28 May 2020
EMA/CHMP/333708/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bavencio

International non-proprietary name: avelumab

Procedure No. EMEA/H/C/004338/II/0013

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Steps taken for the assessment		
Description	**Planned date**	**Actual Date**
Start of procedure:	30 Dec 2019	30 Dec 2019
CHMP Rapporteur Assessment Report	28 Jan 2020	29 Jan 2020
PRAC Rapporteur Assessment Report	31 Jan 2020	31 Jan 2020
PRAC members comments	05 Feb 2020	n/a
Updated PRAC Rapporteur Assessment Report	06 Feb 2020	n/a
PRAC endorsed relevant sections of the assessment report	13 Feb 2020	13 Feb 2020
CHMP members comments	17 Feb 2020	17 Feb 2020
Updated CHMP Rapporteur Assessment Report	20 Feb 2020	20 Feb 2020
Request for supplementary information	27 Feb 2020	27 Feb 2020
Submission of MAH's responses	27 Mar 2020	26 Mar 2020
Re-start of procedure:	30 Mar 2020	30 Mar 2020
CHMP Rapporteur Assessment Report	28 Apr 2020	28 Apr 2020
PRAC Rapporteur Assessment Report	30 Apr 2020	30 Apr 2020
PRAC members comments	06 May 2020	n/a
Updated PRAC Rapporteur Assessment Report	07 May 2020	n/a
PRAC endorsed relevant sections of the assessment report	14 May 2020	14 May 2020
CHMP members comments	18 May 2020	n/a
Updated CHMP Rapporteur Assessment Report	20 May 2020	n/a
Opinion	28 May 2020	28 May 2020

Procedure resources	
CHMP Rapporteur:	Filip Josephson
PRAC Rapporteur:	Hans Christian Siersted

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Europe B.V. submitted to the European Medicines Agency on 29 November 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of section 5.1 of the SmPC in order to update efficacy information following results from study EMR100070-003 Part B listed as a specific obligation in the Annex II; this is a Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma. With this submission the company is also taking the opportunity to update annex-II proposing deletion of the specific obligation and proposing the switch from conditional to full marketing authorisation. The package leaflet and the RMP (version 2.1) are updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

In accordance with the SOB, the MAH submitted the final results of the primary analysis for part B of study EMR100070-003 (May 2019).

The primary analysis demonstrated that the effect of avelumab monotherapy in 1L metatstaic Merkel Cell Carcinoma (mMCC), based on the interim analysis evaluation of 29 patients for a minimum of 13 weeks' follow-up in March 2017, was overestimated: the durable response rate (DRR objective responses lasting at least 6 months) dropped from 83% to 30%; Objective Response rate (ORR) from 62% to 40%; and median Progression Free Survival (mPFS) from 9.1 to 4.1 months. The safety profile remains unchanged

Despite the lower effect estimates, the data still support a positive Benefit/Risk (B/R) for Bavencio both in the first line and the previously treated mMCC. In this context it is noted that avelumab remains to the date of this assessment the only approved drug for mMCC in EU, and the only non-chemotherapy option.

The MAH provided answers to the request of supplementary information. The differences in ECOG and PD-L1 status between the 29 patients in the IA and the 87 accrued afterwards until EOS are highlighted. It seems reasonable that the difference may be at least partially explained by the baseline characteristics of early versus late recruited patients.

The relevant specific obligation is considered fulfilled and the data confirm that the benefits of Bavencio both in the first and next line treatment of mMCC continue to outweigh the risks. On that basis, the CHMP is of the view that there are no remaining grounds for the marketing authorisations to remain conditional and therefore recommends the granting of a marketing authorisation no longer subject to specific obligations.

The SmPC has been updated to include the data from study EMR100070-003 in section 5.1 and is considered acceptable.

The RMP version 2.2.1. is considered acceptable.

The benefit-risk balance of Bavencio remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of section 5.1 of the SmPC in order to update efficacy information following results from study EMR100070-003 Part B listed as a specific obligation in the Annex II; this is a Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma. With this submission the company is also taking the opportunity to update annex-II proposing deletion of the specific obligation and proposing the switch from conditional to full marketing authorisation. The package leaflet and the RMP (version 2.1) are updated accordingly.

is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended. The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II to the Opinion:

Description	**Due date**
In order to confirm the efficacy for chemotherapy-naïve treated patients, the MAH should submit the final results of study EMR 100070-003 – Part B.	30th January 2020

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Bavencio-H-C-004338-II-13

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

The application dossier for avelumab monotherapy in mMCC, which yielded a CMA for a line-agnostic indication, consisted of one single-arm, two-cohort study (EMR100070-003):

- Part A: a study in mMCC patients previously treated with at least one line of chemotherapy and progressing after the most recent regimen. Primary endpoint: ORR
- Part B includes treatment naïve MCC patients in the metastatic setting who may have received adjuvant systemic therapy >6 months prior to study start. The primary endpoint is durable response rate, DRR, with a minimum duration of 6 months. Assuming a true DRR of 45% the probability to observe lower bound of the exact 95% CI above 20% would be >99% and above 30% would be 90%. The study has been designed to have 1 planned interim analysis at 3 months after the accrual of the 25th subject, with additional interim analyses possible. The primary analysis was planned to be conducted 15 months after the accrual of the last subject (object of this submission in fulfilment of the SOB). Subject follow-up for progression and survival is planned to continue until 5 years after the last subject receives the last dose of avelumab or the last subject dies, whichever occurs first.

At the time of the CMA (2017), there were no approved therapies for mMCC. The most commonly used first-line chemotherapy regimen in disseminated disease is a platinum compound ± etoposide, resulting in high response rates (60-70%), but poor duration of response. With respect to relapsed disease, study data are sparse, but the ORR is much lower than in the first-line setting and duration is brief. Historic control in the JRAR: Iyer *et al.* Cancer Medicine 2016:

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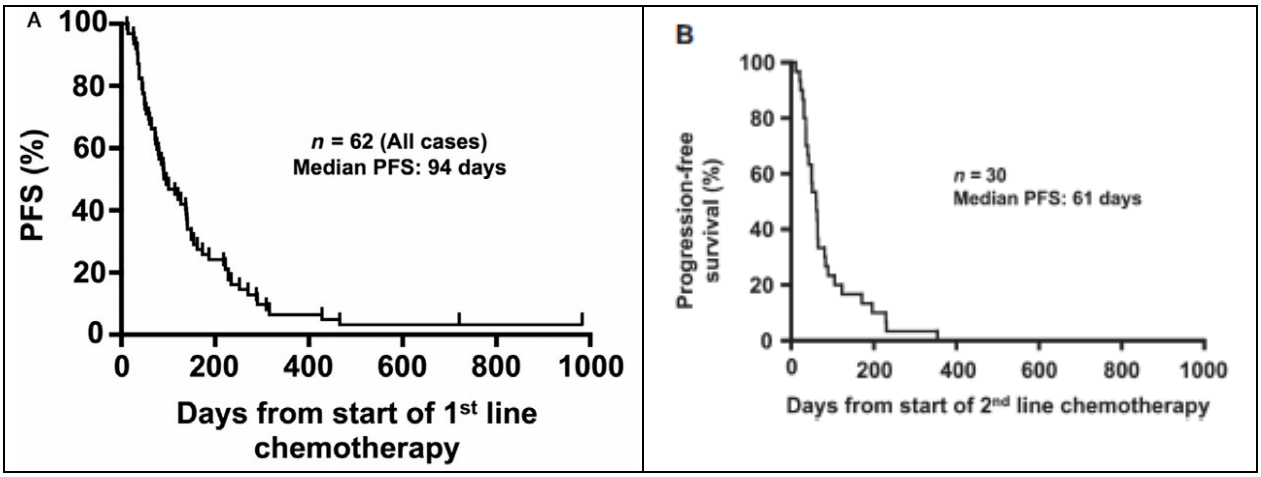


6. Clinical Pharmacology aspects

Study EMR100070-003 is an ongoing global Phase II, open-label, single-arm study of avelumab 10 mg/kg in subjects with metastatic Merkel cell carcinoma (mMCC) conducted in 2 parts (Parts A and B). Part B enrolled 116 subjects with MCC who are treatment-naïve to chemotherapy in the metastatic setting and were treated with avelumab 10 mg/kg every 2 weeks. The clinical pharmacology results

are only for part B, as part A had been reported previously in the initial submission in support of the initial Marketing Authorisation.

