Non-Interventional Study Report

Title	Non-interventional cohort study to assess the characteristics and management of patients with Merkel cell carcinoma (MCC) in Germany
Study Number	MS100070-0031
Version identifier of the final study report	Version 1.0
Date of last final version of the study report	27 November 2024
EU PAS register number	EUPAS25338
Sponsor	Merck Europe B.V. Gustav Mahlerplein 102 1082 MA Amsterdam The Netherlands
Coordinating Investigator/ Principal Investigator(s)	PPD 60549 Frankfurt am Main Germany
Active substance	Avelumab (L01XC)
Medicinal product	Bavencio®
Product reference	EMEA/H/C/004338
Procedure number	EMEA/H/C/004338/MEA/002.1
Marketing authorization holder(s)	Merck Europe B.V. Gustav Mahlerplein 102 1082 MA Amsterdam The Netherlands
Joint PASS	No
Research question and objectives	This study is a non-interventional cohort study performed to comprehensively assess characteristics and management of patients with MCC in Germany. Among other objectives, this cohort study includes the following PASS specific objectives: • Characterization of disease outcomes by means of response (complete remission [CR], partial remission [PR], stable disease [SD], progressive disease [PD]) and survival (real-

	world progression-free survival [rwPFS], overall survival [OS]) analyses per treatment line and overall, and specifically in the subgroup of immune compromised patients treated with avelumab. • Description of the safety events of interest (e.g. immune-related adverse drug reactions [irADRs]) overall and specifically in the subgroup of immune compromised patients treated with avelumab. Exploratory objectives are: • Comparison of the safety and effectiveness profile of immune compromised patients with the profile of immune competent patients, all of whom are treated with avelumab.
Country(-ies) of study	Germany
Author	PPD Senior Epidemiologist Global Research & Development, Clinical Measurement Sciences (CMS), PRWE (Patient Focused Real-World Evidence), Merck Healthcare KGaA 64293 Darmstadt, Germany
Marketing authorization holder(s)	Merck Europe B.V. Gustav Mahlerplein 102 1082 MA Amsterdam The Netherlands
MAH contact person	PPD PPD

Approval Page - Project Lead Merck

Final Study Report:

MS100070-0031

Non-interventional cohort study to assess the characteristics and management of patients with Merkel cell carcinoma (MCC) in Germany

Short title: MCC TRIM (Tissue Registry in Merkel cell carcinoma)

Final Study Report Date / Version 27 November 2024 / Version 1.0

I approve the final study report.

_____ _____

Signature Date of Signature

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Table of Contents

Table of In-Text Tables

Table of In-Text Figures

1 Abstract

Title:

Non-interventional cohort study to assess the characteristics and management of patients with Merkel cell carcinoma (MCC) in Germany.

Study Number:

MS100070-0031

Marketing Authorization Holder:

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Keywords:

Merkel cell carcinoma, avelumab, patient characteristics, adverse drug reaction.

Rationale and Background:

Merkel cell carcinoma (MMCC) is a rare and aggressive neuroendocrine tumor of the skin. The European Commission (EC) granted conditional marketing approval for avelumab (Bavencio®) as a monotherapy for the treatment of adult patients with metastatic MCC (mMCC) on 18 September 2017. However, during the market authorization review process by the European Medicines Agency (EMA), the need to further assess the safety and efficacy of avelumab in the specific subgroup of immune compromised ICS-) patients with mMCC arose. To address the question, the Sponsor adapted a planned longitudinal non-interventional cohort study of patients with MCC in Germany, leveraging the structure already set up for a more general skin cancer registry, Arbeitsgemeinschaft Dermatologische Onkologie REGistry (ADOREG).

The data collection model for this study was thus based on a mixed data collection model i.e. secondary use of data from the ADOREG with additional primary data collection. Therefore, this study aimed to provide a nation-wide approach of real-world data collection from MCC patients recruited and treated at numerous sites across Germany to answer questions on the safety and effectiveness of avelumab in the subgroup of patients who are immune compromised.

Research Question and Objectives:

Among other objectives, this cohort study includes the following PASS specific objectives:

- Characterization of disease outcomes by means of response and survival analyses, overall and per treatment line, and specifically in the subgroup of immune compromised patients treated with avelumab.
- Description of the safety events of interest, specifically in the subgroup of immune compromised patients treated with avelumab.

The exploratory objectives include:

- Comparison of the safety and effectiveness profile of immune compromised patients with immune competent patients, all treated with avelumab.

Study Design and Population:

This was a 5-year non-interventional (observational), longitudinal, multi-site cohort study focusing on epidemiological and clinical outcomes assessed in patients diagnosed with MCC in Germany. The study has an open cohort study design. Patients were recruited based on a diagnosis of MCC only (all stages and ages), irrespective of treatment and MCC diagnosis tool utilized, from study start (30 April 2019) until 30 September 2023. The study population was recruited by healthcare providers (HCPs) participating in ADOREG, mainly dermato-oncologists, treating and managing patients with MCC in Germany. Enrolled patients were followed until either death, withdrawal from the study or end of the study (31 March 2024), whichever occurred first. This inclusion period allowed for a potential minimum follow-up of 6 months for each patient.

The study initially aimed to enroll a total of about 540 patients with MCC from approximately 45 sites in Germany. During the study, the enrollment target was extended to (maximum) 1,000 patients to have more patients with advanced MCC specifically for the PASS objectives.

Data collection:

Data was collected both retrospectively at the enrolment visit and prospectively during follow-up visits. Demographic data, tumor characteristics, comorbidities, concomitant medication, MCC-related oncology treatments, disease outcomes (response, progression) and HRU data are collected.

Statistical Analysis:

For categorical variables the numbers and percentages within each category (with a category for missing data) of the parameter are presented. For continuous variables, the mean, standard deviation (StDev), median, first and third quartile, minimum and maximum values are derived. All time-to-event analyses are performed by using Kaplan-Meier methods including calculation of median survival times and 95% confidence intervals (CIs).

Safety analysis involves assessment of incidence rates of fatal and non-fatal ADRs, including immune-related ADRs.

The Full Analysis Set (FAS) is subdivided into the Early-Stage Analysis Set (ESAS) and the Advanced-Stage Analysis Set (ASAS). The ASAS is defined as patients with unresectable stage III or stage IV MCC. The ESAS contains all patients in the FAS who are not included in the ASAS.

The Safety Analysis Set (SAS) includes all enrolled patients who had received at least one dose of any systemic oncology treatment and is subdivided into the Analysis Set of patients not considered immune compromised (ICS+), incl. the Analysis Set of ICS+ patients treated with avelumab, and the immune compromised (ICS-) Analysis Set, incl. the immune compromised Analysis Set treated with avelumab.

Additional analyses were performed for investigation of potential impact of the leading site (Universitätsklinikum Essen) on the overall results. Study outcomes were analyzed in strata of center (center 1: Universitätsklinikum Essen vs. center 2: all remaining sites pooled).

Results:

At the end of data collection (31 March 2024), 41 sites had enrolled 875 patients. Of these, 599 are included in the ESAS and 276 in the ASAS. The SAS comprised 311 patients: 247 ICS+ (189 of them treated with avelumab) and 64 ICS- (54 of them treated with avelumab). 243 patients were treated with avelumab. All avelumab-treated patients were with stage III or IV MCC except for 5 stage II patients and 2 patients with stage unknown.

Descriptive analysis of patients' characteristics and relevant comorbidities in patients treated with avelumab stratified by center revealed differences. Patients in center 2 were on average older than patients treated with avelumab in center 1 (mean age 76.1 years and 71.0 years, respectively); a higher proportion of patients with ECOG score of 0 was reported in center 1 than in center 2 (90.5% vs. 56.3%). Impact of the leading site (center 1: Universitätsklinikum Essen) on the overall results was explored in analyses of study outcomes.

Comorbidities or concomitant medications relevant for selecting patients into the ICS-Analysis Set treated with avelumab (n=54), were the following: 34 patients reportedly had a concurrent malignancy, 3 patients had organ transplantation, 2 patients an infection with HIV, 20 patients received systemic corticosteroids, 4 patients cytostatics, 3 patients received a calcineurin inhibitors and 2 patients IMDH inhibitors.

Real-world Progression Free Survival (rwPFS) and Overall Survival (OS) was calculated among patients who initiated a new line of systemic treatment on/after the date of enrollment. In patients treated with avelumab, first-line rwPFS was 7.9 (95% CI: 4.0, 11.6) months in ICS+ and 4.3 (95% CI: 1.0, 7.8) month in ICS- subpopulation. First-line treatment with avelumab resulted in OS 38.2 (95% CI: 15.7, NE) months and 9.9 (95% CI: 4.8, 29.8) months in ICS+ and ICS- subpopulation, respectively.

Objective Response Rate (ORR, CR and PR combined) to first-line avelumab therapy was 34.7% in the ICS+ and 28.6% in ICS- subpopulation. No differences in treatment response between the 2 study centers was not identified in the exploratory regression analyses.

ADRs associated with the use of avelumab included 19 SADRs and 43 non-serious ADRs. The incidence rate for all ADRs associated with the use of avelumab was estimated to be 0.94 (95% CI 0.72 to 1.22) events per person-year. Exploratory regression analysis showed that the incidence rate of ADRs related to avelumab was significantly higher in center 1 than in center 2.

Discussion and Conclusion:

MCC TRIM is the largest study on MCC patients in Germany to our knowledge.

The study confirmed safety of avelumab in patients treated for advanced MCC. No major differences in the safety profiles between ICS+ and ICS- patients were detected as a similar proportion of patients and incidence rates of ADRs related to avelumab was yielded. Effectiveness of systemic treatment with avelumab in advanced MCC in terms of treatment response was confirmed for ICS+ as well as for ICS- patients. Numerically better survival outcomes were observed in ICS+ patients treated with avelumab than ICS- patients.

2 List of Abbreviations

Abbreviation	Full Terminology
ADO	Arbeitsgemeinschaft Dermatologische Onkologie
ADOREG	Arbeitsgemeinschaft Dermatologische Onkologie REGistry
ADR	adverse drug reaction
AE	adverse event
ASAS	Advanced-Stage Analysis Set
CI	confidence interval
CR	complete remission
eCRF	electronic case report form
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
ESAS	Early-Stage Analysis Set
EU	European Union
FDA	Food and Drug Administration
FAS	full analysis set
HIV	Human immunodeficiency virus
HRU	healthcare resource utilization
ICAS	Immune Compromised Analysis Set
ICD	International Classification of Disease
ICI	immune checkpoint inhibitor
ICS+	immune competent patients
ICS-	immune compromised patients
IEC	Independent Ethics Committee
IMDH	inosine monophosphate dehydrogenase
MCPyV	merkel cell polyomavirus
MCC	merkel cell carcinoma
MCC TRIM	tissue registry in merkel cell carcinoma
mMCC	metastatic merkel cell carcinoma
MR	mixed response

Abbreviation	Full Terminology
NCCN	National Comprehensive Cancer Network
NE	not estimable
NED	no evidence of disease
ORR	objective response rate
OS	overall survival
PAS	Post-Authorisation Studies
PASS	Post-Authorization Safety Study
PD	progressive disease
PD-1	programmed cell death receptor
PD-L1	programmed death-ligand 1
PR	partial remission
PRAC	The Pharmacovigilance Risk Assessment Committee
PT	preferred term
RCC	renal cell carcinoma
rwPFS	real-world progression-free survival
SADR	serious adverse drug reaction
SAS	safety analysis set
SAP	statistical analysis plan
SCC	squamous cell carcinoma
SD	stable disease
SOC	system organ class
StDev	standard deviation
TRIM	Tissue Registry in Merkel cell carcinoma
UC	urothelial carcinoma

3 Investigators

Refer to Appendix D.

4 Other Study Responsible Parties

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Coordinating Investigator	PPD 60549 Frankfurt am Main, Germany

5 Milestones

Table 1 Study Milestones

Milestone	Planned date	Actual date	Comments
Final Protocol	Q2 2018	26 February 2018	Version 1.0 dated 25 October 2017; Update (V2.0) dated 26 February 2018; Update (V3.0) dated 26 August 2018; Amendment (V4.0) dated 03 December 2018; Amendment (V5.0) dated 10 August 2021; Amendment (V6.0) dated 20 November 2022
Registration in the EU PAS register	Q3 2018 (Within 2 months after final protocol)	28 August 2018	N/A
Independent Ethics Committee (IEC) approval	Q3 2018	28 September 2018	N/A
Final SAP	Q4 2018	24 April 2019	V2.0 dated 17 July 2020; V3.0 dated 23 August 2021; V4.1 dated 06 October 2022; V5.0 dated 11 August 2023
Start of data collection	Q1 2019	29 April 2019	First-patient in
Interim data cuts	Yearly, with the first one in Q3 2019	1st 20 September 2019; 2nd 30 September 2020; 3rd 30 September 2021; 4th 30 September 2022; 5th 30 September 2023	N/A
End of data collection	Q1 2024 (5 years after start of the data collection)	31 March 2024	N/A
PASS Annual progress reports	Yearly, with the first one expected in Q1 2020	25 February 2020; 22 February 2021; 21 February 2022; 07 March 2023;	N/A
Final report of study results	Q4 2024	xx December 2024	N/A

N/A–Not applicable; Q–quarter; EU PAS register - European Union electronic Register of Post-Authorisation Studies; SAP–Statistical Analysis Plan

6 Rationale and Background

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine cancer of the skin (Goessling 2002; Harms 2018; Nghiem 2016). Due to the concordance of many histopathologic and ultrastructural characteristics, MCC is thought to arise from the Merkel cells of the epidermis (Becker 2014). MCC is predominantly diagnosed in elderly patients (median age > 70 years) with only 4% of patients being ≤ 49 years (Albores-Saavedra 2010) and with a higher proportion of males being diagnosed than females (Paulson 2018). Globally, the incidence of MCC is low with 0.13/100,000 person-years in the EU, and 0.79/100,000 person-years in United States (Schadendorf 2017). However, it is increasing by 5% to 10% per year and generally occurs more commonly in men than women (Lemos 2007; National Comprehensive Cancer Network 2021; Santamaria-Barria 2013; Youlden 2014). About 80% of MCCs harbor a clonally integrated polyomavirus(Feng, 2008); however, sun and ultraviolet light exposure, immunosuppression and other cancers are also risk factors (reviewed in Becker 2010; Harms 2018; Hughes 2014).

In Germany, the incidence rate of MCC was reported for the region of Schleswig-Holstein before and after the implementation of a skin cancer screening program: the age-standardized incidence rates between 1998 and 2010 were 0.1 per 100,000 and 0.3 per 100,000, respectively in women, and 0.2 per 100,000 and 0.4 per 100,000, respectively in men (Eisemann 2014).

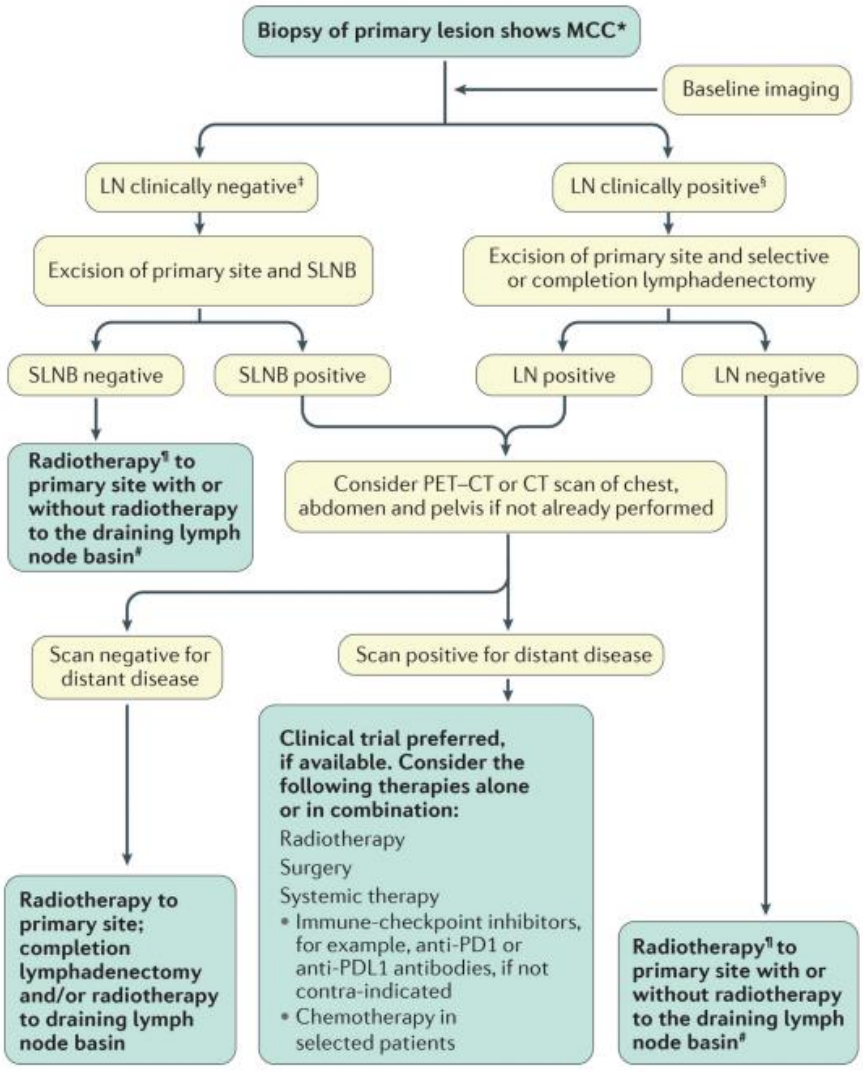
Since clinical features hardly contribute to the diagnosis of MCC, histopathological examination of biopsy material is mandatory, ideally supplemented with immunohistochemical staining of relevant markers. Staging of MCC involves “unknown primary status”, loco-regional lymph node and total body scanning examinations.

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology (National Comprehensive Cancer Network 2021) states that after having confirmed the MCC diagnosis via a biopsy, the choice of treatment for a primary MCC depends on the assessment of the extent of the disease spread. Indeed, the therapeutic strategy is defined after having examined the lymph nodes of the draining basin (clinically and/ or with ultrasonography), as the following management steps should consider whether they are clinically positive (enlarged) or negative. As a result of this assessment, the following treatment options, alone or in combination, are considered:

- Wide local excision of the primary tumor
- Wide-field adjuvant radiotherapy to the site of the primary tumor and, in some cases, to the draining lymph node basin
- Systemic therapy, with chemotherapy (the most common therapy for metastatic MCC not amenable to surgery before the introduction of immunotherapy) or immune checkpoint inhibitors (ICIs). Within this context, avelumab is indicated as monotherapy for the treatment of adult patients with metastatic MCC (mMCC).

The algorithm for the diagnostic and. therapeutic decisions for managing patients with MCC is presented below in Figure 1.

Figure 1 **Evaluation and Treatment of Primary Merkel Cell Carcinoma**



Algorithm for diagnostic and therapeutic decisions for managing patients with Merkel cell carcinoma (MCC). The flowchart begins with the assessment of the extent of disease spread to distant sites (baseline imaging) and regional nodal disease (typically including pathological assessment of clinically negative nodes). After staging is complete, the appropriate therapy can be identified. LN=lymph node; PD1 = programmed cell death protein 1; PDL1 = PD1 ligand 1; SLNB = sentinel lymph node biopsy. *Consider baseline Merkel cell polyomavirus serology for prognostic significance and to track disease. ‡No pathologically enlarged nodes on physical examination and by imaging study. §Pathologically enlarged nodes on physical examination or by imaging study. Radiotherapy is indicated in most patients, except for low-risk disease (for example, primary tumor ≤1 cm on the extremities or trunk, no lymphovascular invasion or negative surgical margin) in patients who are not immunosuppressed. #Consider radiotherapy to the nodal basin in high-risk patients. (Becker 2017)

Early stage disease can be treated with surgical resection and radiotherapy. In Europe and before approval of avelumab, metastatic MCC had been lacking an effective treatment, as responses to chemotherapy were not durable. Regarding treatment options after having MCC diagnosis, a national S2-guideline has recently been developed in Germany (Becker 2019), which is concordant with the recommendations of the NCCN. Due to its rarity, MCC is classified as an orphan disease (ORPHA79140 under http://www.orpha.net/consor/cgi-bin/index.php).

