequent treatments were reported in the CS for either Part A or Part B of JAVELIN Merkel 200. The ERG notes that there are no data on the long-term safety and efficacy of avelumab, and the data on OS in 1L mMCC are immature and are based on small patient numbers (n=39). However, the ERG also acknowledges that JAVELIN Merkel 200 Part A and Part B at this time, represent the best available evidence on the clinical effectiveness of avelumab.

The ERG has concerns around the generalisability of JAVELIN Merkel 200 Part A and Part B results to the population in England most likely to be eligible for treatment with avelumab as there were no study sites in England. In addition, it is considered that a high proportion of patients in both studies had an ECOG PS of 0 compared to that expected in mMCC patients in England and there was no information on subsequent treatments received following study drug discontinuation. However, the ERG considers that the results of JAVELIN Merkel 200 suggest that in both the 1L and 2L+ populations, avelumab is associated with favourable efficacy outcomes in terms of response rate although it is impossible to tell how it compares to chemotherapy and BSC due to the efficacy data being only from single-arm studies. In addition, the ERG considers it should be remembered that avelumab was associated with a high level of TRAEs (as of 3 March 2016, 75.0% of the 2L+ patients had experienced an AE that was deemed to be a TRAE, and in the 1L cohort, as of 30 December 2016, 71.8% patients had experienced a TRAE).

The company reported that to address the comparison of avelumab with BSC requested in the 2L+ population in the NICE final scope they have assumed that the efficacy data from chemotherapy

regimens are equal to those of BSC. The company cited clinical experts' opinion stating that, "efficacy outcomes with BSC and chemotherapy are likely to be very similar due to very poor patient performance with both". Nevertheless, the ERG notes that there were no clinical data to inform this comparision of avelumab versus BSC in the 2L+ population.

The 2L+ subgroup analyses reported in the CS for the subgroups of number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status were highlighted by the company in the forest plot in the CS. The ERG considers these highlighted subgroups suggest there may be within subgroup differences in ORR with avelumab although the ERG acknowledges the differences were not statistically significant but some subgroups comprised a very low number of patients. The ERG considers that these subgroups should have been explored further by the company before they concluded that a naïve comparison of the JAVELIN Merkel 200 avelumab trial and chemotherapy trials was appropriate.

At the request of the ERG, the company attempted to adjust the outcomes of interest in the 2L+ population for potential confounders, albeit with a limited selection. The ERG considers the small number of patients in the regression analyses presented by the company in CS appendix 10 means that there is a large amount of uncertainty around the results purely based on an initial small sample size. The ERG, therefore, considers that caution should be taken when drawing conclusions from the statistically non-significant results from the regression analyses, as they could be a result of the small patient numbers rather than the absence of a subgroup effect (prognostic indicator). The ERG considers that subgroups identified in the subgroup analyses (CS page 83, Figure 18), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, the company should have adjusted outcomes appropriately.

The ERG is concerned that Study 100070-Obs001 included immunosuppressed patients, whereas none of the JAVELIN Merkel 200 avelumab patients were immunosuppressed. In addition, the ERG considers that 1L and 2L+ patients had a better baseline ECOG status in JAVELIN Merkel 200 compared to in Study 100070-Obs001. The ERG is concerned that these differences in baseline characteristics are not accounted for in the naïve comparisons presented in the CS.

The ERG considers the regression analysis to be a more robust analysis of avelumab versus chemotherapy compared to the naïve comparison and propensity score matching because it adjusts for a greater range of likely covariates. However, the ERG would have preferred an analysis with further potential prognostic factors adjusted for such as line of therapy 2L or third line and beyond (3L+), and PD-L1 status. The ERG considers that the inclusion of further covariates would confirm the robustness of the company's preferred option, the naïve comparison of study level data from JAVELIN Merkel 200 for avelumab with pooled data from Study 100070-Obs001 for chemotherapy if the results of both

analyses were similar. In addition, the ERG considers that the later data cut that the company anticipates taking place in [redacted], is likely to have an increase in patient number and an increase in the events of interest. The ERG considers this later dataset is likely to provide the basis for a more robust assessment of avelumab versus chemotherapy in 1L patients. However, the ERG also considers that any analysis should be adjusted for potential observed treatment-effect modifiers with justification provided for the variables used.

The economic analysis performed by the company was thorough and generally of a high standard. The ERG's main concerns lie with the uncertainty in the treatment effectiveness comparison caused by a lack of data with potentially limited comparability. The lack of a full adjustment for potential imbalances in effect-modifying variables in the sources of data was a key concern, especially for the treatment-naïve population, for which data was seriously limited.

The ERG also has a serious concern about the assumption that PH applies between treatment effectiveness estimates in the populations on different lines of treatment. This assumption appears potentially flawed when considering the lack of proportionality observed in the independently best fitting curves. The treatment-naïve population analyses are very uncertain given the lack of data, and the results are difficult to fully interpret until more data become available.

The modelling undertaken was generally sound, however, some of the assumptions were considered implausible by the ERG, causing potentially underestimated ICERs for both populations. The key issues relate to the estimate of treatment effectiveness, where the company fitted a curve that they considered to have an implausible tail, and chose to correct this implausibility by imposing a series of truncations to the curve. The ERG's clinical experts considered this to be implausible and was not likely to reflect clinical practice in the UK. The ERG's preferred base case incorporates a similarly good fitting curve but with a more plausible extrapolation, resulting in higher expected treatment costs than those estimated in the company's analysis.

The ERG considers the analysis for the treatment-naïve population to have potentially serious uncertainty given the lack of data and considers it very unreliable for assessing the cost effectiveness of avelumab in this population. For the treatment-experienced population, the analysis is more reliable but still has a degree of uncertainty that should be considered when interpreting the results for the decision analysis.

8.1 Implications for research

The ERG notes that the avelumab JAVELIN Merkel 200 trial is ongoing with further data-cuts and analyses planned.

The ERG considers there is a need for further research to:

- confirm the relative effectiveness of avelumab compared with BSC in the 2L+ population;
- confirm the relative effectiveness of avelumab compared with chemotherapy in the 1L population;
- confirm the efficacy and safety of avelumab in the population of England and Wales;
- provide long-term efficacy and safety data on avelumab, in particular, to confirm its impact on OS.

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10 APPENDICES

10.1 Quality assessment

Table 81. Company's Downs and Black quality assessments of 18 cohorts and single-arm studies identified in the effectiveness SLR. 45 included case reports and case series were not assessed (adapted from CS Appendix 4, Table 6)

Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	T
Bhatia 2015[167]	1	1	1	1	0	1	0	1	1	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	1	**12**
Iyer 2014[30]	1	1	1	1	0	1	1	1	1	0	1	0	1	0	0	0	1	1	1	1	1	0	0	0	0	1	**16**
Satpute 2014[43]	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	**7**
Nghiem 2016[56]	1	1	1	1	1	1	1	1	0	0	1	0	1	0	0	0	0	1	1	1	1	1	0	0	0	1	**16**
Becker 2016[47]	1	1	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	**8**
Sabol 2016[20]	1	0	1	1	0	1	0	0	0	1	1	0	1	0	0	0	0	0	1	1	0	1	0	0	0	0	**10**
Kaufman 2016[52]	1	1	1	1	2	1	1	1	1	1	1	0	1	0	0	0	0	1	1	1	1	1	0	0	0	1	**19**
Cowey 2016[3]	1	1	1	1	0	1	1	0	0	0	1	0	1	0	0	0	0	0	1	1	0	1	0	0	0	0	**11**
Timmer 2016[89]	1	1	1	1	0	1	0	0	0	0	1	0	1	0	0	0	0	1	0	1	1	1	0	0	0	0	**11**
Bhatia 2016b[66]	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	**5**
Di 1995[32]	1	1	1	1	0	1	0	0	0	0	1	1	1	0	0	1	0	0	0	1	1	0	0	0	0	0	**11**
Samlowski 2010 (S0331 study)[36]	1	1	1	1	0	1	1	1	1	0	1	0	1	0	0	1	0	1	0	1	0	0	0	0	0	0	**13**
Savage 1997[54]	1	1	1	1	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0	**9**
Shah 2009[57]	1	1	1	1	0	1	0	1	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	**9**
Woll 2009[61]	1	0	0	1	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	**5**
Nathan 2016[73]	1	1	1	1	0	1	1	1	1	0	1	0	1	0	0	0	0	1	0	1	1	0	0	0	0	0	**13**
Bhatia 2016a[46]	1	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	**7**
Shah 2016[31]	1	1	1	1	0	1	1	1	0	0	1	0	1	0	0	0	0	1	0	1	0	1	0	0	0	0	**12**

Abbreviations: ID, identifier; T, total score; SLR, systematic literature review; CS, company submission

1: Is the hypothesis/objective of the study clearly described?; 2: Are the main outcomes to be measured clearly described in the introduction or methods section?; 3: Are the characteristics of the patients included in the study clearly described?; 4: Are the interventions of interest clearly described?; 5: Are the distributions of principal confounders in each group of subjects to be compared clearly described?; 6: Are the main findings of the study clearly described?; 7: Does the study provide estimates of the random variability in the data for the main outcomes?; 8: Have all important adverse events that may be a consequence of the intervention been reported?; 9: Have the characteristics of patients lost to follow-up been described?; 10: Have actual probability values been

reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?; 11: Were the subjects asked to participate in the study representative of the entire population from which they were recruited?; 12: Were those subjects who were prepared to participate representative of the entire population from which they were recruited?; 13: Were the staff, places and facilities where the patients were treated representative of the treatment the majority of the patients receive?; 14: Was an attempt made to blind study subjects to the intervention they received?; 15: Was an attempt made to blind those measuring the main outcomes of the intervention?; 16: If any results of the study were based on "data dredging" was this made clear?; 17: In trials and cohort studies, do the analyses adjust for different lengths of follow up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?; 18: Were the statistical tests used to assess the main outcomes appropriate?; 19: Was compliance with the interventions reliable?; 20: Were the main outcomes measures used accurate (valid and reliable)?; 21: Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case control studies) recruited from the same population?; 22: Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case control studies) recruited over the same period of time?; 23: Were study subjects randomized to intervention groups?; 24: Was the randomized intervention assignment concealed from both patients and healthcare staff until recruitment was complete and irrevocable?; 25: Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?; 26: Were losses of patients to follow-up taken into account?

