NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Avelumab for treating metastatic merkel cell carcinoma [ID1102]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Company submission addendum in response to Appraisal Consultation Document**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Merck
   - NET Patient Foundation
   - Department of Health – no comment

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **ERG critique of company ACD response**

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

Avelumab for treating metastatic Merkel cell carcinoma

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient and professional consultee	NET Patient Foundation	Having Avelumab available through the CDF would be of great benefit to patients, our concern is that this has been given a 3 year review date, at which point even though NICE consider this a life extending end of life treatment with costs that are beneath the ICER there is a chance it could be removed.	Thank you for your comment. The recommendations have changed. Please see FAD section 1 for more details. In addition, the guidance will be reviewed when more JAVELIN data become available. Please see FAD sections 5 and 6.
2	Patient and professional consultee	NET Patient Foundation	We are concerned the uncertainties raised by NICE regarding further data to reduce uncertainties will not be met whilst the drug is on the CDF. The study performed is already the largest clinical trial in MCC and the data for avelumab as a second line treatment is already fairly mature.The concerns about uncertainties of patient numbers and comparators for second line treatments wont be resolved whilst it is on the CDF. As stated throughout, MCC is a rare cancer and within the patient group those suitable for Avelumab are going to be an even smaller number.	Thank you for your comment. The recommendations have changed. Please see FAD section 1. Second line and beyond treatments with avelumab are recommended for routine commissioning.
3	Company	Merck	**Previously-treated mMCC patients should be able to access avelumab through routine commissioning; the CDF will not reduce any of the remaining uncertainties, and no further datacuts of JAVELIN 200 are planned for this cohort.** Merck/Pfizer do not consider that the CDF will resolve the clinical uncertainties associated with second-line plus treatment as outlined in the ACD and addressed individually below: **Maturity of the data** The avelumab data for treatment-experienced metastatic MCC patients (Part A) is as mature as it will get. All patients have reached the primary endpoint, median survival has been reached and only 19 (22%) of patients are at risk of a PFS event. At the time of submission, 18-months follow-up date was provided for the full cohort of 88 treatment-experienced (2L+) patients from Part A of the JAVELIN Merkel 200 trial. Among the 88 patients treated with avelumab, 83%	Thank you for your comments. Second line and beyond treatments with avelumab are recommended for routine commissioning. Please see FAD section 1 for more details.

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			discontinued treatment; 47.7% (42/88) progressed and 11.4% (10/88) died. There are only 19 subjects remaining in the study from whom to expect additional data, 15 of which continued to receive treatment as of the March 2017 data-cut (see Table 14 in the NICE submission document). The 24th March data-cut already represents a mature data-set where median OS was reached (12.6 months) and shows a 12-month OS rate of 40%; this is more than double the median OS of 4.3-5.7 months expected with chemotherapy and greater than the 12-month OS rate of 0% from the start of second-line chemotherapy (Cowey 2017; Becker 2016; Iyer 2016). Since submission on the 1st August a further data cut was taken on 26th September, the interim findings show: [redacted] This data-cut is the last planned analyses with no further cuts expected for the 2.3 year duration in which avelumab would be in the CDF. The ERG's ICER for treatment-experienced patients is £37,629 and therefore already considered cost-effective. When revised to account for NICE's preferred assumptions this slightly increases the ICER to £37,846 per QALY gain but still well below the EoL willingness to pay threshold and therefore not an obvious CDF candidate. To strengthen the confidence in the treatment-experienced ICER some scenarios have been conducted to demonstrate how much better the comparator will need to be in order to make the ICER cost-ineffective (please see comment 3 below and section 1.2 of the addendum). This analysis shows that best supportive care would need to demonstrate on average a survival benefit of 12.6 months (at constant utility) which is more than double the mean OS benefit of 5.1 months projected in the model.	

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			Patient numbers JAVELIN Merkel 200 is the largest registrational trial in metastatic Merkel Cell Carcinoma (MCC) to date. Metastatic MCC is an ultra-rare neuroendrocrine skin cancer estimated to affect as little as 75 patients a year in England (across all lines of therapy). Due to the small patient numbers and the challenges in recruiting patients into a clinical trial, the single arm study design of the JAVELIN Merkel 200 trial allowed for the collection of a larger cohort of patient data than would otherwise have be obtained through randomised control trials (RCTs). While the small patient numbers and single-arm design present some limitations in the context of an HTA[1], these challenges are no different to those faced in the majority of assessments of ultra-rare conditions. Whilst some short term data collection of newly treated 2L+ avelumab patients may be possible in the CDF, the small numbers of patients overall and short term 'follow up' mean this will be of limited benefit. **Comparator data** JAVELIN Merkel 200 is a single arm study and therefore does not allow a traditional indirect treatment comparison to be conducted. The absence of direct comparative data is common among trials for ultra-orphan conditions due to the challenges in designing and recruiting patients to large RCTs. The true uncertainty lies in the comparator arm where there is a paucity of data available in the form of retrospective registry data and limited aggregate data. Merck took the most robust approach to generating comparator data by conducting observational studies (Becker 2016 and Cowey 2017). These were described in detail in section 4.9 in the original submission and accepted by the Committee as the most appropriate comparator data for the JAVELIN trial.	

[1] 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.

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			To address the inherent uncertainty in this appraisal, Merck KGaA/Pfizer have sought advice from a range of clinical and health economics experts[2], generated and undertaken robust analysis of comparator data. The options for formally comparing the comparator data with the JAVELIN trial were explored by economic experts and a naïve comparison was deemed appropriate as reported in Appendix 10 of the submission. To summarise, the analysis found that regardless of treatment received in the second-line plus setting, outcomes were uniformly poor. Furthermore, the analysis found that apart from line of treatment, 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. Finally, and more importantly, if avelumab for 2L+ were to enter the CDF, collection of comparator data would not be possible and this uncertainty would remain unaddressed. In conclusion, putting avelumab for the treatment of metastatic MCC in 2L+ into the CDF will provide no value from a data perspective. It will not address the uncertainty associated with the comparator arm and the issue of 'small' patient numbers which is inherent to rare diseases. The September 26 data is as mature as it will get and demonstrates survival projections in line with the economic model. This is the last planned analyses with no further cuts expected for the 2.3 year duration in which avelumab would be in the CDF. Finally, putting this cost-effective indication into the CDF will prevent access of the drug to patients in Wales and Northern Ireland who cannot benefit from the fund.	
4	Company	Merck	**The conclusion of cost-effectiveness in treatment-experienced patients is a robust one and only clinically implausible assumptions are likely to change it**	Thank you for your comments. Second line and beyond treatments with avelumab are recommended for routine commissioning. Please see FAD section 1 for more details.

[2] Validation is discussed in detail in Section 5.10; in summary: [redacted] advised on clinical assumptions and model inputs and a modelling steering committee comprising [redacted] advised on modelling methodology, in particular outcome extrapolation.

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			Section 3.25 of the ACD states that the key uncertainties have arisen due to the single-arm trial design of JAVELIN Merkel 200, small number of patients and the reliance on a naïve indirect comparison. Two of these uncertainties cannot be quantified through analysis of available data; these are: the single-arm trial design of JAVELIN Merkel 200 and the small number of patients, which are reflective of the ultra-rare condition for which the estimates are derived. However, the third uncertainty pertaining to the naïve indirect comparison can be explored further through additional analysis. In an appendix to this comment (see section 1.2 of addendum), we have provided an analysis which aims to address how good survival outcomes would need to be for treatment-experienced patients receiving BSC in order to produce an ICER such that avelumab would no longer be considered cost-effective. Available data in this patient population receiving chemotherapy[3] suggests that average survival is approximately 5-6 months, with clinical expert opinion suggesting an estimate of 5 months may even be overly optimistic. The outcome of the analysis demonstrates that average survival for patients treated with BSC would have to be more than double (i.e. in the region of 12 to 13 months) the currently estimated value to produce an ICER of £50,000 per QALY gained. Furthermore, among the 77 patients from which chemotherapy OS survival data is available, only three had an OS of at least 12 months. This highlights that although estimates of survival derived via a naïve indirect comparison are associated with uncertainty, the average survival in patients receiving BSC would have to be considerably greater than is currently evident in order to produce an ICER for avelumab that would no longer be considered cost effective. This is clinically implausible.	
5	Company	Merck	**Correction of an incorrect assumption about how Merck/Pfizer model comparator data for treatment-experienced patients** There is some confusion as to which comparator data for treatment-	Thank you for your comment. The FAD has been amended to reflect this. Please see FAD section 3.13 for more details.

[3] In the absence of data on BSC, chemotherapy data was used as a proxy for BSC.

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			experienced patients was used in the company's economic model. The ACD states "*the company used pooled data from study 100070-Obs001 (part A) and 6 additional studies to estimate progression-free and overall survival for chemotherapy*". In fact, the model only uses comparator data from the Merck/Pfizer observational studies and the use of the term "pooled" observational study refers to the pooling of both the EU 2L (Becker et al. 2016) and US 2L (Cowey 2017) data. Comparator data for treatment-naïve patients used the US Cowey 2017 study (the EU study did not collect data in treatment-naïve patients) and figure 51 in the company's submission should read "Cowey treatment-naïve parametric survival curves and Kaplan-Meir plots for OS" not "Pooled treatment-naïve parametric survival curves and Kaplan-Meir plots for OS"	
6	Company	Merck	**Correction to the apparent assumption by the ERG that BSC is the appropriate comparator for treatment-naïve patients; instead ICERs relating to chemotherapy are more appropriate (as concluded in the scope and acknowledged by the Committee in the ACD).** In Section 3.2 of the ACD, it is stated that the appropriate comparator for treatment-naïve mMCC is chemotherapy: *"The committee concluded that the appropriate comparator for first-line treatment is chemotherapy"* However, elsewhere in the ACD, frequent reference is made to the base-case comparator for treatment-naïve patients being BSC (Sections 3.18 and 3.25). It is important to acknowledge that within UK clinical practice, the most relevant comparator for consideration is chemotherapy. As such, the ACD should be updated when discussing ICERs for the treatment-naïve population to use the relevant comparator (chemotherapy). It must also be noted, that there is no literature which describes the outcomes of treatment-experienced or treatment-naïve metastatic MCC patients who are treated with BSC. In the absence of this data, the company used chemotherapy as a proxy for BSC. While in the second line setting survival outcomes are broadly the same regardless of treatment given, the same is not true in the first-line setting. As such, this is a very conservative assumption because chemotherapy is considered to have a beneficial effect	Thank you for your comment. The FAD has been updated to reflect this. Please see FAD sections 3.2 and 3.17 for more details.