For EMR100070-003 Part B, sparse blood samples were collected prior to each drug infusion through Week 7, then at 6-week intervals until Week 25 (Day 169), and afterwards at 12-week intervals while on treatment for determination of C_{trough}. Post-infusion samples were collected at the end of infusion on Weeks 1, 7, and 25 for determination of C_{EOI}.

6.1. Methods – analysis of data submitted

Quantification of avelumab in human serum

An addendum to the previously validated bioanalysis method for the quantification of avelumab in human serum was provided (report 15-GR023-V0, 218-1407 Addendum 4). To assess the selectivity in the paediatric population, blank human serum samples from ten healthy paediatric volunteers was measured. Acceptance criteria were met at 750 ng/mL and ULOQ but failed at 250 ng/mL (125% LLOQ) due to over-recovery in many of the individual lots (103.2-176.0%). Method 218-1407 is not suitable to analyse paediatric samples. Selectivity at 750 ng/mL passed, and the method may be suitable for analysing paediatric samples with a truncated assay range and an appropriate validation will be performed (218-1823).

Amendment 2 (report 15-GR023-V0, 218-1407) demonstrated stability for up to 8 freeze/thaw cycles. The impact of the presence of PD-L1 (target) was evaluated at the LLOQ, LQC, and ULOQ with 5 concentrations of PD-L1: 0, 5, 10, 25, and 50 ng/mL. At the 0 ng/mL level, all results were BQL. At the LLOQ and ULOQ levels, all samples recover within 20% of the nominal concentration. At the LQC level, in the presence of 0, 10, 25, and 50 ng/mL PD-L1, the samples recovered within 20% of the nominal concentration, but not at 5 ng/mL PD-L1. Overall, this indicates that there is no interference from PD-L1 up to 50 ng/mL.

A bioanalytical study report (218-1502) was provided containing the study results and within study validation which all passed the acceptance criteria, including incurred sample reproducibility which was passed for 176 out of 184 reportable ISR results (95.7%).

Immunogenicity – Anti drug antibodies (ADA)

Two ADA methods were used for study EMR100070-003 and were split between two laboratories (Covance [Covance, New Jersey, United States] and QPS [QPS LLC, Delaware, United States]) Parts A and B, respectively. To afford clarity of interpretation of the ADA titer results, it was decided to retiter at QPS all screened and confirmed positives previously determined at Covance. Therefore, all titer results for Study EMR100070-003 are provided by QPS; the screening and confirming results were split between Covance and QPS, Part A and Part B, respectively. The respective method validations are summarised in Table 1.

Step-wise method (Covance)

Samples from studies EMR100070-001, EMR100070-002, and EMR100070-003 Part A were analysed using the step-wise ECL assay at Covance beginning 18 July 2014. Samples from studies EMR100070-001 and EMR100070-003 previously evaluated against the NHV cut point factor were reprocessed using the ST cut point factor in 2017, and additional confirmatory and titer assays were performed on the new screen positive samples as applicable.

The validated method is a step-wise electrochemiluminescence (ECL) assay. In brief, biotinylated avelumab is captured on the streptavidin-coated plates. The samples and quality controls are incubated with acid to dissociate complexes of antibody and avelumab, then neutralized, and then

incubated with the coated plates, where the analyte is specifically captured with Ruthenium sulfo-tag-labelled avelumab, and then quantified by ECL detection. Samples that test positive in the screening assay are subsequently tested in a confirmatory assay to ensure that signal is decreased in the presence of excess avelumab. Samples that confirm positive are further characterized to determine the titer of ADA present.

*Homogenous method (QPS)**[new]***

Samples from study EMR100070 003 Part B were analysed using the homogeneous ECL assay at QPS beginning 15 May 2018.

The validated method is a homogeneous bridging format ECL assay. In brief, unknown and control samples, after minimal required dilution, are mixed and incubated with acid buffer to dissociate complexes of antibody and avelumab, improving the drug tolerance of the assay. Subsequently, a mix of capture/detection reagents (i.e., avelumab conjugated with Biotin and SULFO-TAG) is added along with neutralization buffer allowing the bridging binding between ADA and labeled-drugs to be formed. The bridged ADA-avelumab complexes are captured on a streptavidin pre-coated/pre-blocked MSD microplate allowing for detection after a wash step.

The assay result is based on the comparison between sample readout and a plate-specific screening cut-point. The screening assay results are reported as "putative positive" (equal or above cut-point) or "negative" (below cut-point). Positive ("putative") samples are tested for specificity where these samples undergo competition testing in the presence and absence of avelumab. Titers are determined for confirmed positive samples.

Drug tolerance enabled detection of 20 ng/mL of antibody in the presence of 25 µg/mL avelumab and both 250 and 500 ng/mL of antibody was detected in the presence of 100 µg/mL avelumab. Based on the median concentration at trough, the level of drug tolerance was anticipated to be sufficient to support the clinical development program.

Selectivity was established in both adult and paediatric patient serum (see Table 1).

Table 1: Validation Summary of Immunogenicity Methods for the Clinical Development of Avelumab

Analyte/ Laboratory	ADA/ Covance	ADA/QPS **[new]**	nAb/ QPS Old method
Reports	TNJS13-170 Amendment 1	15-GR077V0 Amendment 3	16-QPD065V0
Assay principle	Step-wise bridging immuno-assay on MSD® platform	Homogeneous bridging immune-assay on MSD® platform	Competitive ligand-binding assay
Studies	EMR100070-001 EMR100070-002 EMR100070-003 (Part A) screen confirm	EMR100070-003 (Part A) titer EMR100070-003 (Part B) screen confirm and titer	EMR100070-001 EMR100070-002 EMR100070-003
Cut point factor	Floating 1.80 NHV (n=50) 1.17 Japan 1.25 ST	Floating 1.12 Solid Tumor Patient (STP) Serum (n=50)	Floating 0.71 ST and NHV
Sensitivity (LOD)	15.5 ng/mL in NHV; 4.85 ng/mL in Japan; 5.12 ng/mL in ST	10 ng/mL (2.3 ng/mL)	297 ng/mL
Drug tolerance	0.25 µg/mL at 31.3 µg/mL avelumab in NHV, at 125	20 ng/mL at 25 µg/mL avelumab in STP serum, at	297 ng/mL at