Table 82. Company's quality assessments of 12 RCTs in melanoma identified in the safety SLR (adapted from CS Appendix I, Table 1, provided at the clarification stage)

Study ID	Trial name	Randomisation	Allocation concealment	Baseline comparability	Blinding	Dropouts between groups	More outcomes than reported	Intention to treat
Chang 1993[60]	NA	YES	NOT CLEAR	YES	NOT CLEAR	NO	NO	NO
Flaherty 2013[143]	NA	YES	YES	YES	YES	NO	YES	YES
Hamid 2014[144]	NA	YES	NOT CLEAR	YES	NO	YES	NO	NO
Hauschild 2009[145]	NA	YES	YES	YES	YES	NO	NO	YES
Kim 2012[147]	BEAM	YES	YES	YES	YES	YES	NO	YES
O'Day 2013[152]	SYMMETRY	YES	YES	YES	YES	YES	YES	YES
O'Day 2009[154]	NA	YES	YES	YES	NO	YES	YES	YES
Ribas 2015[153]	KEYNOTE-002	YES	YES	YES	YES	YES	NO	YES
Ribas 2016[157]	KEYNOTE-001	NA	NA	NO	NA	YES	YES	NO
Robert 2014[156]	NA	YES	YES	YES	NO	NO	NO	YES
Zimpfer-Rechner 2003[158]	NA	YES	NOT CLEAR	YES	NO	NO	NO	NOT CLEAR
Robert 2015[163]	KEYNOTE-006	YES	YES	YES	NO	YES	YES	YES

Abbreviations: ID, identifier; RCTs, randomised controlled trials; SLR, systematic literature review; CS, company submission

Table 83. Company's quality assessments of 48 RCTs in SCLC identified in the safety SLR (adapted from CS Appendix I, Table 2, provided at the clarification stage)

Study ID	Randomisation	Allocation concealment	Baseline comparability	Blinding	Dropouts between groups	More outcomes than reported	Intention to treat
Allen 2012[159]	YES	NO	NOT CLEAR	NO	YES	YES	NO
Ardizzoni 2005[90]	YES	NOT CLEAR	YES	NO	NO	YES	YES
Dimitroulis 2008[92]	YES	NOT CLEAR	YES	NO	NO	NO	YES
Eckhardt 2007[95]	YES	NO	NOT CLEAR	NO	NO	YES	YES
Eckhardt 2006[97]	YES	NO	YES	NO	NO	YES	YES
Ansari 1995 (citation not supplied)	YES	YES	YES	YES	NO	NO	YES
Artal-Cortes 2004[96]	YES	NOT CLEAR	YES	NO	NO	NO	YES
Ettinger 1992[93]	YES	NO	NO	NO	NO	YES	NO
Evans 2015[98]	YES	NO	YES	NO	NOT CLEAR	YES	YES
Hanna 2006[99]	YES	NO	YES	NO	NO	YES	
Inoue 2008[106]	YES	NOT CLEAR	YES	NO	NOT CLEAR	NO	NO
Guo 2013[108]	YES	NO	NO	NO	NO	NO	NO
Gervais 2015[104]	YES	NO	YES	NO	NO	NO	YES
Goto 2014[102]	YES	NO	NOT CLEAR	NO	YES	NOT CLEAR	NO
Hainsworth 1995[103]	YES	NO	YES	NO	NO	YES	NO
Johnson 1991[105]	YES	NO	YES	NO	NO	YES	NO
Jotte 2011[110]	YES	NOT CLEAR	YES	NO	NOT CLEAR	NO	NO
Lara 2009[111]	YES	NO	YES	NO	NO	YES	YES
Johnson 1987[112]	YES	NO	NOT CLEAR	NO	YES	NO	NO
Lowenbrau 1994[109]	YES	NO	YES	NO	NO	NO	NO
Lu 2015[113]	YES	NO	YES	NO	NOT CLEAR	NO	NO
Mavroudis 2001[114]	YES	YES	NOT CLEAR	YES	NO	NO	YES
McIllmurray 1989[116]	YES	NO	YES	NO	NOT CLEAR	NO	NO
Mau-Sorensen 2014[117]	YES	NO	YES	NO	NO	YES	NOT CLEAR
Niell 2005[115]	YES	YES	NO	YES	NO	NO	NO

Noda 2002[118]	YES	YES	YES	YES	NO	NO	NO
O'Brien 2006[119]	YES	YES	YES	YES	YES	YES	NO
Nagel 2011[120]	YES	YES	YES	YES	NO	YES	NO
Okamoto 2005[164]	YES	YES	YES	YES	NOT CLEAR	YES	NOT CLEAR
O'Brien 2011[166]	YES	NO	YES	NO	NO	YES	NO
Oh 2013[165]	YES	NO	NOT CLEAR	NO	NOT CLEAR	YES	NOT CLEAR
Pawel 1999[121]	YES	YES	YES	YES	NOT CLEAR	YES	NO
Rudin 2008[139]	YES	YES	YES	NOT CLEAR	NO	NO	NO
Schmittel 2011[123]	YES	NOT CLEAR	NOT CLEAR	NOT CLEAR	YES	YES	NO
Schmittel 2006[127]	YES	NOT CLEAR	YES	NOT CLEAR	NO	NO	NO
Sculier 2002[126]	YES	YES	YES	YES	NO	YES	YES
Schaefer 2003[128]	YES	NOT CLEAR	NOT CLEAR	NOT CLEAR	YES	YES	NO
Schiller 2001[124]	NOT CLEAR	NOT CLEAR	YES	NOT CLEAR	YES	NOT CLEAR	NO
Sekine 2014[125]	YES	NO	YES	NO	NO	NO	NO
Socinski 2009[129]	YES	NO	YES	NO	NO	NO	NO
Steele 2001[182]	YES	NO	YES	NO	NOT CLEAR	YES	NO
Sun 2016[135]	YES	YES	YES	NO	NO	NO	YES
Sun 2013[136]	YES	NO	YES	NO	NOT CLEAR	YES	NOT CLEAR
Von Pawel 2014[142]	YES	NO	YES	NO	NOT CLEAR	YES	YES
Von Pawel 2001[138]	YES	YES	YES	YES	NO	YES	YES
Cheng 2014[137]	YES	NOT CLEAR	NOT CLEAR	NOT CLEAR	NO	NO	NOT CLEAR
Spigel 2014[94]	YES	NOT CLEAR	YES	NOT CLEAR	NOT CLEAR	YES	NOT CLEAR
Yoon 2014[133]	YES	NOT CLEAR	YES	NOT CLEAR	NOT CLEAR	YES	NOT CLEAR
Abbreviations: ID, identifier; RCT, randomised controlled trials; SCLC, small cell lung cancer; SLR, systematic literature review; CS, company submission							

Table 84. Company's Downs and Black quality assessments of 9 non-RCTs in melanoma identified in the safety SLR (adapted from CS Appendix J, Tables 1–7, provided at the clarification stage)

Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	T
Hofmann 2016[167]	1	1	1	1	2	1	0	1	1	0	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0	0	**12**
Hwang 2016[148]	1	1	1	1	2	1	0	1	1	0	0	0	0	0	0	1	1	1	0	1	1	1	0	0	1	1	0	**17**
Karydis 2016[149]	1	0	1	1	2	1	0	1	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0	0	**11**
Wen 2016[151]	1	1	1	1	2	1	0	1	0	0	0	0	0	0	0	1	1	0	0	1	1	1	0	0	0	0	0	**13**
Zimmer 2016[161]	1	1	1	1	2	1	0	1	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0	0	**12**
Shoushtari 2015[162]	0	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	**5**
Perdon 2015[160]	0	1	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	0	**9**
Hassel 2016[155]	0	1	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	**7**
Jansen 2016[146]	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	**3**

Abbreviations: ID, identifier; T, total score; RCT, randomised controlled trial; SLR, systematic literature review; CS, company submission

1: Is the hypothesis/objective of the study clearly described?; 2: Are the main outcomes to be measured clearly described in the introduction or methods section?; 3: Are the characteristics of the patients included in the study clearly described?; 4: Are the interventions of interest clearly described?; 5: Are the distributions of principal confounders in each group of subjects to be compared clearly described?; 6: Are the main findings of the study clearly described?; 7: Does the study provide estimates of the random variability in the data for the main outcomes?; 8: Have all important adverse events that may be a consequence of the intervention been reported?; 9: Have the characteristics of patients lost to follow-up been described?; 10: Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?; 11: Were the subjects asked to participate in the study representative of the entire population from which they were recruited?; 12: Were those subjects who were prepared to participate representative of the entire population from which they were recruited?; 13: Were the staff, places and facilities where the patients were treated representative of the treatment the majority of the patients receive?; 14: Was an attempt made to blind study subjects to the intervention they received?; 15: Was an attempt made to blind those measuring the main outcomes of the intervention?; 16: If any results of the study were based on "data dredging" was this made clear?; 17: In trials and cohort studies, do the analyses adjust for different lengths of follow up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?; 18: Were the statistical tests used to assess the main outcomes appropriate?; 19: Was compliance with the interventions reliable?; 20: Were the main outcomes measures used accurate (valid and reliable)?; 21: Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case control studies) recruited from the same population?; 22: Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case control studies) recruited over the same period of time?; 23: Were study subjects randomized to intervention groups?; 24: Was the randomized intervention assignment concealed from both patients and healthcare staff until recruitment was complete and irrevocable?; 25: Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?; 26: Were losses of patients to follow-up taken into account?; 27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

Table 85. Company's Downs and Black quality assessments of 12 non-RCTs in SCLC identified in the safety SLR (adapted from CS Appendix J, Tables 8 – 14, provided at the clarification stage)

Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	T
Altinbas 2012[167]	1	1	1	1	2	0	0	1	0	1	0	0	0	0	0	1	0	1	0	1	1	0	0	0	0	0	0	**12**
Faria 2010[91]	1	1	1	1	2	1	0	1	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0	0	**12**
Garst 2005[100]	1	1	1	1	2	1	0	1	0	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	0	0	0	**11**
Huber 2006[101]	1	1	1	1	2	1	0	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	**10**
Inoue 2008[107]	1	1	1	1	2	1	0	1	0	1	0	0	0	0	0	1	0	1	0	1	1	1	1	0	1	0	0	**16**
Guo 2013[108]	1	1	1	1	2	1	0	1	0	1	1	0	0	0	0	1	0	1	1	1	1	1	1	0	0	0	0	**17**
Park 2013 (citation not supplied)	1	1	0	1	0	1	0	1	0	1	0	0	0	0	0	1	0	1	0	1	1	1	0	0	0	0	0	**11**
Pereira 2013[104]	1	1	0	1	0	1	0	1	0	1	0	0	0	0	0	1	0	0	0	1	1	0	0	0	0	0	0	**9**
Shah 2007[122]	1	1	1	1	2	1	0	1	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	**11**
Shi 2015[130]	1	1	1	1	2	1	0	1	0	1	0	0	0	0	0	0	0	1	0	1	0	0	1	0	0	0	0	**12**
Stathopoulo 2010[131]	1	1	1	1	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**8**
Yilmaz 2011[134]	1	1	1	1	2	0	0	1	0	1	0	0	0	0	0	1	0	1	0	0	0	0	1	0	0	0	0	**11**

Abbreviations: ID, identifier; T, total score; RCT, randomised controlled trial; SLR, systematic literature review; SCLC, small cell lung cancer; CS, company submission