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			on patient outcomes in the treatment-naïve setting.	
7	Company	Merck	**Provision to the Committee of the revised ERG's ICERs for treatment-naïve patients, fully incorporating Committee discussion and correcting minor model errors** In the ACD, the Committee's preferred base-case regarding the cost-effectiveness of avelumab in the treatment-naïve population contains a number of features that have not actively been applied within the ERG's base-case cost-effectiveness results, as well a correction of a model error not captured within the ERG's analysis. These features are: • **Updated administration cost** As per explanation for the treatment-experienced population (please see comment 1, above) • **Proportion of patients continuing treatment beyond 2 years** As per explanation for the treatment-experienced population (please see comment 1, above). In the base-case projection of time on treatment for treatment-naïve patients, this was over-estimated at approximately 8.5% at 2 years. • **Model error regarding application of background mortality** Following the Appraisal Committee Meeting held on Thursday 2nd November 2017, a model error was noted regarding the application of background mortality for patients treated with chemotherapy or BSC: o In the patient flow sheets of the cost-utility model, a very small proportion of patients treated with chemotherapy or BSC were predicted to live for the duration of the modelled time horizon (approximately 0.34%), whereas patients treated with avelumab were assumed to all have died. o This is because of a modelling error, where the application of background mortality was erroneously omitted from the calculations concerning chemotherapy and BSC. This error featured in the submitted model, as well as the version of the model used by the ERG- which was not picked up during their review.	Thank you for your comments. The FAD has been updated to include the company's amendments to the ERG's revised base-case. Please see FAD section 3.17 for more details.

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			Therefore, we have updated the cost-effectiveness model to consider the *"true"* base-case preferences of the committee, and corrected for this model error. The base-case cost-effectiveness results including costs, QALYs and LYs are presented in an appendix to this response- see section 2.2 of the addendum. • **Original ICER:** £72,033 (avelumab versus chemotherapy) • **Revised ICER:** £67,293 (avelumab versus chemotherapy) These model changes demonstrate notably different cost-effectiveness results for the treatment-naïve cohort of patients, hence it is important that the Committee have access to the exact numbers from which decision-making can be based. Reference to the most appropriate comparator for decision-making is also an important aspect within the ACD, as the current text within the ACD may be potentially misleading.	
8	Company	Merck	**ICERs from the ERG's economic model for treatment-naïve patients are implausible due to their perverse projections of benefit for this patient cohort** The ERG's preferred extrapolations of OS, PFS and ToT are each associated with limitations, primarily relating to the use of data from JAVELIN Merkel 200: Part B alone in their derivation. In the manufacturer's response to the ERG clarification questions, the immaturity of the data in this patient population was discussed along with reference to the small patient sample size (n=39). It was explained that fitting parametric curves to data from JAVELIN Merkel 200 Part B would not form an accurate basis from which long-term extrapolation may be considered to inform the cost-effectiveness analysis. The supporting addendum outlines the main issues identified in the ERG's treatment-naïve model and in particular their survival projections which in turn has resulted in implausible ICERs. In Section 2.3 of the addendum to these comments, we explore the underlying hazard functions for the OS extrapolations in the ERG's treatment-naïve and treatment-experienced models and find that unfortunately the ERG's model projects that the hazard of death for the treatment-naïve population is consistently greater than the hazard of death for the treatment-experienced (2L+) population beyond 1.74 years, i.e. that 1L patients do worse with	Thank you for your comments. The FAD has been updated to include the company's assumptions for OS extrapolation. Please see FAD section 3.17 for more details.

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			avelumab than 2L+ patients (see figure 8 in supporting document). A further analysis was conducted looking at the subset of patients in the JAVELIN Merkel 200: Part A study who had only received one line of prior therapy (i.e. second-line only patients). The repeated analysis showed that the hazard of death for treatment-naïve patients projected in the ERG's model consistently exceeded that of second-line only patients after 1.09 years (see Figure 10 in supporting document). Clinical opinion and indeed the OS trend observed between 2L only and 2L+ in JAVELIN Merkel 200 Part A shows that greater OS benefits are realised the earlier the treatment is used in the pathway. Our analysis therefore suggests that the ERG's base case projection for OS in treatment-nave patients lacks clinically validity, given that patients who are treatment-naïve are expected to derive outcomes at least as good as those who are treatment-experienced, if not better. For time on treatment, the lack of long-term follow up with a large number of patients at risk may lead to parametric analysis "over-fitting" the tail of the Kaplan-Meier function. The ERG's base-case extrapolation using data for treatment-naïve patients from JAVELIN Merkel 200 Part B predicts that 8.5% of patients are still on treatment at 2 years. This is greater than clinical expectation, the committees preferred assumptions that 5% of patients are still receiving treatment beyond 2 years and the companies base-case extrapolation of 5.4%. Within the appendix, an example is presented where the same analysis (as the ERG's) is repeated but only using data up until 3 months which represents the majority of patients in this cohort (n=29) (all remaining patients, n=14 were censored at this time). The resultant extrapolation shows a lower estimate of time on treatment, more aligned with clinical expectation (though clearly based on shorter overall follow up).	
9	Company	Merck	**Provision of a clinically plausible maximum/upper bound ICER for treatment-naïve patients; still conservative but still consistent with evidence and clinical opinion** Based on the limitations of the current ERG treatment-naïve model (outlined in comment 6 above and the findings from the analysis in section 2.3 of the addendum), the following amends are proposed; the ERG's preferred	Thank you for your comments. The committee considered the company's new base case and concluded that both the company's new base case and the ERG's revised base case are plausible. Please see FAD sections 3.17 and 3.22 for more details.

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			extrapolation of treatment-naïve data is the basis, but beyond the time points where their model projected patients would do ***worse*** than previously-treated patients, we assume instead the actual hazards of death in the treatment-experienced (2L+) and second-line only populations in two separate analyses. Effectively this model uses observed 1L data and then assumes that unobserved benefits will be no better than those seen in the 2L+ and 2L populations (separately). (1) Using the treatment-experienced (2L+) hazards from 1.74 years (the point at which the hazard of death for 1L is greater than 2L+) gives an ICER of £58,315 for avelumab versus chemotherapy. (2) Using the second-line only hazards from 1.09 years gives an ICER of £52,506 for avelumab versus chemotherapy. Both scenarios use the ERG's preferred extrapolation of the JAVELIN Merkel Part B time on treatment data; although it should be recognised that this is highly conservative and is predicting that 8.5% of patients are still on treatment at 2 years. We propose that the clinically plausible maximum ICER cannot be the one suggested by the ERG (given the limitations in their model) and is more reasonably estimated with the following parameters: • Chemotherapy as the appropriate comparator • Updated cost of treatment administration • 5% of patients continuing treatment beyond 2 years, and all patients assumed to have stopped treatment by 5 years • Correction of model error in comparator data regarding application of background mortality • Use of hazards derived via the base-case extrapolation for treatment-experienced (2L+) beyond the time of 1.74 years, such that the hazard of death for treatment-naïve patients is at most equal to the hazard of death for treatment-experienced patients • Continuing to use ERG's time on treatment projection (based on data from treatment-naïve JAVELIN Merkel 200 Part B) This analysis yields an ICER of avelumab versus chemotherapy for treatment-naïve patients of £58,315 per QALY gained. The use of treatment-experienced	

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			(2L+) hazards over the use of second-line only hazards was selected as this scenario utilizes all available data available (i.e. the whole population of the JAVELIN Merkel 200: Part A trial [n=88]), and offers the most conservative estimate of survival for treatment-naïve patients. It represents the plausible *upper bound* for cost-effectiveness in treatment-naïve patients. In conclusion, the most plausible ICER for treatment-naïve patients is likely to lie between £48,148 per QALY gained (per the original base-case) and £58,315 per QALY gained (per this revised upper bound) which conservatory assumes that in the long term the hazards of OS or PFS event are no better than 2L+.	
10	Web comment	NHS professional	The response rates appear to be higher first line which makes the likelihood of this drug being more clinically and cost effective first line the most likely outcome.	Thank you for your comment.
11	Web comment	NHS professional	CC is an aggressive cancer with a high disease mortality rate. Cytotoxic chemotherapy offers short lived responses that are not durable. There is a strong radionale for using immunotherapy in MCC. There is a high mutational rate leading to neoantigen formation in addition to the exhaustion of TILS that may be reversible using checkpoint inhibition. Although the part A Javelin Merkel 200 study enrolled 88 patients with previously treated MCC, there were also 39 treatment naÃ¯ve patients with MCC with responses. The data support the use of Avelumab in the second line setting. It is thought that earlier use of Avelumab in the first line setting may demonstrate slightly better response rates compared with chemotherapy. We have noted that earlier use of checkpoint inhibition in other tumour types may be more beneficial and it is hoped that this may also hold true for MCC. Approval of Avelumab in the first line therapy will allow us to prospectively evaluate the data in this rare group of patients with significant unmet need.	Thank you for your comments. The recommendations have changed. Please see FAD section 1. Second line and beyond treatments with avelumab are recommended for routine commissioning, and first-line treatment is recommended for use within the Cancer Drug Fund.
12	Commentator	Department of Health & Social Care	“No comment” response.	Thank you for your response.

Merck Response to:

National Institute for Health and Care Excellence

Appraisal Consultation Document – Avelumab for treating metastatic Merkel cell carcinoma [ID1102]

December 2017

Executive summary

We thank NICE and the Committee for the opportunity to review the ACD and to provide further analyses to allow for a comprehensive consideration of the most plausible ICERs in the treatment-experienced and treatment-naïve mMCC patient populations. This document contains additional analyses to supplement our full response (the comments form and this addendum), all summarised here.

2L+ / treatment-experienced patients

Merck/Pfizer propose that treatment-experienced patients should be funded through routine commissioning (not through the CDF) for the following reasons:

- Part A of the JAVELIN Merkel 200 trial (i.e. treatment-experienced patients) has already met its primary endpoint; no further data will be available from this cohort during the period for which it would be funded in the CDF
- The dataset can be considered mature (more mature in fact than other datasets which have led to routine commissioning decisions, e.g. nivolumab in advanced melanoma [TA384] and pembrolizumab in advanced melanoma [TA366 and TA357]); median PFS and OS have been reached and 83% of patients have discontinued treatment. There are only 19 subjects remaining in the study (15 of which are still receiving treatment) from whom to expect additional data beyond that already presented
- Uncertainty associated with the comparator treatment cannot be reduced by any length of time in the CDF and is an inevitability of analyses using historic controls (necessary because of the single arm trial design in an ultra-rare condition)
- In the treatment-experienced cohort, avelumab is cost-effective; the Committee, ERG and Merck agree that the most plausible ICER estimate is well below the cost-effectiveness threshold for end of life medicines

1L / treatment-naïve patients

We agree with the Committee that maturing data from treatment naïve/Part B patients would reduce uncertainty in this cohort. After the first ACM, the Committee were minded to accept that the upper bound of the plausible ICER for avelumab in treatment naïve patients versus BSC could be close to the ERG's revised ICER of £75,526/QALY. Merck/Pfizer wish to highlight to the

Committee key logical and clinical limitations of the ERG's economic model which underpins this estimate and render it implausible:

1. The ERG's model projections do not account for the expected immune-oncology (IO) plateau which has been demonstrated with longer follow up in all IOs including avelumab's treatment experienced data. This results in poorer survival estimates in treatment-naïve patients than has been accepted for treatment-experienced patients; contrary to evidence, logic and clinical opinion that IO's used early on in the treatment pathway will yield better survival outcomes The ERG's ICER is high because of this clinically unreasonably and unjustifiably conservative assumption.
2. The ICER mentioned in the ACD response is versus BSC when the appropriate comparator in the treatment-naïve setting – as identified in the scope for this appraisal and highlighted in the ACD – is chemotherapy.