The treatment landscape for MCC has been changing rapidly over the last decade with the introduction of new therapeutic options in Europe and the United States. PD-L1 is expressed in about 50% of MCC tumor cells and tumor infiltrating lymphocytes in MCC patients (Lipson 2013). Therefore, PD-1, PD-L1 inhibitors seems effective as treatment. The PD-1 inhibitor pembrolizumab was approved by the European Commission (EC) for melanoma in July 2015. Pembrolizumab was approved by the Food and Drug Administration (FDA) in December 2018 to treat locally advanced or metastatic MCC. Until now, pembrolizumab has not been approved to treat MCC in Europe. The PD-L1 inhibitor retifanlimab was granted accelerated approval by FDA for metastatic or recurrent locally advanced MCC in March 2023; it was designated as an orphan medicine for the treatment of Merkel cell carcinoma in the European Union in January 2023. Retifanlimab (ZYNYZ) received EC approval as monotherapy for first-line treatment of adult patients with advanced MCC not amenable to curative surgery or radiation therapy in April 2024.

Merck Healthcare KGaA and Pfizer were co-developing avelumab, an investigational fully human anti-programmed death-ligand 1 (PD-L1) immunoglobulin-G1 (IgG1) monoclonal antibody, which belongs to a class of drugs that activate the immune system to attack malignant tumors and are used to treat many types of cancer. Merck and Pfizer (former Co-Sponsors) were investigating avelumab for multiple cancer types as possible indications, either as monotherapy or in combination with other therapies. The alliance between Merck Healthcare KGaA and Pfizer for Bavencio, was terminated in June 2023 and thereafter, Merck regains exclusive worldwide rights to develop, manufacture and commercialize avelumab.

The FDA granted accelerated approval of avelumab for the treatment of adult and pediatric patients 12 years and older with mMCC. On 6 September 2023, Merck Healthcare KGaA, Darmstadt, Germany received approval to convert the accelerated approval into full approval of Avelumab for the treatment of mMCC and fulfilled accelerated approval requirements for this indication. Avelumab is the first product to receive full approval for mMCC indication by FDA. On 23 March 2017, and locally advanced or metastatic urothelial carcinoma in those whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy on 9 May 2017. On 14 May 2019, the FDA approved avelumab in combination with axitinib for first-line treatment of patients with advanced RCC. Most recently, on 30 June 2020, avelumab was approved by the FDA as maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy. Regarding the European Union (EU), the EC approved avelumab as monotherapy for the treatment of adult patients with mMCC on 18 September 2017. At that time, it was the first approved immunotherapy for this rare and aggressive type of skin cancer. In Europe, avelumab (Bavencio®) was made commercially available to patients by prescription within few weeks following its approval in some countries, with initial access in Germany and the United Kingdom (UK) as soon as October 2017. Since then, the EC approved avelumab in combination with axitinib for first-line treatment of adult patients with advanced RCC, on 28 October 2019. On 25 January 2021, avelumab was approved by the EC as first-line maintenance treatment of adult patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy, adding one more solid cancer indication to the avelumab label in the EU.

Considering the changing landscape of MCC treatment in Europe, more comprehensive information on patients with advanced MCC and their tumor characteristics, as well as effectiveness and safety outcomes from a large sample size of patients, in the real-world setting in Europe, is needed.

This study established a real-world dynamic cohort of patients with MCC in Germany. A German national skin cancer registry (ADOREG) operated by ADO (Arbeitsgemeinschaft Dermatologische Onkologie, [in English: Dermatological Cooperative Oncology Group, DeCOG]) in cooperation with IQVIA, was established in 2014. The decision was taken to expand the scope of skin cancers collected and, consequently, patients with MCC started to be enrolled in ADOREG from March 2018. ADOREG currently records data on patient and tumor characteristics, as well as treatments received and treatment outcomes. For the dynamic cohort study, a study-specific electronic case report form (eCRF) was added to collect additional data on tumor samples, immunosuppressive conditions and immunosuppressive medications, adverse drug reactions (ADR) and healthcare resource use.

By using the existing network of sites reporting into ADOREG and collecting additional data via a dedicated eCRF, this dynamic cohort study, named MCC TRIM (Tissue Registry in Merkel cell carcinoma), enabled a better description of patients with MCC in Germany, and thereby contributes to the understanding of this rare disease.

The Pharmacovigilance Risk Assessment Committee (PRAC) classified part of this study as a PASS (category 3) as some objectives of the dynamic cohort study have been used to specifically answer the question regarding the safety and efficacy of avelumab in the subset of immune compromised patients, a group of patients which was not included in the pivotal clinical trial (Kaufman 2018). As a voluntary PASS, the study was notified to the relevant local regulatory authority in Germany (Paul Ehrlich Institute) after approval by the PRAC. In this PASS report, only sections related to PASS objectives are reported.

7 Research Question and Objectives

This cohort study identified and followed patients with MCC using routinely collected ADOREG data as well as additional study-specific data via primary data collection. Among the other questions, the study aimed to address the following questions specifically for the subgroup of immune compromised (ICS-) patients:

- What is the safety profile of avelumab in the treated ICS- patients with MCC in the real-life setting in Germany, and is this profile (both from a safety and effectiveness perspective) comparable to that of immune competent (ICS+) patients?

7.1 Primary Study Objectives

The primary objectives for Study MS100070-0031 were:

- Describe, relevant patient and tumor characteristics in patients diagnosed with MCC in Germany

- Estimate background prevalence rates of relevant comorbidities in this study patient population
- Describe MCC-related oncology treatments for all types and lines of therapy since initial diagnosis of MCC
- Describe relevant common comorbidities in patients entering advanced disease stage *
- Describe relevant concomitant medications, i.e. used as premedication or for management of adverse drug reactions (ADRs), in patients entering advanced disease stage*

* Patients entering advanced disease stage are defined as unresectable Stage III to IV MCC.

The specific PASS objectives for the patients treated with avelumab were:

- Characterization of disease outcomes by means of response (complete remission [CR], partial remission [PR], stable disease [SD], progressive disease [PD]) and survival (real-world progression-free survival [rwPFS], overall survival [OS]) analyses per treatment line and overall, and specifically in the specific subgroup of immune compromised patients treated with avelumab**;
- Description of the safety events of interest (e.g. immune-related adverse drug reactions [irADRs]) overall and specifically in the subgroup of ICS- patients treated with avelumab**.

** ICS- patients are defined based on relevant comorbidities and medications within a certain time period (see section 9.10.2).

7.2 Exploratory Objectives

- Comparison of the safety and effectiveness profile of ICS- patients with the profile of ICS+ patients, all of whom are treated with avelumab**.

8 Amendments and Updates

The amendments/updates mentioned below were made to the study protocol.

Table 2 Protocol Amendments and Updates

Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
1	25 October 2017	N/A	First version	N/A
2	26 February 2018	Throughout	Update	General revision in response to comments received from the PRAC
3	26 August 2018	Throughout	Update	Quality check
4	03 December 2018	Study timelines, Section 14.4, Section 11	Amendment	To better describe the interaction between the existing skin cancer national registry, ADOREG, now expanded to enroll MCC patients, and the dynamic cohort study, aka MCC TRIM, and the fact that the data used for this study will come from ADOREG (where some of the data are

Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
				already collected as part of the routine data collection, and then considered as secondary data for the study), complemented by a primary data collection, specifically for the purpose of this study (as not part of the routinely collected data in ADOREG). A clarification about which data are coming from which sources has been added in section 14.4 related to the eCRFs; To adapt the study timelines, due to a delay of around 6 months compared to the initial timelines, for the start of data collection and all subsequent milestones, partially linked to the acquisition of the CRO, ONKODATAMED, by the company IQVIA (changes also implemented in the current version), acquisition which has triggered additional contractual discussions before the concrete implementation of the study; To clarify the section 11 on the Management and Reporting of Adverse Drug Reactions by deleting all references to adverse events that were remaining from standard text, and to ensure that it is clearer now that only ADRs are collected and reported (no AE should be collected or reported) as agreed with the PRAC; To correct some inconsistencies between different sections of the protocol.
5	10 August 2021	Study size, Section 9.5	Amendment	The protocol amended in December 2018 (Version 4.0) has been amended to Version 5.0 to adapt the study size (see Section 9.5) due to higher recruitment rate than expected for the overall population and update administrative aspects.
6	20 November 2022	Milestones, Section 6	Amendment	The protocol amended in August 2021 (Version 5.0) has been amended to Version 6.0. Actual project timelines have been added to Section 6.

N/A= Not applicable, EMA= European Medicines Agency, MCC= Merkel cell carcinoma, TRIM= Tissue Registry in Merkel cell carcinoma, eCRF= Electronic case report form, CRO= Contract research organization, ADR= Adverse drug reaction, AE= Adverse event, PRAC= Pharmacovigilance Risk Assessment Committee

9 Research Methods

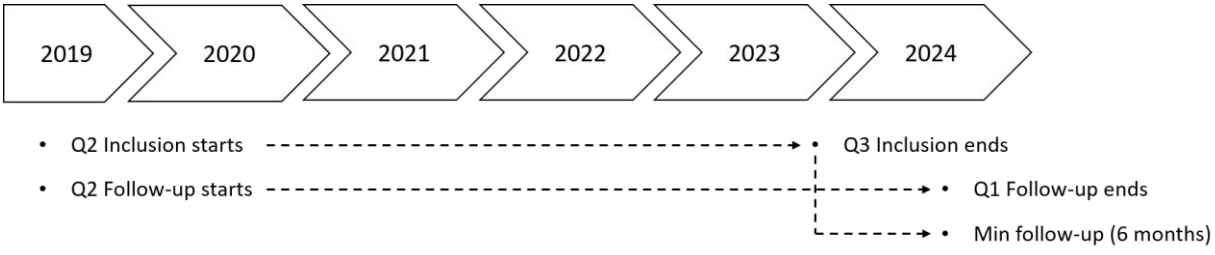
9.1 Study Design

This study is a non-interventional (observational), longitudinal cohort study conducted in multiple sites in Germany. The design is an open cohort with continuous enrollment during the study inclusion period starting in Q2 2019 through end of Q3 2023, allowing for a minimum follow-up of 6 months for each patient as the follow-up of all patients ended with study closure by end of Q1 2024. Throughout the whole study period, data on parameters of interest from routine clinical practice was regularly (with a minimum periodicity of 6 months) documented in the study-specific eCRF for each patient, starting after individual study inclusion. Patients were not assigned per protocol to a particular treatment or intervention. Treatment decision lay within the discretion of the treating physician and was independent from the decision to include the patient in the study. Data analyses were performed annually for annual progress reports and analysis for the final report was conducted after the study closure (Q1 2024). Data are either registered directly as part of ADOREG routinely collected data (in the ADOREG eCRF), or in the specific eCRF built for the cohort study to collect additional data needed for this study. Individual patient data from the ADOREG database was sourced into the study database, hence the study database contains all data required for the study purpose.

For quality assurance, and specifically to confirm diagnosis and potential biomarkers, central histopathological and molecular analysis of routine tumor samples collected at initial diagnosis and progression of the disease were performed. These analyses also include the prognostic marker Merkel cell polyomavirus (MCPyV) status. Consent to the analysis of tumor tissue for research purposes was requested within the informed consent and was mandatory for participation in the study. However, in cases when only limited or no tumor material at all was available, the central analysis was restricted to confirmation of the diagnosis or had to be waived, in agreement with the central laboratory.

The overall study plan is summarized below in Figure 2.

Figure 2 Overview of Study Design



Q= quarter; Min=minimum

Further information on the ADOREG could be find in section 9.4 of the study protocol version 6.0.

All male and female patients diagnosed with MCC were invited to participate by the contracted study sites in Germany and included in the study if fulfilled inclusion criteria. All these sites also participate in ADOREG. Patients were included in the study irrespective of their MCC stage, diagnostic test for MCC, and their prior and/ or current treatments, allowing for the assessment of any disease stage and treatment history.

9.2 Setting

The study was conducted in real-world setting.

The study population was enrolled by healthcare providers (HCPs), mainly dermatologists, who treat and manage patients with MCC in Germany. Further details are given in section 9.5.

9.3 Subjects

The study population was identified according to the inclusion criteria below. No exclusion criterion was applied for this study. Patients had to fulfil all of the following inclusion criteria:

- Being diagnosed with MCC, regardless of stage, age and the diagnostic MCC tool/test used;
- Providing written and signed informed consent to collect and process data in a pseudonymized manner either by him/ herself or by the legal guardian if aged <18 years;
- Providing written and signed informed consent to collect and process tumor specimens in a pseudonymized manner either by him/ herself or by the legal guardian if aged <18 years.

9.4 Observation Period

The study period (first-patient in) started on 30 April 2019 and continued for the duration of 5 years (end of Q1 2024). Patients contributing to this final study report were included from the study start (30 April 2019) until end of recruitment period (30 September 2023) and observed until the end of data collection period (31 March 2024). During this timeframe, up to 9 follow-up recordings were possible. All patients were followed from the time of study inclusion through to death, loss to follow-up, consent withdrawal, or end of data collection period (whichever came first).

9.5 Data Sources and Measurements

ADOREG collects relevant epidemiological and clinical data of all patients visiting the participating sites through an online web-based secure electronic documentation system. In this system, data safety and protection measures have been implemented and approved.

ADOREG comprises the following sub-registries:

- Malignant melanoma
- Basal cell carcinoma
- Squamous cell carcinoma

- Cutaneous lymphoma
- MCC

Further information on the ADOREG is in section 9.4 of the study protocol version 6.0. To achieve high data quality and to avoid potential heterogeneity in data collection, parameter value types were based on code lists or specified value ranges where possible. Classifications that were used comprise e.g. the International Classification of Disease 10th Revision (ICD-10) for relevant comorbidities, as described in section 9.6. Automated edit checks defined in the data validation plan have been implemented in the eCRFs, where possible. In addition, definitions for some variables were provided directly in the eCRFs to provide clarity. Finally, the sites also had access to an eCRF-manual, which was regularly updated and available for download in the ADOREG documentation system. This way of collecting data could limit the potential difference in data collection and ensures alignment of information measured between the different sites.

9.6 Variables

The following variables were considered as the key (most important) variables, especially to adequately describe the safety and effectiveness of avelumab, overall and in the sub-group of ICS- patients.

Tumor characteristics: Date of initial diagnosis, localization of primary tumor (according to ICD10), Tumor Node Metastasis classification and tumor stage (according to the American Joint Committee on Cancer (AJCC) staging) at time of inclusion, histology of primary tumor, MCPyV status, PD-L1 test performed and result if available. In case of metastatic disease at the time of inclusion: Description of metastases (lymph node, satellite/ In-transit, distant [including localization of distant metastases]).

MCC-related oncology treatments: Name, type, standard dose, and duration (if applicable number of cycles) of oncology treatment for all lines of oncology treatment since initial diagnosis of MCC (including surgery, radiation, and systemic therapy), and treatment situation (neoadjuvant, adjuvant, curative, maintenance, palliative).

Date of tumor evaluation, method used for tumor evaluation, results of tumor evaluation, CR, PR, SD, PD (method chosen for tumor assessment can be asked, e.g. immune-related response, imaging, Response Evaluation Criteria in Solid Tumors (RECIST), other method), rwPFS, and OS. Evaluation at time of relapse/ progression: Date of relapse/ progression, description of metastases (lymph node, satellite/ In-transit, distant [including localization of distant metastases]).

Safety variables: ADRs in relation to oncology treatments (causality assessment) including immune-mediated ADRs as assessed by the investigators, start and end dates of ADR, outcome of ADR and seriousness and reason for seriousness classification. More specifically, for this study, the following adverse drug reactions are considered:

- Immune-related Adverse Drug Reactions (irADRs)
- Infusion-related reactions (IRRs)

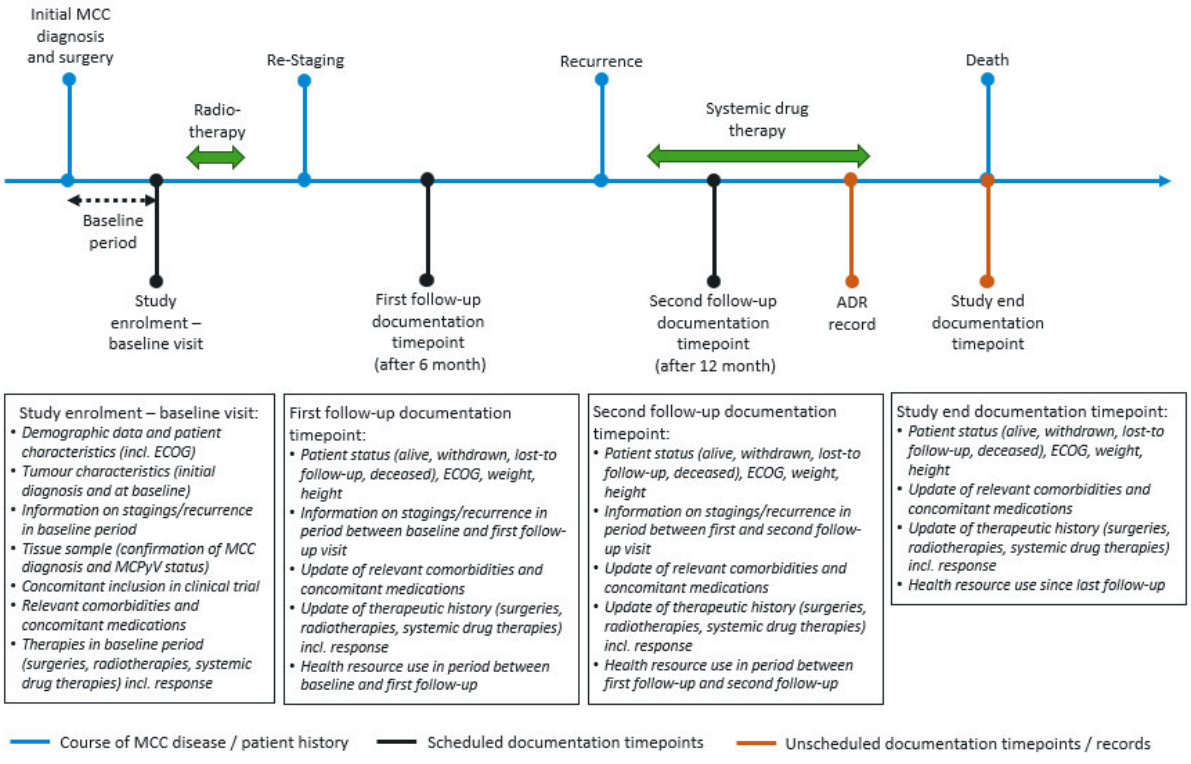
Comorbidities (in patients entering advanced disease stage, i.e. unresectable stages III-IV): Relevant comorbidities were assessed using the ICD-10 codes, and specifically to allow differentiation between immune competent and immune compromised patients.

Concomitant medications (in patients entering advanced disease stage, i.e. unresectable stages IIIIV): Prior or concomitant medications of particular interest (i.e. to capture immune compromised patients).

Refer to Section 9.3 of the protocol (version 6.0) as well as in Section 4.1 and the Table 1 of the SAP version 5.0 for further details.

Figure 3 describes a course of one exemplary MCC patient and how events and relevant treatments are captured via scheduled and unscheduled data recording timepoints.

Figure 3 **Course of An Exemplary Merkel Cell Carcinoma Patient, Study Visits and Data Recordings**



Source: Appendix F, Figure 3

MCC = Merkel Cell Carcinoma; ECOG = Eastern Cooperative Oncology Group score; MCPyV = Merkel Cell Polyomavirus; ADR = Adverse Drug Reaction

9.7 Bias

Considering the observational design of the study, possibility of selection and information bias cannot be discarded.

To reduce possibility of selection bias and to reflect the real-world treatment situation of MCC, eligibility criteria for this study were kept as broad as possible, no exclusion criteria were applied.

To minimize selection bias, sites participating in ADOREG were selected as representing most of the large as well as small dermatology departments in Germany.

Enrollment of patients consecutively during prospective recruitment period until all or maximum number of eligible patients were included contributed to minimization of possible selection bias.

The study had also potential for information bias consistent with the observational design.

The study was carried out using data recorded during routine clinical care. Under consideration of observational design, timing of data collection could be not consistent across the study population; no standardized and comparable assessment over all study centers was implemented. Heterogeneity between the leading study center (Universitätsklinikum Essen) and other centers with regards to the outcome parameters (effectiveness, safety) was explored in regression analysis.

In the routine clinical care, some records are expected to be incomplete. Missing information on patient characteristics and study outcomes during this observational study could introduce source of biased results. In particular, missing information on death among patients considered lost to follow-up could impact results of survival analyses. Study centers were actively engaged on an ongoing basis to minimize missing data.