1: Is the hypothesis/objective of the study clearly described?; 2: Are the main outcomes to be measured clearly described in the introduction or methods section?; 3: Are the characteristics of the patients included in the study clearly described?; 4: Are the interventions of interest clearly described?; 5: Are the distributions of principal confounders in each group of subjects to be compared clearly described?; 6: Are the main findings of the study clearly described?; 7: Does the study provide estimates of the random variability in the data for the main outcomes?; 8: Have all important adverse events that may be a consequence of the intervention been reported?; 9: Have the characteristics of patients lost to follow-up been described?; 10: Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?; 11: Were the subjects asked to participate in the study representative of the entire population from which they were recruited?; 12: Were those subjects who were prepared to participate representative of the entire population from which they were recruited?; 13: Were the staff, places and facilities where the patients were treated representative of the treatment the majority of the patients receive?; 14: Was an attempt made to blind study subjects to the intervention they received?; 15: Was an attempt made to blind those measuring the main outcomes of the intervention?; 16: If any results of the study were based on "data dredging" was this made clear?; 17: In trials and cohort studies, do the analyses adjust for different lengths of follow up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?; 18: Were the statistical tests used to assess the main outcomes appropriate?; 19: Was compliance with the interventions reliable?; 20: Were the main outcomes measures used accurate (valid and reliable)?; 21: Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case control studies) recruited from the same population?; 22: Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case control studies) recruited over the same period of time?; 23: Were study subjects randomized to intervention groups?; 24: Was the randomized intervention assignment concealed from both patients and healthcare staff until recruitment was complete and irrevocable?; 25: Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?; 26: Were losses of patients to follow-up taken into account?; 27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Avelumab for Merkel cell carcinoma [ID1102]

You are asked to check the ERG report from BMJ Technology Assessment Group (BMJ-TAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 18 October 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Avelumab licence

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
The EMA approval details are out of date	*On page 17 of the report, the ERG state:* *"The company anticipated that final approval would be received on 23 September 2017; however, the ERG notes that on 5 October 2017, avelumab was still on the pending European Commission decisions list on the EMA website."* This should be corrected to state the following: *"The company received full EMA license for avelumab in metastatic Merkel cell carcinoma on 20th September 2017"* This error needs to be corrected on page 17 and 42.	Amendment of this error correctly provides the dates in which an EMA licence was granted.	Not a factual error. However, the ERG has updated the text on pages 17 and 42 to reflect the additional information provided by the company. The sentence *"The company* [redacted] *"* has been replaced with, *"The ERG notes that the company received full EMA license for avelumab in mMCC on 20 September 2017."*

Issue 2 Patient characteristics analysed for inclusion in adjustment

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
The ERG suggests throughout the document that Merck should have adjusted for characteristics such as PD-L1 status and tumour burden. In the response to ERG questions (Question A10) it was made clear that these variables were not included in the observational dataset (NA – Not Available), and as such could not be analysed and subsequently adjusted for. Examples include page 16: “number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, the company should have adjusted outcomes appropriately.” And page 23 “The ERG is unclear why the company did not explore using alternative variables for matching ... such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status”.	The ERG report should be revised to state that whilst comparison of PD-L1 status, stage at diagnosis and other factors would have been desirable, these were not captured in either the trial, observational dataset, or both. The only overlapping variables being age and gender. These changes should be made throughout the report.	The requested data fields were not included in both datasets, as made clear in the tables requested by the ERG and in our response to the clarification questions.	Not a factual error.

Issue 3 Inaccurate description of company approach to identifying prognostic patient characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
The ERG report is inconsistent in the description of the company approach to identifying prognostic characteristics in the observational dataset, at times misrepresenting this. The description however is correct at other points in the report. Whilst some sections in the report (mostly commonly in the economic section) state the company used regression analysis but excluded non-significant variables, page 125 and onwards (correctly) states that as well as univariate and multivariate regression, visual inspection of Kaplan-Meier curves was used to identify any trends that may not have reached statistical significance due to the low patient numbers.	The description of the approach of regression (for example on page 28) should be corrected to accurately reflect that no observable trends were seen (regardless of significance), and in addition no variables reached statistical significance, as opposed to implying that statistical significance was used as the sole characteristic on which prognostic variables were identified. Whilst this is accurately presented in several places (most notably page 114 where it is stated that curves for immunosuppression crossed multiple times), it is incorrectly reported on pages 28, 29, 40, 98 and others. We accept that further data beyond the approximately 60 patients analysed in both treatment naïve and treatment experienced groups would have more power to detect differences by patient characteristics. That Kaplan-Meier plots overlap rather than separate however indicates this is unlikely.	The methods discussed were not used in isolation, with trends investigated using Kaplan-Meier data, and not rejected on the basis of statistical significance alone. The current description, particularly in the economic section, hints that there were signals that different characteristics were prognostic, but that the result did not reach p=0.05 and thus were ignored. Kaplan-Meier curves overlapped, with no identifiable trends that would fit with expected outcomes.	The ERG report should be considered in its totality rather than in isolated paragraphs. However, the text on page 29 has been amended. The text on the other pages mentioned is not factually inaccurate.

Issue 4 Provision of results in the ERG report for treatment-naïve patients receiving chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In parts of the ERG report, results are presented for the treatment-naïve and treatment-experienced cohorts with the incorrect parameters as per the final NICE scope. More specifically, comparisons to chemotherapy for treatment-naïve patients are erroneously omitted. Comparisons to chemotherapy	We ask that the ERG include the comparison to chemotherapy for treatment-naïve patients. These results are omitted in Tables 1, 71, 72, 73, 77, 78.	Chemotherapy is one of the two comparators specified in the scope of the appraisal, and is of most importance for the comparison to avelumab for treatment-naïve patients. It is	Thank you for highlighting this inaccuracy. These tables have been updated to reflect the results relevant to the comparisons outlined by the NICE scope.

for treatment-experienced patients are not included within the final scope, though presenting these results is acceptable given the small proportion of patients who may receive chemotherapy.		acknowledged that omission of this comparison was likely an unintentional error, but these results are important to present.	

Issue 5 Discussion of the cost-effectiveness analysis results for treatment-naïve patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The results of the cost-effectiveness analysis for treatment-naïve patients are unfairly described as *"unreliable"* within the ERG report, based on the uncertainties associated with the evidence base. The language used by the ERG does not fairly represent the evidence base, nor does it reflect the true underlying issue the ERG is discussing.	On page 153 of the report, the ERG state: *"The cost-effectiveness analysis, therefore, should be considered with caution, as these results will be at least as unreliable as the effectiveness estimates upon which they are based."* This should be amended to the following: *"The cost-effectiveness analysis, therefore, should be considered with caution, as these results are prone to at least the same degree of uncertainty as per the effectiveness estimates upon which they are based."*	The data available for treatment-naïve patients receiving avelumab is relatively immature compared to the data available for treatment-experienced patients. Consequently, any analyses made based upon these data are clearly prone to uncertainty, though this is not analogous to them being *"unreliable"*. This amendment is suggested to reiterate the true concern with the results – that is, the results of any analysis of uncertain data are clearly subject to at least the same degree of uncertainty.	Not a factual error.

Issue 6 Interpretation of the hazard function

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG raises a concern with the company's justification for the use of spline-based models, but in doing so erroneously suggests that the company stated spline-based models are	On page 155 of the report, the ERG state: *"The ERG considers the company's justification that splines are required when hazards are shown to be monotonic to be incorrect, as there are flexible standard parametric models that can produce non-monotonic functions, such as the log-logistic, lognormal or the generalised gamma."* This should be amended to the following:	Though it is accepted that the existence of non-monotonic hazards alone is not reason enough to warrant the use of spline-based models, the company did not suggest spline-based models should be applied where monotonic hazards are exhibited.	Thank you for highlighting this error. The text has been amended as suggested.

required when hazards are shown to be monotonic. This is incorrect.	*"The ERG considers the company's justification that splines are required when hazards are shown to be non-monotonic to be incorrect, as there are flexible standard parametric models that can produce non-monotonic functions, such as the log-logistic, lognormal or the generalised gamma."*		

Issue 7 Error in reported results based on economic model

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG comment</th></tr>
<tr><td>The results produced by the ERG in the following scenario are incorrect:
Table 74: Results of scenario 1 (Treatment-experienced): Weibull treatment duration curve (without truncation).</td><td>On page 197 of the report, the ERG present cost-effectiveness results using the following settings within the model (on the 'Controls' sheet):
- Time on treatment (distribution) [F57] = Log-logistic
- Estimated discontinuation time for the majority of patients [F58] = 40 year(s)
- Proportion of patients expected to remain on treatment after this time [F59] = 100%
- Maximum expected treatment duration [F60] = 40 year(s)

This is not what the ERG scenario aims to achieve – the distribution applied for time on treatment should be Weibull instead of log-logistic. The correct results associated with this scenario are presented below (changed values highlighted in yellow):

<table>
<tr><th>Therapy</th><th>Total costs</th><th>Total LYs</th><th>Total QALYs</th><th>Incremental costs</th><th>Incremental LYs</th><th>Incremental QALYs</th><th>ICER</th></tr>
<tr><td>Avelumab</td><td>£92,557</td><td>3.53</td><td>2.22</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Chemotherapy</td><td>£9,838</td><td>0.41</td><td>0.30</td><td>£82,718</td><td>3.11</td><td>1.92</td><td>£43,060</td></tr>
<tr><td>BSC</td><td>£7,465</td><td>0.41</td><td>0.31</td><td>£85,091</td><td>3.11</td><td>1.91</td><td>£44,584</td></tr>
<tr><td colspan="8">Abbreviations in table: BSC. best supportive care; LY, life years; QALYs, quality-adjusted life years.</td></tr>
</table>

The values in Table 74 of the ERG report should be updated in line with the figures presented in the table above. In doing so, these results will match those provided by the ERG in Table 79.</td><td>The values presented currently in Table 74 are incorrect, and should be amended for accuracy.</td><td>Thank you for highlighting this inaccuracy. The results in Table 74 have now been updated.</td></tr>
</table>

Issue 8 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
	On page 136 of the report, the ERG state:		

The ERG report contains some minor typographical errors.	*"The remainder of this section provides a detailed description of the company's methods and data sources used to model the cost-effectiveness of aveluamb in mMCC patients, as well as the ERG's critique of those methods and data sources."* Avelumab is spelled incorrectly.	Amending typographical errors aims to improve clarity of report.	Thank you for highlighting these typographical errors. They have now been corrected.
	On page 175 of the report, the ERG state within Table 49 that the average dose of avelumab per administration is 869 mg. This was also presented in the company's submission on page 159 in Table 50. The average dose is stated as 869mg, which is a typographical error, as this should be 849 mg (calculated using the method of moments). The value of 849mg is consistent with the submitted cost-effectiveness model		

Issue 9 Assumptions regarding time on treatment

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG comment**
The ERG states the assumption made by the manufacturer regarding treatment discontinuation as part of their overall critique, but do not make reference to the extensive clinical validation process that formed the basis of the assumptions.	On page 159 of the report, the ERG state: *"The assumption that two thirds of patients currently on treatment at two years immediately discontinue is a very strong assumption and is likely to have a great impact on the results of the cost-effectiveness results. The ERG's clinical experts stated that there is no evidence to suggest that treatment should be discontinued after two years and considered it to be a morally difficult decision to withdraw treatment from patients who are receiving a benefit from it."* This should be amended to the following: *"The assumption that two thirds of patients currently on treatment at two years immediately discontinue is a very strong assumption and is likely to have a great impact on the results of the cost-effectiveness results. The ERG's clinical experts stated that there is no evidence to suggest that treatment should be discontinued after two years and considered it to be a morally difficult decision to withdraw treatment from patients who are receiving a benefit from it. However, the company's clinical experts suggested that two years is a natural point at which physicians will discuss with patients stopping treatment and that it is highly unlikely that patients will still be on treatment at 5 years."*	The ERG fails to state the company's clinical validation of the treatment discontinuation assumption when critiquing the approach, and then refer to the opinion of their own clinical experts which contradicts the opinion of the clinical experts consulted by the manufacturer. This is a biased presentation of the opinion of the clinical community as a whole. By amending the statement by the ERG to acknowledge that there is no clear consensus across the clinical community, a clear and unbiased representation of clinical expert opinion is provided.	Not a factual error.