Merck provides a revised maximum/upper bound estimate of the cost-effectiveness in treatment-naïve patients. This estimate is still based on a conservative, yet in this case clinically plausible, assumption that beyond the observed data, projections of benefit in treatment-naïve patients *never exceed* those in treatment-experienced patients, i.e. avelumab is only as good in treatment-naïve patients as it is in treatment-experienced patients (2L+), never better. Furthermore, this estimate takes into account the Committee's preferred treatment duration assumption (95% of avelumab patients stop treatment by 2 years) and an amendment to the administration costs following Peter Clark's identification of an underestimate. The result of this analysis suggest that the plausible *upper bound* for cost-effectiveness in treatment-naïve patients is £58,315 versus chemotherapy.

A minor error in Merck's original model where background mortality was erroneously omitted from the calculations concerning comparator data has also been corrected and is reflected in the estimate above.

Proposed CDF agreement

Merck/Pfizer are currently in late-stage discussions with NHSE about a commercial arrangement which will ensure that the manufacturer (not the CDF) is underwriting the risk associated with the uncertainty in the 1L data whilst the JAVELIN Merkel 200 trial is maturing. We are proposing to provide avelumab to the NHSE/CDF at a lower vial price for treatment-naïve patients, one which renders the most plausible ICER < £50,000/QALY for the duration of the CDF term. Conceptually, the agreement is satisfactory to all parties and the exact details and numbers depend on the outcome of discussions at the second Appraisal Committee Meeting.

Dear Joanna,

We would like to thank NICE for granting Merck/Pfizer the opportunity to comment on, and provide additional analyses relating to, the Appraisal Consultation Document (ACD) published on 27 November 2017 for the ongoing single technology appraisal (STA) for avelumab for treating metastatic Merkel cell carcinoma (mMCC) [ID1102]. The ACD states that the appraisal committee are interested in receiving comments regarding the following:

- Has all of the relevant evidence been taken into account?

The Committee is yet to see cost-effectiveness results for its preferred analysis (discussed in Section 3.20 of the ACD). Here in this response, the cost-effectiveness results for the Committee's preferred base-case analysis are explicitly provided.

Most importantly, we do not believe that the Committee's preferred base-case analysis for patients with treatment-naïve mMCC is plausible because the underlying economic model predicts that avelumab treatment will be worse in treatment-naïve patients than in treatment-experienced patients; this is not clinically plausible and is contradictory to clinical opinion, avelumab evidence and evidence from all other IOs. As such, Merck/Pfizer have revised the ERG's treatment-naïve patient base case, providing what we believe to be the most conservative plausible analysis – one which utilises treatment-naïve data for as long as possible (the observed period) and from then on assumes that benefits will be no better than (i.e. only as good as) seen in treatment-experienced patients.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries of the clinical and cost-effectiveness of avelumab for treating mMCC are primarily factually accurate. However, there are some aspects of the ACD which may be hindered by misinterpretations and/or misunderstandings relating to the available data, which we aim to address in this response.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

We do not consider the recommendations made at present to be suitable for guidance to the NHS, specifically in relation to the Committee's conclusion that it could not recommend avelumab second-line in routine commissioning. The Committee are concerned about the uncertainties in the clinical data, the small number of patients and the limitations of the naïve comparison, and about the reliability of the long-term modelling results. There are several reasons why uncertainties in the previously-treated cohort will not be reduced by any period of time in the CDF. We present these in the ACD response form, along with further analyses in this addendum to allow for discussion about the true level of uncertainty.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

We have no concerns relating to the unlawful discrimination against any group of patients.

The remainder of this addendum includes the following key components:

- Section 1: Comments regarding the treatment-experienced mMCC population

  Section 1.1 [COMMENT 1 in ACD comments table]: Committee-preferred base-case cost-effectiveness analysis results (as per ACD)

  Section 1.2 [COMMENT 3 in ACD comments table]: Quantification of the uncertainty associated with the clinical evidence base, for treatment-experienced mMCC

- Section 2: Comments regarding the treatment-naïve mMCC population

  Section 2.1: Committee-preferred base-case cost-effectiveness analysis results (as per ACD) [COMMENT 6 in ACD comments table]

  Section 2.2: Issues with extrapolation of JAVELIN Merkel 200: Part B data [COMMENT 7in ACD comments table]

  Section 2.3: Top line 1L results from the September 26 data cut of JAVELIN Merkel 200- Part B

  Section 2.4: Revised base-case cost-effectiveness analysis results (based on contents of this response) [COMMENT 8 in ACD comments table]

Yours sincerely,
Amerah Amin
Health Economist
Merck

1 Treatment-experienced mMCC

1.1 Committee-preferred base case analysis (as per ACD)

Corresponding to comment 1 in the ACD comments table

In the ACD, the Committee's preferred base-case contains a number of features that have not actively been shown within the ERG's base-case cost-effectiveness results. The nature of these revisions have been addressed in comment 1 of the ACD comments table document and in summary include an update of the administration costs of avelumab, implementation of the Committee's preferred assumption about the proportion of patients continuing treatment beyond 2 years and correction of a small modelling error relating to the application of background mortality in the comparator arm.

Updated base-case results are provided for treatment-experienced patients in Table 1.

Table 1: Revised base-case model results as per NICE preferred assumptions outlined in the ACD: treatment-experienced patients

Treatment	Total			Incremental (avelumab vs.)			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
ERG revised base-case (as per ACD)							
Avelumab	£78,822	3.53	2.22				
BSC	£7,413	0.43	0.32	£71,409	3.10	1.90	£37,629
Updated ERG revised base-case (as per committee preferences)							
Avelumab	£79,233	3.53	2.22				
BSC	£7,413	0.43	0.32	£71,821	3.10	1.90	£37,846

ERG revised base-case (as per ACD): ICER vs. chemotherapy is £36,246
Updated ERG revised base-case (as per committee preferences): ICER vs. chemotherapy is £36,255

Key: ACD, Appraisal Consultation Document; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

1.2 Quantification of uncertainty through updated analyses (treatment-experienced)

Corresponding to comment 3 in ACD comments form

JAVELIN Merkel 200: Part A was an uncontrolled clinical trial of avelumab in mMCC. This design was specifically chosen in acknowledgement of the issues associated with recruiting patients with an ultra-orphan disease, such as mMCC. Merck/Pfizer conducted a retrospective observational study to collect data in clinically-matched patients receiving chemotherapy in order to elicit a reasonable comparison to the UK standard of care (typically best supportive care [BSC]) and its associated outcomes.

As data in this patient population are limited, a variety of analyses were undertaken in an attempt to quantify the uncertainty associated with outcomes

in patients treated with chemotherapy, including a naïve comparison to the observational data, a propensity-matched analysis and a Weibull regression. The latter of these analyses was used to inform the base-case cost-effectiveness estimates.

While the Weibull regression was preferred, there is still clear uncertainty in the estimation of survival for treatment-experienced patients receiving BSC. In the absence of data on BSC, chemotherapy data was used as a proxy for BSC. Literature suggests median survival for patients receiving chemotherapy/BSC would be between 4 and 6 months.[1-4] Clinical expert opinion suggested that a median survival of 5 months, with 10% of patients surviving 6 to 7 months, is optimistic for a typical second-line patient.[5]

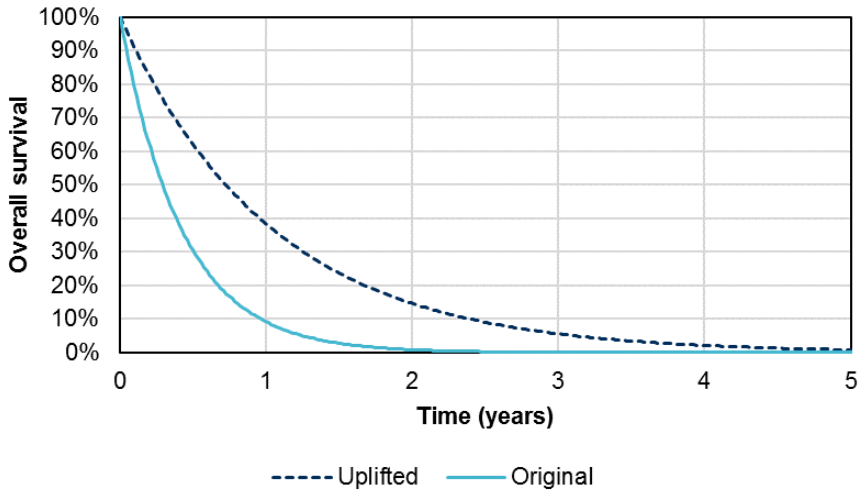
With this in mind, an analysis was performed to establish how good survival would need to be for patients treated with BSC in order for avelumab to no longer be cost-effective in treatment-experienced patients (i.e. to produce an ICER greater than or equal to £50,000 per QALY gained; given that avelumab meets the-end-of life criteria, as confirmed in Section 3.24 of the ACD).

In this analysis, a hazard ratio was applied to the base-case OS curve (based on the Weibull regression supplied in response to the clarification questions) as a proxy for the improvement that would need to be seen in survival for BSC patients. The Solver functionality integrated within Excel was used to derive the HR required to apply to the OS curve such that the ICER produced for avelumab versus BSC was £50,000 per QALY gained.

The outcome of this analysis yielded a HR of approximately 0.4011 required to achieve an ICER of £50,000 per QALY gained. This HR shifts median OS for BSC patients from approximately 3.5 months to approximately 8.6 months; and shifts mean OS from approximately 5.1 months to 12.6 months. Therefore, average survival would need to more than double in order for the ICER obtained to be £50,000.

A plot of the difference in the curves is presented in Figure 1, with the corresponding headline model results presented in Table 2.

Figure 1: Extrapolation results – Improvement in OS for comparator arm required to produce an ICER of £50,000 per QALY gained (treatment-experienced patients)



Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year.

Table 2: Scenario model results – Improvement in OS for comparator arm required to produce an ICER of £50,000 per QALY gained (treatment-experienced patients)

Treatment	Total			Incremental (avelumab vs.)			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
ERG revised base-case (as per ACD)							
Avelumab	£78,822	3.53	2.22				
BSC	£7,413	0.43	0.32	£71,409	3.10	1.90	£37,629
Updated ERG revised base-case (as per committee preferences)							
Avelumab	£79,233	3.53	2.22				
BSC	£7,413	0.43	0.32	£71,821	3.10	1.90	£37,846
Scenario: improvement in BSC OS to obtain an ICER of £50,000 per QALY gained							
Avelumab	£79,233	3.53	2.22				
BSC	£7,642	1.05	0.79	£71,591	2.48	1.43	£50,000

Key: ACD, Appraisal Consultation Document; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

The outcome of this analysis demonstrates that the OS for treatment-experienced patients receiving BSC would have to be considerably greater than available data and clinical expert opinion suggest in order to produce an ICER that would no longer be within the range that could be considered cost effective.