Misclassification of patient characteristics or outcomes may be due to systematic or random measurement error. To minimize this type of bias in the current study, instructions were provided to all investigators to harmonize the way data are collected in the eCRF.

Underreporting of ADRs is known with respect to spontaneous reporting (Crestan 2020). On-site monitoring visits to the sites were performed in the current study to assess the accuracy of the reporting and possibly increase the reporting rate.

For further details on study limitations please refer to section 11.2.

9.8 Study Size

Based on the analysis of the North Rhine-Westphalia epidemiologic tumor registry of patients with MCC in Germany (for details, see study protocol section 9.5, study size), an enrollment of 120 patients per year was envisaged (estimated to be about 25% of total new MCC diagnosis in Germany per year) by the projected 45 sites to be contracted for this study.

It is estimated that around 30% to 40% of patients will have been diagnosed with advanced stage MCC at the time of inclusion or will subsequently have disease progression to advanced stages (Kukko 2012). Thus, a total of around 540 patients were expected to be included during the 4.5-year inclusion period of this study, with 160 to 200 patients with mMCC either at inclusion or during the follow-up period.

The assumption was that most of the patients with mMCC were to be treated with avelumab, and between 8 to 10% were expected to be immune compromised (Heath 2008; Paulson 2013). Therefore, the size of the primary subgroup of interest to answer the specific request from the Committee for Medicinal Products for Human Use regarding information on the efficacy and safety profile of immune compromised patients treated with avelumab should be around 15 to 20 patients. For the exploratory objective, around 140 to 180 patients considered not immune compromised and treated with avelumab were expected to be evaluated over the entire study period (Q2 2019 to Q1 2024).

However, after around 2 years, the study team observed a higher recruitment rate (around 19 patients per month), and slightly lower proportion of patients in advanced stages (around 27%) compared to the initial assumptions; therefore, it has been agreed to continue enrollment up to the planned end of the study inclusion period (Q3 2023) or (at maximum) 1000 patients, whichever will come first.

9.9 Data Transformation

Categorical variables were created by the grouping of reported values of discrete or continuous parameters (e.g. variable “age group” in 7 categories based on continuous parameter “age”).

Detailed methods for data transformation and data management are documented in the SAP, available in Appendix E.

9.10 Statistical Methods

9.10.1 Main Summary Measures

All analyses were conducted using SAS version 9.4, except the Sankey diagram rendering, which was conducted using R, version 4.2.1.

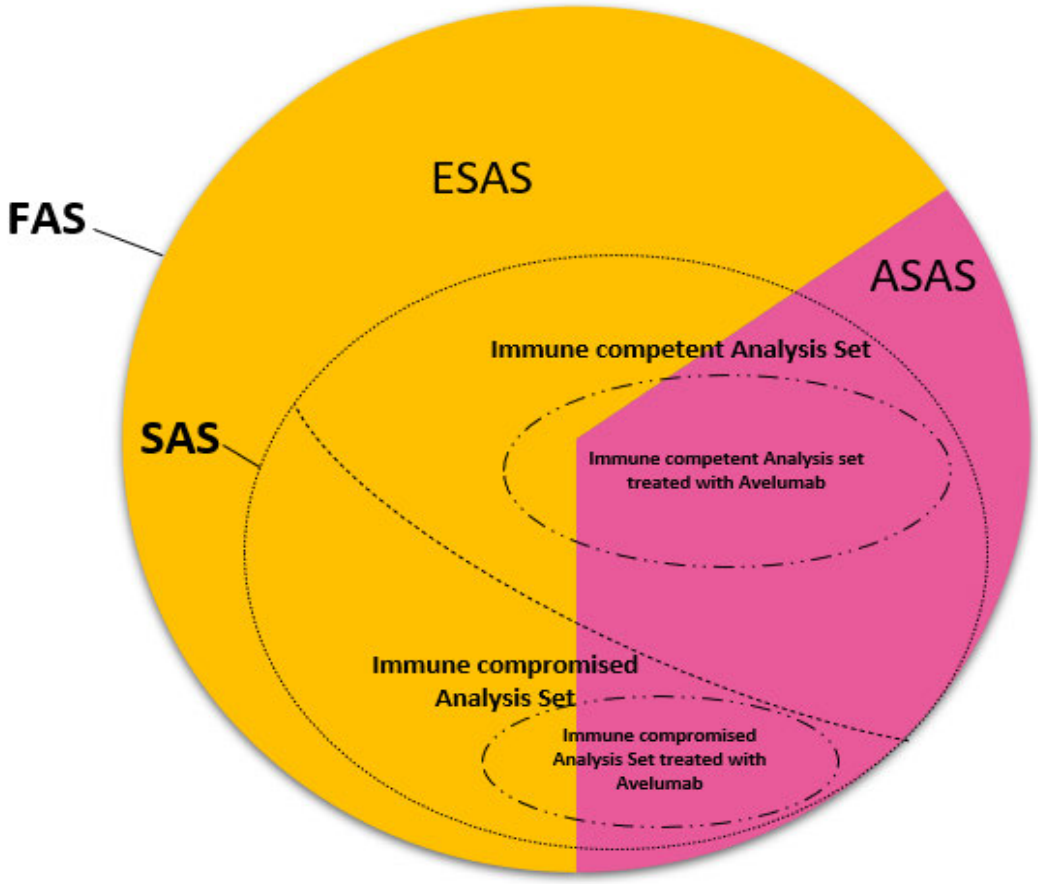
Summary statistics including demographics and characteristics at study inclusion were tabulated. Frequencies and percentages were used to describe categorical variables. Continuous variables were described as means and standard deviations as well as medians and interquartile ranges, minimum and maximum. Where appropriate, two-sided 95% confidence intervals (CIs) were presented. Where possible, graphical representation was used to illustrate results. The number of patients with non-missing data and number of patients with missing data were also reported.

Rates and proportions were calculated for study outcomes. Kaplan-Meier survival estimates were used for time to event analyses, including study survival outcomes.

9.10.2 Analysis Sets

Analysis sets are visualized in Figure 4 below.

Figure 4 Graphical display of Analysis Sets



FAS - Full Analysis Set; ESAS – Early-Stage Analysis Set; ASAS – Advanced-Stage Analysis Set; SAS - Safety Analysis Set. Please note that the proportion observed in the figure is not intended to reflect the proportions of each Analysis Set of the study.

Full Analysis Set (FAS)

The FAS contained all patients enrolled in the study who fulfilled all inclusion criteria for the study.

Safety Analysis Set (SAS)

The SAS contained all enrolled patients who had received at least one dose of any systemic oncology treatment, including avelumab.

Advanced-Stage Analysis Set (ASAS) And Early-Stage Analysis Set (ESAS)

The ASAS contained all patients in the subpopulation of the FAS, defined as patients with unresectable Stage III or Stage IV MCC. Patients with unresectable Stage III / IV MCC were operationalized as follows:

- Recorded Stage III and systemic oncology treatment with palliative/curative intention documented in the eCRF, or
- Stage IV cancer.

The ESAS contained all patients in the FAS who are not included in the ASAS.

Analysis Sets of patients not considered immune compromised and Immune compromised Analysis Sets

These Analysis Sets were based on the SAS.

Patients in these sets were classified as immune compromised (and included in the immune compromised Analysis Set) when one or more concomitant comorbidities or concomitant medications were recorded for these patients at the time the patients received any systemic oncology treatment, including avelumab as described in section 5.4 of the SAP (Appendix E) and Table 3.

Table 3 Comorbidities or concomitant medications that are considered for the ICS- analysis sets.

Comorbidities	Concomitant medications:
• HIV (testing positive for HIV or known AIDS • CD4 count ≤500 any time from 12 months prior diagnosis date to most recent follow-up • Organ transplantation (incl. allogeneic stem-cell transplantation) • Concurrent malignancy excluding Squamous cell carcinoma in situ	• Systemic corticosteroids (corticosteroids for systemic use, plain and, combinations) • Calcineurin inhibitors • mTOR inhibitors (sirolimus, everolimus, temsirolimus) • IMDH inhibitors (azathioprine, leflunomide, mycophenolic acid) • Biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, natalizumab, ituximab, secukinumab, tocilizumab, ustekinumab, vedolizumab) • Monoclonal antibodies (basiliximab, daclizumab, muromonab-CD3) • Cytostatics (methotrexate, cyclophosphamide) • Other (dimethyl fumarate)

CD4: Cluster of differentiation 4, HIV: Human immunodeficiency virus, AIDS: Acquired Immunodeficiency Syndromem, TOR: Mammalian target of rapamycin, IMDH: Inosine monophosphate dehydrogenase

Patients included in the SAS and not considered immune compromised according to the above criteria were categorized as not immune compromised and included into the Analysis Set of patients not considered immune compromised.

Patients classified as immune compromised and treated with avelumab at any time were included into the Immune compromised Analysis Set treated with avelumab. Likewise, patients not considered immune compromised treated with avelumab at any time were included into the Analysis Set of patients not considered immune compromised treated with avelumab. This PASS report focuses on the results of the last 2 Analysis Sets.

9.10.3 Main Statistical Methods

9.10.3.1 Analyses According to PASS Study Objectives

9.10.3.1.1 Description of Relevant Patient and Tumor Characteristics in Patients Diagnosed with MCC in Germany

Patient and tumor characteristics were analyzed using the FAS and ASAS (described in section 9.10.2). Patient and tumor characteristics were reported once at study inclusion and for time-varying characteristics also when entering advanced stage (as defined for the ASAS), e.g. Eastern Cooperative Oncology Group (ECOG) score. For some patients, values at study inclusion and when entering advanced stage were the same, as their diagnosis at study inclusion was already advanced MCC. The baseline period was defined as the time between the initial diagnosis date and the inclusion date.

For variables where a patient may have more than one category due to multiple responses per patient and if not stated otherwise in the table footer, the proportion of patients included in each category was calculated using all patients as the denominator. Therefore, the total frequency across categories may not equal the total number of all patients in the population and the sum of proportions over all categories may exceed 100%.

For the complete list of characteristics and the respective statistics that were reported for the characteristics refer to section 4.1 of the SAP (Appendix E).

9.10.3.1.2 Estimation of Background Prevalence of Relevant Comorbidities in this Study Patient Population

Prevalence proportions and prevalence rates of comorbidities at study inclusion were analyzed using the FAS and ASAS (described in section 9.10.2). Frequencies, percentages and rates (and the respective 95% CI) of patients with relevant comorbidities (1) at study inclusion and (2) entering advanced stage were reported by groups of comorbidities and by specific comorbidities, the full list is described in the protocol, section 14.4, eCRF (anticipated/minimum list of variables) and in the SAP Section 4.2.

Person-years at risk considered for prevalence rates are calculated from initial MCC diagnosis to enrollment date for the FAS and from initial MCC diagnosis to entering advanced stage disease for the ASAS.

9.10.3.1.3 Description of Relevant Common Comorbidities in the Immune Compromised Analysis Set and the Immune Compromised Analysis Set Treated with Avelumab

These analyses were performed on ESAS and ASAS patients included in the immune compromised Analysis Set and the Immune compromised Analysis Set treated with avelumab (for definitions see section 9.10.2).

The immunosuppressive comorbidities listed in section 4.4 of the SAP were analyzed.

Any record of the listed comorbidities in the patient's history up until the most recent follow-up coinciding with drug therapy were considered relevant for this analysis.

Frequencies and percentages (and the respective 95% CI) were reported by immunosuppressive comorbidity condition.

9.10.3.1.4 Description of Relevant Concomitant Medications in the Immune Compromised Analysis Set And the Immune Compromised Analysis Set Treated with Avelumab

These analyses were performed on ESAS and ASAS patients included in the immune compromised Analysis Set and the Immune compromised Analysis Set treated with avelumab (for definitions see section 9.10.2).

Any record of "ongoing" immunosuppressive concomitant medications listed in section 4.5 of the SAP when the patient simultaneously was treated with MCC-related drug therapy was considered relevant for this analysis.

Frequencies and percentages (and the respective 95% CI) of medication use were reported overall (use of at least one concomitant medication) and by drug class.

9.10.3.1.5 Characterization of Disease Outcomes

Response analyses

These analyses were performed on ESAS and ASAS patients as well as patients included in the immune compromised and not considered immune compromised Analysis Sets treated with avelumab (for definitions see section 9.10.2).

Information on treatments and outcomes was stratified by cancer stage. For each stratum, a contingency table was generated, reporting counts and percentages of response (CR, PR, MR, SD, PD, NED, unratable) by treatment (radiotherapy, neoadjuvant systemic therapy, adjuvant systemic therapy, systemic therapies [L1, L2, L3]). In case if number of observations in a group was too low to produce meaningful results ($n \leq 10$), the results are not provided in this report.

Survival analyses (rwPFS, OS)

These analyses were performed among patients in SAS (for definitions see section 9.10.2), having received their first administration of systemic treatment after study inclusion.

Main analysis for rwPFS

rwPFS was calculated per line of treatment (1 L, 2 L, 3 L). rwPFS was defined as the time (in months) from day of first systemic treatment administration to the date of the first documentation of progressive disease (PD) or death due to any cause, whichever occurs first.

The rwPFS was censored on the start date of the subsequent line (initiation of a new anticancer therapy, leading to a change in line) if a subsequent line was recorded and there was no indication of progressive disease (e.g. the new line was initiated due to toxicities), loss to follow-up or at the end of follow-up (end of study period).

Sensitivity analyses on rwPFS

In some cases, the exact PD date may be unknown but the response for the respective line was rated as PD. These cases were not considered as events in the primary rwPFS analysis. To be able to evaluate the impact of probably missing PD dates, a sensitivity analysis was performed, where in these cases the stop date of the respective treatment line was used as the event date as a surrogate for the missing PD date (Obj 6b-2).

An additional sensitivity analysis regarding rwPFS was performed, where the initiation of a new line of treatment was not considered as a censoring event (Obj 6b-3).

Analyses of rwPFS and OS from first-line treatment with avelumab stratified by immune compromised status (patients not considered immune compromised [ICS+) vs. patients considered immune compromised [ICS-]) were conducted.

Kaplan-Meier curves

Kaplan-Meier curves showing rwPFS for all SAS patients having received their first administration of first-line systemic treatment after study inclusion were rendered, as well as curves showing overall survival (irrespective of treatment line, first, second and third-line). In case if number of events in survival analyses in some strata was too low to produce meaningful results (≤10 events per stratum), they have not been displayed and are not provided in the report.

For detailed description of survival analyses please refer to section 4.6 of SAP (Appendix E).

9.10.3.1.6 Description of the Safety Events of Interest Overall and Specifically in the Subgroup of Immune Compromised Patients Treated with Avelumab.

The Analysis Sets considered for Objective 7 analyses were: (i) patients receiving any systemic therapy to treat MCC (SAS), (ii) the Analysis Set of patients not considered immune compromised, (iii) the immune compromised Analysis Set, (iv) the Analysis Set of patients not considered immune compromised treated with avelumab and (v) the Immune compromised Analysis Set treated with avelumab. However, patients in each analysis set were only included in Objective 7 analyses, if their last dose of systemic treatment was within 90 days prior to enrollment, if they had an ongoing systemic treatment at enrollment or if they received systemic treatment after enrollment. Both totals of patients with at least one ADR as well as relative proportions and incidence rates of ADRs were analyzed. This PASS report focuses on results for the last 2 Analysis Sets.

9.10.3.2 Exploratory Analyses

9.10.3.3 Comparison of Safety and Effectiveness Profiles Between Immunocompromised and Immunocompetent Patients Treated with Avelumab

Patients receiving avelumab were stratified by their immune competence status at initiation of avelumab therapy (see section 9.10.2). Responses (CR, PR, MR, SD, PD) to avelumab treatment by immunocompetence have been visualized in a contingency table. Differences in proportions of specific responses and CIs were calculated. With respect to safety events, totals of patients with at least one ADR, number, and incidence rates of ADRs were analyzed.

9.10.3.4 Annual Analyses

Data analyses comprised all objectives. Where low sample sizes did not allow for specific analyses, this is stated in the respective sections within the reports.

9.10.3.5 Final Analysis

All planned final analyses are performed in 2024 after the end of study data collection on 31 March 2024.

9.10.4 Missing Values

Missing data were not imputed for this study.

9.10.5 Sensitivity Analyses

Sensitivity analyses were performed as described in section 9.10.3.1.5 in relation to rwPFS.

9.10.6 Amendments to the Statistical Analysis Plan

The relevant version of the SAP was version 5.0, provided in Appendix E. As suggested by the agency during the review of the annual progress reports, the amendments made during the latest SAP update and implemented in the current analysis were undertaken in order to address a certain degree of heterogeneity between the leading study center (Universitätsklinikum Essen, the reference center in Germany with the highest recruitment) and other centers, and to explore the impact of the leading center on overall study results (effectiveness, safety).

The PASS related objectives are assessed in ICS- and ICS+ patients treated with avelumab and stratified by binary center variable (center 1: Universitätsklinikum Essen vs. center 2: all other centers pooled together).

Therefore, descriptive patients' and tumor characteristics as well as patients' effectiveness and safety profile have been explored within center by immune status. Exploratory regression analyses with independent parameters for immune compromised status, center and interaction

term were applied in case of differences identified in descriptive characteristics (multinomial regression models for treatment response and Poisson regression model for Incidence rate of ADRs). Under consideration of exploratory character of analyses (no hypotheses testing was planned), no adjustment for multiple testing was performed.

9.11 Quality Control

Standard procedures were used to ensure data quality and integrity, including quality control and archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, description of available data, and extent of validation of outcomes. In addition to the quality checks already described in 9.15 (e.g., data plausibility checks, monitoring of data), this dynamic cohort study was conducted according to the rules of 'Good Pharmacoepidemiology Practice' (Public Policy Committee, International Society of Pharmacoepidemiology 2016).

The investigators complied with the confidentiality policy as described in the site contracts and with the requirements described in the protocol. The treating physicians were ultimately responsible for the conduct of all aspects of the study at the local level and verified the integrity of all data transmitted to ADOREG or collected as supplementary information for the MCC TRIM study.

9.12 Management and Reporting of Adverse Reactions

Recording of Adverse Drug Reactions in the Case Report Form

For this study, only ADRs (serious and non-serious) were recorded. The recording of unrelated AEs was not considered necessary in order to achieve the study objectives.

ADRs were considered for recording if patient had last dose of systemic treatment within 90 days prior to inclusion in the study (date of signature of first informed consent) and continued until the end of the mandatory safety-follow-up period, which is 90 days after the last drug administration.

Each serious ADR, as specified in section 11 of the protocol version 6.0, occurring during the study, had to be documented by the investigator within 24 hours of awareness and recorded in the eCRF, including its description, seriousness, severity (grading), duration (onset and resolution dates), causal relationship, any other potential causal factors, actions taken with the drug (e.g. dose reduction, withdrawal), required treatment and outcome of the event. Nonserious ADRs had to be recorded within 30 days of awareness and otherwise documented in the eCRF following the same principles as for serious ADRs.

Regulatory Reporting to the Health Authorities

After ADRs recording by the investigator in the eCRF, ADRs related to avelumab (serious and non-serious) were reported to the Sponsor by the investigator. To send the report, the investigator approved the ADR report via e-signature in the eCRF. Expedited reporting of serious and non-

serious ADRs to Health Authorities was performed by the Sponsor according to applicable global and local requirements.

In addition, the investigator had to comply with any applicable local pharmacovigilance requirements to report appropriate safety data to national pharmacovigilance systems, as required by German specific reporting requirements.

9.13 Ethics

The Ethics Committee of Universitätsklinikum Essen approved the conduct of this study in Germany on 28 September 2018. However, each participating study site also had the option to follow their local requirements and obtain ethics approval for the conduct of the study at their respective sites.

9.13.1 Health Authorities

The protocol and any applicable documentation (Subject Information and Consent Form) were submitted or notified to the National Health Authorities (Paul Ehrlich Institute) in accordance with the regulations of Germany.

9.13.2 Patient Information and Informed Consent

Prior to obtaining informed consent from eligible patients, the investigator or his/ her delegate had the obligation to inform patients about, but not limited to, the aim of the study and their rights of participation in the study. An information sheet in the local language (German) was provided to the patient for the purpose of obtaining informed consent.

The informed consent form had to be signed and personally dated by the patient or his/her legal guardian if aged <18 years and the investigator. The signed and dated declaration of informed consent remained at the investigator's site and had to be safely archived by the investigator. A copy of the signed and dated information and consent form had to be provided to the patient prior to study participation.

Whenever important new information became available that might be relevant to the patient's consent, the written patient information sheet and any other written information provided to patients had to be revised by the Sponsor and submitted again to the IEC for review and approval.