		µg/mL avelumab in Japan and ST	250 and 500 ng/mL at 100 µg/mL avelumab in STP serum	31.3 ng/mL avelumab
Validation QC conc (µg/mL)		NC 0.25 (LPC) 2.0 (MPC) 5.0 (HPC)	NC 0.020 (LPC) 0.20 (MPC) 0.5 (HPC)	NC NHV 0.297 NHV 0.297 ST 1.0 NHV 1.0 ST
Selectivity[a]		10/10 10/10 NT NT	10/11 and 8/11 spiked at 20 and 500 ng/mL in adult STP matrix 8/11 and 5/11 spiked at 20 and 500 ng/mL in paediatric STP matrix	NT 11-okt 10/11 4/11 15/21
CV% precision at QC concentrations	**Inter-assay (signal) mean**	40.2 42.0 41.2 42.8	75 274.9 NA 5029	21.0 NT NT NT NT
	Intraassay	6.8 to 12.8 3.7 to 8.6 1.8 to 8.6 1.1 to 11.5	0 to 16.5 0.3 to 7.9 NA 0.4 to 10.6	0.3 to 12.6 0.3 to 9.5 NT 0.7 to 6.8 NT
	Interassay (S/N) mean	NA NT NT NT	NA 3.8 NA 67.5	NA 6.2 NT 18.4 NT
Stability		202 day at -80°C 27.5 hr at RT 24 hr at 5°C 7 F/T	24 hr at RT 24 hr at 4°C 7 F/T	24 hr at RT 7 F/T

Source: TNJS13-170 Amendment 1 Section 2; 15-GRO77-V0 Amendment 3 Section 2, IP190 Table 7, Table 11, and Table 12; IP373 Table 4, Table 5; 16QPD065-V0 Section 2.

ADA: anti-drug antibodies; Covance: Covance, New Jersey, US; F/T: freeze-thaw cycles; HPC: high positive control; LOD: limit of detection; LPC: low positive control; MPC: mid positive control; MSD: Mesoscale Discovery; NA: not applicable; nAb: neutralizing antibody; NC: negative control; NHV: normal healthy volunteer; NT: not tested; PC: positive control; QC: quality control; QPS: QPS LLC, Delaware, US; RT: room temperature; S/N: signal to noise as measured by positive control divided by negative control, ST: solid tumor. [a] Selectivity in this table includes individuals and pools.

An immunoanalytical study report (218-1802) was provided containing the study results (screen, confirmation, titration) and within study validation which all passed the acceptance criteria.

A recently developed competitive ligand-based neutralising ADA (nAb) assay with improved drug tolerance was validated at QPS. Results from this assay will be reported at the completion of this study. For the current study, all nAb determinations were performed by QPS using the previously validated method described in Table 1. An immunoanalytical study report (218-1614) was provided containing the study results for neutralising antibodies and within study validation which all passed the acceptance criteria.

6.2. Results

Pharmacokinetics (EMR100070-003 Part B)

In patients treated with avelumab 10 mg/kg every 2 weeks, the geometric means of C_{EOI} (end of infusion) and C_{trough} of avelumab after the first dose were 237 µg/mL and 22.2 µg/mL, respectively (Table 2 and Table 3). C_{EOI} appeared to be stable over time. The geometric mean and mean of C_{trough} appeared to increase with time and reach plateau at Week 25, which was in line with previous observations. Observed geometric coefficients of variation (CV%) for C_{EOI} ranged from 27.7% to 32.1% (Table 2). There was a large interindividual variability in observed C_{trough}. The geometric CV% for C_{trough} ranged from 21.4% to 130.4% (Table 3). The values and variability of C_{EOI} and C_{trough} were consistent with those observed in Part A (C_{EOI} 252µg/mL, range 107 - 1108µg/mL, 13.8 - 34.7%; C_{trough} 23.8µg/ml, range 1.58 - 245µg/mL, CV% 12.8 - 101.6%).

Table 2: Summary Table of Avelumab Serum Concentration at End of Infusion (CEOI) over Nominal Time – PK Analysis Set

Dose Group	Day (Week)	N	GM (µg/mL)	CV% GM	Mean (µg/mL)	Median (µg/mL)	StDev (µg/mL)
10 mg/kg	1 (W1)	104	237	31.1	240	231	146.5
	43 (W7)	78	244	32.1	253	256	56.71
	169 (W25)	41	255	27.7	265	260	79.27

Source: Study EMR100070-003 Part B CSR, Table 15.4.1.1.
C_{EOI}: concentration at end of infusion; CV%: percent coefficient of variation; GM: geometric mean; StDev: standard deviation.

Table 3: Summary Table of Avelumab Serum Trough Concentrations (Ctrough) over Nominal Time – PK Analysis Set

Dose Group	Day (Week)	N	GM (µg/mL)	CV% GM	Mean (µg/mL)	Median (µg/mL)	StDev (µg/mL)
10 mg/kg	15 (W3)	100	22.2	57.5	25.2	24.2	12.54
	29 (W5)	86	27.8	80.2	35.6	30.2	42.98
	43 (W7)	76	27.5	89.4	33.7	31.9	18.43
	85 (W13)	61	29.4	130.4	37.2	38.1	19.60
	127 (W19)	54	37.0	65.6	42.1	39.0	19.18
	169 (W25)	45	45.6	60.3	54.0	42.6	39.02
	253 (W37)	47	39.9	53.0	44.3	39.7	20.27
	337 (W49)	36	39.5	37.3	42.2	37.4	17.31
	421 (W61)	24	43.6	30.3	45.7	40.3	15.73
	505 (W73)	14	41.8	30.4	40.3	42.0	16.12
	589 (W85)	4	57.5	24.1	58.7	61.0	13.10
	673 (W97)	5	44.9	21.4	45.7	50.8	9.076

Source: Study EMR100070-003 Part B CSR, Table 15.4.1.1, Table 15.4.1.2.
CV%: percent coefficient of variation; GM: geometric mean; StDev: standard deviation.
C_{trough} refers to the concentration of the 336 hour sample post last dosing.

Immunogenicity

Immunogenicity incidence for study EMR100070-003 is presented in Table 4 (data cut-off 02 May 2019). Samples for evaluation of ADA response using the homogeneous bridging format assay were available for 116 subjects. One subject had a positive ADA response at baseline, but the response was not boosted upon treatment. Eight of 110 subjects (7.3%) had treatment-emergent ADA response. Three of those 8 subjects were transient positives and the remaining 5 were persistent positives. The titers were generally low, with two notable exceptions: one transient positive had a titer of 14,580 on a single occasion, and a second persistent positive had a maximum titer of 43,740 but by end of treatment the titer was only 180. Three of 9 ADA ever-positive subjects with mMCC responded to avelumab treatment in Study EMR100070-003 Part B, all with partial responses.

Due to the low incidence of immunogenicity and few PK assessments after onset due to sparse sampling, the potential association of immunogenicity with PK was not analysed in the current study but will be evaluated in an integrated assessment across clinical studies.