Issue 10 Impact of adverse events on health-related quality of life

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG state that avelumab treatment-related adverse events have a zero impact on the QALYs estimated for avelumab. While the impact is very small, it is not equal to zero.	On page 165 of the report, the ERG state: *"In this scenario, TRAEs have zero impact on the QALYs estimated for avelumab and cause a 0.01 decrement in QALYs for treatment-naive patients receiving chemotherapy."* This should be amended to the following: *"In this scenario, TRAEs have a negligible impact on the QALYs estimated for avelumab and cause a 0.01 decrement in QALYs for treatment-naive patients receiving chemotherapy."*	The impact of treatment-related adverse events on health-related quality of life for patients treated with avelumab is small, though it is not zero. The amendment clarifies that treatment-related adverse events have been accounted for within the analysis, but the impact is very small.	Thank you for highlighting this inaccuracy. The text has now been amended as requested.

Issue 11 Consideration of proxy diseases within the estimation of health-related quality of life

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG state that HSUVs were not compared to other publications identified in the SLR. However, one publication identified in the SLR by O'Brien *et al.*, (2006) was considered as an alternative setting for including HSUVs within the model (though sub-optimal, this allowed the use of the pre-progression utilities from the JAVELIN Merkel 200 trial, with decrements taken from related literature).	On page 165 of the report, the ERG state: *"However, the company did not attempt to compare the HSUVs used in the model to those reported in the publications identified in the SLR carried out for HRQoL which would have been a useful validation exercise, given that the company in more than one instance reports that these patient populations are considered to be a proxy to mMCC."* This should be amended to the following: *"The company did provide an analysis using a utility decrement upon progression based on one of the studies identified in the SLR: O'Brien et al., 2006. However, the company did not compare the specific HSUVs used in the model to those reported in the publications identified in the SLR carried out for HRQoL which would have been a useful validation exercise, given that the company in more than one instance reports that these patient populations are considered to be a proxy to mMCC."*	It is acknowledged that the direct HSUVs from the literature were not compared to those in the literature. This was not performed, as clinical expert opinion suggested direct comparability of HSUVs would be inappropriate. For example, one clinician stated: *"deterioration would be more rapid and utility decrements would therefore be larger in MCC patients than in melanoma patients."* However, the company did provide one analysis attempting to use available literature in combination with the JAVELIN Merkel 200 trial data. This amendment should clarify which analyses were attempted and which were not.	Not a factual error.

Issue 12 Premedication treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG refers to premedication treatment with paracetamol and chlorpheniramine, as per the JAVELIN Merkel 200 trial and clinical expert opinion. However, the dose of 1mg is an error – a 1g dose was administered to patients.	On page 36 of the report, the ERG state: *"The ERGs clinical experts reported that in England, the premedication is likely to be 1g of paracetamol given orally (or intravenously [IV]), and 10mg of IV (or oral equivalent dose) chlorpheniramine."* This is correct, however on pages 197 and 198 1mg of paracetamol is suggested instead. These should be amended to match the actual dose of 1g.	Amendment of this very minor discrepancy should avoid confusion with the dose of paracetamol administered.	Thank you for highlighting this inaccuracy. The text has now been corrected.

Issue 13 Patients enrolled in JAVELIN Merkel 200 – Part B

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
The ERG refers to the maximum number of treatment-naïve patients in JAVELIN Merkel 200 from the latest data-cut as n=29 with at least 3 months follow up. This is incorrect – in total, 39 patients have enrolled (as of latest follow-up date) and n=14 patients have at least 6 months of follow-up data.	On page 23 of the report, the ERG state: *"The ERG considers it difficult to draw any conclusions relating to OS or PFS for avelumab compared to chemotherapy in 1L mMCC because the data for avelumab are extremely limited due to the lack of long-term follow-up and small number of patients in the analysis (maximum n=29, and only 14 patients with 6 months or longer follow-up)."* This should be corrected to state the following: *"The ERG considers it difficult to draw any conclusions relating to OS or PFS for avelumab compared to chemotherapy in 1L mMCC because the data for avelumab are extremely limited due to the lack of long-term follow-up and small number of patients in the analysis (39 patients in total, 29 patients with 3 months or longer follow-up, and only 14 patients with 6 months or longer follow-up)."*	Amendment of this error correctly demonstrates the sample sizes available in the treatment-naïve cohort.	The ERG has amended the text on page's 23, 100, 112 and 127 as suggested by the company, replacing the text, "*(maximum n=29,"* with *"…..(39 patients in total, 29 patients with 3 months or longer follow-up,…."*.

Issue 14 Avelumab efficacy compared with chemotherapy and BSC

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
The ERG's statement that it is impossible to tell how avelumab compares to chemotherapy and BSC is an unfair statement. It mentions that conclusions around comparative effectiveness should not be made from single arm studies based on small patient numbers (<100). The language used by the ERG does not fairly represent the evidence base, nor does it reflect the true underlying issue the ERG is discussing.	*On page 123 of the report, the ERG state:* *"avelumab is associated with favourable efficacy outcomes in terms of response rate although it is impossible to tell how it compares to chemotherapy and BSC due to the efficacy data being only from single-arm studies."* This should be corrected to state the following: *"avelumab is associated with favourable efficacy outcomes in terms of response rate although there is an additional layer of uncertainty due to cross study comparisons."*	It is impossible from any trial to reach a definitive conclusion on efficacy, as there is always the play of chance. Randomised controlled trials (RCT) and larger trials try to restrict that chance. JAVELIN Merkel 200 is the largest ever registrational trial in metastatic MCC. It was supplemented with observational studies to collect as much data as possible in this ultra-rare disease. Part A of the trial includes 88 patients which is a greater number than the 70-81 patients per year estimated to be diagnosed with metastatic MCC in the UK. It would have been impossible as well as unethical (as advised by regulatory authorities) to conduct an RCT with sufficient power to identify significant treatment differences. While we recognise the data is limited, this is not uncommon for rare diseases. Merck has made	Not a factual error.
	On page 132 of the report the ERG state: *"The ERG considers that results of the company's naïve comparisons should be interpreted with caution because they are based on non-randomised data and are at a high risk of bias. In addition, conclusions around comparative effectiveness of interventions should not be made from results from single-arm studies and the results for mMCC are based on small patient numbers (<100 patients) thus the evidence base is extremely limited for drawing any conclusions relating to avelumab in 1L or 2L+ mMCC.".* This should be corrected to state the following: *"The ERG considers that results of the company's naïve comparisons should be interpreted with caution because they are based on non-randomised data and are at a high risk of bias. In addition, conclusions around comparative effectiveness of interventions is restricted to a single-arm study based on small patient numbers (<100 patients) thus the evidence base is extremely limited for drawing any conclusions relating to avelumab in 1L or 2L+ mMCC.".*		Not a factual error.

		considerable effort to fill in the data gaps.	

Issue 15 Avelumab data-cuts

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
Inconsistent data-cuts used in the ERG report (page 20). When listing TRAE and serious AEs the ERG use December and March data cuts, respectively	*On page 20 of the report, the ERG state:* *"In the 1L cohort, as of 30 December 2016, 79.3% (23/29) patients had experienced a TRAE. The ERG notes that the most common treatment-emergent adverse (TEAE) was fatigue in the 2L+ cohort (39.8%), with both fatigue and constipation being the most common TEAEs in the 1L population (23.1%). In terms of serious TEAEs, 42 patients (47.7%) in the 2L+ cohort experienced a serious TEAE and 8.0% (7/88) of the serious TEAEs were deemed to be related to treatment with avelumab based on the 18-month follow-up data set. In the 1L cohort, 30.8% (12/39) of patients experienced a serious TEAE and 10.3% (4/39) of these were attributed to avelumab (3-month follow-up data set)."* This should be corrected to state the following*:* *"In the 1L cohort, as of 24 March 2017, 71.8% (28/39) patients had experienced a TRAE. The ERG notes that the most common treatment-emergent adverse (TEAE) was fatigue in the 2L+ cohort (39.8%), with both fatigue and constipation being the most common TEAEs in the 1L population (23.1%). In terms of serious TEAEs, 42 patients (47.7%) in the 2L+ cohort experienced a serious TEAE and 8.0% (7/88) of the serious TEAEs were deemed to be related to treatment with avelumab based on the 18-month follow-up data set. In the 1L cohort, 30.8% (12/39) of patients experienced a serious TEAE and 10.3% (4/39) of these were attributed to avelumab (3-month follow-up data set)."* This error needs to be corrected on page 20, 28, 94, 124, 13 and 204.	Amendment of this error correctly reflects the most up to date safety information consistently across all outcomes from the latest 1L data cut	Not a factual error.

Issue 16 Avelumab safety

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
The ERG consistently mentions the high proportion of patients that have TRAE but fail to specify that the majority of these are low grade (1-2), even though they mention later that grade 3-4 AEs have the highest impact on QoL	*On page 28 of the report, the ERG state:* *"The ERG notes that there were high levels of TRAEs in Part A and Part B of JAVELIN Merkel 200: as of 3 March 2016, 70.5% of the 2L+ patients had experienced an AE that was deemed to be a TRAE, and in the 1L cohort, as of 30 December 2016, 79.3% patients had experienced a TRAE."* This should be corrected to state the following: *"The ERG notes that there were high levels of TRAEs in Part A and Part B of JAVELIN Merkel 200: as of 3 March 2016, 70.5% of the 2L+ patients had experienced an AE that was deemed to be a TRAE, and in the 1L cohort, as of 24 March 2017, 71.8% patients had experienced a TRAE. The majority of these TRAEs are grade 1-2 with 9.1% (8/88) and 20.5% (8/39) related to grade 3 or more in the 2L+ and 1L patients, respectively. There were no deaths deemed to be related to avelumab"* This error needs to be corrected on page 28, 123 and 131	There were no new safety signals compared to other immune-oncology agents. Furthermore, the majority of TRAE are low grade and are generally manageable by U.K. Oncologists; minimising the impact on QoL. This has been better explained on page 94 of the ERG report	Not a factual error.