Average survival for patients treated with BSC (expected to be in the region of 5 to 6 months) would have to more than double (i.e. be in the region of 12 to 13 months) in order for the ICER of avelumab versus BSC to no longer be considered cost-effective. Furthermore, of the 77 patients from which data for OS are available, only three had an OS of at least 12 months.

2 Treatment-naïve mMCC

2.1 Committee-preferred base case analysis (as per ACD)

Corresponding to comment 6 in the ACD comments table

In the ACD, the Committee's preferred base-case contains a number of features that have not actively been shown within the base-case cost-effectiveness results, as well a correction of a model error not captured within the ERG's analysis. The nature of these revisions are discussed in comment 6 of the ACD comments form and in summary include updated administration costs, apply the Committee's preferred treatment duration assumption and correct a modelling error related to the application of background mortality for chemotherapy and BSC.

It is important to acknowledge that within UK clinical practice, the most relevant comparator for consideration is chemotherapy. Furthermore, as stated in section 3.2 of the ACD "The committee concluded that the appropriate comparator for first-line treatment is chemotherapy". However, elsewhere in the ACD, frequent reference is made to the base-case comparator for treatment-naïve patients being BSC (Sections 3.18 and 3.25). As such, the ACD should be updated when discussing ICERs for the treatment-naïve population to use the relevant comparator (chemotherapy). The results below are therefore presented for avelumab versus chemotherapy.

Updated base-case results are provided in Table 3.

Table 3: Revised base-case model results – treatment-naïve patients

Treatment	Total			Incremental (avelumab vs.)			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
ERG revised base-case (as per ACD)							
Avelumab	£102,812	4.16	2.65				
Chemotherapy	£10,608	2.02	1.37	£92,204	2.14	1.28	£72,033
Updated ERG revised base-case (as per committee preferences)							
Avelumab	£98,863	4.16	2.65				
Chemotherapy	£11,116	1.94	1.34	£87,747	2.22	1.30	£67,293

ERG revised base-case (as per ACD): ICER vs. BSC is £75,526
Updated ERG revised base-case (as per committee preferences): ICER vs BSC is £71,053

Key: ACD, Appraisal Consultation Document; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

2.2 Issues with extrapolation of data from JAVELIN Merkel 200: Part B

Corresponding to comment 7 in the ACD comments table

In the manufacturer's response to the clarification questions, the immaturity of the data in this patient population was discussed (maximum follow-up of approximately 11 months, minimum follow-up of 3 months), along with reference to the small sample size (n=39).

In the summary of the analysis presented, we explained that fitting parametric curves to data from JAVELIN Merkel 200: Part B is associated with numerous caveats and limitations. Therefore, the data were not considered to represent an accurate basis from which long-term extrapolation may be considered to inform the cost-effectiveness analysis. We undertook an analysis of the ERG's projected hazards of death in treatment-naïve patients, described below.

Comparison of hazards of death: treatment-naïve and treatment-experienced, second line plus (2L+)

To illustrate some of the issues with extrapolating such short-term data, the hazard of death for the ERG's preferred base-case OS curves (for both treatment-experienced and treatment-naïve patients) were calculated using the formula shown in Equation 1.

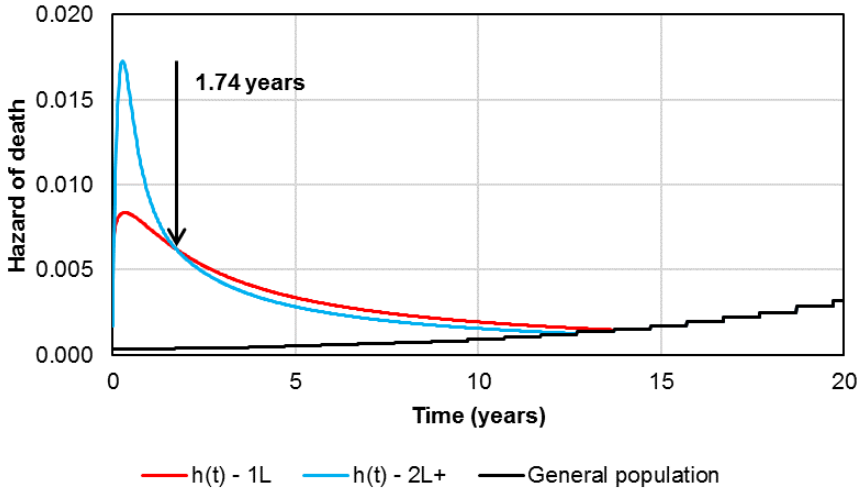
Equation 1: Estimated hazard function formula

$$\hat{h}(t) \cong 1 - \left(\frac{\hat{S}(t+1)}{\hat{S}(t)}\right)$$

Key: $\hat{h}(t)$, estimated hazard function at time t; $\hat{S}(t)$, estimated survivor function at time t.
Note: Here, t refers to the cycles used in the cost-effectiveness model (1 week).

A plot of this function over the range of time $t \in [0,20]$ years is shown in Figure 2.

Figure 2: Estimated hazard function for treatment-naïve and treatment-experienced ERG-base case projections (for avelumab)



Key: 1L, treatment-naïve; 2L+, treatment-experienced; ERG, Evidence Review Group; h(t); estimated hazard function at time t.

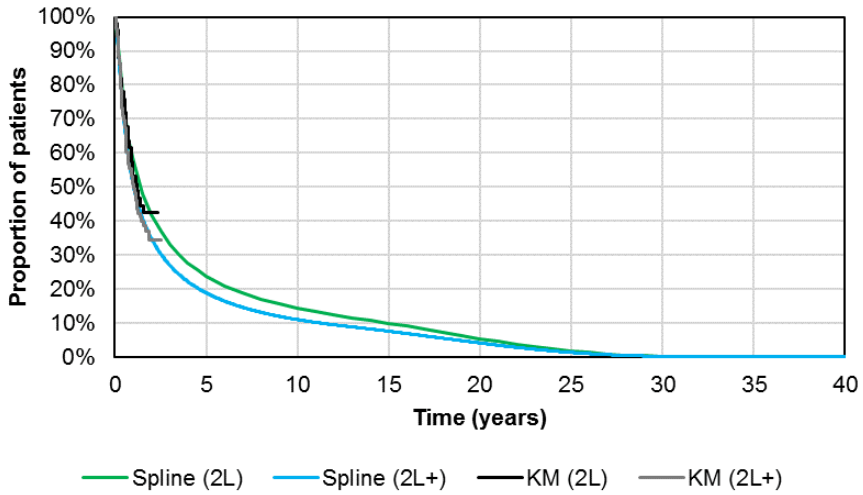
Figure 2 demonstrates that beyond a time of 1.74 years, the hazard of death for treatment-naïve patients is consistently predicted to be greater than the hazard of death for treatment-experienced patients (shown by the lines in the plot crossing at this time).

Comparison of hazards of death: treatment-naïve and treatment-experienced, second-line only (2L)

To further illustrate this issue, an additional analysis looking at only second-line patients was undertaken to compare the predicted hazards over time, and to illustrate the expectation of improved outcomes for patients who are less heavily pre-treated. Of the total cohort of patients in JAVELIN Merkel 200: Part A (n=88), 52 patients had previously received one prior systemic anticancer treatment. The spline-based models assessed for the entire cohort from JAVELIN Merkel 200: Part A were re-fitted, and the same base-case choice of curve (the 1-knot odds-based spline model) was selected based on Akaike and Bayesian Information Criteria (AIC and BIC, respectively).

An overview of the Kaplan-Meier curves for second-line patients and all treatment-experienced patients are presented in Figure 3, alongside the 1-knot odds-based spline extrapolations. While the ability to compare these curves is limited (given that one is a subgroup of the other), the second-line curve demonstrates the expected directional effect of removing patients with a greater number of previous treatment lines (i.e. removing later-line patients results in an expected improvement in OS).

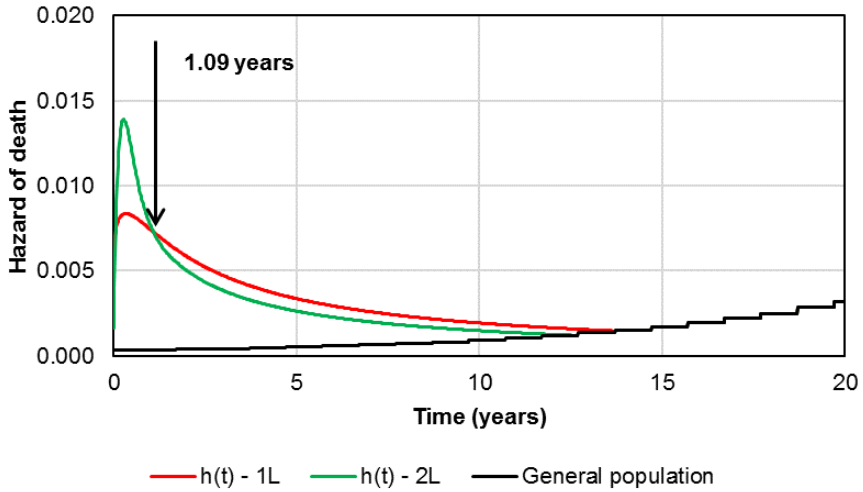
Figure 3: Kaplan-Meier and extrapolation for second-line patients (subset of treatment-experienced) versus all treatment-experienced patients (for avelumab)



Key: 2L, second-line only patients (subset of treatment-experienced); 2L+, treatment-experienced; KM, Kaplan-Meier.

A plot of the estimated hazard function for the second-line patients versus treatment-naïve patients over the range of time $t \in [0,20]$ years is shown in Figure 4.

Figure 4: Estimated hazard function for treatment-naïve and second-line (subset of treatment-experienced) ERG-base case projections (for avelumab)



Key: 1L, treatment-naïve; 2L, second-line only patients (subset of treatment-experienced); ERG, Evidence Review Group; h(t); estimated hazard function at time t.

Figure 4 demonstrates that beyond a shorter time of 1.09 years, the hazard of death for treatment-naïve patients is consistently predicted to be greater than the hazard of death for second-line patients (shown by the lines in the plot

crossing at this time). This again demonstrates that the ERG's long-term predictions are implausible, at least beyond 1.09 years.

Extrapolation of time on treatment

In the manufacturer's submission, approximately two-thirds of patients were assumed to discontinue treatment at 2 years. This was based on clinical expert opinion that at 2 years, the majority of patients will have discontinued treatment and only a small proportion would continue thereafter.

The ERG's base-case extrapolation using data for treatment-naïve patients from JAVELIN Merkel 200: Part B predicts 8.5% of patients to still be on treatment at 2 years. Conversely, the company's base-case extrapolation for treatment-experienced patients from JAVELIN Merkel 200: Part A predicts 5.4% of patients would still be on treatment at 2 years. This is presented in Figure 5.

Figure 5: Base-case extrapolations for ToT (treatment-naïve and treatment-experienced patients)

Key: 1L, treatment-naïve; 2L+, treatment-experienced; KM, Kaplan-Meier; ToT, time on treatment.