Table 4: Immunogenicity Incidence for Subjects Treated with 10 mg/kg Avelumab for Individual Studies and Integrated Safety Summary

Studies	EMR100070-003 Part A (N=88) n/N (%)	EMR100070-003 Part B (N=116) n/N (%)
ADA Ever positive n/N0 (%)	5/88 (5.7)	9/116 (7.8)
ADA Pre-existing n/N1 (%)	0/86	1/106 (0.9)
ADA Treatment boosted n/N2 (%)	0/80	0/103
ADA Treatment-emergent n/N3 (%)	5/82 (6.1)	8/110 (7.3)
ADA Transient n/N3 (%)	1/82 (1.2)	3/110 (2.7)
ADA Persistent n/N3 (%)	4/82 (4.9)	5/110 (4.5)

Source: Module 2.7.2 addendum April 2017; Part B csr-emr100070-003 Part B Section 12.5.4 Table 40 ADA = antidrug antibody; mMCC = metastatic Merkel Cell Carcinoma; N0 = The number of treated subjects.
N1 = The number of subjects with valid baseline result.
N2 = The number of subjects with valid baseline and at least 1 valid post-baseline result.
N3 = The number of subjects with at least 1 valid post-baseline result and without positive baseline results (including missing, NR).

A total of 10 confirmed ADA positive samples previously tested at Covance and 20 confirmed ADA positive samples (new assay, QPS) were analysed for neutralising antibodies. Of the 29 screened samples, 6 samples screened positive for neutralizing antibody, and 1 sample was insufficient volume (ISV) for analysis and a backup aliquot was analysed. A recently developed competitive ligand-based neutralizing antibody assay with improved drug tolerance was validated and results from this assay will be reported at the completion of this study.

6.3. Discussion

Bio- and immuno- analytical methods and reports were provided and are considered adequate for the intended use.

The concentrations measured at the end of infusion and trough in part B are similar to previous observations for part A. The interindividual variability, which is high, in particular for $C_{trough,}$ is also in the same range as in part A. Of note, data of part A was included in the population PK model in the original application, and overall inter individual variability was considered moderate. Given that the clinical pharmacology profile of avelumab did not change in Study EMR100070-003 Part B, the new clinical pharmacology data has no impact on the benefit/risk profile.

Overall, the updated analysis for Part B is consistent with data previously reported from Part A, with a low incidence of immunogenicity. Since only sparse sampling was available, no new analyses of the impact of immunogenicity on PK were provided. The impact on PK remains low.

This new data does not result in a change to SmPC section 5.2, which is acceptable.

7. Clinical Efficacy aspects

EMR100070-003 is an ongoing, multicenter, international, single-arm, open-label, Phase II study in 2 parts (Part A and Part B) that was designed to evaluate the efficacy and safety of avelumab in subjects with metastatic Merkel Cell Cancer (mMCC). In Part B (subject of this report), patients were treatment-naïve to systemic therapy in the metastatic setting.

The primary objective for Part B was to evaluate the clinical activity of avelumab as first-line treatment for metastatic or distally recurrent Merkel cell carcinoma (MCC) as determined by the durable response rate (DRR), defined as an objective response lasting at least six months. Up to 112 patients were planned to be enrolled.

Table 4 **Selected Key Demographic and Baseline Characteristics – Full Analysis Set**

Characteristic	Avelumab N=116 (100%)
Sex, n (%)	
Male	81 (69.8)
Female	35 (30.2)
Race, n (%)	
White	75 (64.7)
Black or African American	2 (1.7)
Asian	3 (2.6)
Not collected at the site	35 (30.2)
Unknown	1 (0.9)
Age (years)[a], n (%)	116 (100.0)
Median	74.0
Minimum, maximum	41, 93
Age category, n (%)	116 (100.0)
< 65 years	22 (19.0)
≥ 65 years	94 (81.0)
65 to < 75	37 (31.9)
75 to < 85	43 (37.1)
≥ 85	14 (12.1)
Geographic Region	
North America	29 (25.0)
Western Europe	75 (64.7)
Australia	9 (7.8)
Asia	3 (2.6)
ECOG PS, n (%)	116 (100.0)
0	72 (62.1)
1	44 (37.9)

Table 5 Merkel Cell Carcinoma Disease History – Full Analysis Set	
Characteristic	Avelumab N=116 (100%) n (%)
Site of primary tumor	
Lymph nodes	1 (0.9)
Skin	104 (89.7)
Missing	11 (9.5)
Visceral metastases at baseline per IERC	
Present	79 (68.1)
Absent	35 (30.2)
Missing	2 (1.7)
Lymph node disease only at baseline per IERC	
Yes	25 (21.6)
No	89 (76.7)
Missing	2 (1.7)
Time since first metastatic disease (months)	
n	116 (100.0)
Mean ± standard deviation	5.1 ± 7.29
Median	2.2
Quartile 1; quartile 3	1.1; 6.2
Minimum, maximum	0.4, 49.6
Time since last disease progression of disease prior to study entry (months)	
n	102 (87.9)
Missing	14 (12.1)
Mean ± standard deviation	1.4 ± 1.18
Median	1.1
Quartile 1, quartile 3	0.7, 1.7
Minimum, maximum	0.0, 6.2
M stage at study entry	
M0	0
M1	116 (100.0)
MX	0
Missing	0

Results

Avelumab as first-line therapy in subjects with mMCC produced durable responses in a clinically meaningful proportion of subjects with 35 of 116 patients, for a DRR of 30.2% (95% CI: 22.0, 39.4).

ORR was 39.7% (95% CI: 30.7, 49.2) according to IERC assessment.

The median duration of response of 18.2 months (95% CI: 11.3, -); the maximum duration as of the cutoff date was ongoing at 28.3 months.

The following table offers a comparison between the data at the time of approval and the data available as of May 2019.

	Approval			PAM
Part A, systemically previously treated mMCC pat				
	Primary analysis, n=88, Sept. 2016			May 2019
	ORR at min. 12 mo FU	33% (95% CI 23.3-43.8)	-	-
	- CR	11.4% (95% CI 6.6-19.9)	-	-
	- PR	21.6% (95% CI 13.5-31.7)	-	-
	DRR	31% (95% CI 21; 44%)	-	-
	PFS	2.7 mo (95% CI 1.4-6.9)	-	-
	DOR	40.5 mo (18-NE)	-	No update
	OS	NA	-	12.6 mo (7.5-17.1)
Part B, systemically not previously treated				
	Prespecified IA*, n=39, March 2017 29/39 enrolled patients had >13 weeks min FU and were thus included in the IA		Subsequent IA, n=116, Sept. 2018	Primary analysis, n=116, May 2019
	DRR	83% (95% CI 46-96)	27.6% (19.7, 36.7)	30.2% (22-39.4)
	ORR	62% (95% CI 42-79)	39.7% (30.7-49.2)	39.7% (30.7-49.2)
	-CR	14%	13.8%	16.4%
	- PR	48%	25.9%	23.3%
	DOR	NE	15.2 (10.2-NE)	18.2 mo (11.3-NE)
	PFS	9.1 mo (1.9-NE)	4.1 mo (1.4-6.1)	4.1 mo (1.4-6.1)
	OS	-	-	20.3 mo (12.4-NE)

Issue 1, CMA

The underlying arguments for the CMA approval were at the time:

- The first-line data were very limited, but the response rate (back then similar to chemotherapy) and the apparent durability of responses were considered favourable in a comparison with intensive chemotherapy.

As part of the SOB, the primary analysis for part B (May 2019) has been submitted by the MAH.

The effect of avelumab monotherapy in 1L mMCC, based on the evaluation of 29 patients for a minimum of 13 weeks' follow-up in March 2017, was overestimated compared to the final outcome: the DRR dropped from 83% to 30%; ORR from 62% to 40% and mPFS from 9.1 to 4.1 months.