9.14 Subject Identification and Privacy

A unique pseudonym was assigned to each patient at inclusion. This pseudonym served as the patient's identifier in the study as well as in ADOREG. A separate unique identifier connected to the first assigned pseudonym was used in the MCC TRIM study database.

The site investigator ensured that the patients' anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, patients were not identified by their names or other identifiers but rather by their assigned pseudonyms. If names were included on copies of

documents submitted to the Sponsor, the names were obliterated, and the assigned patient pseudonym added to the documents. Documents not relevant for submission to the Sponsor, such as signed informed consent forms, were maintained in strict confidence by the site investigator.

Only authorized persons had access to identifiable personal details, if required for data verification. The investigators agreed to provide direct access to these documents to the Sponsor and to Health Authority representatives only where these were required, i.e. during audits. The investigator was responsible for retrieving information from personal medical records.

Data protection and privacy regulations were observed in capturing, forwarding, processing, and storing patient data. Patients were informed accordingly and were requested to give their consent on data handling procedures in accordance with national regulations.

9.15 Data Management

An Electronic Data Capture (EDC) system was used for this study. Study variables were entered in the study-specific eCRF by authorized site personnel, first at the time of study inclusion, and then regularly during follow-up visits (with a planned periodicity of 6 months). After documentation of baseline data, the participating study site documented relevant data according to the requirements of the eCRF until death or end of study participation due to other reasons (e.g. withdrawn consent).

The authorization of the investigator to enter data into the eCRFs was verified by his/her password. Data consistency and accuracy was ensured by real-time checks running at time of data entry in the eCRF. Additionally, regular data quality checks for mandatory fields were performed outside of the EDC system as specified in the data management plan and the data validation plan. Implausible and incomplete data were addressed by queries. All investigators ensured that queries were dealt with promptly. All corrections on the eCRFs were automatically tracked and the audit trail function allowed the changes and clarifications to be viewed and audited. A Data Monitoring Plan was written, describing in detail all data checks performed on completeness, plausibility and consistency for collected data and all steps necessary from raw data to final database (with data coming from both ADOREG and the additional data collection, via linked eCRFs) such as, but not limited to, database development, additional data collection process, medical coding considerations and conventions, query edition and database validation.

Telephone and e-mail support are provided for questions concerning technical, organizational, and scientific issues.

9.16 Monitoring

Ten on-site monitoring visits were performed during the study period (30 April 2019 to 31 March 2024), with the focus on informed consent checks and ADR reporting. Active sites were contacted for remote monitoring activities, including review of patient enrollment, ADR recording and reporting, query resolution, data completeness and availability of essential study documents (e.g. the delegation log).

Remote monitoring included checks programmed in SAS and provided as data listings and report for review by the Data Manager. This review was conducted in monthly intervals. Missing and/ or implausible data for mandatory fields were requested per query by the site and the site would answer the queries within 2 weeks.

10 Results

10.1 Study Subjects

10.1.1 Patient Enrollment

Overall, 58 sites were contacted during the recruitment period, 14 of them rejected participation and 1 site was not responsive, resulting in 43 activated sites out of the initially projected 45 ADOREG sites (Figure 5). The main reason of participation rejection was insufficient resources for conduct of study.

The target enrollment was defined at the initiation of this study as 540 patients and then increased in July 2021 up to maximum 1,000 patients for end of September 2023 (refer to Protocol version 6). Excluding 5 patients enrolled erroneously (violation of inclusion criteria: 3 had diagnosis other than MCC and 2 did not correctly signed informed consent), 41 enrolling sites have enrolled a total of 875 patients.

Site activation in 2020 was slowed down by the COVID-19 pandemic, due to longer review times of e.g. contracts due to re-organization of work at sites and ethics committees. Following the decision to increase the study size to up to maximum 1000 patients, start-up activities were re-initiated to activate up to 3 additional sites by Q4 2022; 2 of them were activated in Q3 and Q4 (sites Wuerzburg and Giessen, correspondingly), one site (Kiel) was not initiated. The reasons for non-activation of this (Kiel) site until 30 September 2023 (end of study recruitment period) was nonresponse of the PI.

However, delays in site activation and the COVID-19 pandemic did not impact patients' enrollment (Table 4 and Figure 6).

Figure 5 **Projected and Actual Site Activations, First-Patient In (30 April 2019) Until End of Enrollment Period (30 September 2023)**

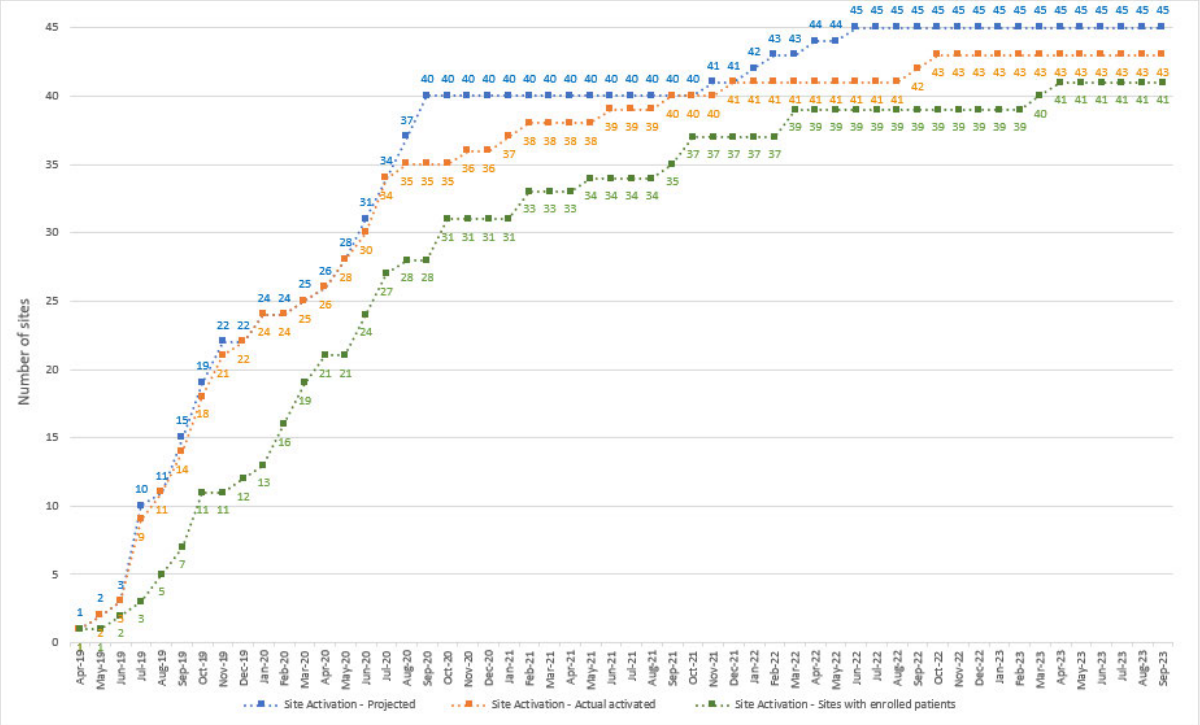


Figure 6 **Projected and actual patient enrollment, first-patient in (April 2019) until end of enrollment period (30 September 2023)**

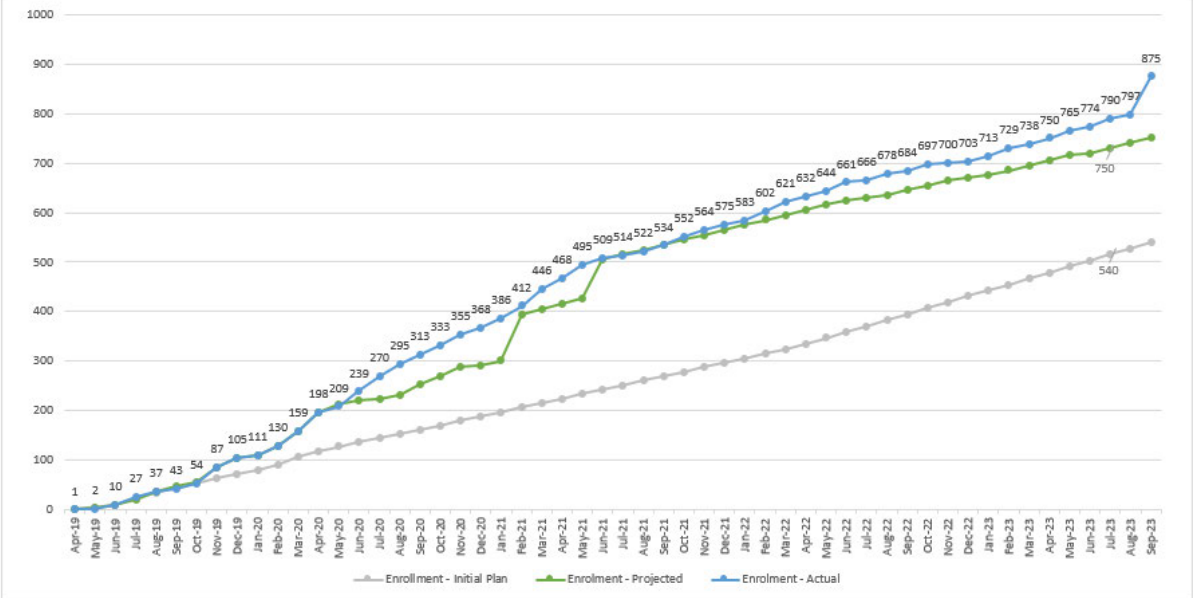


Table 4 Summary of the 41 Active Sites Enrolling 875 Patients with Merkel Cell Carcinoma During Interim Analyses and for the Final Study Report

Site name / Report	Number of MCC patients enrolled				
	1st interim report 2019	2nd interim report 2020	3rd interim report 2021	4th interim report 2022	Final report 2024
MCC TRIM Study	41 (100%)	312 (100%)	534 (100%)	684 (100%)	875 (100%)
Universitätsklinikum Essen*	27 (65.9%)	77 (24.7%)	98 (18.4%)	114 (16.7%)	138 (15.8%)
Universitätsklinikum des Saarlandes, Homburg	6 (14.6%)	22 (7.0%)	32 (6.0%)	42 (6.1%)	59 (6.7%)
Universitätsklinikum Mainz	0 (0.0%)	23 (7.3%)	41 (7.7%)	48 (7.0%)	57 (6.5%)
Universitätsklinikum Heidelberg	0 (0.0%)	24 (7.7%)	45 (8.4%)	47 (6.9%)	56 (6.4%)
Universitäts-Hautklinik Tübingen	0 (0.0%)	30 (9.6%)	42 (7.9%)	45 (6.6%)	55 (6.3%)
Universitätsklinikum Hamburg-Eppendorf	0 (0.0%)	0 (0.0%)	17 (3.2%)	28 (4.1%)	40 (4.6%)
Klinikum Minden	0 (0.0%)	0 (0.0%)	3 (0.6%)	22 (3.2%)	32 (3.7%)
Universitätsklinikum Freiburg	0 (0.0%)	0 (0.0%)	16 (3.0%)	26 (3.8%)	31 (3.5%)
Klinikum Dortmund	0 (0.0%)	9 (2.9%)	13 (2.4%)	19 (2.8%)	28 (3.2%)
Fachklinik Hornheide, Münster	0 (0.0%)	21 (6.7%)	27 (5.1%)	27 (3.9%)	27 (3.1%)
Elbe Klinikum Buxtehude	5 (12.2%)	9 (2.9%)	17 (3.2%)	20 (2.9%)	26 (3.0%)
Medizinische Fakultät Carl Gustav Carus der TU Dresden	0 (0.0%)	7 (2.2%)	15 (2.8%)	22 (3.2%)	25 (2.9%)
Helios Klinikum Erfurt	0 (0.0%)	8 (2.6%)	13 (2.4%)	19 (2.8%)	25 (2.9%)
Universitätsklinikum Schleswig-Holstein, Campus Lübeck	1 (2.4%)	10 (3.2%)	15 (2.8%)	17 (2.5%)	25 (2.9%)
DRK Krankenhaus Chemnitz-Rabenstein	0 (0.0%)	5 (1.6%)	15 (2.8%)	22 (3.2%)	23 (2.6%)
Universitätshautklinik Magdeburg	0 (0.0%)	3 (1.0%)	20 (3.7%)	21 (3.1%)	23 (2.6%)
Klinikum Bremerhaven Reinkenheide	0 (0.0%)	9 (2.9%)	11 (2.1%)	17 (2.5%)	22 (2.5%)
Klinikum Nürnberg Nord	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	18 (2.1%)
Klinikum der Universität München	0 (0.0%)	6 (1.9%)	8 (1.5%)	15 (2.2%)	17 (1.9%)
Medizinische Hochschule Hannover	0 (0.0%)	11 (3.5%)	14 (2.6%)	14 (2.0%)	14 (1.6%)
Helios St. Elisabeth Klinik Oberhausen	1 (2.4%)	3 (1.0%)	6 (1.1%)	11 (1.6%)	12 (1.4%)
Martin-Luther-Universität Halle-Wittenberg	0 (0.0%)	0 (0.0%)	6 (1.1%)	10 (1.5%)	11 (1.3%)
Helios Klinik Schwerin	0 (0.0%)	5 (1.6%)	10 (1.9%)	10 (1.5%)	11 (1.3%)
Universität Leipzig AöR	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	10 (1.1%)
Helios Klinikum Duisburg	0 (0.0%)	1 (0.3%)	3 (0.6%)	6 (0.9%)	10 (1.1%)
Klinikum Augsburg Süd	0 (0.0%)	0 (0.0%)	1 (0.2%)	7 (1.0%)	9 (1.0%)
Universitätsklinikum Würzburg	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (0.9%)
Klinikum Bayreuth	0 (0.0%)	3 (1.0%)	6 (1.1%)	6 (0.9%)	7 (0.8%)
Klinikum Quedlinburg	0 (0.0%)	7 (2.2%)	7 (1.3%)	7 (1.0%)	7 (0.8%)
Universitätsklinikum Mannheim	1 (2.4%)	6 (1.9%)	7 (1.3%)	7 (1.0%)	7 (0.8%)
Universitätsklinikum Düsseldorf	0 (0.0%)	3 (1.0%)	6 (1.1%)	6 (0.9%)	6 (0.7%)

Site name Report	Number of MCC patients enrolled				
	1st interim report 2019	2nd interim report 2020	3rd interim report 2021	4th interim report 2022	Final report 2024
Universitätsklinikum Erlangen	0 (0.0%)	0 (0.0%)	2 (0.4%)	3 (0.4%)	6 (0.7%)
Westfälsche Wilhelms-Universitätsklinikum Münster	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	5 (0.6%)
Universitätsklinikum Ulm	0 (0.0%)	1 (0.3%)	3 (0.6%)	5 (0.7%)	5 (0.6%)
Krankenhaus Dresden Friedrichstadt	0 (0.0%)	2 (0.6%)	4 (0.7%)	4 (0.6%)	4 (0.5%)
Klinikum der Stadt Ludwigshafen am Rhein	0 (0.0%)	4 (1.3%)	4 (0.7%)	4 (0.6%)	4 (0.5%)
Universitätsklinikum Regensburg	0 (0.0%)	2 (0.6%)	3 (0.6%)	3 (0.4%)	3 (0.3%)
Helios Klinikum Wuppertal	0 (0.0%)	0 (0.0%)	3 (0.6%)	3 (0.4%)	3 (0.3%)
Hauttumorzentrum Hamburg-Krankenhaus Tabea/HOPA	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	3 (0.3%)
Universitätsklinikum Gießen	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Katholisches Klinikum Bochum St. Josef-Hospital	0 (0.0%)	1 (0.3%)	1 (0.2%)	1 (0.1%)	1 (0.1%)

Source: Appendix F Table 4

*Universitätsklinikum Essen is one of the key/referral sites for the treatment and management of patients with MCC in Germany, which may explain why this site has the largest sample size representation.

Percentages are provided with the total number of patients enrolled in the MCC TRIM study in the respective analysis as denominator.

10.1.2 Study Subjects in Analysis Sets

At the time of this final analysis (end of data collection: 31st March 2024), 875 subjects were recruited in 41 enrolling sites from 29 April 2019 to 30 September 2023. 243 patients were treated with avelumab. 236 out of 243 avelumab-treated patients were with stage III (107) or IV (129) MCC, 5 patients were with stage II and stage was unknown for 2 patients. Among the 243 patients treated with avelumab, 54 were ICS- and 189 were ICS+.

Table 5 provides an overview of the patient distribution in the analyses sets and patient counts presented in tables of results per objective.

Table 5 Overview of patients included in analyses sets

Definition population	Patients matching population definition (FAS)	
	N 875	% patients 100
Patients not diagnosed with unresectable Stage III MCC or Stage IV MCC (ESAS)	599	68.5%
Patients diagnosed with unresectable Stage III MCC or Stage IV MCC (ASAS)	276	31.5%
Patients receiving any systemic therapy to treat MCC (SAS)	311	35.5%
Patients receiving avelumab to treat MCC at any time	243	27.8%

Definition population	Patients matching population definition (FAS)	
	N **875**	**% patients** **100**
Patients considered immune competent and receiving any systemic therapy (ASNCIC)	247	28.2%
Patients considered immune competent and treated with avelumab (ASNCICA)	189	21.6%
Patients considered immune compromised and receiving any systemic therapy (ICAS)	64	7.3%
Patients considered immune compromised and treated with avelumab (ICASA)	54	6.2%

Source: Appendix G Attrition Table

N=Number; FAS= Full Analysis Set; ASAS = Advanced Stage Analysis Set; ASNCIC = Analysis Set of patients not considered immune compromised; ASNCICA = Analysis Set of patients not considered immune compromised treated with avelumab; ESAS = Early-Stage Analysis Set; FAS = Full Analysis Set; ICAS = Immune compromised Analysis Set; ICASA = Immune compromised Analysis Set treated with avelumab.

Among the 875 patients included in FAS, 599 (68.5%) patients were in ESAS and 276 (31.5%) patients were in ASAS including 162 patients with Stage IV MCC. MCC diagnosis was confirmed via tumor tissue analysis for 718 patients (82.1%). For 157 (17.9%) patients, the analysis was either inconclusive (9 patients) or impossible due to too little or no material available. Among the 162 patients, 119 (13.6%) patients had stage IV MCC at enrollment, 43 patients progressed to mMCC during the course of the study.

Of the 311 patients in the SAS, 173 patients were included in survival analyses, as these patients initiated a new line of systemic treatment on/after their date of enrollment (first-line: 137 patients, second-line: 56 and third-line: 26 patients). Likewise, only 267 patients of the SAS were evaluated for safety events as they reportedly had their last dose of systemic treatment within the pre-specified safety period of 90 days prior to enrollment, had ongoing systemic treatment at enrollment or initiated systemic treatment after enrollment.

Patients from the SAS were subsequently distributed based on the immune status as follows:

- Patients not considered immune compromised (ICS+) in the SAS were included in the Analysis Set of patients not considered immune compromised (ASNCIC, n=247, 79.4%)
- Patients considered immune compromised (ICS-) in the SAS were included into the immune compromised Analysis Set (ICAS, n=64, 20.6%).

64 patients in the study were considered ICS- and received any systemic therapy, 54 were treated with avelumab. 28 had Stage IV MCC, 25 had Stage III MCC and the stage was unknown for 1 patient.

247 patients in the study were considered ICS+ and received any systemic therapy, 189 were treated with avelumab. 101 had stage IV MCC, 82 had stage III and 5 patients were reported to have stage II.

Among 54 ICS- avelumab-treated patients, 7 were treated in center Universitätsklinikum Essen (center 1), and 47 in other study sites (center 2, as defined in section 9.10.6); corresponding numbers of patients not considered immune compromised (ICS+) were 37 and 152, respectively.

10.2 Descriptive Data

10.2.1 Patient and Tumor Characteristics

Refer to Table 1 in Appendix G for patient and tumor characteristics of all patients in FAS at study inclusion (n=875). Over the baseline period, the median time between the initial diagnosis date and the inclusion date was 34 days (Q1-Q3: 0 to 378) in FAS. The median follow-up time since study inclusion was 18.1 months (Q1-Q3: 6.7 to 34.1).

The results for patients treated with avelumab (n=243) stratified by (a) immune compromised status and (b) center are summarized in this report.