These extrapolations were revised in accordance with the anticipation of approximately 5% of patients remaining on treatment at 2 years (as discussed in Section 2.1), shown in Figure 6.

Figure 6: Revised base-case extrapolations for ToT (treatment-naïve and treatment-experienced patients; 5% on treatment at 2 years)

Key: 1L, treatment-naïve; 2L+, treatment-experienced; KM, Kaplan-Meier; ToT, time on treatment.

The extrapolation of ToT based on data from JAVELIN Merkel 200: Part B is based on a small number of patients still at risk, and is therefore prone to over-fitting to the tail of the curve. For illustrative purposes, the numbers at risk at 3-monthly intervals are provided alongside the base-case extrapolation and Kaplan-Meier curve in Figure 7.

Figure 7: ToT over period of observed data (treatment-naïve)

Key: 1L, treatment-naïve; KM, Kaplan-Meier; ToT, time on treatment.

In order to prevent the curve over fitting, the base-case extrapolation was re-fitted to the observed ToT data with data censored at 3 months (i.e. ToT values greater than 3 months were assumed to be a censor point at 3 months). A plot of this curve is provided in Figure 8.

Figure 8: Base-case extrapolation for ToT over two years versus extrapolation based on 3 months of follow up data only (treatment-naïve)

Key: 1L, treatment-naïve; 3mo, 3 months; KM, Kaplan-Meier; ToT, time on treatment.

An extrapolation based on 3-months of follow-up data also has numerous limitations and associated caveats. However, the analysis illustrates that the current projection of ToT for treatment-naïve patients may over-predict ToT during the period between 3 and 24 months.

2.3 JAVELIN Merkel Part B top line results from the September 26 data cut

The new data cut further supports the company's view that treatment outcomes in 1L metastatic MCC are in line with or even superior to outcomes seen in 2L+ patients. The data is showing the following:

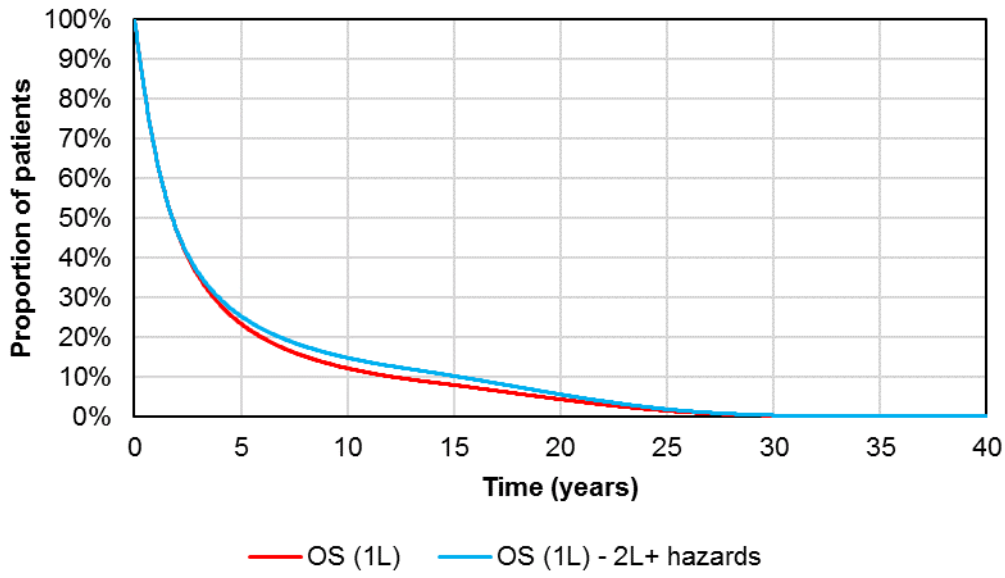
2.4 Revised cost-effectiveness analysis results using appropriate hazards

Corresponding to comment 8 in the ACD comments form

To address this issue with the underlying hazard function of the extrapolation methods, the hazard of an OS or PFS event from the ERG's preferred extrapolation was capped at the point at which it becomes implausible (1.74 years) by the corresponding hazard of OS or PFS event for the treatment-experienced (2L+) cohort of patients. We consider that this continues to be a conservative assumption, as the hazard of an event for treatment-naïve patients is expected to be at most the same as the hazard of an event for treatment-experienced patients, and we expect it to be lower.

The resultant survival curve from this analysis is presented in Figure 9.

Figure 9: Amended OS curve for treatment-naïve patients (using hazards from treatment-experienced patients, for avelumab)

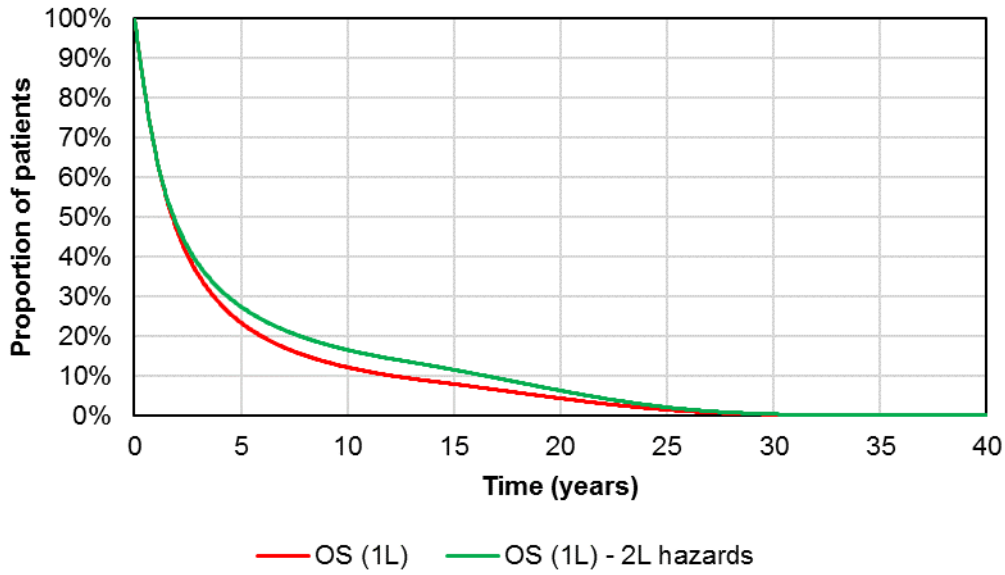


Key: 1L, treatment-naïve; 2L+, treatment-experienced; OS, overall survival.

A scenario analysis was also conducted using the hazards for the 2L-only cohort of patients (i.e. beyond 1.09 years, the hazard of death was taken from the 2L-only extrapolation). It should be noted that this is also a conservative assumption, as the hazard of an event for treatment-naïve patients is expected to be at most the same as the hazard of an event for second-line patients, though it may actually be lower.

The resultant survival curve from this analysis is presented in Figure 10.

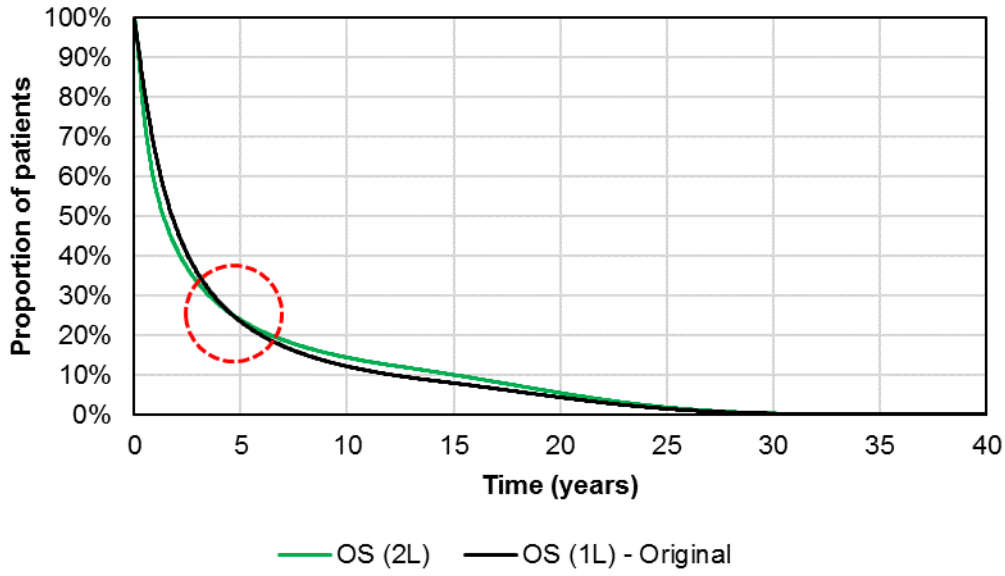
Figure 10: Scenario: amended OS curve for treatment-naïve patients (using hazards from second-line patients, for avelumab)



Key: 1L, treatment-naïve; 2L, second-line; OS, overall survival.

The predicted-long term survival estimates demonstrate face validity and are aligned with clinical expectation. The OS extrapolations for treatment-naïve and second-line patients no longer cross, as was the case for the ERG's base-case extrapolation (shown in Figure 11).

Figure 11: ERG base-case OS curve for treatment-naïve patients versus OS curve for second-line patients (for avelumab)



Key: 1L, treatment-naïve; 2L, second- line only patients (subset of treatment-experienced); OS, overall survival.

Furthermore, the 5-year OS of approximately 25.3% to 27.5% (when using either treatment-experienced 2L+ or second-line only hazards) is similar to the manufacture's submitted base-case projection of approximately 26.3% (using a clinically-validated HR of 0.8 versus the treatment-experienced extrapolation).

The associated cost-effectiveness results from the model when using appropriate hazards are presented in Table 4.

Table 4: Revised base-case model results– treatment-naïve patients

Treatment	Total			Incremental (avelumab vs.)			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
1: ERG revised upper bound ICERs (as per ACD)							
Avelumab	£102,812	4.16	2.65				
Chemotherapy	£10,608	2.02	1.37	£92,204	2.14	1.28	£72,033
2: Updated ERG revised upper bound ICERs (fully incorporating Committee preferences)							
Avelumab	£98,863	4.16	2.65				
Chemotherapy	£11,116	1.94	1.34	£87,747	2.22	1.30	£67,293
3: #2 + treatment-experienced hazards applied beyond 1.74 years							
Avelumab	£99,610	4.58	2.86				
Chemotherapy	£11,116	1.94	1.34	£88,494	2.64	1.52	£58,315
4: #2 + second-line hazards applied beyond 1.09 years							
Avelumab	£99,900	4.89	3.04				
Chemotherapy	£11,116	1.94	1.34	£88,784	2.96	1.69	£52,506

1: ERG revised upper bound ICERs (as per ACD): ICER vs. BSC is £75,526
2: Updated ERG revised upper bound ICERs (fully incorporating Committee preferences): ICER vs. BSC is £71,053
3: #2 + treatment-experienced hazards applied beyond 1.74 years: ICER vs. BSC is £61,455
4: #2 + second-line hazards applied beyond 1.09 years: ICER vs. BSC is £55,272

Key: ACD, Appraisal Consultation Document; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

Revised maximum likely ICERs for treatment-naïve patients

In

Table 5 we present *plausible* upper bound ICERs for treatment-naïve patients (we do not accept that the ERG's current ICERs are plausible). In this analysis we assume that beyond 1.74 years (the time point at which the ERG's model predicts that benefit in 1L patients is worse than in 2L+ patients)[*], patients are benefiting only as much as they do in 2L+ (not worse or better). For completeness, this analysis includes the following amends to the ERG's model:

- Highlighting the primary comparator for consideration as chemotherapy
- Updated cost of treatment administration

[*] The use of treatment-experienced (2L+) hazards over the use of second-line only hazards was selected as this scenario utilizes all available data available (i.e. the whole population of the JAVELIN Merkel 200: Part A trial [n=88]).