The effect estimate for the primary analysis is thus substantially lower than at the interim analysis. The B/R estimation is revised and narrowed, yet remains positive.

Issue 2, biomarkers

Table 14 Summary of Efficacy Results by Combined PD-L1 Expression Status and Merkel Cell Polyoma Virus Status (Immunohistochemistry) – Full Analysis Set

	Avelumab (N = 116)				
	PD-L1 (≥ 1% Cutoff) / MCV Status[a]				
Efficacy Parameter	+/+ n=11 (100%)	+/- n=10 (100%)	-/+ n=59 (100%)	-/- n=27 (100%)	NA n=9 (100%)
Durable Response Rate[b]					
Number of subjects with durable response, n (%)	5 (45.5)	5 (50.0)	14 (23.7)	8 (29.6)	3 (33.3)
95% CI (exact)[c]	16.7, 76.6	18.7, 81.3	13.6, 36.6	13.8, 50.2	7.5, 70.1
Objective Response Rate[b]					
CR + PR (response rate, %)	6 (54.5)	7 (70.0)	18 (30.5)	11 (40.7)	4 (44.4)
95% CI (exact)[c]	23.4, 83.3	34.8, 93.3	19.2, 43.9	22.4, 61.2	13.7, 78.8
Odds ratio (+/+ over -/+)	2.73				
95% CI	0.60, 12.75				
p-value[d]	0.1686				
Odds ratio (+/- over -/+)		5.31			
95% CI		1.04, 34.55			
p-value[d]		0.0293			
Odds ratio (-/- over -/+)				1.57	
95% CI				0.54, 4.44	
p-value[d]				0.4615	
Duration of Response (subjects with response), n (%)	6 (54.5)	7 (70.0)	18 (30.5)	11 (40.7)	4 (44.4)
Median, months (95% CI)[e]	ne (4.0, -)	ne (2.8, -)	16.5 (6.9, -)	18.2 (4.9, -)	12.5 (5.6, 12.5)
Minimum, maximum	4.0, 28.3	1.2, 22.1	2.8, 19.3	2.8, 26.3	5.6, 12.5
Progression-Free Survival (subjects with events), n (%)	7 (63.6)	4 (40.0)	45 (76.3)	21 (77.8)	7 (77.8)
Median, months (95% CI)[e]	8.7 (1.3, -)	ne (1.3, -)	1.4 (1.4, 4.2)	2.6 (1.4, 7.0)	8.3 (1.2, 13.8)
Minimum, maximum	0.03, 29.6	1.35, 24.9	0.03, 20.6	0.79, 27.6	1.25, 15.1
Hazard ratio (+/+ over -/+)	0.58				
95% CI	0.26, 1.30				
Hazard ratio (+/- over -/+)		0.36			
95% CI		0.13, 0.99			
Hazard ratio (-/- over -/+)				0.94	
95% CI				0.56, 1.58	

Overall Survival, n (with event)	6 (54.5)	2 (20.0)	31 (52.5)	15 (55.6)	4 (44.4)
Median, months (95% CI)[e]	20.3 (8.4, -)	ne (6.9, -)	16.1 (6.1, -)	15.9 (6.2, -)	ne (2.0, -)
Minimum, maximum	2.00, 31.3	6.93, 32.2	0.49, 34.9	0.79, 28.8	2.04, 34.7
Hazard ratio (+/+ over -/+)	0.87				
95% CI	0.36, 2.09				
Hazard ratio (+/- over -/+)		0.26			
95% CI		0.06, 1.08			
Hazard ratio (-/- over -/+)				1.05	
95% CI				0.57, 1.95	

Sources: Table 15.2.1.21, Table 15.2.2.15, Table 15.2.3.17, Table 15.2.4.14, Table 15.2.5.15.

CI: confidence interval; CR: complete response; IERC: Independent Endpoint Review Committee; MCV: Merkel cell polyoma virus; N/n: number of subjects; ne: not estimable; PD: progressive disease; PR: partial response; RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SD: stable disease.

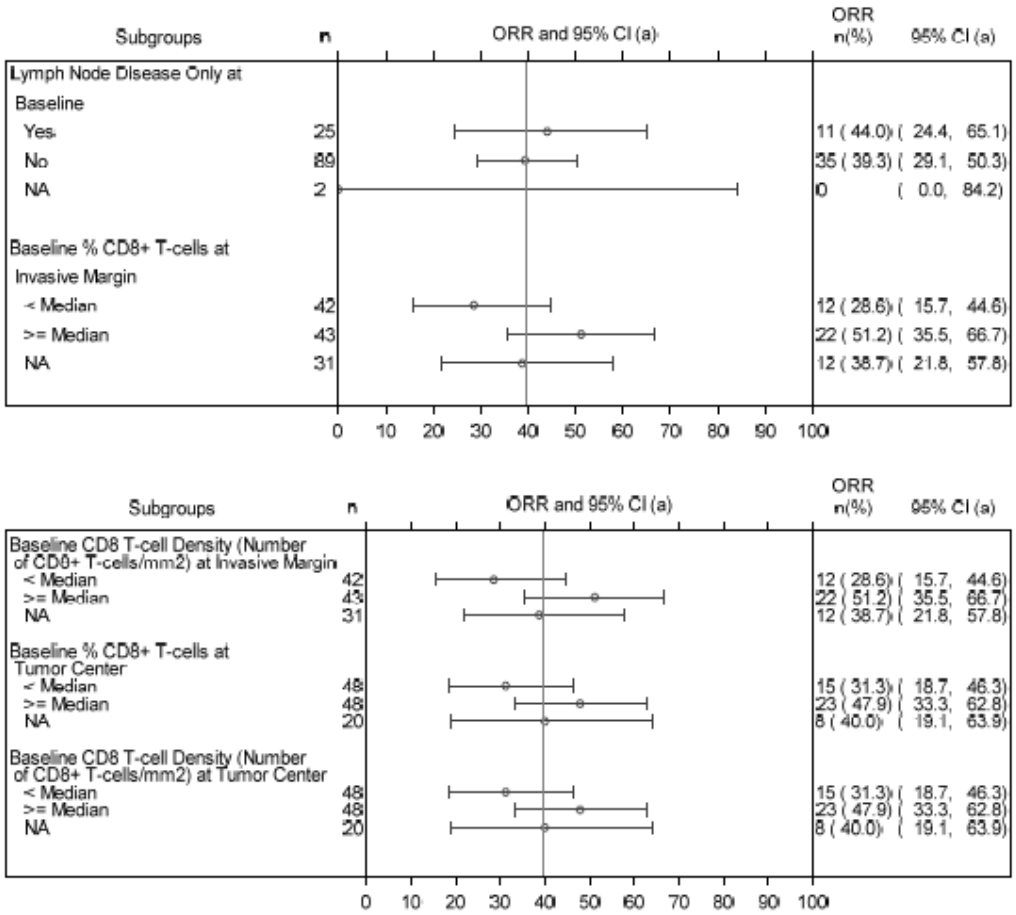
a Subjects were considered PD-L1-positive if ≥ 1% of the tumor cells showed ≥ 1+ PD-L1 membrane staining intensity or PD-L1-negative if < 1% of the tumor cells showed ≥ 1+ PD-L1 membrane staining intensity. Tumor MCV status determined by baseline IHC sample.

b According to IERC assessments per RECIST 1.1.

c 95% exact CI using Clopper-Pearson method.

d P-value using Fisher's exact test.

e Product-limit (Kaplan-Meier) estimates.