Issue 17 Avelumab Solid Tumor trial safety data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Comment
The ERG has stated that no data on the AEs from the Solid Tumor study were provided in the CS or appendices	*On page 93 of the report, the ERG state:* *"The methodology for the JAVELIN Solid Tumor trial was provided in Appendix 11 of the CS but no data on the AEs from the study were provided in the CS or its appendices."* This should be corrected to state the following:	Safety data on both the Solid Tumor Trial and JAVELIN Merkel 200 (including over 1700 patient's worth of data) has been reported in the SPC provided in appendix 1	The ERG has amended the text on page 93. The text, *"but no data on the AEs from the study were provided in the CS or its appendices."* has been replaced with, *"and AEs*

	"The methodology for the JAVELIN Solid Tumor trial was provided in Appendix 11 of the CS and AEs from the study were provided in Appendix 1 of the CS." This error needs to be corrected on page 93 (reported twice on this page)		*from the study were provided in Appendix 1 of the CS."* In addition, the text, "*However, the reference details provided with the CS do not reflect the statement made by the company and no clinical data from the JAVELIN Solid Tumor study are presented in the CS and so the ERG is unclear of its relevance to the appraisal of avelumab in mMCC."* Has been replaced with *"However, the only clinical data from the JAVELIN Solid Tumor study are presented in the appendices of the CS."*

Avelumab for treating metastatic Merkel cell carcinoma

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 16/134/09

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
17	Issue 1: EMA approval details amended
23	Issue 13: JAVELIN Merkel 200 sample size amended
29	Issue 3: Description of company approach to identify prognostic factors amended.
30-31	Issue 4: Correcting cost effectiveness results to reflect appropriate comparisons in line with the NICE scope and company submission.
42	Issue 1: EMA approval details amended
93	Issue 17: Provision of adverse event details amended
110	Issue 13: JAVELIN Merkel 200 sample size amended
112	Issue 13: JAVELIN Merkel 200 sample size amended
127	Issue 13: JAVELIN Merkel 200 sample size amended
136	Issue 8: Typographical error.
155	Issue 6: Correction in text to "non-monotonic".
165	Issue 10: Text stating "zero impact" corrected to "negligible impact".
175	Issue 8: Dose of avelumab corrected.
196-202	Issue 4: Correcting cost effectiveness results to reflect appropriate comparisons in line with the NICE scope and company submission. ERG correction to Table 77 where the first change for the ERG preferred base case has been amended to only remove the truncation to the ToT curve. Initially this changed the curve to the Weibull also, however, this change is overridden in the second change in the table that uses alternative curves. The description row in Table 77 for the second change has also been edited to state that the ToT curve is also changed in addition to the PFS and OS. ERG edits to text surrounding the scenario analyses and ERG base cases to add clarity.

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of avelumab (BAVENCIO®; Merck Serono/Pfizer) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of avelumab for treating metastatic Merkel cell carcinoma (mMCC).

The company submission (CS) states that a European marketing authorisation application (MAA) for avelumab to treat mMCC in adults was submitted to the European Medicines Agency (EMA) in October 2016 and avelumab received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 21 July 2017 for avelumab as a monotherapy for the treatment of adult patients with mMCC. The The ERG notes that the company received full EMA license for avelumab in mMCC on 20 September 2017. The ERG notes that avelumab has received accelerated approval by the FDA (23 March 2017) for the treatment of adults and paediatric patients (over 12 years) with mMCC.

The key clinical trial informing the safety and efficacy of avelumab in patients with mMCC is the JAVELIN Merkel 200 trial. Avelumab was administered in the trial at a dose of 10 mg/kg as a 60-minute intravenous (IV) infusion once every 2 weeks with the dose of avelumab calculated based on the weight of the patient on the day of administration. Premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab was mandatory in JAVELIN Merkel 200 in line with the anticipated SmPC guidance.

JAVELIN Merkel 200 was conducted in two parts, Part A comprised patients at second-line or beyond treatment (2L+) and Part B comprised patients at first-line treatment (1L) for mMCC. The two parts of JAVELIN Merkel 200 restricted trial entry to adults with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 who had mMCC meeting the trial entry criteria. The final scope issued by NICE specified the population of interest to be patients with mMCC with different comparators requested for the 1L and 2L+ populations. The Evidence Review Group (ERG) considers the populations in JAVELIN Merkel 200 Part A and Part B to be relevant to the decision problem. In addition, all clinically relevant outcomes were reported in the CS, with the exception of health-related quality of life (HRQoL) data for 1L patients.

In the final scope issued by NICE, the comparator of interest was identified as chemotherapy for the 1L population and best supportive care (BSC) for the 2L+ population. The ERG notes that no trial level data were presented in the CS for BSC. The company presented the results of studies of chemotherapy as a surrogate for BSC, reporting that these were the best available equivalent and were likely to over-

concerned that the inclusion of Samlowski 2010 introduces clinical heterogeneity as the Samlowski trial population comprises a mix of 1L (n=9) and 2L+ (n=14) patients.

The results for the 1L population of the naïve comparison of avelumab from JAVELIN Merkel 200 Part B with chemotherapy suggest avelumab is associated with improved ORR, PFS and OS outcomes compared to chemotherapy in Study 100070-Obs001 and in Iyer 2016. However, as discussed previously, this comparison is based on small patient numbers for avelumab, and long term follow-up data for avelumab is lacking. The ERG, therefore, considers that the 1L results should be interpreted with caution.

In total, there were seven studies that the company identified from the SLRs and their own observational studies with OS or PFS (or both) data on chemotherapy in 1L mMCC patients (Study 100070-Obs001; Iyer 2016; Voog 1999; Satpute 2014; Santamaria-Barria 2013; Fields 2011; Allen 2005) that were used in a naïve pooling in the economic modelling. The company reported that, "this results in increased patient numbers for analysis, and likely the most generalisable results". The ERG considers that the approach is likely to introduce unnecessary heterogeneity into the analysis although it is not possible to predict the likely direction of the resulting bias. The ERG considers it difficult to draw any conclusions relating to OS or PFS for avelumab compared to chemotherapy in 1L mMCC because the data for avelumab are extremely limited due to the lack of long-term follow-up and small number of patients in the analysis (39 patients in total, 29 patients with 3 months or longer follow-up, and only 14 patients with 6 months or longer follow-up).

[redacted]

In response to clarification questions, the company conducted a propensity score matching analysis and a regression analysis for PFS and OS for the 2L+ population. In the propensity score matching analysis, the 2L+ patients from Study 100070-Obs001 (US 2L - Part A and EU 2L - Part B; n=54) were matched on a 1:1 basis with 2L+ patients in JAVELIN Merkel 200 (Part A; n=88). The only variables which the company used in the matching process to calculate the propensity score, were age and sex, [redacted] The ERG is unclear why the company did not explore using alternative variables for matching. The ERG considers that subgroups identified in the subgroup analyses (CS page 83, Figure 18), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, included as characteristics for matching. The ERG considers there to be a notable difference in the propensity scores of the unmatched and matched patients between the two studies (Study 100070-Obs001 and JAVELIN Merkel 200). However, the

[redacted]

[redacted]

conclusions from the statistically non-significant results from the regression analyses, as they could be a result of the small patient numbers rather than the absence of a subgroup effect (prognostic indicator). The ERG considers that subgroups identified in the subgroup analyses (CS page 83, Figure 18), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, the company should have adjusted outcomes appropriately.

The ERG is concerned that Study 100070-Obs001 included immunosuppressed patients, whereas none of the JAVELIN Merkel 200 avelumab patients were immunosuppressed. In addition, the ERG considers that 1L and 2L+ patients had a better baseline ECOG status in JAVELIN Merkel 200 compared to in Study 100070-Obs001. The ERG is concerned that these differences in baseline characteristics are not accounted for in the naïve comparisons presented in the CS.

The ERG considers the regression analysis to be a more robust analysis of avelumab versus chemotherapy compared to the naïve comparison and propensity score matching because it adjusts for a greater range of likely covariates. However, the ERG would have preferred an analysis with further potential prognostic factors adjusted for such as line of therapy 2L or third line and beyond (3L+), and PD-L1 status. The ERG considers that the inclusion of further covariates would confirm the robustness of the company's preferred option, the naïve comparison of study level data from JAVELIN Merkel 200 for avelumab with pooled data from Study 100070-Obs001 for chemotherapy if the results of both analyses were similar.

The later data cut that the company anticipates taking place in [redacted], is likely to have an increase in patient number and an increase in the events of interest. The ERG considers this later dataset is likely to provide the basis for a more robust assessment of avelumab versus chemotherapy in 1L patients. However, the ERG also considers that any analysis should be adjusted for potential observed treatment-effect modifiers with justification provided for the variables used.

Economic

The lack of adjustment for imbalances in potential effect modifiers or prognostic indicators between the data sources was a key limitation of the company's analysis. The justification that there were no statistically significant prognostic effects and no trends observed for the variables included in a regression analysis was not considered sufficient by the ERG due to the small sample size included in the analyses.

The assumptions applied for time on treatment were considered implausible by the ERG and clinical expert opinion suggested that there was no evidence to suggest discontinuation at two years was suitable and believed it would be unethical without that evidence.

The key issue for the treatment-naïve population is the limited data, but the use of a Cox proportional hazards model to estimate a relative treatment effect between populations was considered to be potentially implausible without evidence to justify a constant relative effect.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

The ERG's preferred base case ICERs, presented cumulatively as each change is applied to the company's base case, are presented in Table 1 and Table 2 for the treatment-experienced and treatment-naïve populations, respectively. The results differ from the company's base case analyses as a result of changes to the company's approach for the estimation of treatment effectiveness and time on treatment, as well as the addition of premedication costs for avelumab, which were not considered in the company's model.