- Implementation of the assumption that 5% of patients continue treatment beyond 2 years, and all patients assumed to have stopped treatment by 5 years
- Correction of model error regarding application of background mortality
- Use of hazards derived via the base-case extrapolation for treatment-experienced patients beyond the time of 1.74 years, such that the hazard of death for treatment-naïve patients is at most equal to the hazard of death for treatment-experienced patients
- Continued use of ERG's approach to modelling time on treatment (i.e. extrapolation of observed ToT data from JAVELIN Merkel 200 Part B)

This analysis incorporates the most conservative plausible estimate of survival for treatment-naïve patients and therefore represents the plausible *upper bound* for cost-effectives in 1L patients. The ICER versus chemotherapy in this analysis is £58,315 per QALY gained.

In conclusion, it is plausible to assume that the maximum ICER (at the current avelumab price) for treatment-naïve patients lies between £48,148 per QALY gained (company original base case) and £58,315 per QALY gained (revised ERG upper bound).

Table 5: Revised base-case model results + use of pooled comparator data – treatment-naïve patients

Treatment	Total			Incremental (avelumab vs.)			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER
Avelumab	£99,610	4.58	2.86				
Chemotherapy	£11,116	1.94	1.34	£88,494	2.64	1.52	£58,315

Key: ACD, Appraisal Consultation Document; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

References

1. Iyer JG, Blom A, Doumani R, et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. *Cancer Med*. 2016; doi: 10.1002/cam4.815.

2. Samlowski WE, Moon J, Tuthill RJ, et al. A phase II trial of imatinib mesylate in merkel cell carcinoma (neuroendocrine carcinoma of the skin): A Southwest Oncology Group study (S0331). *AmJ Clin Oncol*. 2010; 33(5):495-9.

3. Cowey CL, Mahnke L, Espirito J, et al. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. *Future Oncol*. 2017.

4. Becker JC, Lorenz E, Haas G, et al. Evaluation of Real World Treatment Outcomes in Patients with Metastatic Merkel Cell Carcinoma (MCC) Following Second Line Chemotherapy. *Ann Oncol*. 2016; 26((Suppl 3) Abstract#2602).

5. Merck KGaA. DATA ON FILE Consultant Oncologist Avelumab in Metastatic Merkel Cell Carcinoma, Validation Meeting Report. 2017.

Avelumab for treating metastatic Merkel cell carcinoma [ID1102]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by 5pm on 18 December 2017 **email:** TACommA@nice.org.uk NICE DOCS

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

The Appraisal Committee is interested in receiving comments on the following:

- has all of the relevant evidence been taken into account?
- are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- are the provisional recommendations sound and a suitable basis for guidance to the NHS?

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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Merck
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Amerah Amin E-mail: amerah.amin@merckgroup.com Phone: +44 208 818 7574

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Provision to the Committee of the final ICERs for treatment-experienced patients, fully incorporating Committee discussion and correcting minor model errors** In the ACD, the Committee's preferred base-case regarding the cost-effectiveness of avelumab in the treatment-experienced population contains a number of features that have not actively been incorporated within the base-case cost-effectiveness results, as well a correction of a model error not captured within the ERG's analysis (see comment 5 below). These features are: • **Updated administration cost** Section 3.17 of the ACD states: *"The committee noted the NHS England submission that the company used incorrect administration costs for chemotherapy."* The ACD suggests that the cost may have been underestimated by approximately £100 per administration. An updated cost of £253 per administration (compared to the previous cost of £199) has been incorporated within the model, reflecting the cost of a day case chemotherapy

	administration appointment in the NHS reference costs database (previously this was costed as simple parenteral chemotherapy per an outpatient appointment) • **Proportion of patients continuing treatment beyond 2 years** Section 3.14 of the ACD states: *"The clinical experts explained that they expect 95% of patients having avelumab to stop treatment by 2 years."* This assumption is discussed again in relation to the revised base-case settings for the cost-effectiveness model for first-line patients in Section 3.18: *"At the meeting, the committee heard that the clinical experts expect 95% of patients having avelumab to stop treatment by 2 years (see section 3.14). It therefore requested the ERG to revise their base case accordingly."* The model was only capable of estimating a proportion of patients discontinuing at 2 years, and was not able to assume 5% of patients were on treatment at 2 years. In the base-case projection of time on treatment for treatment-experienced patients, this was over-estimated at approximately 5.4% at 2 years. Therefore, we have updated the cost-effectiveness model to consider the *"true"* base-case preferences of the Committee for treatment-experienced patients. • **Original ICER:** £37,629 (avelumab versus BSC) • **Revised ICER:** £37,846 (avelumab versus BSC) While the model changes do not yield substantially different cost-effectiveness results for the treatment-experienced cohort of patients, we consider it important that the Committee have access to the exact numbers upon which decision-making can be based. In particular, these changes demonstrate that correcting the discontinuation at 2 years and revising the administration cost essentially cancel each other out.
2	**Previously-treated mMCC patients should be able to access avelumab through routine commissioning; the CDF will not reduce any of the remaining uncertainties, and no further datacuts of JAVELIN 200 are planned for this cohort.** Merck/Pfizer do not consider that the CDF will resolve the clinical uncertainties associated with second-line plus treatment as outlined in the ACD and addressed individually below: **Maturity of the data** The avelumab data for treatment-experienced metastatic MCC patients (Part A) is as mature as it will get. All patients have reached the primary endpoint, median survival has been reached and only 19 (22%) of patients are at risk of a PFS event. At the time of submission, 18-months follow-up date was provided for the full cohort of 88 treatment-experienced (2L+) patients from Part A of the JAVELIN Merkel 200 trial. Among the 88 patients treated with avelumab, 83% discontinued treatment; 47.7% (42/88) progressed and 11.4% (10/88) died. There are only 19 subjects remaining in the study from whom to expect additional data, 15 of which continued to receive treatment as of the March 2017 data-cut (see Table 14 in the NICE submission document). The 24th March data-cut already represents a mature data-set where median OS was reached (12.6 months) and shows a 12-month OS rate of 40%; this is more than double the median OS of 4.3-5.7 months expected with chemotherapy and greater than the 12-month OS rate of 0% from the start of second-line chemotherapy (Cowey 2017; Becker 2016; Iyer 2016). Since submission on the 1st August a further data cut was taken on 26th September, the interim findings show: [redacted]

[redacted]

This data-cut is the last planned analyses with no further cuts expected for the 2.3 year duration in which avelumab would be in the CDF.

The ERG's ICER for treatment-experienced patients is £37,629 and therefore already considered cost-effective. When revised to account for NICE's preferred assumptions this slightly increases the ICER to £37,846 per QALY gain but still well below the EoL willingness to pay threshold and therefore not an obvious CDF candidate.

To strengthen the confidence in the treatment-experienced ICER some scenarios have been conducted to demonstrate how much better the comparator will need to be in order to make the ICER cost-ineffective (please see comment 3 below and section 1.2 of the addendum). This analysis shows that best supportive care would need to demonstrate on average a survival benefit of 12.6 months (at constant utility) which is more than double the mean OS benefit of 5.1 months projected in the model.

Patient numbers
JAVELIN Merkel 200 is the largest registrational trial in metastatic Merkel Cell Carcinoma (MCC) to date.

Metastatic MCC is an ultra-rare neuroendrocrine skin cancer estimated to affect as little as 75 patients a year in England (across all lines of therapy). Due to the small patient numbers and the challenges in recruiting patients into a clinical trial, the single arm study design of the JAVELIN Merkel 200 trial allowed for the collection of a larger cohort of patient data than would otherwise have be obtained through randomised control trials (RCTs). While the small patient numbers and single-arm design present some limitations in the context of an HTA[1], these challenges are no different to those faced in the majority of assessments of ultra-rare conditions.

Whilst some short term data collection of newly treated 2L+ avelumab patients may be possible in the CDF, the small numbers of patients overall and short term 'follow up' mean this will be of limited benefit.

Comparator data
JAVELIN Merkel 200 is a single arm study and therefore does not allow a traditional indirect treatment comparison to be conducted. The absence of direct comparative data is common among trials for ultra-orphan conditions due to the challenges in designing and recruiting patients to large RCTs.

The true uncertainty lies in the comparator arm where there is a paucity of data available in the form of retrospective registry data and limited aggregate data. Merck took the most robust approach to generating comparator data by conducting observational studies (Becker 2016 and Cowey 2017). These were described in detail in section 4.9 in the original submission and accepted by the Committee as the most appropriate comparator data for the JAVELIN trial.

[1] 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.

	To address the inherent uncertainty in this appraisal, Merck KGaA/Pfizer have sought advice from a range of clinical and health economics experts[2], generated and undertaken robust analysis of comparator data. The options for formally comparing the comparator data with the JAVELIN trial were explored by economic experts and a naïve comparison was deemed appropriate as reported in Appendix 10 of the submission. To summarise, the analysis found that regardless of treatment received in the second-line plus setting, outcomes were uniformly poor. Furthermore, the analysis found that apart from line of treatment, 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. Finally, and more importantly, if avelumab for 2L+ were to enter the CDF, collection of comparator data would not be possible and this uncertainty would remain unaddressed. In conclusion, putting avelumab for the treatment of metastatic MCC in 2L+ into the CDF will provide no value from a data perspective. It will not address the uncertainty associated with the comparator arm and the issue of 'small' patient numbers which is inherent to rare diseases. The September 26 data is as mature as it will get and demonstrates survival projections in line with the economic model. This is the last planned analyses with no further cuts expected for the 2.3 year duration in which avelumab would be in the CDF. Finally, putting this cost-effective indication into the CDF will prevent access of the drug to patients in Wales and Northern Ireland who cannot benefit from the fund.
3	**The conclusion of cost-effectiveness in treatment-experienced patients is a robust one and only clinically implausible assumptions are likely to change it** Section 3.25 of the ACD states that the key uncertainties have arisen due to the single-arm trial design of JAVELIN Merkel 200, small number of patients and the reliance on a naïve indirect comparison. Two of these uncertainties cannot be quantified through analysis of available data; these are: the single-arm trial design of JAVELIN Merkel 200 and the small number of patients, which are reflective of the ultra-rare condition for which the estimates are derived. However, the third uncertainty pertaining to the naïve indirect comparison can be explored further through additional analysis. In an appendix to this comment (see section 1.2 of addendum), we have provided an analysis which aims to address how good survival outcomes would need to be for treatment-experienced patients receiving BSC in order to produce an ICER such that avelumab would no longer be considered cost-effective. Available data in this patient population receiving chemotherapy[3] suggests that average survival is approximately 5-6 months, with clinical expert opinion suggesting an estimate of 5 months may even be overly optimistic. The outcome of the analysis demonstrates that average survival for patients treated with BSC would have to be more than double (i.e. in the region of 12 to 13 months) the currently estimated value to produce an ICER of £50,000 per QALY gained. Furthermore, among the 77 patients from which chemotherapy OS survival data is available, only three had an OS of at least 12 months. This highlights that although estimates of survival derived via a naïve indirect comparison are associated with uncertainty, the average survival in patients receiving BSC would have to be considerably greater than is currently evident in order to produce an ICER for avelumab that would no longer be considered cost effective. This is clinically implausible.