10.2.1.1 Patients Treated with Avelumab in Strata by ICS+/ ICS-

Among patients treated with avelumab (n=243), 189 (77.8%) patients were considered ICS+ and 54 (22.2%) were considered ICS-. The proportion of male patients was similar in between the 2 groups. The following differences were noted between the 2 groups:

- The proportion of patients aged 70 to 89 years was numerically higher in the ICS- than in ICS+ subpopulation (83.3% and 68.8%, respectively).
- The proportion of patients with Stage IV disease at enrolment was slightly higher in the ICS- than in ICS+ patients 40.7% and 37.6% respectively.
- 6.1% of ICS+ and 13.0% of ICS- patients were reported with baseline ECOG score of 2 or higher.

Table 6 Patient and Tumor characteristics of Avelumab-treated Patients

Characteristics	ICS+ (n = 189)	ICS- (n = 54)
Total Patients Treated with Avelumab, n (%)	189 (77.8%)	54 (22.2%)
Proportion of Male Patients, % (95% CI)	64.6% (57.7% to 71.4%)	64.8% (52.1% to 77.6%)
Mean Age at Initial Diagnosis, years (stdev)	74.8 (10.2)	76.4 (8.1)
Age 70-79 Years, % (95% CI)	32.8% (26.1% to 39.5%)	46.3% (33.0% to 59.6%)
Age 80-89 Years	36.0% (29.1% to 42.8%)	37.0% (24.2% to 49.9%)
Median Time from Diagnosis to Staging, days (Q1-Q3)	161 (0 to 440)	185 (0 to 585)
Stage III Disease at Enrollment, % (95% CI)	42.3% (35.3% to 49.4%)	35.2% (22.4% to 47.9%)
Stage IV Disease at Enrollment, % (95% CI)	37.6% (30.7% to 44.5%)	40.7% (27.6% to 53.8%)
Baseline ECOG Score '0', % (95% CI)	65.0% (57.7% to 72.4%)	56.5% (42.2% to 70.8%)
Skin Phototype II, % (95% CI)	72.2% (64.0% to 80.4%)	58.3% (42.2% to 74.4%)
Primary Tumor Location; % (95% CI)		

Characteristics	ICS+ (n = 189)	ICS- (n = 54)
Lower limb including hip:	23.3% (17.3% to 29.3%)	14.8% (5.3% to 24.3%)
Upper limb including shoulder:	20,6% (14.9% to 26.4%)	31.5% (19.1% to 43.9%)
Distant Metastasis; % (95% CI)	54.6% (46.1% to 63.2%)	64.7% (48.6% to 80.8%)
MCPyV Test Positive; % (95% CI)	70.8% (63.6% to 78.0%)	65.2% (51.5% to 79.0%)
Small Cell Histological Subtype of MCC, % (95% CI)	34.6% (24.2% to 44.9%)	38.5% (19.8% to 57.2%)
Tumor Infiltration with Lymphocytes, % (95% CI)	38.6% (26.0% to 51.2%)	26.7% (4.3% to 49.0%)
Median Follow-up Time, months (Q1-Q3)	14.3 (6.4 to 29.4)	8.9 (4.2 to 22.8)

Source: Table 1 in Appendix G

CI= Confidence interval, ECOG= Eastern Cooperative Oncology Group MCC= Merkel Cell Carcinoma, n= number, Q1= Quarter 1, Q3= Quarter 3, MCPyV= Merkel Cell Polyomavirus.

10.2.1.2 Patients Treated with Avelumab in Strata by Center

Patient and tumor characteristics of patients treated with avelumab (n=243) stratified by center were analyzed. The number of patients by 2 centers is presented in Table 7 below.

Table 7 Number of Patients Treated with Avelumab Stratified by Center

	Total	ICS+	ICS-
Center 1 (Site Essen)	44	37	7
Center 2 (all remaining sites together)	199	152	47
Total	243	189	54

Differences between 2 centers have been identified with regards to some patients' and tumor characteristics.

- Patients in center 1 were on average younger than in center 2. Mean (StDev) patients' age was 71.0 (11.1) years in center 1 and 76.1 (9.2) years in center 2.
- Higher proportion of patients with ECOG score '0' was reported in center 1 than in center 2: 90.5% (95% CI 81.6% to 99.4%) and 56.3% (95% CI 48.8% to 63.8%) of patients with available information, respectively.
- Histologically, small cell type was the most frequently reported type of MCC in center 2 (39.4% [95% CI 29.5% to 49.2%] of patients with available information in center 2 vs. 7.7% [95% CI 0.0% to 22.2%] in center 1) whereas patients in center 1 were most frequently reported with unknown primary (76.9% [95% CI 54.0% to 99.8%] of patients with available information in center 1 vs. 21.3% [95% CI 13.0% to 29.6%] in center 2).

Completeness of documentation in the real-world setting can vary between study sites. Some differences between 2 centers could be caused by heterogeneity of study sites regarding data collection/ documentation. Information on ECOG, metastases status, was less frequently reported in center 2 than in center 1: ECOG was not recorded for 16.1% (95% CI 11.0% to 21.2%) of patients in center 2 and for 4.5% (95% CI 0.0% to 10.7%) of patients in center 1; information on metastases was not available for 17.4% (95% CI 11.4% to 23.4%) and 2.7% (95% CI 0.0% to

7.9%) of patients at enrollment in center 2 and center 1, respectively. Some other parameters were less frequently documented in center 1 than in center 2, e.g. skin phototype was not reported in 63.6% (95% CI 49.4% to 77.9%) of cases in center 1 and in 32.2% (95% CI 25.7% to 38.7%) in center 2, histology of tumor was not recorded for 70.5% (95% CI 57.0% to 83.9%) in center 1 and for 52.8% (95% CI 45.8% to 59.7%) in center 2, respectively; information on conduct of PD-L1 test was unavailable in 43.2% (95% CI 28.5% to 57.8%) and 19.6% (95% CI 14.1% to 25.1%) of patients in center 1 and center 2, respectively.

Proportion of patients enrolled in 2019 in center 1 (38.6%, 95% CI 24.2% to 53.0%) was higher than in center 2 (9.0%, 95% CI 5.1% to 13.0%). Correspondingly, the median duration of follow-up in this study was longer in center 1 than in center 2 (16.9 months vs. 12.6 months).

Under consideration of identified differences, possible impact of the leading site (center 1) on the overall study results was explored in analyses of study outcomes (effectiveness and safety). The results are presented in the corresponding sections of this report.

10.2.2 Estimation of Background Prevalence of Relevant Comorbidities

Refer to Table 2 in Appendix G for the background prevalence proportions of relevant comorbidities (as listed in section 9.10.3.1.2.) for all patients in FAS in the study.

10.2.2.1 Patients Treated With Avelumab in Strata by ICS+/ ICS-

Skin cancers other than MCC as well as other malignancies were numerically more frequently reported in ICS- vs. in ICS+ avelumab Analysis Set (see Table 8). The most frequently reported nononcologic comorbidities in both analysis sets were diabetes and ischemic heart disease/ myocardial infarction (see Table 8).

Table 8 Prevalence Proportions and Rates of Relevant Comorbidities in Avelumab-treated Patients

	ICS+, n=189		ICS-, n=54	
Condition	**Percentage [95% CI]**	**Rate per Person-Year [95% CI]**	**Percentage [95% CI]**	**Rate per Person-Year [95% CI]**
SCC	6.3% [2.9% to 9.8%]	0.05 [0.03 to 0.10]	18.5% [8.2% to 28.9%]	0.14 [0.07 to 0.27]
Basal Cell Carcinoma	7.4% [3.7% to 11.1%]	0.06 [0.03 to 0.11]	16.7% [6.7% to 26.6%]	0.12 [0.06 to 0.25]
Actinic Keratosis	6.9% [3.3% to 10.5%]	0.06 [0.03 to 0.11]	11.1% [2.7% to 19.5%]	0.08 [0.03 to 0.20]
Melanoma	1.1% [0.0% to 2.5%]	0.01 [0.00 to 0.04]	5.6% [0.0% to 11.7%]	0.04 [0.01 to 0.14]
Other Solid Tumors	6.3% [2.9% to 9.8%]	0.05 [0.03 to 0.10]	13.0% [4.0% to 21.9%]	0.10 [0.04 to 0.22]

	ICS+, n=189		ICS-, n=54	
Condition	**Percentage [95% CI]**	**Rate per Person-Year [95% CI]**	**Percentage [95% CI]**	**Rate per Person-Year [95% CI]**
Other Hematological Malignancy	1.6% [0.0% to 3.4%]	0.01 [0.00 to 0.05]	25.9% [14.2% to 37.6%]	0.19 [0.11 to 0.34]
Diabetes	19.0% [13.4% to 24.6%]	0.16 [0.11 to 0.23]	25.9% [14.2% to 37.6%]	0.19 [0.11 to 0.34]
Ischemic Heart Disease/Myocardial Infarction	11.1% [6.6% to 15.6%]	0.09 [0.06 to 0.15]	14.8% [5.3% to 24.3%]	0.11 [0.05 to 0.23]

Source: Table 2 in Appendix G, SCC= squamous cell carcinoma, CI= confidence interval

10.2.2.2 Patients Treated with Avelumab in Strata by Center

No differences in prevalence rates and frequency distribution of oncological and nononcological comorbidities between centers have been identified based on assessment of 95% CIs. The most frequent comorbidity was diabetes with 25.0% (95% CI 12.2% to 37.8%) of patients (rate 0.19 per person-year [95% CI 0.09 to 0.36]) in center 1 and 19.6% (95% CI 14.1% to 25.1%) of patients (rate 0.17 per person-year [95% CI 0.12 to 0.23]) in center 2, followed by ischemic heart disease/ myocardial infarction in center 1 (20.5% [95% CI 8.5% to 32.4%], rate 0.15 per person-year [95% CI 0.07 to 0.32]) and ischemic heart disease/ myocardial infarction or basal cell carcinoma in center 2 (10.1% each [95% CI 5.9% to 14.2%], rate 0.08 per person-year [95% CI 0.05 to 0.14]).

Proportion of patients reported to be immunocompromised due to immunosuppressive conditions or immunosuppressive medications any time during medical history was similar in 2 centers 2 centers (11.4% [95% CI 2.0% to 20.7%], rate 0.09 per person-year [95% CI 0.03 to 0.22] in center 1 and 9.0% [95% CI 5.1% to 13.0%], rate 0.08 per person-year [95% CI 0.05 to 0.13] in center 2).

10.3 Outcome Data

10.3.1 Common Comorbidities for Immune Compromised Patients

Refer to Table 4 in Appendix G for common comorbidities for ICS- patients in the study.

54 avelumab-treated patients were considered ICS- including 53 patients from the ASAS set and 1 patient from ESAS. The 1 patient with ESAS did not have any relevant conditions listed in Table 4 in Appendix G. 34 out of the 53 patients (63.0% of 54 patients) were reported to have a concurrent malignancy (excluding SCC or a carcinoma in situ). 3 patients (5.6%) had an organ transplant and 2 ASAS patients (3.7%) had HIV infection.

Patients had also additional comorbidities, but only comorbidities determining immune compromised state are considered and reported in Table 4 in Appendix G.

10.3.2 Concomitant Medications for Immune Compromised Patients

Concomitant medications included premedication or for management of adverse drug reactions.

Refer to Table 5 in Appendix G for concomitant medications for ICS- patients in the study.

Among the 54 patients treated with avelumab and were ICS-, 19 ASAS patients (35.2%) reportedly received systemic corticosteroids, 4 ASAS patients (7.4%) received cytostatics, 3 patients (5.6%) calcineurin inhibitors and 2 ASAS patients (3.7%) received IMDH inhibitors. One ESAS patient (1.9% of 54 patients) received systemic corticosteroids and was therefore selected into the Immune compromised Analysis Set treated with avelumab.

10.4 Main Results

10.4.1 Primary Objectives

10.4.1.1 Characterization of Disease Outcomes

10.4.1.1.1 Tumor Response

Characterization of disease outcomes in the ASAS (n=276) by means of tumor response per treatment received (in overall and stratified by immune compromised status) is summarized in Table 6a in Appendix G.

The response for patients who were treated with avelumab as first-line treatment are summarized in Table 9. The ORR for the 167 ICS+ patients treated with avelumab as first-line treatment was 34.7% (95% CI: 27.5%, 42.0%) with 42 CRs (25.1%, 95% CI: 18.6%, 31.7%) and 16 PRs (9.6% 95% CI: 5.1%, 14.0%). The ORR for the 49 ICS- patients treated with avelumab as first-line treatment was 28.6% (95% CI: 15.9%, 41.2%) with 9 CRs (18.4%, 95% CI: 7.5%, 29.2%) and 5 PRs (10.2%, 95% CI: 1.7%, 18.7%).

The response for ICS+ patients who were treated with avelumab as second-line treatment (n=11, 100%) had 3 CR and 3 ‘unratable’ responses, 2 SD, 2 PD and 1 MR. The ORR was 27.3% (95% CI 1.0% to 53.6%, n=3). The results for second-line avelumab in stages III and IV as well as for third-line therapy are not reported here because of very low number of patients (n <10) in these analyses.

The results for second- and third-line therapy with avelumab in ICS- patients are not reported here because of very low number of treated patients (n <10) in these analyses.

Table 9 Response in Patients Treated with Avelumab as First-line Treatment

	ICS-			ICS+		
Response	**Overall**	**ICS- Stage III**	**ICS- Stage IV**	**Overall**	**ICS+ Stage III**	**ICS+ Stage IV**
n	49	25	24	167	74	89
ORR, n, % (95% CI)	28.6% (15.9% to 41.2%)	40.0% (20.8% to 59.2%)	16.7% (1.8% to 31.6%)	34.7% (27.5% to 42.0%)	43.2% (32.0% to 54.5%)	25.8% (16.7% to 34.9%)
CR, n, % (95% CI)	9, 18.4% (7.5% to 29.2%)	7, 28.0% (10.4% to 45.6%)	2, 8.3% (0.0% to 19.4%)	42, 25.1% (18.6% to 31.7%)	24, 32.4% (21.8% to 43.1%)	16, 18.0% (10.0% to 26.0%)
PR, n, % (95% CI)	5, 10.2% (1.7% to 18.7%)	3, 12.0% (0.0% to 24.7%)	2, 8.3% (0.0% to 19.4%)	16, 9.6% (5.1% to 14.0%)	8, 10.8% (3.7% to 17.9%)	7, 7.9% (2.3% to 13.5%)
SD, n, % (95% CI)	3, 6.1% (0.0% to 12.8%)	1, 4.0% (0.0% to 11.7%)	2, 8.3% (0.0% to 19.4%)	25, 15.0% (9.6% to 20.4%)	11, 14.9% (6.8% to 23.0%)	13, 14.6% (7.3% to 21.9%)
PD, n, % (95% CI)	17, 34.7% (21.4% to 48.0%)	8, 32.0% (13.7% to 50.3%)	9, 37.5% (18.1% to 56.9%)	48, 28.7% (21.9% to 35.6%)	14, 18.9% (10.0% to 27.8%)	34, 38.2% (28.1% to 48.3%)
Unratable, n, % (95% CI)	13, 26.5% (14.2% to 38.9%)	5, 20.0% (4.3% to 35.7%)	8, 33.3% (14.5% to 52.2%)	33, 19.8% (13.7% to 25.8%)	16, 21.6% (12.2% to 31.0%)	17, 19.1% (10.9% to 27.3%)
MR, n, % (95% CI)	2, 4.1% (0.0% to 9.6%)	1, 4.0% (0.0% to 11.7%)	1, 4.2% (0.0% to 12.2%)	3, 1.8% (0.0% to 3.8%)	1, 1.4% (0.0% to 4.0%)	2, 2.2% (0.0% to 5.3%)

Source: Table 6a in Appendix G

CI= Confidence interval, CR=complete response, ICS= Immune competent patients, MR=mixed response, PD=progressive disease, PR= Partial Remission, ORR=objective response rate, SD=stable disease.

10.4.1.1.2 ICS+ and ICS- Patients Treated with Avelumab in Strata by Center

Analysis of treatment response to the first-line systemic therapy with avelumab has not provided meaningful differences between 2 center strata. The ORR was similar in ICS+ subpopulation with 30.3% (95% CI 14.6% to 46.0%) in center 1 and 35.8% (95% CI 27.7% to 43.9%) in center 2. In the ICS- subpopulation of center 2, the ORR was 27.3% (95% CI 14.1% to 40.4%). The results for ICS- subpopulation of center 1 are not presented because of very low number of patients in this stratum (n=7). Noticeable is high proportion of 'unratable' response to avelumab in center 2 (23.9% [95% CI 16.7% to 31.1%] in ICS+ to 29.5% [95% CI 16.1% to 43.0%] in ICS- subpopulation in first-line) which is higher than in overall avelumab Analysis Set (19.8% [95% CI 13.7% to 25.8%] in ICS+ to 26.5% [95% CI 14.2% to 38.9%] in ICS- in first-line). Analysis in the second and third-line therapy does not provide conclusive results because of very low number of treated patients.

Possible effect of the leading study center on treatment response was additionally explored in multinomial regression analysis performed for first-line and second-line+ treatment with avelumab. No statistically significant differences between 2 center strata could be identified in analyses with 5 response categories (CR, PR, MR, SD, PD), as well as with 4 response categories, where CR and PR were combined in the category ORR. No significant differences between ICS+ and ICS- subpopulations in overall as well as within each of 2 centers were identified. The results of these analyses are presented in Tables 6a-2 and 6 a-3 of Appendix G, respectively. The results of additional (sensitivity) analyses (including response category 'unratable') were consistent with the main results.

10.4.1.1.3 Survival Analyses

rwPFS

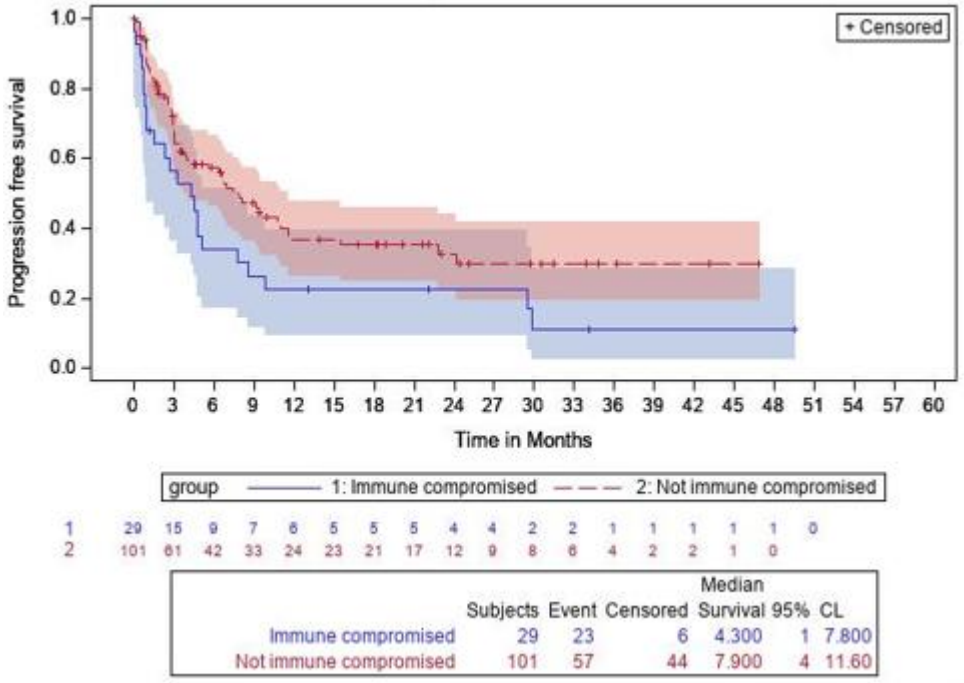
Table 10 summarizes the Kaplan-Meier estimates for rwPFS for avelumab-treated patients. The rwPFS for first-line treatment with avelumab (n=130) is shown in Figure 7, stratified by ICS+/ICS- status. Sensitivity analysis 1, as described in Section 9.10.3.1.5, confirmed the results (Figure 8). Figure 9 describes the results of first-line rwPFS in patients treated with avelumab in disease stage IV, also stratified by ICS+/ICS-.