Table 1. ERG base case ICER (treament-experienced)

	Avelumab	BSC	Incremental value
Company's base case			
Total costs (£)	£78,752	£7,465	£71,287
QALYs	2.22	0.31	1.91
ICER			£37,350
Weibull time on treatment curve (without truncation)			
Total costs (£)	£92,557	£7,465	£85,091
QALYs	2.22	0.31	1.91
ICER			£44,584
Weibull regression models for PFS and OS			
Total costs (£)	£92,537	£7,413	£85,124
QALYs	2.22	0.32	1.90
ICER (compared with base case)			£37,582
ICER with all changes incorporated			£44,857
Addition of pre-medication costs			
Total costs (£)	£92,644	£7,413	£85,232
QALYs	2.22	0.32	1.90
ICER (compared with base case)			£37,397
ICER with all changes incorporated			£44,914
ERG's alternative base case ICER			
ICER with all changes incorporated			**£44,914**

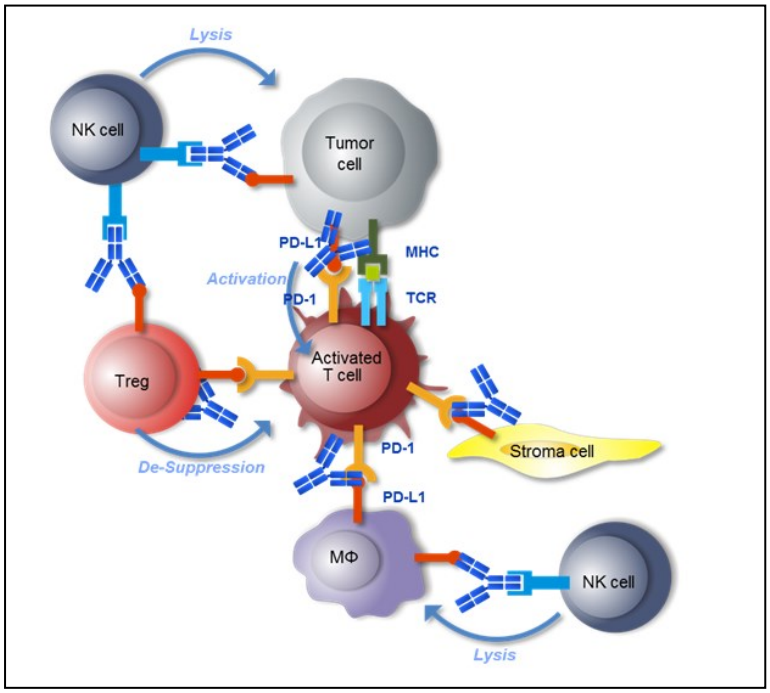
Abbreviation used in the table: BSC, best supportive care; ERG, evidence review group; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year.

Table 2. ERG base case ICER (treatment-naïve)

	Avelumab (1)	**Chemotherapy (2)**	**BSC (3)**	**Incremental value (1-2)**	**Incremental value (1-3)**
Company's base case					
Total costs (£)	£78,588	£10,608	£7,217	£67,979	£71,371
QALYs	2.93	1.37	1.38	1.56	1.55
ICER				£43,553	£46,148
Removal of truncation to time on treatment curve					
Total costs (£)	£141,523	£10,608	£7,217	£130,915	£134,306
QALYs	2.93	1.37	1.38	1.56	1.55
ICER				£83,882	£86,851
Parametric curves for PFS, OS and ToT					
Total costs (£)	£159,375	£10,608	£7,217	£148,766	£152,158
QALYs	2.65	1.37	1.38	1.28	1.27
ICER (compared with base case)				£71,938	£75,430
ICER with all changes incorporated				£116,235	£120,228
Addition of pre-medication costs					
Total costs (£)	£159,570	£10,608	£7,217	£148,962	£152,353
QALYs	2.65	1.37	1.38	1.28	1.27
ICER (compared with base case)				£43,610	£46,206
ICER with all changes incorporated				£116,388	£120,383
ERG's alternative base case ICER					
ICER with all changes incorporated				**£116,388**	**£120,383**

Abbreviation used in the table: BSC, best supportive care; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

Figure 1. Proposed mechanism of actions of avelumab (reproduced from the CS page 31, Figure 1)



Abbreviations: ADCC: Antibody-dependent cell-mediated cytotoxicity; ADCP: Antibody-dependent cellular phagocytosis; MHC: Major histocompatibility complex; NK: Natural killer; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1; TCR: T-cell receptor

The company reported that, "avelumab was granted Orphan Drug designation for the treatment of metastatic MCC by the Food and Drug Administration (FDA) (25 September 2015) and the European Medicines Agency (EMA) (6 June 2016; EU Orphan designation number: EU/3/15/1590), as well as Fast Track and Breakthrough Therapy Designations in October 2015 and November 2015, respectively[17, 18]". The company stated that these designations reflect the efficacy of avelumab in patients with mMCC, the poor outcomes associated with mMCC, and the limited treatment options available.

The CS states that a European marketing authorisation application (MAA) for avelumab to treat mMCC in adults was submitted to the European Medicines Agency (EMA) in October 2016 and avelumab received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 21 July 2017 for avelumab as a monotherapy for the treatment of adult patients with mMCC. The ERG notes that the company received full EMA license for avelumab in mMCC on 20 September 2017.

The ERG notes that avelumab has received accelerated approval by the FDA (23 March 2017) for the treatment of adults and paediatric patients (over 12 years) with mMCC. This approval is reported by the company to be based on 1L and 2L+ data from JAVELIN Merkel 200. The ERG also notes that avelumab for mMCC treatment will be submitted to the Scottish Medicines Consortium (anticipated

4.3.6 Adverse effects

The company reported that the safety of avelumab was initially investigated in the JAVELIN Solid Tumor study[176, 177] which was a Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics (PK), and biological and clinical activity of avelumab in patients with metastatic or locally advanced solid tumours. The methodology for the JAVELIN Solid Tumor trial was provided in Appendix 11 of the CS and AEs from the study were provided in Appendix 1 of the CS. The ERG notes that the initial dose escalation phase of the trial enrolled 53 patients with avelumab doses ranging from 1 mg/kg to 20 mg/kg. There was also a subsequent expansion phase of the study which enrolled 1,452 patients with multiple tumour types, across 16 expansion cohorts, all of whom received at least one dose of avelumab (10 mg/kg). The company stated that the expansion cohorts did not include any patients with MCC but that it did not expect any major difference in the safety of avelumab across different types of solid tumours. In addition the company stated that, "Consequently the safety data base consisting of a total of 1,540 patients treated with the proposed dose and treatment schedule of 10 mg/kg every 2 weeks is considered of an acceptable magnitude for identifying the safety profile of avelumab in the short-term perspective".[17] However, the only clinical data from the JAVELIN Solid Tumor study are presented in the appendices of the CS. There were safety data available on avelumab in mMCC from JAVELIN Merkel 200 and these were summarised in the CS. The ERG therefore only discusses the JAVELIN Merkel 200 avelumab safety data in this report.

The JAVELIN Merkel 200 safety analyses were conducted using the safety analysis set, which included all patients in the 2L+ cohort (Part A) and 1L cohort (Part B) who had received at least one dose of avelumab. The data cut-off for safety analyses was 18-months follow-up for the 2L+ cohort, and 3-months follow-up for the 1L cohort. The CS provided limited summary data on the AEs in JAVELIN Merkel 200 and so the ERG has supplemented the CS data with additional data from the primary publications of the 1L and 2L+ data,[3, 178] although these had earlier data cut-offs than the March 2017 analyses presented in the CS (30 December 2016 and 3 March 2016, respectively).

The median duration of therapy for the 2L+ cohort was [redacted] with a median number of infusions of [redacted]. The median duration of therapy in the 1L cohort was [redacted] with a median number of infusions of [redacted]. [redacted]. The ERG notes that the company reported most patients (both 1L and 2L+) received between [redacted] of the planned dose per cycle although numerical data in support of this were not provided in the CS. In addition, it

Abbreviations: BOR: Best overall response; CI: Confidence interval; CR: Complete response; DoR: Duration of response; DRR: Durable response rate; KM: Kaplan-Meier; NR: Not reached; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1; SD: Stable disease

Figure 2 and **Error! Reference source not found.** show the KM plots for the avelumab data from the 1L patients in JAVELIN Merkel 200 compared to the chemotherapy data from the Study 100070-Obs001 1L patients for OS and PFS, respectively. It should be noted that Study 100070-Obs001 only contained 1L data from US patients, and the ERG's clinical experts reported that they may over-estimate the efficacy of chemotherapy, as treatment in the US is considered to be more aggressive. The ERG considers it important to highlight that the OS data for avelumab are extremely limited due to the lack of long-term follow-up data for JAVELIN Merkel 200 1L patients and the small number of patients in the analysis (39 patients in total, 29 patients with 3 months or longer follow-up, and only 14 patients with 6 months or longer follow-up). The ERG, therefore, considers it difficult to draw any conclusions relating to OS for avelumab compared to chemotherapy in 1L mMCC patients.

Figure 2. OS KM plot for avelumab versus chemotherapy in 1L patients (JAVELIN Merkel 200 and Study 100070-Obs001 [US data]; produced by the ERG based on CS Appendix 10 pg 7, Figure 2)

The KM plots for PFS in the 1L population suggest that beyond approximately 3 months, avelumab may be associated with longer PFS compared to chemotherapy (**Error! Reference source not found.**). However, as discussed previously, this comparison is based on small patient numbers for avelumab, and long term follow-up data for avelumab is lacking. The ERG, therefore, considers that the 1L results should be interpreted with caution.

and visual inspection". The company considered that the additional six chemotherapy studies had similar outcomes to Study 100070-Obs001 and so they naïvely pooled the data from all the studies and fit parametric curves to inform the base-case analysis in 1L patients. The company reported that, "this results in increased patient numbers for analysis, and likely the most generalisable results". The ERG considers that the approach is likely to introduce unnecessary heterogeneity into the analysis although it is not possible to predict the likely direction of the resulting bias.

The resulting parametric curves and goodness of fit statistics are discussed further in Section 5 but the KM plots for the pooled chemotherapy study data are presented in Figure 3 and **Error! Reference source not found.**. The ERG considers it difficult to draw any conclusions relating to OS or PFS for avelumab compared to chemotherapy in 1L mMCC because the data for avelumab are extremely limited due to the lack of long-term follow-up and small number of patients in the analysis (39 patients in total, 29 patients with 3 months or longer follow-up, and only 14 patients with 6 months or longer follow-up). However, the ERG considers that the OS and PFS KM plots for the pooled 1L chemotherapy studies are similar to those of the Study 100070-Obs001 US 1L data.

Figure 3. OS KM plot for avelumab versus chemotherapy in 1L patients (JAVELIN Merkel 200 and pooled chemotherapy study data; produced by the ERG based on CS Appendix 10 pg 27, Figure 10)

Obs001 (OS approximately 1.25 years versus approximately 0.75 years, respectively; and PFS approximately 0.75 years versus approximately 0.5 years, respectively). However, the ERG is concerned that the inclusion of Samlowski 2010 introduces clinical heterogeneity as the Samlowski trial population comprises a mix of 1L (n=9) and 2L+ (n=14) patients.

The results for the 1L population of the naïve comparison of avelumab from JAVELIN Merkel 200 Part B with chemotherapy suggest avelumab is associated with improved ORR, PFS and OS outcomes

compared to chemotherapy in Study 100070-Obs001 and in Iyer 2016. However, as discussed previously, this comparison is based on small patient numbers for avelumab, and long term follow-up data for avelumab is lacking. The ERG, therefore, considers that the 1L results should be interpreted with caution.