[2] Validation is discussed in detail in Section 5.10; in summary [redacted] advised on clinical assumptions and model inputs and a modelling steering committee comprising [redacted] advised on modelling methodology, in particular outcome extrapolation.

[3] In the absence of data on BSC, chemotherapy data was used as a proxy for BSC.

Avelumab for treating metastatic Merkel cell carcinoma [ID1102]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by 5pm on 18 December 2017 **email:** TACommA@nice.org.uk NICE DOCS

4	**Correction of an incorrect assumption about how Merck/Pfizer model comparator data for treatment-experienced patients** There is some confusion as to which comparator data for treatment-experienced patients was used in the company's economic model. The ACD states "*the company used pooled data from study 100070-Obs001 (part A) and 6 additional studies to estimate progression-free and overall survival for chemotherapy*". In fact, the model only uses comparator data from the Merck/Pfizer observational studies and the use of the term "pooled" observational study refers to the pooling of both the EU 2L (Becker et al. 2016) and US 2L (Cowey 2017) data. Comparator data for treatment-naïve patients used the US Cowey 2017 study (the EU study did not collect data in treatment-naïve patients) and figure 51 in the company's submission should read "Cowey treatment-naïve parametric survival curves and Kaplan-Meir plots for OS" not "Pooled treatment-naïve parametric survival curves and Kaplan-Meir plots for OS"
5	**Correction to the apparent assumption by the ERG that BSC is the appropriate comparator for treatment-naïve patients; instead ICERs relating to chemotherapy are more appropriate (as concluded in the scope and acknowledged by the Committee in the ACD).** In Section 3.2 of the ACD, it is stated that the appropriate comparator for treatment-naïve mMCC is chemotherapy: *"The committee concluded that the appropriate comparator for first-line treatment is chemotherapy"* However, elsewhere in the ACD, frequent reference is made to the base-case comparator for treatment-naïve patients being BSC (Sections 3.18 and 3.25). It is important to acknowledge that within UK clinical practice, the most relevant comparator for consideration is chemotherapy. As such, the ACD should be updated when discussing ICERs for the treatment-naïve population to use the relevant comparator (chemotherapy). It must also be noted, that there is no literature which describes the outcomes of treatment-experienced or treatment-naïve metastatic MCC patients who are treated with BSC. In the absence of this data, the company used chemotherapy as a proxy for BSC. While in the second line setting survival outcomes are broadly the same regardless of treatment given, the same is not true in the first-line setting. As such, this is a very conservative assumption because chemotherapy is considered to have a beneficial effect on patient outcomes in the treatment-naïve setting.
6	**Provision to the Committee of the revised ERG's ICERs for treatment-naïve patients, fully incorporating Committee discussion and correcting minor model errors** In the ACD, the Committee's preferred base-case regarding the cost-effectiveness of avelumab in the treatment-naïve population contains a number of features that have not actively been applied within the ERG's base-case cost-effectiveness results, as well a correction of a model error not captured within the ERG's analysis. These features are: • **Updated administration cost** As per explanation for the treatment-experienced population (please see comment 1, above) • **Proportion of patients continuing treatment beyond 2 years** As per explanation for the treatment-experienced population (please see comment 1, above). In the base-case projection of time on treatment for treatment-naïve patients, this was over-estimated at approximately 8.5% at 2 years.

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	• **Model error regarding application of background mortality** Following the Appraisal Committee Meeting held on Thursday 2nd November 2017, a model error was noted regarding the application of background mortality for patients treated with chemotherapy or BSC: ○ In the patient flow sheets of the cost-utility model, a very small proportion of patients treated with chemotherapy or BSC were predicted to live for the duration of the modelled time horizon (approximately 0.34%), whereas patients treated with avelumab were assumed to all have died. ○ This is because of a modelling error, where the application of background mortality was erroneously omitted from the calculations concerning chemotherapy and BSC. This error featured in the submitted model, as well as the version of the model used by the ERG- which was not picked up during their review. Therefore, we have updated the cost-effectiveness model to consider the *"true"* base-case preferences of the committee, and corrected for this model error. The base-case cost-effectiveness results including costs, QALYs and LYs are presented in an appendix to this response- see section 2.2 of the addendum. • **Original ICER:** £72,033 (avelumab versus chemotherapy) • **Revised ICER:** £67,293 (avelumab versus chemotherapy) These model changes demonstrate notably different cost-effectiveness results for the treatment-naïve cohort of patients, hence it is important that the Committee have access to the exact numbers from which decision-making can be based. Reference to the most appropriate comparator for decision-making is also an important aspect within the ACD, as the current text within the ACD may be potentially misleading.
7	**ICERs from the ERG's economic model for treatment-naïve patients are implausible due to their perverse projections of benefit for this patient cohort** The ERG's preferred extrapolations of OS, PFS and ToT are each associated with limitations, primarily relating to the use of data from JAVELIN Merkel 200: Part B alone in their derivation. In the manufacturer's response to the ERG clarification questions, the immaturity of the data in this patient population was discussed along with reference to the small patient sample size (n=39). It was explained that fitting parametric curves to data from JAVELIN Merkel 200 Part B would not form an accurate basis from which long-term extrapolation may be considered to inform the cost-effectiveness analysis. The supporting addendum outlines the main issues identified in the ERG's treatment-naïve model and in particular their survival projections which in turn has resulted in implausible ICERs. In Section 2.3 of the addendum to these comments, we explore the underlying hazard functions for the OS extrapolations in the ERG's treatment-naïve and treatment-experienced models and find that unfortunately the ERG's model projects that the hazard of death for the treatment-naïve population is consistently greater than the hazard of death for the treatment-experienced (2L+) population beyond 1.74 years, i.e. that 1L patients do worse with avelumab than 2L+ patients (see figure 8 in supporting document). A further analysis was conducted looking at the subset of patients in the JAVELIN Merkel 200: Part A study who had only received one line of prior therapy (i.e. second-line only patients). The repeated analysis showed that the hazard of death for treatment-naïve patients projected in the ERG's model consistently exceeded that of second-line only patients after 1.09 years (see Figure 10 in supporting document). Clinical opinion and indeed the OS trend observed between 2L only and 2L+ in JAVELIN Merkel 200 Part A shows that greater OS benefits are realised the earlier the treatment is used in the pathway. Our analysis therefore suggests that the ERG's base case projection for OS in treatment-nave patients

	lacks clinically validity, given that patients who are treatment-naïve are expected to derive outcomes at least as good as those who are treatment-experienced, if not better. For time on treatment, the lack of long-term follow up with a large number of patients at risk may lead to parametric analysis "over-fitting" the tail of the Kaplan-Meier function. The ERG's base-case extrapolation using data for treatment-naïve patients from JAVELIN Merkel 200 Part B predicts that 8.5% of patients are still on treatment at 2 years. This is greater than clinical expectation, the committees preferred assumptions that 5% of patients are still receiving treatment beyond 2 years and the companies base-case extrapolation of 5.4%. Within the appendix, an example is presented where the same analysis (as the ERG's) is repeated but only using data up until 3 months which represents the majority of patients in this cohort (n=29) (all remaining patients, n=14 were censored at this time). The resultant extrapolation shows a lower estimate of time on treatment, more aligned with clinical expectation (though clearly based on shorter overall follow up).
8	**Provision of a clinically plausible maximum/upper bound ICER for treatment-naïve patients; still conservative but still consistent with evidence and clinical opinion** Based on the limitations of the current ERG treatment-naïve model (outlined in comment 6 above and the findings from the analysis in section 2.3 of the addendum), the following amends are proposed; the ERG's preferred extrapolation of treatment-naïve data is the basis, but beyond the time points where their model projected patients would do ***worse*** than previously-treated patients, we assume instead the actual hazards of death in the treatment-experienced (2L+) and second-line only populations in two separate analyses. Effectively this model uses observed 1L data and then assumes that unobserved benefits will be no better than those seen in the 2L+ and 2L populations (separately). (1) Using the treatment-experienced (2L+) hazards from 1.74 years (the point at which the hazard of death for 1L is greater than 2L+) gives an ICER of £58,315 for avelumab versus chemotherapy. (2) Using the second-line only hazards from 1.09 years gives an ICER of £52,506 for avelumab versus chemotherapy. Both scenarios use the ERG's preferred extrapolation of the JAVELIN Merkel Part B time on treatment data; although it should be recognised that this is highly conservative and is predicting that 8.5% of patients are still on treatment at 2 years. We propose that the clinically plausible maximum ICER cannot be the one suggested by the ERG (given the limitations in their model) and is more reasonably estimated with the following parameters: • Chemotherapy as the appropriate comparator • Updated cost of treatment administration • 5% of patients continuing treatment beyond 2 years, and all patients assumed to have stopped treatment by 5 years • Correction of model error in comparator data regarding application of background mortality • Use of hazards derived via the base-case extrapolation for treatment-experienced (2L+) beyond the time of 1.74 years, such that the hazard of death for treatment-naïve patients is at most equal to the hazard of death for treatment-experienced patients • Continuing to use ERG's time on treatment projection (based on data from treatment-naïve JAVELIN Merkel 200 Part B) This analysis yields an ICER of avelumab versus chemotherapy for treatment-naïve patients of £58,315 per QALY gained. The use of treatment-experienced (2L+) hazards over the use of second-line only hazards was selected as this scenario utilizes all available data available (i.e. the whole population of

	the JAVELIN Merkel 200: Part A trial [n=88]), and offers the most conservative estimate of survival for treatment-naïve patients. It represents the plausible *upper bound* for cost-effectiveness in treatment-naïve patients. In conclusion, the most plausible ICER for treatment-naïve patients is likely to lie between £48,148 per QALY gained (per the original base-case) and £58,315 per QALY gained (per this revised upper bound) which conservatively assumes that in the long term the hazards of OS or PFS event are no better than 2L+.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Avelumab for treating metastatic Merkel cell carcinoma [ID1102]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NET Patient Foundation
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to Disclose
Name of commentator person completing form:	Lindsey Devlin