Source: Figure 15.2.12.1.

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; FAS; Full Analysis Set; IHC: immunohistochemistry; MCV: Merkel cell polyoma virus; n: number of subjects; NA: not available; ORR: objective response rate; PD-L1: programmed death ligand 1; SLD: sum of longest diameter.

a 95% exact CI using Clopper-Pearson method.

The differential effect of avelumab (DRR, ORR) by biomarker subgroup (PD-L1 expression in tumor cells; density of CD8+ T cells at invasive margin; and Merkel cell virus tumor status) and their

combination should be discussed by the MAH. The MAH should discuss biomarker subgroups of patients for whom avelumab therapy should not be indicated.

Discussion

The primary analysis demonstrated that the effect of avelumab monotherapy in 1L mMCC, based on the interim analysis evaluation of 29 patients for a minimum of 13 weeks' follow-up in March 2017, was overestimated: the durable response rate (DRR objective responses lasting at least 6 months) dropped from 83% to 30%; ORR from 62% to 40%; and mPFS from 9.1 to 4.1 months in the final primary analysis provided with the SOB data. The safety profile remains unchanged.

Despite the lower effect estimates, the data still support a positive B/R for Bavencio both in the first line and the previously treated mMCC. In this context it is noted that avelumab remains to the date of this assessment the only approved drug for mMCC in EU, and the only non-chemotherapy option.

The MAH provided answers to the request of supplementary information. The differences in ECOG and PD-L1 status between the 29 patients in the IA and the 87 accrued afterwards until EOS are highlighted. It seems reasonable that the difference may be at least partially explained by the baseline characteristics of early versus late recruited patients.

8. Clinical Safety aspects

The safety profile of avelumab as a single agent in systemic therapy-naïve subjects with recurrent or metastatic MCC was well characterized in 116 subjects with at least 15 months of follow up in Part B of Study EMR100070-003.

The most frequently reported TEAEs of any grade were constipation, cough, fatigue, and asthenia. TEAEs were generally manageable and mild to moderate in severity. Grade $\geq$ 3 treatment-related TEAEs were reported for 21 subjects (18.1%), and 12.1% of subjects discontinued avelumab treatment permanently due to a treatment-related TEAE. There were no avelumab-related Grade 5 TEAEs.

Based on the mechanism of action and the known safety profile of avelumab, irAEs were expected. Immune-related AEs occurred in 35 subjects (30.2%). In all treated subjects, most irAEs were reported in the subcategories of immune-related rash (18 subjects, 15.5%) and immune-related endocrinopathies: thyroid disorders (7 subjects, 6.0%). The number of subjects with high-grade (Grade $\geq$ 3) irAEs was low (7 subjects, 6.0%) and most were reported for the subcategory of immune-related hepatitis. A single subject was reported with a Grade 4 irAE of dermatitis psoriasiform. There were no Grade 5 irAEs.

Infusion-related reactions were reported in 34 subjects (29.3%). Most IRRs were either mild or moderate in severity. Only 1 subject reported a Grade 3 IRR, and there were no Grade 4 or 5 IRRs. In most subjects the initial IRR was associated with the first infusion of avelumab and resolved within 1 day after onset of the event. All IRRs resolved except for one which resolved with sequelae. Three subjects (2.6%) permanently discontinued study treatment due to IRRs.

These updated safety analysis results are consistent with those reported previously. The overall safety profile of avelumab in mMCC also remains consistent with the overall safety profile of the pooled data set based on 1738 subjects with advanced solid tumor malignancies (refer to Module 2.7.4 in the initial

MAA). These data continue to confirm a manageable safety profile of avelumab in mMCC.

In conclusion the data do not raise any new safety concerns for avelumab.

9. Risk management plan

The MAH submitted an updated RMP version with this application. The main proposed RMP changes were the following:

- Part IV and Part VI.II.C.1 are no longer applicable after the submission of the primary analysis of study report EMR 100070-003/Part B
- Annex 5 is no longer applicable after the submission of the primary analysis of study report EMR 100070-003/Part B

9.1. Overall conclusion on the RMP

☒ The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information in section 11 are submitted.

The RMP Version 2.1 (PDF format) has not been updated in Part IV with the proposed deletion of Table 21, as in the RMP working document.

1. The MAH is required to update the RMP with all changes as proposed in the working document.

2. The RMP Version 2.1 contains outdated information in multiple sections, and a general revision/update of the RMP is required.

Examples of outdated information in the RMP Version 2.1

The removal of educational material for HCPs was approved as part of the assessment of the RMP Version 2.0 (EMEA/H/C/004338/II/0009/G).

The reclassification of immune-related pancreatitis to an important identified risk was approved as part of the assessment of the RMP Version 2.0 (EMEA/H/C/004338/II/0009/G).

10. Changes to the Product Information

As a result of this variation, section 5.1. of the SmPC is being updated to add efficacy information following results from study EMR100070-003 Part B listed as a specific obligation in the Annex II. Please refer to the attached, annotated SmPC.

11. Request for supplementary information

11.1. Other concerns

Clinical aspects

1. In part B of the pivotal study, the estimated DRR and ORR differs widely between the patients (n=29) included in the March 2017 interim analysis, and the primary analysis results (n=116) for which patients were subsequently accrued. Please present data for outcomes in that complementary subgroup of 87 patients that were not included in the IA, and discuss the baseline disease and demographic characteristics, including prognostic and predictive factors (such as PD-L1 expression), or any other aspects of study conduct, with respect to potential reasons for the difference in outcomes between these two subsets of the study population.

2. The differential effect of avelumab (DRR, ORR) by biomarker subgroup (PD-L1 expression in tumor cells, density of CD8+ T cells at invasive margin; and Merkel cell virus tumor status) and their combination should be discussed by the MAH. Please discuss implications for clinical utility in these subpopulations, including the potential value of such biomarkers for making treatment decisions.

3. A number of amendments to the proposed changes in section 5.1 of the SmPC are proposed (see separate document).

Risk management plan

1. The MAH is required to update the RMP with all changes as proposed in the working document.

2. The RMP Version 2.1 contains outdated information in multiple sections, and a general revision/update of the RMP is required.

12. Assessment of the responses to the request for supplementary information

Clinical aspects

Comment 1

In Part B of the pivotal study, the estimated DRR and ORR differ widely between the patients (n=29) included in the March 2017 interim analysis, and the primary analysis results (n=116) for which patients were subsequently accrued. Please present data for outcomes in that complementary subgroup of 87 patients that were not included in the IA, and discuss the baseline disease and demographic characteristics, including prognostic and predictive factors (such as PD-L1 expression), or any other aspects of study conduct, with respect to potential reasons for the difference in outcomes between these two subsets of the study population.

Response

The estimated ORR and DRR were higher for the group of subjects included in the March 2017 interim analysis than in the complementary subgroup (Table 1 and Table 2).