In total, there were seven studies that the company identified from the SLRs and their own observational studies with OS or PFS (or both) data on chemotherapy in 1L mMCC patients (Study 100070-Obs001; Iyer 2016; Voog 1999; Satpute 2014; Santamaria-Barria 2013; Fields 2011; Allen 2005) that were used in a naïve pooling in the economic modelling. The company reported that, "this results in increased patient numbers for analysis, and likely the most generalisable results". The ERG considers that the approach is likely to introduce unnecessary heterogeneity into the analysis although it is not possible to predict the likely direction of the resulting bias. The ERG considers it difficult to draw any conclusions relating to OS or PFS for avelumab compared to chemotherapy in 1L mMCC because the data for avelumab are extremely limited due to the lack of long-term follow-up and small number of patients in the analysis (39 patients in total, 29 patients with 3 months or longer follow-up, and only 14 patients with 6 months or longer follow-up).

[redacted]

In response to clarification questions, the company conducted a propensity score matching analysis and a regression analysis for PFS and OS for the 2L+ population. In the propensity score matching analysis, the 2L+ patients from Study 100070-Obs001 (US 2L - Part A and EU 2L - Part B; n=54) were matched on a 1:1 basis with 2L+ patients in JAVELIN Merkel 200 (Part A; n=88). The only variables which the company used in the matching process to calculate the propensity score, were age and sex, [redacted] The ERG is unclear why the company did not explore using alternative variables for matching. The ERG considers that subgroups identified in the subgroup analyses (CS page 83, Figure 18), such as number of prior systemic therapies, disease burden at baseline and tumour PD-L1 expression status should have been explored further and if possible, included as characteristics for matching. The ERG considers there to be a notable difference in the propensity scores of the unmatched and matched patients between the two studies (Study 100070-Obs001 and JAVELIN Merkel 200). However, the

[redacted]

[redacted]The ERG considers the search carried out by the company to be appropriate, and sufficient to identify any published cost-effectiveness studies for treatments of mMCC.

1.7 Overview and critique of company's economic evaluation

The company submitted a *de novo* economic model to assess the cost-effectiveness of avelumab compared to chemotherapy or best supportive care (BSC) in treatment-naïve patients with mMCC, and compared to BSC in treatment-experienced patients with mMCC.

The evidence for the effectiveness of avelumab is based on the single arm JAVELIN Merkel 200 trial,[136] with comparator evidence for chemotherapy estimated from observational studies, some of which were conducted by the company given a lack of published evidence identified through the SR. No head-to-head trials were available so a naïve comparison of these data sources was used to inform the company's base case analysis.

The remainder of this section provides a detailed description of the company's methods and data sources used to model the cost-effectiveness of avelumab in mMCC patients, as well as the ERG's critique of those methods and data sources.

1.7.1 NICE reference case checklist

Table 3 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope outlined in Section 3.

Table 3. NICE reference case checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-utility analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes. The time horizon was set at 40 years, which was deemed sufficient to capture the lifetime of patients on with mMCC.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Synthesis of evidence on outcomes	Systematic review	Yes. A systematic review was conducted to identify data sources for outcome measures including disease progression, mortality and quality of life.

The company considered a range of different survival curves and assessed the hazard functions of the data using log-log plots to choose appropriately fitting curves. The ERG considers the company's justification that splines are required when hazards are shown to be non-monotonic to be incorrect, as there are flexible standard parametric models that can produce non-monotonic functions, such as the log-logistic, lognormal or the generalised gamma. However, given the flexibility of spline-based survival models, and the range of different splines that were considered by the company, the ERG considers it unlikely that a better fitting model to the data could have been found. However, a more plausible extrapolation may have been possible and the ERG considers it more appropriate to assess all available survival functions. In general, however, the ERG considered the company's chosen curves for PFS and OS for the treatment-experienced population to have generally good fits with plausible extrapolations.

Another issue the ERG notes, is that the company's base case analysis uses different survival functions for the avelumab and comparator groups for both OS and PFS. This is highlighted in NICE technical support document 14 as requiring substantial justification, as different functions can produce very different shaped curves, which may be implausible. However, given the mode of action of avelumab causes an immune response, this may suitably justify the use of a different distribution. Further to this, given that the comparator data are complete and do not need extrapolation, the uncertainty in the shape of the curves is limited to only the avelumab curves. The ERG, therefore, considers this approach to be reasonable.

1.7.2 Treatment discontinuation

To accurately calculate treatment costs, the time for which patients receive the treatment needs to be considered. Patients can discontinue for numerous reasons, including disease progression, intolerable toxicity or death. Therefore, time on treatment (ToT) data are required to estimate the proportion of patients receiving treatment at each model cycle in order to accurately apply the costs of treatment. The company's approach is described for each comparator at each line of treatment in the following sub-sections. The treatment duration for chemotherapy is discussed in Section **Error! Reference source not found.**.

1.7.2.1 Treatment-experienced (second line)

1.7.2.1.1 Avelumab time on treatment

The proportion of patients remaining on treatment for patients receiving avelumab was modelled in the same way as PFS and OS, by fitting survival curves to the ToT KM data shown in **Error! Reference source not found.**.

for their condition. However, the HSUVs applied to patients in the model were around 0.71 and 0.77, in the groups closest to death and further from death, respectively. One of the ERG's clinical experts stated that he would expect patients to have the same HSUV as the general population, making the 0.77 assumed in patients with more than 100 days to die, seem plausible. Furthermore, while the HSUVs applied in the model may be high, the company applies the same values regardless of treatment group, so the difference in HSUVs between health states is the key issue rather than the baseline magnitude, and this difference is plausible.

During the clarification stage the ERG asked the company to clarify whether the impact of adverse events on quality of life is incorporated in the base case analysis. The company explained that the time-to-death approach used does not differentiate whether patients are on or off treatment. However, the ERG notes that this indicates that the resultant HSUVs implicitly include the effect of TRAEs on quality of life as the EQ-5D data collected in the trial are from patients regardless of whether they were experiencing TRAEs or not. Furthermore, the company clarified that the scenario in the model in which HSUVs are based on progression status of patients QALY decrements attributed to TRAEs are incorporated in the PF-on treatment state. In this scenario, TRAEs have a negligible impact on the QALYs estimated for avelumab and cause a 0.01 decrement in QALYs for treatment-naive patients receiving chemotherapy.

The ERG acknowledges that the EQ-5D data from the JAVELIN Merkel 200 trial is the best available source of HRQoL data to inform this analysis, and that the patient demographics in SCLC and melanoma may be different from mMCC. However, the company did not attempt to compare the HSUVs used in the model to those reported in the publications identified in the SLR carried out for HRQoL which would have been a useful validation exercise, given that the company in more than one instance reports that these patient populations are considered to be a proxy to mMCC.

1.7.3 Resources and costs

1.7.3.1 Systematic literature review

The company carried out an SLR to identify studies reporting resource use and costs in mMCC alongside the SLR for cost-effectiveness studies described and critiqued in Section **Error! Reference source not found.**. The company broadened the search further to capture studies reporting resource use and costs for management of SCLC and melanoma, as no studies were identified that reported resource use and costs for mMCC. This approach was take based on input by the company's clinical experts, who stated that SCLC and mMCC are disease analogues. The company reports using data from SCLC studies where available, and only using data from melanoma studies when no SCLC sources were identified.

The relative dose intensity (RDI) of avelumab in the JAVELIN Merkel 200 trial was 95.43%, which the company defines as the proportion of doses received relative to the intended dose of 10 mg/kg. Therefore, the company adjusted the intended dose in the model to 9.543 mg/kg instead of 10 mg/kg when calculating the mean number of vials per patient. The summary statistics of the method of moments calculations are presented in Table 9, which shows the resultant mean number of vials per administration for the European subpopulation to be 4.25 vials. This is the mean number of vials assumed for avelumab in the company's base case analysis. The dose and costs of avelumab are summarised in Table 10.

Table 4. Summary statistics of methods of moments calculation for avelumab (CS, pg 158, Table 49)

Statistic	All patients	European patients
N	88	29
Mean weight (kg)	83.09	78.50
SD	19.15	14.99
SE	2.04	2.78
Average vials	4.46	4.25
Abbreviations in table: : N, number of patients; SD, standard deviation; SE, standard error		

Table 5. Dosing information for avelumab (CS, pg 159, Table 50)

Dose	10 mg/kg
Vial size	200 mg
Cost per vial	£768.00 (Merck)
Cost per mg	£3.84
Average dose per treatment	849 mg*
RDI	95.43%

Average cost per treatment	£3,261.04
Administration information	IV infusion once every 2 weeks[3]
Abbreviations in table: IV, intravenous; kg, kilogram; mg, milligram; RDI, relative dose intensity. * The average dose for avelumab is calculated via the method of moments and incorporates vial wastage.	

There are currently no approved treatments for mMCC, and therefore, the company relied on clinical expert opinion on chemotherapy regimens used to treat SCLC in England, which are also used off-label to treat mMCC. Chemotherapy dosage in the model is based on published literature identified in the SLR (CS, page 164, Table 54), complemented by clinical expert opinion. Treatment-naïve patients in the chemotherapy arm of the model in the base case analysis are assumed to be equally split between two regimens; carboplatin + etoposide and cisplatin + etoposide. Additional chemotherapy regimens are included in the model, to allow the flexibility of selecting alternative regimens if desired.

Chemotherapy dosage is calculated based on body surface area (BSA) for cisplatin and etoposide. The BSA of patients in the model is assumed to be the same as the average BSA of patients in the JAVELIN

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The ERG did not identify any further errors following the company's response to clarification questions, hence, the company's base case around which the ERG's analyses are based is that presented in Section **Error! Reference source not found.**.

6.2 ERG scenario analysis

The ERG conducted a number of scenario analyses around the company's base cases for both the treatment-naïve and treatment-experienced populations. These are presented in Section 6.2.1 and 0, respectively.

6.2.1 Treatment-naïve (First line)

6.2.1.1 Scenario 1: Treatment-experienced Weibull treatment duration curve (without truncation)

This scenario maintains the assumption that ToT for the treatment-naïve population is equivalent to the treatment-experienced population but uses the company's Weibull treatment duration curve without truncation. The results of this analysis are given in Table 6.

Table 6. Results of scenario 1 (Treatment-naïve)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£92,392	4.78	2.93	-	-	-	-
Chemotherapy	£10,608	2.02	1.37	£81,784	2.76	1.56	£52,398
BSC	£7,217	2.02	1.38	£85,176	2.76	1.55	£55,075
Abbreviations in table: BSC. best supportive care; LY, life years; QALYs, quality-adjusted life years.							

6.2.1.2 Scenario 2: Parametric curves for PFS, OS and ToT

The company's best fitting parametric curves were used for PFS, OS and ToT instead of the company's base case approach of applying HRs. The best fitting curve was the 1-knot normal spline for both PFS and OS, and the Weibull for ToT. The results are presented in Table 7.