Table 10 Kaplan-Meier Estimates for rwPFS

	ICS-	ICS+
Total Number of Patients in Analysis	130	
Number of Patients	29	101
Events (PD/Death)	23 (14/9)	57 (44/13)
Censored	6	44
Median rwPFS (95% CI) Months	4.3 (1.0, 7.8)	7.9 (4.0, 11.6)
Stage IV Patients	67	
Number of Patients	12	55
Events (PD/Death)	10 (5/5)	36 (29/7)
Censored	2	19
Median rwPFS (95% CI) Months	1.5 (0.4, 29.5)	3.1 (2.7, 9.4)

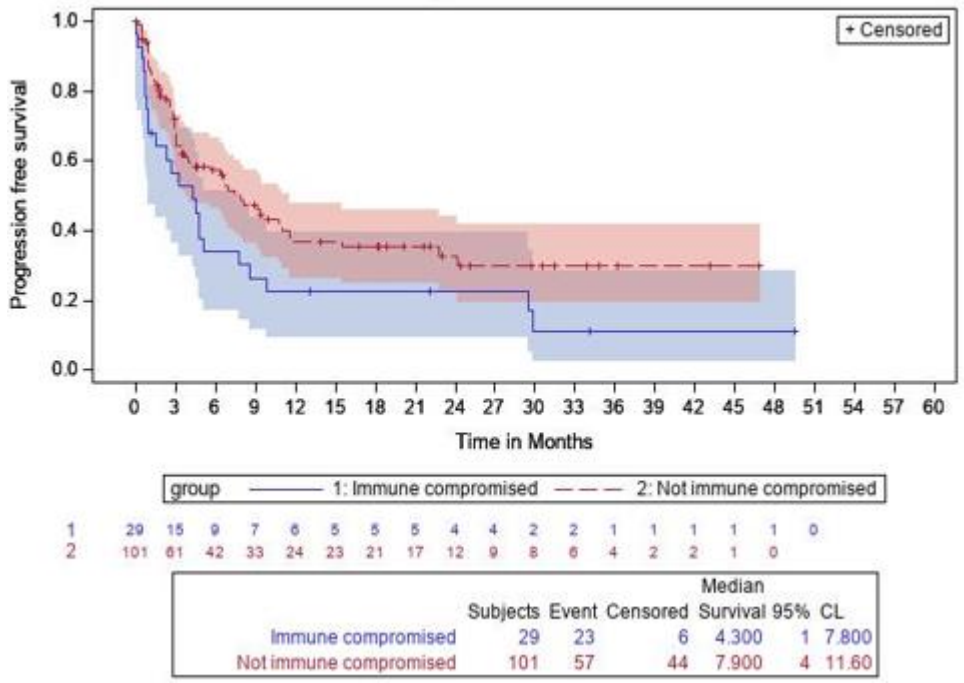
Source: Table 6n in Appendix G.

Figure 7 **Kaplan-Meier Curve for First-Line rwPFS in Patients Receiving Avelumab Stratified by ICS+/ICS- Status**



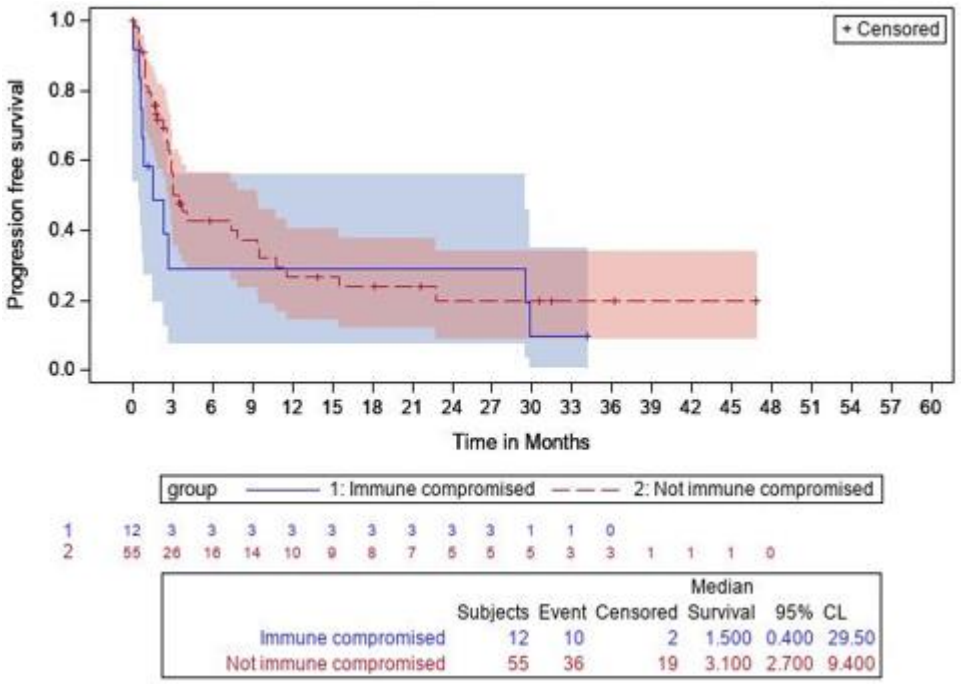
Source: Appendix G, Figure 6l-1

Figure 8 **Kaplan-Meier Curve for First-Line rwPFS in Patients Receiving Avelumab Stratified by ICS+/ICS- Status–Sensitivity Analysis 1**



Source: Appendix G, Figure 6l-2

Figure 9 **Kaplan-Meier curve for first-line rwPFS in patients receiving avelumab in disease stage IV stratified by ICS+/ICS- status**

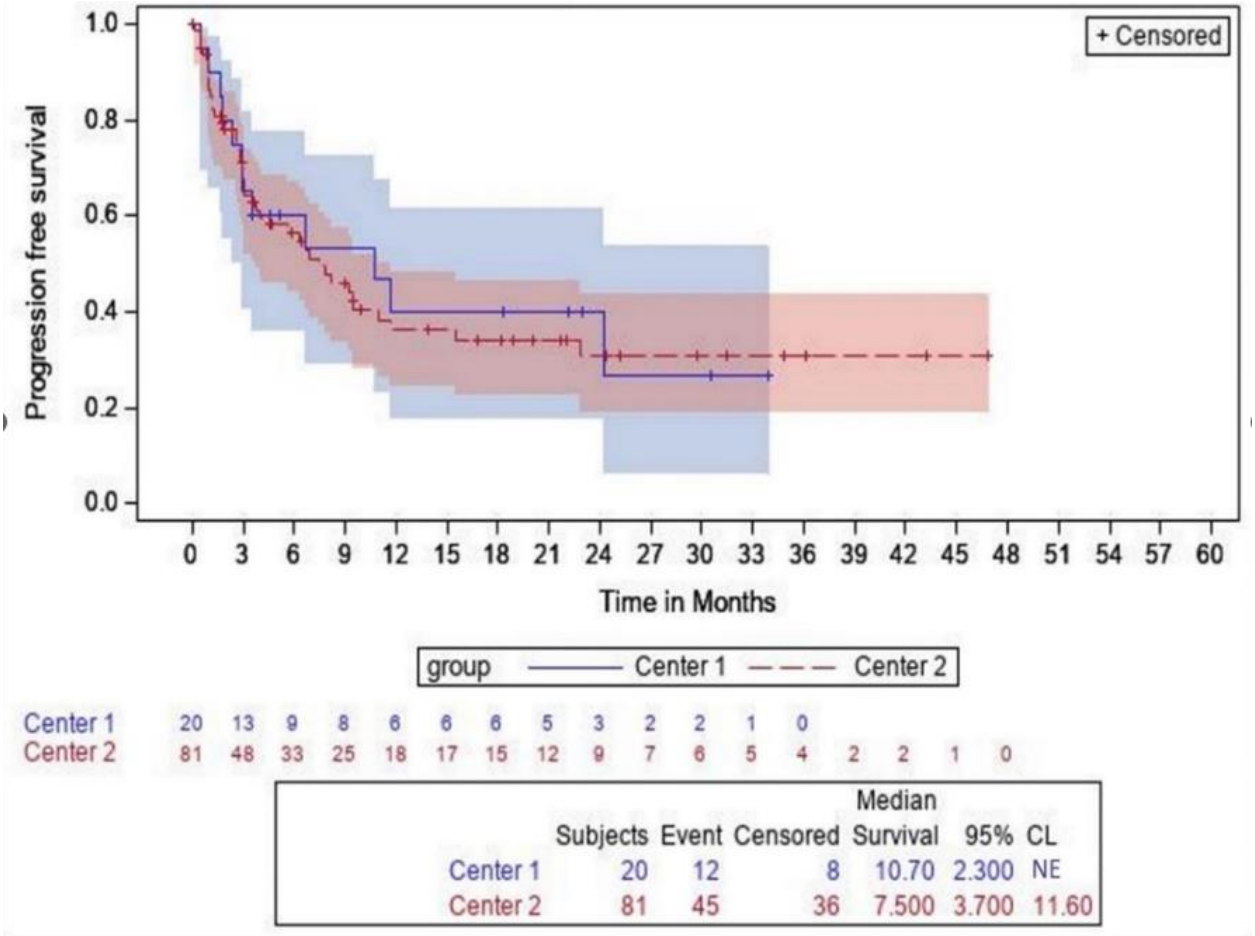


Source: Appendix G, Fig 6I-3

Figure 10 shows the Kaplan-Meier curve for first-line rwPFS in immune competent patients treated with avelumab stratified by center. Of 20 ICS+ patients treated with first-line avelumab in center 1, 12 (60.0%) experienced an event (PD: n=9, death: n=3) and 8 (40.0%) were censored. The estimated median rwPFS (95% CI) time in this analysis was 10.7 (2.3, NE) months, as shown in Table 6n in Appendix G. Of 81 ICS+ patients in center 2, 45 (55.6%) experienced an event (PD: n=35, death: n=10) and 36 (44.4%) were censored. The estimated median rwPFS (95% CI) time in this population was 7.5 (3.7, 11.6) months. The results on first - line rwPFS in ICS- patients stratified by center are not presented because of low number of patients for this analysis in center 1 stratum.

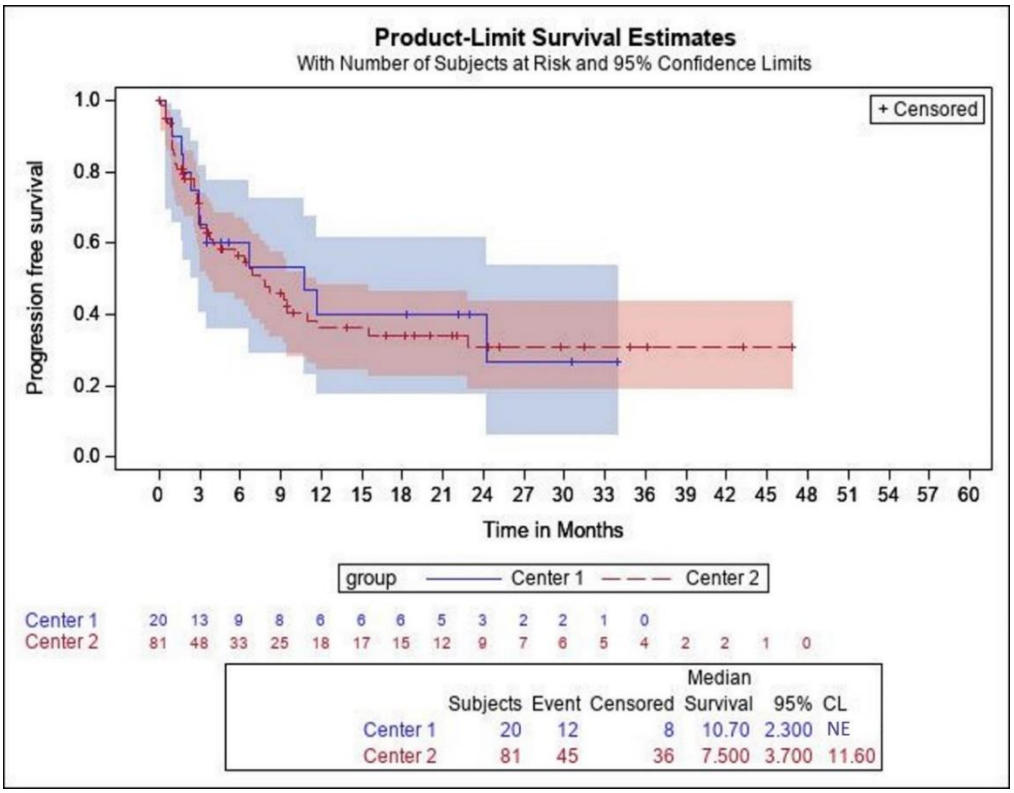
The results of sensitivity analysis 1, as described in Section 9.10.3.1.5, of first-line rwPFS in immune competent patients treated with avelumab stratified by center were identical to the results of the primary analysis (Figure 11).

Figure 10 **Kaplan-Meier Curve for First-Line rwPFS in Immune Competent Patients Receiving Avelumab Stratified by Center**



Source: Appendix G, Figure 6l-6 a

Figure 11 **Kaplan-Meier Curve for First-Line rwPFS in Immune Competent Patients Receiving Avelumab Stratified by Center-Sensitivity Analysis 1**

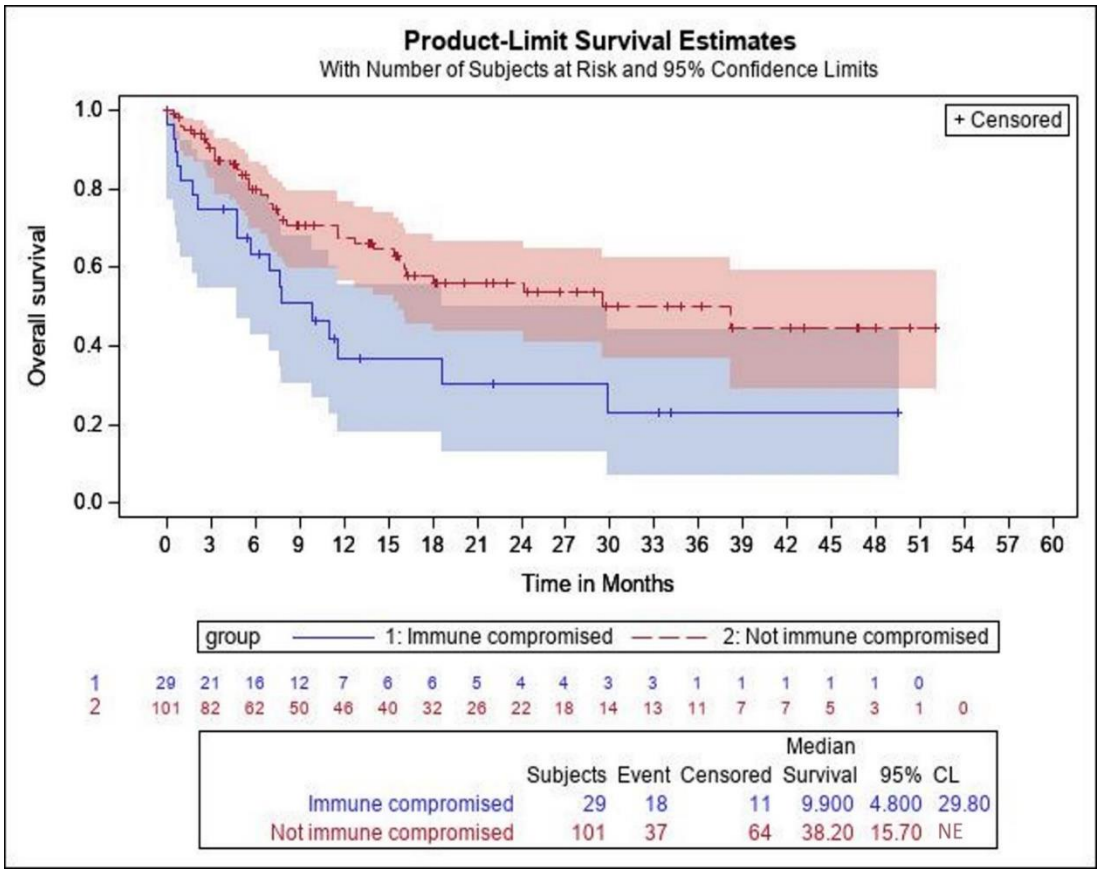


Source: Appendix G, Figure 6l-7 a

OS

Figure 12 shows the Kaplan-Meier curve for overall survival from start of first-line treatment.in patients treated with avelumab stratified by ICS+/ICS- status. Of 101 ICS+ patients treated with first-line avelumab, 37 (36.6%) died and 64 (63.4%) were censored. The estimated median OS (95% CI) time in this analysis was 38.2 (15.7, NE) months, refer to Table 6n in Appendix G. Eighteen (62.1%) of 29 ICS- patients died and 11 (37.9%) were censored. The estimated median OS (95% CI) time in this subpopulation was 9.9 (4.8, 29.8) months. The results on first-line avelumab OS from stage IV stratified by ICS+/ICS- status are not presented because of low number of patients for this analysis in ICS- stratum.

Figure 12 **Kaplan-Meier Curve for Overall Survival from Day of First-Line Treatment Initiation After Enrollment in Patients Receiving Avelumab Stratified By ICS+/ICS- Status**



Source: Appendix G, Figure 6m-1

Further survival analyses were not conducted in accordance with the SAP (section 4.6, Appendix E) because low patient and/or event numbers (≤ 10) in strata by type of therapy (avelumab vs other PD-L1/PD-1 inhibitor therapy vs chemotherapy), ICS- in stage IV avelumab population, ICS- patients treated with avelumab in center 1 would not have allowed to provide reliable estimates. For example, for the first-line rwPFS/ OS analysis stratified by type of systemic therapy there were 130 patients included in the stratum of first-line avelumab therapy, 3 patients in the stratum of first-line chemotherapy and 4 patients in other first-line PD-L1/PD-1 inhibitor therapy; for the first-line avelumab rwPFS and OS analysis stratified by immune status in stage IV only 12 patients with 10 (rwPFS) and 9 (OS) events were identified as immune compromised. 1 immune compromised patient with first-line avelumab was treated in center 1.

Also, the planned comparative Cox regression models were not implemented for the same reason.

10.4.1.2 Description of the Safety Events of Interest (E.g. Immune-related ADRs) Overall and Specifically in the Subgroup of Immune Compromised Patients Treated With Avelumab

Safety Analysis Set

Results on the safety analysis set of 267 patients are presented in detail in Table 7a in Appendix G.

ADRs were recorded in patients from the SAS who received drug therapy within 90 days prior to their study inclusion date, or whose therapy was ongoing at their date of enrollment or who initiated systemic therapy after being enrolled. Refer to Table 7a in Appendix G and section 10.4.1.2 in the full report (Appendix F).

Among 233 participants eligible for safety analysis and treated with avelumab, a total of 62 ADRs in 34 patients were related to avelumab counting for 19 SADRs (incidence rate 0.29, 95% CI 0.17 to 0.47) and 43 non-serious ADRs (incidence rate 0.65, 95% CI 0.47 to 0.89). The overall ADR incidence rate was estimated to be 0.94 (95% CI 0.72 to 1.22) events per person-year. SADRs were most frequently reported in the SOC category of "respiratory, thoracic and mediastinal disorders" (n=5) and "nervous system disorders" (n = 3). The most common SOC categories for the non-serious ADRs were "investigations" (n=10) and "injury, poisoning and procedural complications" (n = 9). Among 25 ADRs in 21 patients identified as immune related by investigators (incidence rate 0.38, 95% CI 0.24 to 0.58), 13 were SADRs (incidence rate 0.20, 95% CI 0.10 to 0.36) and 12 non-serious ADRs (incidence rate 0.18, 95% CI 0.09 to 0.34). The most frequent SOC category was "respiratory, thoracic and mediastinal disorders" (n=4) for serious and nonserious immune related ADRs.

10 infusion related reactions related to avelumab were observed in 7 patients.

Analysis Set of ICS+ patients treated with avelumab and Analysis Set of ICS- patients treated with avelumab

Results are presented in detail in Table 7c in Appendix G.

Overall

27 out of 182 ICS+ patients (14.8%) treated with avelumab experienced at least one ADR that was considered related to avelumab. 53 ADRs related to avelumab comprised 16 SADRs and 37 non-serious ADRs. The incidence rate for ADRs (serious and non-serious) related to avelumab in the Analysis Set of ICS+ patients treated with avelumab was 1.01 (95% CI 0.75 to 1.34) events per person-year (time at risk: 52.7 person-years). Incidence rate of serious and nonserious ADRs related to avelumab among ICS+ patients treated with avelumab was estimated to be 0.30 (95% CI 0.17 to 0.52) and 0.70 (95% CI 0.49 to 0.99), respectively. The most common SOC categories for SADR and non-serious ADRs are identical to the overall analysis set of patients treated with avelumab. 21 ADRs were identified as immune related by investigators in the Analysis Set of ICS+ patients, 11 were SADRs and 10 non-serious ADRs. The estimated incidence rate of immune related ADRs in ICS+ Analysis Set was 0.40 (0.25, 0.63) events per person-year.