Table 1 Confirmed Overall Response by IERC - Study EMR100070-003 Part B

Best Overall Response, n (%)	≥13 w FU March 2017 IA (n=29)	Accrued thereafter (n=87) (b)
Complete Response	7 (24.1)	12 (13.8)
Partial Response	11 (37.9)	16 (18.4)
Stable Disease	3 (10.3)	9 (10.3)
Non CR/ non PD	0	1 (1.1)
Progressive Disease	7 (24.1)	41 (47.1)
Non-Evaluable	1 (3.4)	8 (9.2)
Objective Response Rate		
Response Rate (CR+PR), n (%)	18 (62.1)	28 (32.2)
95% conf. interval (exact) (a)	(42.3, 79.3)	(22.6, 43.1)

(a) 95% exact confidence interval (CI) using the Clopper-Pearson method.
(b) < 13 Weeks Follow-up at the 24 Mar 2017 IA

Table 2 Durable Response Rate by IERC - Study EMR100070-003 Part B

DOR	≥13 w FU March 2017 IA (n=29)	Accrued thereafter (n=87) (b)
Number of subjects with durable response, n (%)	13 (44.8)	22 (25.3)
95% conf. interval (exact) (a)	(26.4, 64.3)	(16.6, 35.7)

(a) 95% exact confidence interval (CI) using the Clopper-Pearson method.
(b) < 13 Weeks Follow-up at the 24 Mar 2017 IA

The evaluation of the group of subjects included in the March 2017 interim analysis and the complementary subgroup revealed a comparable distribution of demographic and baseline disease characteristics (Table 3 and Table 4) such as age and sex. A more unbalanced distribution was observed for ECOG, PD-L1 expression status, and the geographic region where subjects were enrolled.

Table 3 Selected Demographic Characteristics – Study EMR100070-003 Part B

	≥ 13 Weeks Follow-up at 24 Mar 2017 IA (N = 29)	Accrued Thereafter (N = 87) (b)
Sex, n (%)		
Male	21 (72.4)	60 (69.0)
Female	8 (27.6)	27 (31.0)
Race, n (%)		
White	22 (75.9)	53 (60.9)
Black or African American	0	2 (2.3)
Asian	0	3 (3.4)
Not Collected at the Site	6 (20.7)	29 (33.3)
Unknown	1 (3.4)	0
Ethnicity, n (%)		
Hispanic/Latino		
Yes	0	3 (3.4)
No	15 (51.7)	28 (32.2)
Missing	14 (48.3)	56 (64.4)
Japanese		
Yes	0	3 (3.4)
No	0	0
Missing	29 (100.0)	84 (96.6)
Age (Years)		
Mean ±SD	72.2 ±9.89	72.9 ±10.46
Median	75.0	73.0
Q1; Q3	65.0; 79.0	66.0; 80.0
Min; Max	47; 88	41; 93
Age Categories, n (%)		
< 65 years	7 (24.1)	15 (17.2)
≥ 65 years	22 (75.9)	72 (82.8)
65 - < 75 years	6 (20.7)	31 (35.6)
75 - < 85 years	14 (48.3)	29 (33.3)
≥ 85 years	2 (6.9)	12 (13.8)
Geographic Region, n (%)		
North America	18 (62.1)	11 (12.6)

Western Europe	11 (37.9)	64 (73.6)
Australia	0	9 (10.3)
Asia	0	3 (3.4)
ECOG Performance Status at Baseline, n (%) (a)		
0	23 (79.3)	49 (56.3)
1	6 (20.7)	38 (43.7)
Body Mass Index (BMI) (kg/m^2)		
n, (%)	29 (100.0)	83 (95.4)
Missing (%)	0	4 (4.6)
Mean ±SD	28.81 ±4.794	28.05 ±5.231
Median	28.30	26.90
Q1; Q3	25.30; 32.60	24.60; 31.10
Min; Max	21.5; 40.4	19.1; 48.9

Table 4 Selected Baseline Characteristics - Study EMR100070-003 Part B

	≥ 13 Weeks Follow-up at 24 Mar 2017 IA (N = 29)	Accrued Thereafter (N = 87) (a)
Site of Primary Tumor, n (%)		
Lymph Node	0	1 (1.1)
Skin	29 (100.0)	75 (86.2)
Missing	0	11 (12.6)
Tumor Size (cm)		
n (%)	15 (51.7)	42 (48.3)
Unknown (%)	14 (48.3)	44 (50.6)
Missing (%)	0	1 (1.1)
Mean ±SD	3.64 ±1.776	4.42 ±4.571
Median	3.10	3.31
Q1; Q3	2.20; 4.70	2.00; 4.50
Min; Max	1.3; 8.0	0.6; 25.0
Visceral Metastases at Baseline, n (%)		
Present	23 (79.3)	56 (64.4)
Absent	6 (20.7)	29 (33.3)
Missing	0	2 (2.3)
Lymph Node Disease Only at Baseline, n (%)		

Yes	3 (10.3)	22 (25.3)
No	26 (89.7)	63 (72.4)
Missing	0	2 (2.3)
Time from Initial Diagnosis to Study Entry (Months)		
n (%)	29 (100.0)	87 (100.0)
Mean ±SD	20.5 ±25.90	17.5 ±18.92
Median	13.0	10.4
Q1; Q3	7.9; 18.9	3.7; 23.7
Min; Max	0.7; 120.9	0.8; 89.1
Lymphovascular Invasion, n (%)		
Yes	11 (37.9)	19 (21.8)
No	3 (10.3)	18 (20.7)
Unknown	15 (51.7)	49 (56.3)
Missing	0	1 (1.1)
Time Since First Metastatic Disease (Months)		
n (%)	29 (100.0)	87 (100.0)
Mean ±SD	6.0 ±6.56	4.8 ±7.53
Median	3.9	2.1
Q1; Q3	1.1; 9.3	1.1; 5.4
Min; Max	0.6; 27.7	0.4; 49.6
PD-L1 expression at cut-off of 1%, n (%)		
≥ 1%	9 (31.0)	12 (13.8)
< 1%	17 (58.6)	70 (80.5)
Non-evaluable	3 (10.3)	5 (5.7)

Source: Appendix 1 of this response
(a) < 13 Weeks Follow-up at the 24 Mar 2017 IA

Baseline performance status varied substantially between the two groups with 79.3% of subjects included in the March 2017 interim analysis being assessed as ECOG 0 at baseline versus 56.3% of subjects in the complementary subgroup. Improved baseline performance status has been associated with better outcomes in clinical trials of solid tumors with both immunotherapy as well as chemotherapeutic agents. In the overall study population, subjects with a performance status of ECOG 1 overall showed a lower objective response rate compared to subjects assessed as ECOG 0 (27.3% vs. 47.2%; Refer to Table 15.2.1.8) as well as a lower durable response rate (22.7% vs. 34.7%; Refer to Table 15.2.5.7).

Comparison of the two study groups also showed a considerable difference in the distribution of subjects whose tumors expressed PD-L1 with a cutoff of ≥ 1% tumor cell staining. The prevalence of subjects with PD-L1 ≥ 1% in the subset of subjects evaluated in the March 2017 interim analysis was 31.0% vs. 13.8% in the complementary subgroup. PD-L1 expression has been widely discussed as a predictive biomarker in immuno-oncology trials, however, its effect in metastatic MCC has not been validated. The overall study results show numerically higher response rates in the PD-L1 ≥ 1% subgroup compared to the PD-L1-negative subgroup with an objective response rate of 61.9% (95% CI: 38.4,81.9) vs 33.3% (95% CI: 23.6,44.3) and durable response rate of 47.6% (95% CI: 25.7,70.2) vs 25.3% (95% CI: 16.6, 35.7), respectively.