Table 7. Results of scenario 2 (Treatment-naïve)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£102,690	4.16	2.65	-	-	-	-
Chemotherapy	£10,608	2.02	1.37	£92,082	2.14	1.28	£71,938
BSC	£7,217	2.02	1.38	£95,473	2.14	1.27	£75,430
Abbreviations in table: BSC. best supportive care; LY, life years; QALYs, quality-adjusted life years.							

6.2.1.3 Scenario 3: Addition of premedication costs for avelumab treatment

Premedication treatment with 1g of oral paracetamol and 10mg of IV chlorpheniramine for patients treated with avelumab. This was informed by clinical expert opinion. The results are presented in Table 8.

Table 8. Results of scenario 3 (Treatment-naïve)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,678	4.78	2.93	-	-	-	-
Chemotherapy	£10,608	2.02	1.37	£68,069	2.76	1.56	£43,610
BSC	£7,217	2.02	1.38	£71,461	2.76	1.55	£46,206
Abbreviations in table: BSC. best supportive care; LY, life-year; QALYs, quality-adjusted life years.							

6.2.2 Treatment-experienced (Second line)

6.2.2.1 Scenario 1: Weibull treatment duration curve (without truncation)

This scenario uses the company's best fitting Weibull treatment duration curve to the treatment-experienced population data from the JAVELIN Merkel 200 trial. The ERG considers this to provide a more plausible extrapolation than the log-logistic curve used in the company's base case. The results of this analysis are given in Table 9.

Table 9. Results of scenario 1 (Treatment-experienced)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£92,557	3.53	2.22	-	-	-	-
BSC	£7,465	0.41	0.31	£85,091	3.11	1.91	£44,584
Abbreviations in table: BSC. best supportive care; LY, life-year; QALYs, quality-adjusted life years.							

6.2.2.2 Scenario 2: Weibull regression for comparator PFS and OS

The adjusted Weibull regression models were used for PFS and OS for the comparator groups in this scenario. The results of this analysis are given in Table 10.

Table 10. Results of scenario 2 (Treatment-experienced)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,732	3.53	2.22	-	-	-	-
BSC	£7,413	0.43	0.32	£71,319	3.10	1.90	£37,582
Abbreviations in table: BSC. best supportive care; LY, life-year; QALYs, quality-adjusted life years.							

6.2.2.3 Scenario 3: Addition of premedication costs for avelumab treatment

Premedication treatment with 1g of oral paracetamol and 10mg of IV chlorpheniramine for patients treated with avelumab. This was informed by clinical expert opinion. The results are presented in Table 76.

Table 76. Results of scenario 3 (Treatment-experienced)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£78,842	3.53	2.22	-	-	-	-
BSC	£7,465	0.41	0.31	£71,377	3.11	1.91	£37,397
Abbreviations in table: BSC. best supportive care; LY, life-year; QALYs, quality-adjusted life years.							

6.3 ERG base case ICER

6.3.1 Treatment-naïve (First line)

The key changes the ERG has made to the company's model to form the preferred base case are to remove the company's assumption that time on treatment for the treatment-naïve population is equivalent to the time on treatment for the treatment-experienced population, which uses a log-logistic curve but also assumes that two thirds of patients discontinue immediately at two years and then all patients remaining on treatment at 5 years will also immediately discontinue. These assumptions were applied due to the implausible extrapolation produced by the log-logistic distribution. The ERG preferred to use the Weibull curve fitted by the company to the treatment-naïve data from the JAVELIN Merkel 200 trial in response to CQs, as well as removing the truncation used by the company.

The ERG's preferred base case also applies the curves for PFS and OS that the company fitted in response to CQs, as the ERG considered the company's assumption of PH between the two populations was potentially flawed. The ERG acknowledges that, given the lack of data, this analysis is still very uncertain. In addition to this, premedication costs for avelumab were included as 10mg of IV chlorpheniramine and 1g of oral paracetamol.

The ERG's base case ICER is presented with each change incrementally in Table 77.

Table 77. ERG base case ICER (treatment-naïve)

	Avelumab (1)	Chemotherapy (2)	BSC (3)	Incremental value (1-2)	Incremental value (1-3)
Company's base case					
Total 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
Removal of truncation to time on treatment curve					
Total costs (£)	£141,523	£10,608	£7,217	£130,915	£134,306
QALYs	2.93	1.37	1.38	1.56	1.55
LYs	4.78	2.02	2.02	2.76	2.76
ICER				£83,882	£86,851
Parametric curves for PFS, OS and ToT					
Total costs (£)	£159,375	£10,608	£7,217	£148,766	£152,158
QALYs	2.65	1.37	1.38	1.28	1.27
LYs	4.16	2.02	2.02	2.14	2.14
ICER (compared with base case)				£71,938	£75,430
ICER with all changes incorporated				£116,235	£120,228
Addition of pre-medication costs					
Total 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 (compared with base case)				£43,610	£46,206
ICER with all changes incorporated				£116,388	£120,383
ERG's alternative base case ICER					
ICER with all changes incorporated				**£116,388**	**£120,383**

Abbreviation used in the table: BSC, best supportive care; ICER, incremental cost effectiveness ratio; LY, life-year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

6.3.2 Scenario analyses for the treatment-naïve population

One scenario analysis was performed around the ERG's preferred base case for the treatment-naïve population, which was the exclusion of GP visit costs. This was informed by clinical expert opinion, which suggested that these are not required as a regular follow up as patients are seen by the consultant. However, patients may have increased GP attendances themselves as a result of symptoms caused by their disease, and hence this has not been incorporated as part of the ERG's preferred base case. The results of this analysis are given in Table 11.

Table 11. Exclusion of GP costs (Treatment-naïve)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£158,529	4.16	2.65	-	-	-	-
Chemotherapy	£10,608	2.02	1.37	£147,921	2.14	1.28	£115,575
BSC	£7,217	2.02	1.38	£151,312	2.14	1.27	£119,560
Abbreviations in table: BSC. best supportive care; LY, life-year; QALYs, quality-adjusted life years.							

6.3.3 Treatment-experienced (Second line)

For the treatment-experienced population, the changes that the ERG made were similar in that time on treatment truncation was removed and a Weibull curve with a more plausible extrapolation was used instead of the log-logistic curve. For PFS and OS in the comparator group, the Weibull regression models were used, and again, premedication costs were applied as per the treatment-naïve population.

The ERG's base case ICER is presented with each change incrementally in Table 79.

Table 79. ERG base case ICER (treament-experienced)

	Avelumab	BSC	Incremental value
Company's base case			
Total costs (£)	£78,752	£7,465	£71,287
QALYs	2.22	0.31	1.91
LY	3.53	0.41	3.11
ICER			£37,350
Weibull time on treatment curve (without truncation)			
Total costs (£)	£92,557	£7,465	£85,091
QALYs	2.22	0.31	1.91
LY	3.53	0.41	3.11
ICER			£44,584
Weibull regression models for PFS and OS			
Total costs (£)	£92,537	£7,413	£85,124
QALYs	2.22	0.32	1.90
LY	3.53	0.43	3.10
ICER (compared with base case)			£37,582
ICER with all changes incorporated			£44,857
Addition of pre-medication costs			
Total costs (£)	£92,644	£7,413	£85,232
QALYs	2.22	0.32	1.90
LY	3.53	0.43	3.10
ICER (compared with base case)			£37,397
ICER with all changes incorporated			£44,914
ERG's alternative base case ICER			
ICER with all changes incorporated			**£44,914**

Abbreviation used in the table: BSC, best supportive care; ERG, evidence review group; ICER, incremental cost effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

6.3.4 Scenario analyses for the treatment-experienced population

This is equivalent to the scenario analysis for the treatment-naïve population where GP costs are removed. The results of this scenario are given in Table 12.

Table 12. Exclusion of GP visit cost (Treatment-experienced)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Avelumab	£91,537	3.53	2.22	-	-	-	-
BSC	£7,413	0.43	0.32	£84,124	3.10	1.90	£44,330
Abbreviations in table: BSC. best supportive care; ICER, incremental cost effectiveness ratio; LY, life-year; QALYs, quality-adjusted life years.							

NHS England submission on the NICE appraisal of avelumab in the treatment of metastatic Merkel cell carcinoma

1. NHS England notes that the phase II study of avelumab in previously treated metastatic Merkel cell carcinoma was in patients of ECOG performance status 0 or 1 and 30% of patients had been previously treated with 2 chemotherapy regimens and 11% with 3. This is indicative of how selected a group of patients these are as many patients in England after chemotherapy are of poor performance status and rarely are they fit enough for 2nd line chemotherapy.
2. The avelumab study in previously treated patients had a minimum follow-up of 18 months but few progression-free patients are at risk beyond 20 months. Follow-up is therefore immature and NHS England notes that further data cuts/analyses are planned.
3. NHS England notes the analysis of response rates by PD-L1 status that is described in the SPC for previously treated patients and in which the response rate was recorded as 36% in the PD-L1 ≥1% positive group and 19% in the PD-L1 negative subgroup. As only 58 patient were in the PD-L1 positive group and 16 patients in the PD-L1 negative group, NHS England does not think that this analysis is robust enough on which to base any decision making as to benefit or otherwise in PD-L1 subgroups.
4. The company has used the wrong chemotherapy HRG code (SB12Z, 'simple parenteral' treatment) for the administration cost of avelumab and has used 2015-16 figures (£199). Avelumab requires a pre-medication to be administered 30-60 mins before the 60 minute infusion of avelumab, at least for the first 4 cycles. Even if the pre-medication is not necessary, hospital staff on chemotherapy units will be aware of the risk of infusion-related reactions even after the first 4 cycles and this mean that the administration of avelumab will not be regarded as 'simple' in the way that bolus chemotherapy is for example. This means that the code SB13Z should be used and the tariff for 2017-18 is £299.
5. NHS England notes that the company has instituted a maximum treatment duration of 5 years. As NICE knows, several other PD-L1 drugs have 2 year maximum treatment durations in use, particularly in lung cancer. In those diseases in which PD-L1 drugs have been used for the longest, there is an increasing perception amongst clinicians that very long treatment durations may not be necessary and may cause harm in view of the uncommon but potentially very serious immune-related toxicities that are being encountered with prolonged treatment durations.
6. NHS England regards the avelumab data in treatment-naïve patients as being extremely immature with only small numbers of patients having follow-up durations which exceed 3 months.
7. NHS England notes that avelumab in this indication has conditional approval by the EMA and thus carries a black inverted triangle. This conditional approval is as a consequence of the immaturity of the clinical data.

8. NHS England observes that the only patients in the avelumab studies in Merkel cell carcinoma were of performance status 0 or 1 and thus NICE conclusions of clinical and cost effectiveness are based on patients that are physically fit. If NICE recommends avelumab to the NHS for the treatment of metastatic Merkel cell carcinoma, NHS England would wish to commission its use in patients of performance status 0 or 1.

[redacted]

Chair of the NHS England Chemotherapy Clinical Reference Group and National Clinical Lead for the Cancer Drugs Fund

October 2017