7(13.7%) out of 51 ICS- patients treated with avelumab experienced at least one ADR that was considered related to avelumab; 9 ADRs were reported including 3 serious and 6 nonserious. These 9 events resulted in an ADR (serious and non-serious) incidence rate of 0.71 (95% CI 0.32 to 1.45) events per person-year in this Analysis Set (time at risk: 12.68 person-years). The estimated incidence rate of serious and nonserious ADRs related to avelumabin the ICS-avelumab subpopulation was 0.24 (95% CI 0.05 to 0.81) and 0.47 (95% CI 0.17 to 1.14) events per person-year, respectively. 4 ADRs were identified as immune related by investigators in the Analysis Set of ICS- patients, 2 were SADRs and 2 nonserious ADRs. The incidence rate of immune related ADRs in ICS- Analysis Set was 0.32 (0.09, 0.92) events per person-year.

Information on ADRs related to avelumab in ICS+ and ICS- patients treated with avelumab by SOC/PT is summarized in Table 11.

Table 11 Patients with ADRs related to avelumab in ICS+ and ICS- Analysis Sets by SOC and PT

Safety Event	ICS+ Analysis Set treated with avelumab N=182 (100%)						ICS- Analysis Set treated with avelumab N=51 (100%)					
	Any Grade		Grade ≥3		ir AE		Any Grade		Grade ≥3		ir AE	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Subjects with at least one event	27 (14.8%)	9.7%, 20.0%	14 (7.7%)	3.8%, 11.6%	17 (9.3%)	5.1%, 13.6%	7 (13.7%)	4.3%, 23.2%	5 (9.8%)	1.6%, 18.0%	4 (7.8%)	0.5%, 15.2%
INVESTIGATIONS	7 (3.8%)	1.1%, 6.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (2.0%)	0.0%, 5.8%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Blood creatine phosphokinase increased	2 (1.1%)	0.0%, 2.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Blood thyroid stimulating hormone decreased	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	1 (2.0%)	0.0%, 5.8%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Alanine aminotransferase increased	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Blood alkaline phosphatase increased	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Blood thyroid stimulating hormone increased	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Enzyme level abnormal	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Gamma-glutamyltransferase increased	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	1 (2.0%)	0.0%, 5.8%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Hepatic enzyme increased	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-White blood cell count decreased	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5 (2.7%)	0.4%, 5.1%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	2 (3.9%)	0.0%, 9.2%	1 (2.0%)	0.0%, 5.8%	0 (0.0%)	0.0%, 0.0%
-Infusion related reaction	5 (2.7%)	0.4%, 5.1%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	2 (3.9%)	0.0%, 9.2%	1 (2.0%)	0.0%, 5.8%	0 (0.0%)	0.0%, 0.0%

Safety Event	ICS+ Analysis Set treated with avelumab N=182 (100%)						ICS- Analysis Set treated with avelumab N=51 (100%)					
	Any Grade		Grade ≥3		ir AE		Any Grade		Grade ≥3		ir AE	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8 (4.4%)	1.4%, 7.4%	4 (2.2%)	0.1%, 4.3%	7 (3.8%)	1.1%, 6.6%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%
-Immune-mediated lung disease	3 (1.6%)	0.0%, 3.5%	1 (0.5%)	0.0%, 1.6%	3 (1.6%)	0.0%, 3.5%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Interstitial lung disease	2 (1.1%)	0.0%, 2.6%	2 (1.1%)	0.0%, 2.6%	2 (1.1%)	0.0%, 2.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Autoimmune lung disease	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%
-Bronchitis chronic	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Pulmonary embolism	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Pulmonary sarcoidosis	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
NERVOUS SYSTEM DISORDERS	3 (1.6%)	0.0%, 3.5%	3 (%)	0.0%, 3.5%	3 (1.6%)	0.0%, 3.5%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Post viral fatigue syndrome	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Immune-mediated encephalitis	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Neuritis	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Noninfective encephalomyelitis	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%
-Aplastic anaemia	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Leukopenia	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%

Safety Event	ICS+ Analysis Set treated with avelumab N=182 (100%)						ICS- Analysis Set treated with avelumab N=51 (100%)					
	Any Grade		Grade ≥3		ir AE		Any Grade		Grade ≥3		ir AE	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
-Myelosuppression	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Neutropenia	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (2.2%)	0.1%, 4.3%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Fatigue	2 (1.1%)	0.0%, 2.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Asthenia	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Pyrexia	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
GASTROINTESTINAL DISORDERS	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	2 (3.9%)	0.0%, 9.2%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%
-Gastrointestinal inflammation	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%
-Immune-mediated enterocolitis	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Nausea	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	1 (2.0%)	0.0%, 5.8%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (1,1%)	0.0%, 2.6%	0 (0.0%)	0.0%, 0.0%	1 (0.5%)	0.0%, 1.6%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%
-Arthralgia	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Arthritis	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Immune-mediated arthritis	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%	1 (2.0%)	0.0%, 5.8%

Safety Event	ICS+ Analysis Set treated with avelumab N=182 (100%)						ICS- Analysis Set treated with avelumab N=51 (100%)					
	Any Grade		Grade ≥3		ir AE		Any Grade		Grade ≥3		ir AE	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (1.6%)	0.0%, 3.5%	0 (0.0%)	0.0%, 0.0%	2 (1.1%)	0.0%, 2.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Pruritus	2 (1.1%)	0.0%, 2.6%	0 (0.0%)	0.0%, 0.0%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Drug eruption	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
CARDIAC DISORDERS	2 (1.1%)	0.0%, 2.6%	2 (1.1%)	0.0%, 2.6%	2 (1.1%)	0.0%, 2.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Autoimmune myocarditis	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Myocarditis	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
HEPATOBILIARY DISORDERS	2 (1.1%)	0.0%, 2.6%	2 (1.1%)	0.0%, 2.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Hepatitis E	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Immune-mediated hepatitis	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
INFECTIONS AND INFESTATIONS	2 (1.1%)	0.0%, 2.6%	2 (1.1%)	0.0%, 2.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Erysipelas	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Herpes zoster	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
ENDOCRINE DISORDERS	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Hypothyroidism	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
EYE DISORDERS	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%

Safety Event	ICS+ Analysis Set treated with avelumab N=182 (100%)						ICS- Analysis Set treated with avelumab N=51 (100%)					
	Any Grade		Grade ≥3		ir AE		Any Grade		Grade ≥3		ir AE	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
-Eye pruritus	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
METABOLISM AND NUTRITION DISORDERS	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Hyperglycaemia	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
RENAL AND URINARY DISORDERS	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%
-Nephrotic syndrome	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	1 (0.5%)	0.0%, 1.6%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%	0 (0.0%)	0.0%, 0.0%

Source: Appendix G, Table 11

irAE: ADR considered immune-related by investigator; 95% CI: 95% Confidence Interval

Each subject is counted once within each PT or SOC if an adverse event is reported for a given subject more than once during treatment. The PT of worst severity is tabulated.

Disease stage IV

13 (13.4%) out of 97 ICS+ patients with stage IV disease treated with avelumab experienced at least one ADR that was considered related to avelumab. 23ADRs related to avelumab comprised 10 SADRs and 13 non-serious ADRs. The incidence rate for ADRs (serious and non-serious) related to avelumab in stage IV ICS+ patients was 0.89 (95% CI 0.56 to 1.38) events per person-year (time at risk: 25.95 person-years). SADRs (incidence rate 0.39, 95% CI 0.18 to 0.76) were most frequently reported in the SOC category of "respiratory, thoracic and mediastinal disorders" (n=3) and non-serious ADRs (incidence rate 0.50, 95% CI 0.27 to 0.91) in "injury, poisoning and procedural complications" (n = 3). 8 ADRs were identified as immune related by investigators (incidence rate 0.31, 95% CI 0.13 to 0.66), 5 were SADRs (incidence rate 0.19, 95% CI 0.06 to 0.50) and 3 non-serious ADRs 0.12 (95% CI 0.02 to 0.39).

Three (12.0%) out of 25 ICS- patients with stage IV disease treated with avelumab experienced at least 1 ADR that was considered related to avelumab; 3 ADRs were reported including 2 serious (SOC categories "respiratory, thoracic and mediastinal disorders" and "injury, poisoning and procedural complications") and 1 non-serious (SOC category "gastrointestinal disorders"). These 3 events resulted in an overall (serious and non-serious) ADR incidence rate of 0.52 (95% CI 0.11 to 1.78) events per person-year (time at risk: 5.76 person-years). Incidence rate of SADRs was 0.35 (95% CI 0.04 to 1.52) and of non-serious ADRs 0.17 (95% CI 0.00 to 1.25). 1 (serious) immune related ADR was identified by investigators with an incidence rate of 0.17, 95% CI 0.00 to 1.25.

Safety events among patients treated with avelumab in strata by center

12 (34.3%) out of 35 ICS+ patients treated with avelumab in center 1 (Universitätsklinikum Essen) and 15 (10.2%) out of 147 ICS+ patients in center 2 (all remaining study centers pooled together) experienced at least 1 ADR considered related to avelumab. 2 (28.6%) out of 7 ICS- patients treated with avelumab in center 1 and 5 (11.4%) out of 44 ICS- patients in center 2, were reported with at least one ADR.

25 ADRs related to avelumab comprised 7 SADRs (incidence rate 0.81, 95% CI 0.33 to 1.82 events per person-year) and 18 non-serious ADRs (incidence rate 2.08, 95% CI 1.23 to 3.43 events per person-year) in ICS+ patients of center 1; the overall ADR incidence rate was estimated to be 2.89 (95% CI 1.87 to 4.41) events per person-year. The corresponding figures in the ICS+ patients in center 2 were 28 ADRs (9 SADRs and 19 non-serious ADRs) with overall incidence rate 0.64 (95% CI 0.42 to 0.95) events per person-year. The incidence rate of SADRs and non-serious ADRs was 0.20 (95% CI 0.09 to 0.42) and 0.43 (95% CI 0.26 to 0.70) events per person-year, respectively. The incidence rates of ADRs related to avelumab (overall, SADRs, non-serious ADRs) among ICS+ patients were higher in center 1 than in center 2.

2 (both serious) ADRs related to avelumab were reported among ICS- patients in center 1 (incidence rate 1.02, 95% CI 0.12 to 4.48 events per person-year) and 7 ADRs (1 SADR and 6 non-serious ADRs) among ICS- patients in center 2 (overall incidence rate 0.65 [95% CI 0.26 to 1.47] events per person-year). Incidence rate of SADRs in ICS- patients in center 1 was 1.02 (95% CI 0.12 to 4.48) vs 0.09 (95% CI 0.00 to 0.67) in center 2 and of non-serious ADRs was

0.00 events per person-year in center 1 vs 0.56 [95% CI 0.21 to 1.35] in center 2, respectively. The results in ICS- patients in center 1 should be interpreted with caution because of very low number of patients (n=7).

8 Immune-related ADRs related to avelumab were observed in ICS+ patients of center 1 (incidence rate 0.93, 95% CI 0.40 to 1.98 events per person-year), The corresponding figures in the ICS+ patients in center 2 were 13 Immune-related ADRs related to avelumab with the incidence rate of 0.30, 95% CI 0.16 to 0.53. In ICS- patients of center 1, 2 Immune-related ADRs related to avelumab were observed (incidence rate 1.02, 95% CI 0.12 to 4.48 events per person-year), The corresponding figures in the ICS- patients in center 2 were 2 Immune-related ADRs related to avelumab with the incidence rate of 0.19, 95% CI 0.02 to 0.82.

10.4.2 Exploratory Objectives

10.4.2.1 Comparison of the Safety and Effectiveness Profile Between Immune Compromised Patients and Immune Competent Patients Treated With Avelumab

Safety profiles of patients treated with avelumab not considered immune compromised and considered immune compromised presented in Table 7c in Appendix G are described in section 10.4.1.2. The overall incidence rate of ADRs related to avelumab was similar in ICS+ and ICS- avelumab Analysis Sets (incidence rates 1.01 [95% CI 0.75 to 1.34] and 0.71 [95% CI 0.32 to 1.45] events per person-year, respectively). Similar incidence rates of SADRs related to avelumab were observed in both subpopulations with 0.30 (95% CI 0.17 to 0.52) events per person-year in ICS+ and 0.24 (95% CI 0.05 to 0.81) in ICS- patients. No meaningful differences between incidence rates of nonserious ADRs related to avelumab were identified between the ICS+ and ICS- Analysis Sets with 0.70 (95% CI 0.49 to 0.79) events per person-year and 0.47 (95% CI 0.17 to 1.14) events per person-year, respectively.

Incidence rates of ADRs related to avelumab among ICS+ and ICS- patients treated with avelumab by 2 center strata are described in section 10.4.1.2 (definition of center strata in section 9.10.6). Incidence rates of any ADRs, serious, non-serious, immune related (as identified by investigators) ADRs were higher in the ICS+ subpopulation of center 1 than in center 2 based on assessment of 95% CIs. The comparison of ADR incidence rates in ICS- patients between 2 centers has not provided reliable results because of very low number of immune compromised patients in center 1 (n=7).

Possible effect of the leading study center on incidence rate of ADRs in Analysis Set of patients treated with avelumab was investigated in the exploratory regression analysis (Poisson regression models) with independent parameters “immune compromised status” (categories: ICS+/ ICS-), “center” (categories: center 1/ center 2) and the interaction term. The results are presented in Table 7c-2 in Appendix G. Significant differences between 2 study centers could be identified with regards to incidence rate of ADRs related to avelumab (in overall), serious ADRs and ADRs considered immune-related by investigators. Estimated incidence rates in “center 2” stratum was significantly lower than in stratum “center 1” (Incidence Rate Ratio [95% CI]) was 0.37 [0.16, 0.86] for any ADRs, 0.15 [0.04, 0.56] for serious and 0.24 [0.08, 0.71] for immune-

related ADRs). No significant differences in incidence rate of ADRs (overall), serious ADRs and immune-related ADRs could be identified between ICS+ and ICS- subpopulations in overall and within each of 2 centers. Regression models for nonserious ADRs related to avelumab, ADRs considered not immune-related and those with unknown immune status as well as analyses of ADRs not related to avelumab could not be conducted appropriately because the data does not contain sufficient information to estimate parameters for the model in a reliable manner (e.g. all patients have no events in some strata).

To compare the effectiveness profiles, differences in responses to palliative treatment with avelumab in the Analysis Set of patients not considered immune compromised treated with avelumab (n=175) and the Analysis Set of patients considered immune compromised treated with avelumab (n=53) have been evaluated. In addition, analysis of response has been performed in subgroups of disease stages III and IV. The sample sizes being utilized for effectiveness comparisons differ from those available for safety comparisons, as patients needed to have had last dose of systemic treatment within 90 days prior to enrollment, ongoing systemic treatment at enrollment or systemic treatment after enrollment to be considered in safety analyses. However, for the effectiveness analysis patients needed to have received their first administration of systemic treatment after study inclusion.

Responses (CR, PR, MR, SD, PD, 'unratable') to avelumab treatment administered with palliative intent by immune status is summarized in Table 12 for overall populations and by disease stages III and IV separately. In addition, the results stratified by 2 center strata are provided (Table 8 in Appendix G).

A NED response was not observed for avelumab treatment with curative/palliative intent.

Table 12 Differences in Responses to Palliative Treatment with Avelumab between Immune compromised and Immune Competent Patients

	Patient group, n	Response	Proportion	Difference in proportions	95% CI of the difference
		Objective response (CR+PR)			
Overall	ICS+, 175	60	34.3%		
	ICS-, 33	16	30.2%	4.1%	-10.12%,18.32%
Stage III	ICS+, 74	32	43.2%		
	ICS-, 25	10	40.0%	3.2%	-19.03%,25.52%
Stage IV	ICS+, 97	25	25.8%		
	ICS-, 28	6	21.4%	4.3%	-13.17%,21.86%
	ICS+	Complete response (CR)			
Overall	ICS+	43	24.6%		
	ICS-	11	20.8%	3.8%	-8.83%,16.46%
Stage III	ICS+	24	32.4%		
	ICS-	7	28.0%	4.4%	-16.15%,25.01%
Stage IV	ICS+	17	17.5%		
	ICS-	4	14.3%	3.2%	-11.77%,18.25%

	Patient group, n	Response	Proportion	Difference in proportions	95% CI of the difference
		Partial response (PR)			
Overall	ICS+	17	9.7%		
	ICS-	5	9.4%	0.3%	-8.73%,9.29%
Stage III	ICS+	8	10.8%		
	ICS-	3	12.0%	-1.2%	-15.76%,13.38%
Stage IV	ICS+	8	8.3%		
	ICS-	2	7.1%	1.1%	-9.89%,12.1%
		Mixed response (MR)			
Overall	ICS+	4	2.3%		
	ICS-	2	3.8%	-1.5%	-7.08%,4.1%
Stage III	ICS+	1	1.4%		
	ICS-	1	4.0%	-2.7%	-10.77%,5.47%
Stage IV	ICS+	3	3.1%		
	ICS-	1	3.6%	-0.5%	-8.17%,7.21%
		Stable disease (SD)			
Overall	ICS+	26	14.9%		
	ICS-	5	9.4%	5.4%	-4.05%,14.89%
Stage III	ICS+	11	14.9%		
	ICS-	2	8.0%	6.9%	-6.51%,20.24%
Stage IV	ICS+	14	14.4%		
	ICS-	3	10.7%	3.7%	-9.7%,17.14%
		Progressive disease (PD)			
Overall	ICS+	51	29.1%		
	ICS-	18	34.0%	-4.8%	-19.24%,9.6%
Stage III	ICS+	15	20.3%		
	ICS-	8	32.0%	-11.7%	-32.18%,8.72%
Stage IV	ICS+	36	37.1%		
	ICS-	10	35.7%	1.4%	-18.79%,21.58%

Source: Table 8 in Appendix G
ICS+: immune competent, ICS-: immune compromised, CI: confidence interval

Number of observations in the analysis set of immune compromised patients treated with avelumab in disease stage III (n=25) and in stage IV (n=28) was low and results of the comparative response analyses should be interpreted with caution.

In addition, treatment responses in immune compromised and not immune compromised analysis sets in overall and in diseases stages III and IV were described in 2 center strata separately (definition of strata in section 9.10.6). No differences between ICS+ and ICS-subpopulations could be identified in center 2 based on assessment of 95% CIs. The results for center 1 cannot be interpreted appropriately because of very low number of ICS- patients in this center (n=7).

Possible effect of the leading study center on treatment response was investigated in exploratory regression analyses. The results are presented in Table 8-2 in Appendix G. No significant differences between 2 center strata were identified in analyses of ORR, CR, SD and PD. The regression analyses did not confirm any statistically significant differences between ICS+ and ICS- subpopulations in overall as well as within of center strata.

Regression models for PR, MR and "unratable" response could not be executed appropriately because of no patients in response category in some strata.

10.5 Other Analyses

No other analyses were performed.

10.6 Adverse Events/Adverse Reactions

Analysis of patients' safety profiles was one of the main study objectives. The results are presented in sections 10.4.1.2 and 10.4.2.1.

11 Discussion

11.1 Key Results

This cohort study enrolled 875 patients with an MCC diagnosis over a 4.5-year period. For this final study report, 43 sites were activated, and 41 sites contributed to the enrollment. With 875 patients, actual enrollment was significantly above the target enrollment initially planned at the beginning of this study for end of September 2023 (540 patients). The target enrollment was revised to maximum 1,000 patients in July 2021. In this report analysis results for the PASS specific population are reported.

Relevant patient and tumor characteristics

Avelumab Analysis Set: patients in ICS+ and ICS- strata

From 243 patients treated with avelumab, 54 were considered ICS- (22.2%) and 189 patients (77.8%) were ICS+. The ICS- patients were on average slightly older than ICS+. The proportion of patients aged older than 70 was 85.2% in the ICS- and 72.0% in ICS+ subpopulation. A favorable ECOG score of '0' or '1' was reported for 93.8% of assessed ICS+ and 86.9% of ICS- patients. Immune compromised patients had reportedly more frequently distant metastasis (64.7% in ICS- vs. 54.6% in ICS+ Analysis Set). The oncologic and non-oncologic comorbidities were more frequently reported among ICS- patients than in ICS+.

Avelumab Analysis Set: patients in 2 center strata

From 243 patients receiving avelumab, 44 (18.1%) were treated in center 1 and 199 (81.9%) in center 2. Some differences between centers were identified regarding patient and tumor characteristics. Longer median duration of follow-up in center 1 compared to center 2 (16.9 months vs. 12.6 months) could be caused by higher recruitment rate in center 1 in the early stage

of the study which became more balanced at the end of enrollment period due to increased recruitment in other centers.