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Avelumab for treating metastatic Merkel cell carcinoma [ID1102]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Having Avelumab available through the CDF would be of great benefit to patients, our concern is that this has been given a 3 year review date, at which point even though NICE consider this a life extending end of life treatment with costs that are beneath the ICER there is a chance it could be removed.
2	We are concerned the uncertainties raised by NICE regarding further data to reduce uncertainties will not be met whilst the drug is on the CDF. The study performed is already the largest clinical trial in MCC and the data for avelumab as a second line treatment is already fairly mature.The concerns about uncertainties of patient numbers and comparators for second line treatments wont be resolved whilst it is on the CDF. As stated throughout, MCC is a rare cancer and within the patient group those suitable for Avelumab are going to be an even smaller number.
3	
4	
5	
6	

Insert extra rows as needed

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Avelumab for treating metastatic Merkel cell carcinoma [ID1102]

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The response rates appear to be higher first line which makes the likelihood of this drug being more clinically and cost effective first line the most likely outcome.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	
Name	[redacted]
Role	NHS Professional
Other role	Consultant Clinical Oncologist
Organisation	[redacted]
Location	England
Conflict	I am currently setting up a phase 1 clinical study in soft tissue sarcomas using Avelumab that is funded by the manufacturer.
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	CC is an aggressive cancer with a high disease mortality rate. Cytotoxic chemotherapy offers short lived responses that are not durable. There is a strong radionale for using immunotherapy in MCC. There is a high mutational rate leading to neoantigen formation in addition to the exhaustion of TILS that may be reversible using checkpoint inhibition. Although the part A Javelin Merkel 200 study enrolled 88 patients with previously treated MCC, there were also 39 treatment naÃ¯ve patients with MCC with responses. The data support the use of Avelumab in the second line setting. It is thought that earlier use of Avelumab in the first line setting may demonstrate slightly better response rates compared with chemotherapy. We have noted that earlier use of checkpoint inhibition in other tumour types may be more beneficial and it is hoped that this may also hold true for MCC. Approval of Avelumab in the first line therapy will allow us to prospectively evaluate the data in this rare group of patients with significant

	unmet need
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Avelumab for treating metastatic Merkel cell carcinoma

ERG review of ACD response

January 2018

This report was commissioned by the NIHR HTA Programme as project number 16/134/09

BMJ Technology Assessment Group

1 SUMMARY

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the appraisal consultation document (ACD) following the first appraisal committee meeting (ACM) for the appraisal of avelumab for treating people with metastatic Merkel cell carcinoma (mMCC). Each of the eight comments in the company's response are discussed in further detail in Sections 1.1 to 1.8, after an overall summary highlighting the key issues considered by the ERG. A critique of the updated data cut is also provided in Section 2.

For the previously treated population (2L+), the company's changes requested by the committee made very little difference to the previous incremental cost effectiveness ratio (ICER) based on the NICE-requested analysis provided by the ERG for the first ACM. This ICER increased slightly from £37,629 to £37,846, and therefore, is likely to have negligible impact on any recommendation made. The company's opinion that access to treatment via the Cancer Drugs Fund (CDF) would not provide any further information to inform the analysis is one supported by the ERG. Therefore, the ERG considers these results to be the most robust available to inform a decision for routine commissioning.

For the treatment-naïve population (1L), the company provided an updated cost effectiveness analysis based on a number of changes to the NICE-requested analysis, including those requested by the committee and a correction to a model error. Together, these brought the ICER down from £72,033 to £67,293 (compared to chemotherapy). A further analysis to adjust implausible extrapolations brought the ICER down to £58,315. The ERG considers some of the issues raised by the company to be reasonable, however, the methods applied by the company to address these issues do not reduce the uncertainty in the results and the resulting ICER is no more plausible that the original NICE-requested analysis. The issues merely emphasise how uncertainty the results are given the lack of data in the 1L population. The ERG, therefore, considers a routine commissioning decision for this population to be highly uncertain and considers funding via the CDF to potentially provide the opportunity for more mature data to be collected within the JAVELIN 200 trial, hence, reducing some uncertainty in the decision.

The following sections of this document cover the specific issues in further detail, and section numbers (1.1 to 1.8) correspond to the comment numbers (1 to 8) in the company's response to the ACD.

1.1 Updated base case for 2L+ population

The ACD states that an incorrect cost was applied by the company for the administration of chemotherapy (applied for avelumab also), which underestimated the true cost by around £100. The company's original cost was based on an outpatient visit, which they have now updated to include the

cost of a day case attendance instead. This increases the cost of the visit from £199 to £253; less than the difference suggested in the ACD. This increase in cost has only a small impact on the company's base case ICER, increasing it from £37,629 to £38,200. The second change was to reduce the proportion of patients on treatment at two years from 5.4%, based on the company's initial assumptions that two thirds of the remaining patients discontinue at year two, to precisely 5% of patients remaining on treatment at year two. This reduced the company's original base case ICER from £37,629 to £37,280. The combination of these two changes resulted in an ICER of £37,846.

1.2 Applicability of CDF for 2L+ population

The company's second comment was in relation to the relevance of the CDF for avelumab in previously treated patients, after the committee had commented in the ACD that the CDF was the preferred initial funding route for avelumab in both populations. The company considers the CDF to be unnecessary for the 2L+ population given that the data from JAVELIN are mature and no further data cuts are planned. Therefore, none of the remaining uncertainty will be reduced by funding avelumab via the CDF for this population. The ERG considers the company's response to be reasonable and considers the current analysis to be the most robust evidence available to base a decision on routine commissioning.

1.3 Robustness of cost effectiveness evidence in 2L+ population

The company acknowledge the uncertainties that exist because of the single arm trial design and the small number of patients who were recruited into the trial, but they performed a threshold analysis to find the maximum effectiveness of the comparator for which the ICER remains within the £50,000 ICER threshold. The company did this by estimating and applying a hazard ratio (HR) to the Weibull curve fitted to the comparator data (adjusted to the JAVELIN trial population) such that the resulting ICER became £50,000. The estimated HR resulted in an increased median survival of 8.6 months (compared to 3.5 months in the base case) and mean survival of 12.6 months (compared to 5.1 months in the base case). The company regarded this as clinically implausible based on expert opinion and, therefore, deduced that their original analysis is robust.

The ERG notes that this threshold analysis only focuses on changing the effectiveness of the comparator group, and does not consider the uncertainty in the avelumab group. It would take a smaller, potentially more plausible change in each group to cause the same relative effect and result in an ICER of £50,000. It may, therefore, be more useful to consider the difference in mean survival, which shows a change from a mean difference of 37 months to 30 months results in the ICER increasing to £50,000. The ERG also considers there to be remaining uncertainty in the indirect comparison and, therefore, does not consider the company's conclusion that the analysis is robust to be valid. The ERG does, however, acknowledge that there is unlikely to be any possibility for more robust evidence, and therefore, a decision may need to be made based on the analysis as currently presented by the company.

1.4 Clarification of data used for comparator effectiveness

The ERG notes the clarification for the pooled data in the 2L+ population relates only to an inaccuracy in the ACD and was as described in the ERG report and the company submission (CS). For the data used in the 1L population, the company's clarification highlights an inaccuracy in what was described in the CS. However, the data described as clarified in the ACD response is the ERG's preferred data, as outlined in the ERG report, and therefore, the analyses presented are appropriate.

1.5 Appropriate comparator for 1L population

The company propose that the appropriate comparator should be chemotherapy at first line and this was accepted by the committee. The ERG, therefore, accept that the results compared to chemotherapy should be considered rather than the incremental results that show chemotherapy to be dominated by best supportive care (BSC).

1.6 Updated base case for 1L population

The company submitted a revised base case analysis for the 1L population, which included the request by the company to change the administration cost as per the 2L+ population, discussed in Section 1.1, as well as an adjustment to the treatment discontinuation to reduce the proportion on treatment at year two to 5%, from 8.5% in the NICE-requested analyses. In addition to this, the company corrected a model error that resulted in a proportion of patients in the chemotherapy/BSC groups to remain alive at the end of the time horizon because of an omission in background mortality for this group. The results of these changes brought the ICER down from £72,033 compared to chemotherapy to £67,293.

The change in administration costs brought the ICER up to £72,787, while adjusting the proportion on treatment at year two to 5% as well, cause the ICER to reduce to £68,548. The further reduction was caused by the correction to background mortality. The ERG has concerns about the assumption that only 5% remain on treatment at year two because the evidence suggests that a greater proportion of patients are on treatment before this point in the 1L population compared to the 2L+ population, so a greater proportion may remain on treatment at two-years. A value of 8.5% may not be unreasonable.

1.7 Implausibility of the ERG's ICERs for the 1L population

The ERG agrees that there is great uncertainty in fitting parametric survival curves to very limited data, but the company's original approach in no way mitigates this uncertainty and, potentially, imposes further assumptions that could increase that uncertainty. The ERG's approach was chosen in preference to the company's use of a HR, which assumes a constant relative effect that was shown to be unreliable within the trial period and may also be implausible for the extrapolation. The company also suggested that this HR was conservative as it was greater than the HR estimated in a Cox proportional hazards

(PH) model. However, estimating a HR when PH do not hold is a flawed approach to estimate the relative effect and, therefore, the company's approach cannot be determined to be conservative on this basis.

The ERG considers the company's comments that the hazards for the 1L population should not be greater than the 2L+ population may be reasonable. However, this serves to highlight the limitations that arise with such limited data, and attempting to make adjustments in the model to force a more plausible hazard function does not mitigate this uncertainty.

For the time on treatment analysis, the ERG agrees that the uncertain tail of the Kaplan-Meier plot may have an unrealistic influence on the fitted survival curves. However, the ERG is concerned with the company's approach to censor data beyond 3 months to avoid this uncertain tail. This, again, does not mitigate any uncertainty in the data, and may result in greater uncertainty by restricting the data available to just 3 months. The ERG considers the analysis for the 1L to have serious uncertainty resulting from the lack of data available, which may be reduced when further data become available within the JAVELIN 200 trial.

1.8 Clinically plausible upper bound ICER for 1L population

The company put forward an argument for an upper bound for the ICER in the 1L population by capping the hazard of death at the hazard for the 2L+ population, resulting in an ICER of £58,315 compared to chemotherapy. The company concluded that the most plausible ICER is likely to lie between this value and the company's originally submitted ICER of £48,148.

The ERG rejects this argument and does not consider it feasible to estimate a reliable upper bound for the ICER give the level of uncertainty caused by the limited data available. The ICER of £48,148 is based on a flawed assumption of PH and cannot be considered a lower bound for the ICER, while the value of £58,315 cannot be considered an upper bound, as the ICER may be higher than the NICE-requested analysis ICER of £72,033; the uncertainty is too great to provide a reliable ICER or even a reliable range in which it is likely to fall. This analysis needs to be considered with caution if a decision is to be made on the basis of such limited evidence.

2 CRITIQUE OF THE UPDATED JAVELIN TRIAL DATA

2.1 1L results

[redacted]

[redacted]

[redacted]

[redacted]

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. [redacted]

2.2 2L+ results

[redacted]

[redacted]

[redacted]