In summary, the imbalances in PD-L1 ≥1% status and ECOG performance status between the subsets defined by date of enrollment could in part explain the observed difference in ORR and DRR for the two subsets of subjects.

It should be noted though that the number of subjects within the two subgroups varied substantially, with only a quarter of the total study population being reflected in the March 2017 interim analysis. As

the absolute number of subjects was low with only 29 of 116 subjects evaluated at the interim, the direct comparison of the two subsets of subjects is impacted by the wide confidence intervals pertaining to the analyses of the 29 subjects.

Assessment

The Applicant provided the information as requested. The differences in ECOG and PD-L1 status between the 29 patients in the IA and the 87 accrued afterwards until EOS are highlighted. It seems reasonable that the difference may be at least partially explained by the baseline characteristics of early versus late recruited patients.

Issue solved.

Comment 2

The differential effect of avelumab (DRR, ORR) by biomarker subgroup (PD-L1 expression in tumor cells, density of CD8+ T cells at invasive margin and Merkel cell virus tumor status) and their combination should be discussed by the MAH. Please discuss implications for clinical utility in these subpopulations, including the potential value of such biomarkers for making treatment decisions.

Response

Avelumab displays efficacy in Merkel cell carcinoma in all subjects regardless of PD-L1 expression, Merkel cell polyoma virus status, or % CD8+ T cells at the invasive margin. Clinically meaningful objective response rate (ORR) and durable response rate (DRR) results were observed in all analyzed subgroups.

As discussed in Sponsor's Response No. 1 above, observed response rates in the overall study population are higher in the PD-L1 ≥ 1% subgroup compared to the PD-L1-negative subgroup, with an ORR of 61.9% (95% CI: 38.4,81.9) vs 33.3% (95% CI: 23.6, 44.3) and DRR of 47.6% (95% CI: 25.7,70.2) vs 25.3% (95% CI: 16.6,35.7). Despite this trend, the ORR and DRR in the PD-L1-negative subgroup are also substantial and clinically meaningful, obviating the value of PD-L1 as a biomarker for making treatment decisions. As such, the statement, "The clinical utility of PD-L1 as a predictive biomarker in MCC has not been established" is appropriate and the Sponsor proposes that it remains in the EU SmPC as currently included.

Similarly, clinically meaningful results were obtained for all subjects regardless of Merkel cell polyoma virus (MCV) status. The ORR and DRR for subjects with IHC-MCV-positive tumors (n = 70) were 34.3% (95% CI: 23.3,46.6) and 27.1% (95% CI: 17.2,39.1), respectively. Although response rates were lower than those obtained for the subgroup with IHC-MCV-negative tumors (n = 37), which had an ORR of 48.6% (95% CI: 31.9,65.6) and a DRR of 35.1% (95% CI: 20.2,52.5), the IHC-MCV-positive subgroup still derived substantial benefit from treatment and the use of MCV status for making treatment decisions is not supported in Merkel cell carcinoma.

Subjects with a percentage of CD8+ T cells at the invasive margin that was greater than or equal to the median (n = 43) had a higher ORR of 51.2% (95% CI: 35.5,66.7) and DRR of 39.5% (95% CI: 25.0,55.6) compared to subjects with a percentage of CD8+ T cells at the invasive margin less than the median (n = 42) (ORR of 28.6% (95% CI: 15.7,44.6) and DRR of 21.4% (95% CI: 10.3,36.8). As is the case for PD-L1 and MCV, the results for both invasive margin CD8+ T cell density subgroups are clinically meaningful and do not support the use of percentage of CD8+ T cells at the invasive margin as a biomarker for making treatment decisions.

The highest ORR was reported for subjects with PD-L1-positive and IHC-MCV-negative tumors (n = 10) with an ORR of 70.0% (95% CI: 34.8,93.3); the DRR for this subgroup was 50.0% (95% CI: 18.7,81.3). However, each subgroup combining PD-L1 expression and IHC-MCV status that was examined demonstrated efficacy of treatment as evidenced by their DRR and ORR results:

	PD-L1 (≥ 1% Cutoff) / IHC-MCV Status			
Efficacy Parameter	**+/+ (n = 11)**	**+/- (n = 10)**	**-/+ (n = 59)**	**-/- (n = 27)**

DRR (%) (95% CI)	45.5 (16.7,76.6)	50.0 (18.7,81.3)	23.7 (13.6,36.6)	29.6 (13.8,50.2)
ORR (%) (95% CI)	54.5 (23.4,83.3)	70.0 (34.8,93.3)	30.5 (19.2,43.9)	40.7 (22.4,61.2)

Again, there is substantial treatment benefit to all subgroups for which the combined PD-L1 expression and MCV status were evaluated. The use of PD-L1 and MCV status in combination for making treatment decisions is not appropriate.

Moreover, it is important to note that sample sizes within the subgroups presented are small, leading to wide and overlapping confidence intervals in most cases. Because clinically meaningful response rates are observed for all subgroups, the clinical utility of PD-L1, Merkel cell virus tumor status, and density of CD8+ T cells at the invasive margin as biomarkers has not been established and associated diagnostic testing is not indicated for Merkel cell carcinoma.

Finally, the overall study population was dominated by subjects whose tumors were negative for PD-L1 expression at the 1% cutoff. Despite the estimated differences in ORR and DRR when compared against the PD-L1 ≥ 1% subgroup, the observed median overall survival time of 15.9 months (95% CI: 9.6, not estimable (NE)) in subjects with PD-L1 < 1% tumors, versus NE (95% CI: 11.3, not estimable (NE)) in subjects with PD-L1 ≥ 1% tumours, suggests that clinical activity of avelumab in both subgroups defined by PD-L1 status translates into favourable survival time when referenced against reported historical data (refer to Table 5 - Clinical Overview Addendum- Datacut May 2019) in this disease setting.

Assessment

It is reasonable and of interest to the prescriber to know the impact of PD-L1 on efficacy, as this seems to be an important effect modifier.

This is not a claim that the clinical utility of PD-L1 as a predictive biomarker has been established (in fact it is unclear precisely what would be meant by this).

However, conversely, there is no rationale to introduce a statement to deny this, nor to dissuade a clinician that wishes to use PD-L1 status as part of the grounds for clinical decision-making. Therefore this statement should be removed from the SmPc.

The company has provided updated AR addressing the Rapporteurs proposal. The final PI is now acceptable

Issue exhausted.

Comment 3

A number of amendments to the proposed changes in section 5.1 of the SmPC are proposed.

Response

The MAH revised section 5.1 as well as other sections of the avelumab EU PI accordingly, taking the comments from Rapporteur in the EU PI and the responses for the request for supplementary information into consideration. Please refer to Module 1.3.1 SmPC, Labelling, and Package Leaflet.

Assessment

See answer to comment 2.

RMP aspects

Question 1
The MAH is required to update the RMP with all changes as proposed in the working document.

Summary of the MAH's response
The MAH revised the EU RMP as requested.

Assessment of the MAH's response
The MAH has updated the RMP as requested

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 2
The RMP Version 2.1 contains outdated information in multiple sections, and a general revision/update of the RMP is required.

Summary of the MAH's response

The MAH revised the EU RMP as requested.

Assessment of the MAH's response
The MAH has updated the RMP as requested

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

The MAH has provided adequate responses to the PRAC Rapporteurs requests, and the RMP version 2.2.1. is considered acceptable.