Characterization of disease outcomes in the Immune compromised Analysis Set treated with avelumab (n=54)

Response to first-line systemic therapy with avelumab (n=49) was ORR of 28.6% (95% CI 15.9% to 41.2%). The ORR was higher in patients receiving first-line avelumab in stage III than in stage IV disease (40.0% [95% CI 20.8% to 59.2%] vs. 16.7% [95% CI 1.8% to 31.6%]).

No statistically significant differences with regards to treatment response between the 2 study centers as well as between ICS+ and ICS- subpopulations within each of centers could be shown in the exploratory regression analyses.

Survival analyses

The median first-line rwPFS (95% CI) was 7.9 (4.0 to 11.6) months and 4.3 (1.0 to 7.8) months in ICS+ and ICS- subpopulations, respectively.

The median (95% CI) first-line OS among ICS+ patients treated with avelumab was 38.2 (15.7, NE) months whereas in ICS- patients it was 9.9 (4.8, 29.8) months.

Safety events in the Analysis Set of ICS+ patients treated with avelumab and the Analysis Set of ICS- patients treated with avelumab

Among 182 patients from the Analysis Set of ICS+ patients treated with avelumab, the overall ADR incidence rate was estimated to be 1.01 (95% CI 0.75 to 1.34) events per person-year, incidence rate of SADRs and non-serious ADRs was estimated to be 0.30 (95% CI 0.17 to 0.52) and 0.70 (95% CI 0.49 to 0.99), respectively.

Among 51 patients from the Analysis Set of ICS- patients treated with avelumab, the overall incidence rate for ADRs was estimated to be 0.71 (95% CI 0.32 to 1.45) events per person-year, incidence rate 0.24 (95% CI 0.05 to 0.81) for SADRs and 0.47 (95% CI 0.17 to 1.14) events per person-year for nonserious ADRs in this Analysis Set.

The safety profile of ICS+ and ICS- patients was consistent with the known safety profile of the avelumab product information. For both subpopulations, no new safety signal was identified during the follow-up of patients enrolled.

The proportion of patients reported with at least one ADR related to avelumab was higher in center 1 than in center 2 (34.3% vs. 10.2% in ICS+ subpopulation; 28.6% vs. 11.4% in ICS- patients). Incidence rates of ADRs related to avelumab in ICS+ patients in center 1 (Essen) appeared higher than in center 2 (overall: 2.89 [95% CI 1.87 to 4.41] vs. 0.64 [95% CI 0.42 to 0.95] events per person-year. The comparison in immune compromised patients between 2 centers does not provide conclusive results because of very low number of patients in center 1 (n=7). No significant differences between ICS+ and ICS- patients within each of 2 centers were identified in the regression analysis.

Differences in responses to avelumab treatment with palliative intention in the ICS+ Analysis Set of patients treated with avelumab (n=175) and the ICS- Analysis Set of patients treated with avelumab (n=53)

Difference in ORR between the ICS+ and ICS- datasets was 4.1% (95% CI -10.1%, 18.3%); 60 of 175 patients (34.3%) in ICS+ and 16 of 53 patients (30.2%) in ICS- dataset were reported with ORR.

Descriptive comparison of differences in response between 2 centers has not provided reliable results because of low number of ICS- patients considered for this analysis in center 1 (n=7). No statistically significant differences with regards to responses to palliative treatment with avelumab between ICS+ and ICS- subpopulations in center strata could be identified in the exploratory regression analyses. No significant differences between ICS+ and ICS- subpopulations in overall as well as within each of 2 centers were identified in the regression analyses.

11.2 Limitations

A limitation of the study was the relatively short follow-up time of patients with a median of 18.1 months, meaning that 50% of all enrolled patients had a follow-up time of around 1.5 year or less at the end of data collection period (31 March 2024). This has impact in particular by limiting follow-up time available for time to event analyses (OS in particular for early stage) but also on analyses to be undertaken for study objectives depended on follow-up information such as effectiveness, safety and HRU analyses. Time between end of enrollment period (30 September 2023) and end of data collection (31 March 2024) allowed for the follow-up of at least 6 months for all included patients.

Only treatment lines of systemic therapy initiated after enrollment were included in the survival analysis, which could impact results on rwPFS and OS in direction of underestimation.

Study was performed in real-world setting and was based on clinical routine practice data rather than data for research. However, to mitigate this limitation this study was designed to prospectively collect data via the study-specific eCRF and within a defined time-interval for data entry. Documentation is likely to reflect the need for clinical management of the patient rather than the need for standardized and comparable assessment:

- Assessment of response may not occur at standard intervals as is typically scheduled to occur in the clinical trial setting.
- Analysis of time to event outcomes in a non-interventional study may differ somewhat from what would be determined under clinical trial conditions because of variations in timing of treatment start relative to the clinical trial setting. In particular, significant delay in the introduction of treatment in a given line of therapy may have lengthened time to event relative to what would have occurred with implementation of a protocol-defined treatment plan in that setting. Treatment plans in routine clinical practice could be heterogeneous from centers to centers across Germany.

Some measurements may not be consistently available from patient records in the ADOREG data source. According to centers, patient characteristics, may not have been assessed or may have been assessed differently based on patient files (before enrollment). Therefore, it may have an impact in the availability of the medical information even if all have been set to optimize high quality data. In order to address a certain degree of heterogeneity between the leading study center and other centers, the impact of the leading center on outcome parameters (effectiveness, safety) was explored in regression analysis.

Completeness of documentation in the real-world setting can vary between study sites. Comorbid conditions relevant to interpretation of the patients' baseline status may not be documented in the available medical record. Thus, prevalence of such conditions may be underestimated. This may occur because the condition is not considered material to the disease that triggered the data collection. But it may also occur because the comorbid condition (like high frequency of diabetes in some patient groups), though possibly relevant to understanding of outcomes, is not under the direct management of the oncologist.

As the study is restricted to MCC patients treated in Germany, obtained results may not be representative of the treatment landscape and patient management in other countries. However, based on the available treatments and medical guidelines in Europe, the results of this large study in one of the largest European populations, could be extrapolated to other EU member states (Becker 2019).

Misclassification

Misclassification of patient characteristics or outcomes may be due to systematic or random measurement error. To minimize this type of bias in the current study, instructions are provided to all investigators to harmonize the way data are collected in the different eCRFs provided by the Contract Research Organization.

However, misclassification of tumor responses as 'unratable' may still have occurred when response information for a specific line of treatment had been entered before conclusive response information was available. This potential issue was targeted during remote monitoring process to enhance quality of analyzed data. Also, the confirmation of the MCC diagnosis by tissue sample analysis helps to identify and evaluate potential misclassification of the primary diagnosis. At the end of the study, the MCC diagnosis was confirmed via tissue analysis for 718 patients (82.1% of 875 enrolled patients). For 157 (17.9%) patients, the analysis was either inconclusive (9 patients) or impossible due to too little or no material at all available. Available results of the tissue analysis did not point to a potential misdiagnosis of enrolled patients.

Underreporting of Safety Events

Underreporting of ADRs is a well-known phenomenon with respect to spontaneous reporting (Crestan 2020). A meta-analysis of 37 papers concluded that 94% of ADRs were underreported, on average (Hazel 2006) and this may only in part be alleviated by solicited ADR collection methods like in the current study. In addition, to assess the accuracy of the reporting and possibly increase the reporting rate, on-site monitoring visits to the sites with the highest enrollment were

performed in the study. During these visits, a focus of the source data verification was on potential underreporting of ADRs and/or missed reporting of ADRs.

11.3 Interpretation

This study established the largest real-world cohort of patients with MCC in Germany, using data from the national skin cancer registry (ADOREG), as well as additional data not currently collected in ADOREG. The prospective enrollment of patients and collection of data on treatment patterns, comorbidities, concomitant treatments, and disease outcomes plus monitoring the data quality over the course of study made it possible to identify and characterize the MCC population in Germany.

Of the 875 patients enrolled during the 4.5 years study enrollment period, 599 (68.5%) were reported to have either no stage information available at the time of the data cutoff or stage I to III MCC. In total, 276 (31.5%) patients had been diagnosed with unresectable stage III or stage IV MCC and were therefore considered as having advanced MCC. This proportion corresponds to what was anticipated when the study sample size was estimated (between 30-40% of the patients diagnosed with advanced stage MCC at the time of inclusion or will subsequently have disease progression to advanced stages). This number (276 patients) exceeded the number of patients with advanced stage initially planned to be recruited to be able to inform all study objectives with sufficient data (160 to 200 patients). It was possible due to recruitment of meaningfully more patients than originally planned 540. The decision to increase the sample to a maximum of 1000 patients while keeping study timelines was made in 2021 under consideration of an observed higher recruitment rate and lower than expected proportion of patients in advanced stages. It was assumed that most patients with advanced MCC would be treated with avelumab when available, and that 7% to 10% would be immune compromised (Bhanegaonkar 2021; Heath 2008; Paulson 2013; Walker 2020). Hence, the estimated size of the subgroup of interest to provide information on efficacy and safety from immune compromised patients treated with avelumab was 15 to 20 patients over the study period. This subgroup of patients (Immune compromised Analysis Set treated with avelumab) comprised 54 patients (28 of them in disease stage IV) in the final study report, making it over the higher limit of the planned subgroup size (20 patients). Only 51 of those patients were included in safety analyses, as patients needed to have had the last dose of systemic treatment within 90 days prior to enrollment or had an ongoing systemic treatment at enrollment or systemic treatment after enrollment to be considered in safety analyses. Twenty-five of the 54 patients initiated avelumab while having a disease stage III. These treatment patterns reflect the routine clinical practice settings and could be further investigated in frame of further studies 3.

Demographic characteristics at study inclusion were reflective of the typical population of patients with MCC that has been reported in other studies, i.e. it was diagnosed in elderly patients (median age >70 years) (Albores-Saavedra 2010; Kearney 2024; Levy 2019; Lohray 2023) with a higher proportion of males especially in the advanced stages which has also been observed in recent publications (Ghanian 2021; Kearney 2024; Levy 2019; Lohray 2023). Causal role of Merkel Cell Polyomavirus in pathogenesis of MCC (Akaike 2022; Becker 2017; Hernandez 2022; Lewis 2023; Pulitzer 2017) is supported by high proportion of MCC diagnoses confirmed with positive MCPyV test in our study (74.2% of patients with available test results in FAS). The most frequent locations of primary tumor reported in the study were skin of upper

limb (29.5%) and skin of other and unspecified parts of face (23.3%) which is reflecting importance of sunlight (ultraviolet) radiation exposure as a risk factor of MCC in Germany as well as elsewhere (Becker 2017; Patel 2021; Siqueira 2023). Most patients with available information in our study (68.1%) had skin phototype II which is in line with the results of the Genome-Wide Association Study (GWAS) (Farré 2023) where strong association between the fair phototype and non-melanoma skin cancer could be shown. PD-L1 was expressed in 41.4% of tested patients (n=29). This proportion is slightly lower than reported by Lipson 2013. The small number of reportedly tested patients should be taken into account when interpreting these results in our study.

Limitations of non-interventional real-world studies relative to the clinical trials (section 11.2) should be taken into consideration when interpreting rwPFS results of MCC TRIM. as in routine clinical care, tumor assessment is not done according to a schedule in a protocol and therefore can be heterogeneous across different treating sites. Nevertheless, tumor assessments are expected to be done regularly in routine clinical care as well. Furthermore, it should be considered, that only treatment lines of systemic therapy initiated at/after enrollment were included in the survival analysis in MCC TRIM, which could lead to underestimation of rwPFS and OS results (Feifel 2024). As expected, (Paulson 2013, McEvoy 2021), median [95% CI] duration of rwPFS and OS from first-line avelumab was longer in patients not considered immune compromised than in immune compromised subpopulation (rwPFS: 7.9 [4.0, 11.6] months vs. 4.3 [1.0, 7.8] months; OS: 38.2 [15.7, NE] months vs. 9.9 [4.8, 29.8] months). This might be explained by observed differences in several baseline factors, e.g. older age, higher comorbidity rates, worse performance status, and higher proportion of patients with stage IV disease and with distance metastasis in the group of immune compromised patients.

The results on treatment response to avelumab from the MCC TRIM study are comparable with the results reported in the recently published review (Lohray 2023). The reported complete response rate to treatment with avelumab ranged from 10.9% to 37.2% in the review (Lohray 2023) and was 23.1% in the first-line and 31.3% (5 of 16 patients) in the second-line avelumab in our study; ORR varied between 29.1% and 72.1% in (Lohray 2023) and was comparable (32.5% in the first-line and 31.3% in second-line) in the MCC TRIM. The results of the MCC TRIM study were in line with JAVELIN Merkel 200 trial ((D'Angelo 2021; Kaufman 2018), where avelumab resulted in ORR of 39.7% and CR of 16.4% in first-line (32.5% and 23.1% in MCC TRIM) and in ORR 33.0% and CR 11.4% (31.3% ORR and CR in our study) in second-line therapy. MCC TRIM study showed effectiveness of avelumab in patients considered immune compromised with ORR of 28.6% (CR 18.4%, PR 10.2%) in first-line therapy. These results were numerically slightly lower than in the MCC TRIM ICS+ population treated with first-line avelumab (ORR of 34.7%, CR 25.1%, PR 9.6%) and slightly lower than the results from global expanded access program (EAP) (Walker 2020) where ORR in immune compromised patients was 37.5% (CR 18.8%, PR 18.8%). The ORR was higher in stage III than in stage IV MCC in both ICS+ and ICS- subpopulations in MCC TRIM. CR to first-line avelumab in ICS- subpopulation in stages III and IV was very similar to the CR rate from the recently published meta-analysis (Kearney 2024): CR in stage III was 29.4% in both analyses; in stage IV, 16.5% (MCC TRIM) and 16.7% of patients (meta-analysis) were reported with CR. to explore the impact of the leading center on overall study effectiveness results the analyses were conducted as described in section 9.10.6. No meaningful differences were identified between center 1, the leading study center with the largest enrollment (138 patients) and center 2 with

respect to treatment response. This finding was confirmed in regression analysis where no significant differences between 2 center strata as well as between ICS+ and ICS- subpopulations within the centers could be detected.

Safety profile of patients treated with avelumab were similar in the ICS+ and ICS- subpopulations with 14.8% and 13.7% of patients experiencing at least one ADR related to avelumab; 9.3% and 7.8% of patients were reported with ADRs considered as immune related by investigators. The overall proportion of immune related ADRs (9.0%) in 233 patients treated with avelumab was comparable with the recent targeted literature review (Lohray 2023), where 10% to 30% of patients were reported to experience immune related ADRs associated with ICIs such as avelumab. Incidence rates of ADRs related to avelumab were similar between ICS+ and ICS- subpopulations. Proportion of patients experiencing at least 1 ADR and incidence rates of events were reportedly significantly higher in the leading study center (center 1, Universitätsklinikum Essen) than in center 2 (all remaining centers pooled). Universitätsklinikum Essen is a reference center in Germany with the largest number of included patients. It is intensively involved in clinical research and is characterised by very thorough and extensive reporting of adverse events which could influence the results of safety analysis in direction of increased incidence rates. Statistically significant difference between 2 centers with respect to incidence rate of ADRs related to avelumab (overall, serious, immune related) was confirmed in exploratory regression analysis. No significant differences were identified between ICS+ and ICS- patients within center strata.

11.4 Generalizability

Results of this final report are generally in line with previously reported characteristics of patients with MCC that could indicated that patients in this study are likely representative of MCC patients in general in Europe specifically because there was no restriction to include patients into the study in terms of stage or treatment received by patients.

Of 875 patients in the study, 138 (15.8%) were enrolled from Universitätsklinikum Essen. The proportion of other sites in the study population varied between 0.1% and 6.7%. As Universitätsklinikum Essen is one of the reference centers for the management and treatment of patients with MCC in Germany, the expectation was that this center will enroll more patients than any other center in Germany by the end of the inclusion period. Even if there was a possibility for patients with MCC to be referred to different medical specialists including, but not limited to, general practitioners, oncologists, and skin cancer nurse specialist, they would have been mainly in contact with specialized dermato-oncologists for their management and treatment. There are currently 73 centers of excellence for skin cancer in Germany. The vast majority of them are participating in ADOREG; 52 ADOREG centers report to treat MCC patients. All 41 of the 52 ADOREG sites contributing patients to this study are certified centers of excellence for skin cancer. Therefore, the sites included in the study are considered to be representative of the specialized care of MCC in Germany. Furthermore, a collective effort from various EU countries have been ongoing since to develop a harmonized guidance on management of the MCC disease (Lebbe 2015, Spada 2022) that resulted in development of the guidelines from European Society for Medical Oncology (ESMO) on management of MCC patients (Lugowska 2024). This indicates that the treatment pattern for the MCC follows an agreed guidance, and this has been shown in nation-wide real-world evidence from other

European countries e.g. UK (Mistry 2023). Therefore, the data generated from the MCC-TRIM study with a nation-wide approach in Germany could be extrapolated to other EU member states as well.

To minimize selection bias, site investigators are dermatologists and sites participating in ADOREG are selected as representing most of the large as well as small dermatology departments in Germany. In addition, eligibility criteria were selected to be as broad as possible for this study population. The participating study sites were expected to invite all consecutive eligible patients to participate and enroll patients prospectively during the study period. Efforts were made when additional sites were included to ensure geographical variety, which increases generalizability of results. As mentioned before, the study is restricted to MCC patients treated in Germany and does not allow for conclusion regarding the usual care of MCC patients in other countries.

11.5 Other Information

11.5.1 Impact of COVID-19 Pandemic

Site activation in 2020, 2021 and 2022 was slowed down by the COVID-19 pandemic, leading to longer review times of e.g. contracts due to re-organization of work at sites and ethic committees. However, the delay in site activation has not impacted patient enrollment, as 41 sites enrolled 875 patients, representing above expected target enrollment for end of enrollment period (September 2023) defined at the initiation of this study as 540 patients and re-evaluated in July 2021 to 750 to (at maximum) 1,000 patients. Up to the end of data collection (31 March 2024), no data had been marked as being missing or unable to be collected by sites due to the COVID-19 pandemic. Although individual patients visit at clinics may have been delayed or cancelled especially in the period of lockdown in Germany from March 2020 to May 2020, and in the winter months of 2020/2021, study sites provided follow-up data as scheduled (every 6 months for each patient, starting at enrollment). Based on a recent publication, delays in treatment and changes to the routine management of skin cancers due to the COVID-19 pandemic may have a negative impact on the outcome of MCC and other patients with skin cancer (Rashid 2021). The size of the potential impact cannot be estimated.

Reporting of comorbidity with COVID-19 infection was not specifically addressed in the eCRF of this study. No comorbidity with ICD-10 code related to the coronavirus infection (B34.2) was recorded in the data until the end of study period.

12 Conclusion

The current study provided insight into demographic and clinical characteristics of the MCC population in Germany.

Demographic characteristics of the patients at study inclusion were found to be reflective of the typical population of patients with MCC. The number of patients with advanced MCC exceeds the initially planned number considered sufficient to inform the effectiveness and safety outcomes relative to the study objectives specifically the PASS objectives.

Effectiveness of systemic treatment with avelumab in advanced MCC in terms of treatment response was confirmed for immune competent as well as for immune compromised patients. The results of MCC TRIM study are in line with published data, e.g. from the JAVELIN Merkel 200 trial.

In terms of survival outcomes (rwPFS, OS), numerically longer survival has been observed in ICS+ treated with avelumab than in ICS- patients treated with avelumab, which might be explained due to nature of these conditions and the differences between the 2 groups in baseline characteristics. Despite achieving the originally planned number of patients with advanced disease stage, survival outcomes could not be reported for some subpopulations, e.g. OS in ICS- patients treated with avelumab in stage IV, because of still low number of patients or events there at the end of data collection period. The survival characteristics of different types of systemic treatment could not be compared for the same reason (low number of patients on other systemic PD-L1/PD-1 and chemotherapy). Investigation in frame of further studies can be beneficial for gaining further insights into survival characteristics of MCC patients treated with avelumab.

No differences in safety profile of immune compromised patients and patients not considered immune compromised were identified. Incidence rates of ADRs related to avelumab were similar in ICS+ and ICS- subpopulations.

In overall, this dynamic cohort study performed in real-world setting has contributed to characterization of patients' population and treatment characteristics of MCC in Germany. The study results supported effectiveness and safety of avelumab as a treatment option for advanced MCC in real-world setting.

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