Risk Management Plan (RMP) for Bavencio® (Avelumab)

Active substance (s) (INN / Trade Name):	Avelumab / Bavencio®
Name of Company:	**Merck Healthcare KGaA** **Frankfurter Straße 250** **D-64293 Darmstadt** **Germany** **Telephone +49 61 51-72 0** **Telefax +49 61 51-72 69 14** **e-mail: GlobalDrugSafety@merckgroup.com**
RMP version to be assessed as part of this application:	
RMP version number:	9.0
Data lock point for this RMP:	**For Indications:** 09 Jun 2016 (Metastatic Merkel Cell Carcinoma) 20 Jun 2018 (Advanced Renal Cell Carcinoma) 21 Oct 2019 (Locally Advanced or Metastatic Urothelial Carcinoma (1L maintenance therapy)) **For safety concerns** 22 Sep 2019 (Myasthenia gravis/ Myasthenic syndrome) 22 Mar 2023 (Safety in Patients with Autoimmune Disease) 30 May 2024 (Sclerosing cholangitis, Arthritis, Polymyalgia rheumatica and Sjogren's syndrome)
Date of final sign -off:	Document signed electronically, see date of eSignature at the end of the document
Rationale for submitting an updated RMP:	Type II Safety variation: • The risks of immune-mediated sclerosing cholangitis, arthritis, polymyalgia rheumatica and Sjogren's syndrome were added under the important identified risk of 'Immune-mediated adverse reactions' in all the relevant modules. • Risk minimization measures concerning immune-mediated sclerosing cholangitis, arthritis, polymyalgia rheumatica and

[redacted]

CCI [redacted]

	Sjogren's syndrome were updated in the relevant modules of EU RMP in alignment with updated EU SmPC. • Immunogenicity information was updated for all indications in the relevant modules of EU RMP • Part II: Module VII - Section "SVII.3.1. Presentation of important identified risks and important potential risks" was revised and shortened to facilitate the reader's understanding of the safety concerns. • Table V.1 Routine risk minimisation activities and Table V.3 Summary of Risk Minimisation Measures were updated to shift information for immunogenicity from EU SmPC Section 4.8 to Section 5.1. • The term "patient alert card" has been changed to "patient card" according to Version 3 of GVP module XVI.
Summary of significant changes in this RMP:	• The risks of immune-mediated sclerosing cholangitis, arthritis, polymyalgia rheumatica and Sjogren's syndrome were added under the important identified risk of 'Immune-mediated adverse reactions' in all the relevant modules. • Risk minimization measures concerning immune-mediated sclerosing cholangitis, arthritis, polymyalgia rheumatica and Sjogren's syndrome were updated in the relevant modules of EU RMP in alignment with updated EU SmPC. • Immunogenicity information was updated for all indications in the relevant modules of RMP. • Section "SVII.3.1. Presentation of important identified risks and important potential risks" was revised and shortened to facilitate the reader's understanding of the safety concerns.
Other RMP versions under evaluation:	
RMP version number:	8.2

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Details of the currently approved RMP:

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Signatures

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EU QPPV, Head of PV System and QPPV Office

Document signed electronically by the EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved for use in the EEA by the Marketing Authorization Holder's QPPV. The electronic signature is available on file.

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Global Patient Safety, PPD – Avelumab, Global Patient Safety

(Contact person for this RMP)

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List of Abbreviations

ACE	Angiotensin-Converting Enzyme
ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
AJCC	American Joint Committee on Cancer
aRCC	Advanced Renal Cell Carcinoma
BC	Bladder Cancer
BID	Twice a Day
BSC	Best Supportive Care
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CNS	Central Nervous System
CYP	Cytochrome P450
DDI	Drug-drug Interaction
DOR	Duration Of Response
EAP	Early Access Program
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EM	Educational Material
EPAR	European Public Assessment Report
EU	European Union
GC	Gemcitabine and Cisplatin
HAART	Highly Active Antiretroviral Therapy
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
HMG -CoA	3-hydroxy-3-methylglutaryl-coenzym A
HR	Hazard Ratio
ICIs	Immune Checkpoint Inhibitors
IFNγ	Interferon Gamma
IgG1	immunoglobulin G1
IL	Interleukin
imAE	Immune-Mediated Adverse Event
INN	International Nonproprietary Name
IRR	Infusion-Related Reaction
MCC	Merkel Cell Carcinoma
MCPyV	Merkel Cell Polyomavirus
MCP-1	Monocyte Chemoattractant Protein-1
mMCC	Metastatic Merkel Cell Carcinoma
mRCC	Metastatic Renal Cell Carcinoma
mTOR	Mammalian Target of Rapamycin
MVAC	Methotrexate, Vinblastine, Adriamycin, and Cisplatin
nAb	Neutralizing Antibody

NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PASS	Post-Authorization Safety Study
PBMC	Peripheral Blood Mononuclear Cell
PD-1	Programmed Death 1
PD-L1	Programmed Death Ligand 1
PDGF	Platelet Derived Growth Factor
PFS	Progression-Free Survival
PK	Pharmacokinetics
PL	Package Leaflet
PO	Per OS
QPPV	Qualified Person for Pharmacovigilance
RCC	Renal Cell Carcinoma
RMP	Risk Management Plan
SEER	Surveillance, Epidemiology, and End Results
SIR	Standardized Incidence Rate
SmPC	Summary of Product Characteristics
TEAE	Treatment-Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
TNF-α	Tumor Necrosis Factor-Alpha
UC	Urothelial Carcinoma
US	United States
UV	Ultraviolet
UVB	Ultraviolet B
VEGF	Vascular Endothelial Growth Factor
VHL	von Hippel Lindau

Part I: Product Overview

Product Overview

Active substance (INN)	Avelumab
Pharmacotherapeutic group (ATC Code)	Antineoplastic agents, monoclonal antibodies (L01FF04)
Marketing Authorization Holder	Merck Europe B.V. Gustav Mahlerplein 102 1082 MA Amsterdam The Netherlands Tel. +31 (0)207 235 230 Fax +31 (0)207 235 239 e-mail: GlobalDrugSafety@merckgroup.com
Medicinal products to which this RMP refers	1 (Bavencio 20 mg/mL concentrate for solution for infusion)
Invented name in the European Economic Area (EEA)	Bavencio®
Marketing Authorization Procedure	Centralized
Brief description of the product	Chemical class: Programmed death ligand 1 (PD-L1) blocking antibody
	Summary of mode of action: PD-L1 may be expressed on tumor cells and/or tumor-infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD-L1 to the programmed death 1 (PD-1) and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production. Avelumab is a human immunoglobulin G1 (IgG1) monoclonal antibody directed against PD-L1. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the PD-1 and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic $CD8^+$ Tcells, resulting in the restoration of anti-tumor T-cell responses. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth. Avelumab has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity *in vitro*.
	Important information about its composition: Avelumab is a human monoclonal IgG1 antibody directed against the immunomodulatory cell surface ligand protein PD-L1 and produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information	Bavencio Product Information (Module 1.3.1)
Indication(s) in the EEA	Current: Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic merkel cell carcinoma (MCC). Bavencio is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with platinum-based induction chemotherapy. Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose of Bavencio is 800 mg administered intravenously over 60 minutes every 2 weeks.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Concentrate for solution for infusion. Clear, colorless to slightly yellow solution. The solution pH is in the range of 5.0 - 5.6 and the osmolality is between 285 and 350 mOsm/kg. Each mL of concentrate contains 20 mg of avelumab. One vial of 10 mL contains 200 mg of avelumab.
	Proposed: Not applicable
Is the product subject to additional monitoring in the EU?	No

EU=European union, MCC=merkel cell carcinoma, NK=natural killer, PD-1=programmed death 1, PD-L1=programmed death ligand 1, RCC=renal cell carcinoma, UC=urothelial carcinoma

Part II: Safety Specification

Part II: Module SI: Epidemiology of the Indications and Target Populations

Indication: Metastatic Merkel Cell Carcinoma

Bavencio is indicated for the treatment of patients with metastatic Merkel cell carcinoma (MCC).

MCC is a rare neuroendocrine, cutaneous malignancy, which exhibits aggressive clinical features and is associated with a poor prognosis (Saini 2015; Chen 2015; Smith 2012; Toker 1972).

At time of diagnosis the majority of patients (estimated 70-80%) present with localized node negative disease, followed by diagnosis with positive regional lymphadenopathy disease (estimated 24-33%), and least common at diagnosis are distant metastatic disease (estimated 6-9%) (Harms 2016; Allen 2005; Pectasides 2006; Santamaria-Barria 2013; Stokes 2009; Andea 2008; Andea 2010; Fitzgerald 2015). After initial treatment, recurrence is frequent and estimated in as much as 48% of patients at a median time to recurrence 9 months (Allen 2005) and typically observed within the first 3 years following diagnosis (Allen 2005). The most common location of metastasis is the draining lymph node basin, followed by distant skin, lung, central nervous system (CNS), bone, and liver (Allen 2005; Medina-Franco 2001; Voog 1999). Of those with metastatic disease, up to 12% have an unknown primary site of disease.

Distant metastasis occurs in about 21% of patients after initial local or regional nodal disease at diagnosis, and increasing occurrence associated with higher stage at diagnosis. Median survival after presentation of distant metastatic disease is approximately 9 months (Allen 2005).

Comparisons of staging across reports is difficult due to use of multiple inconsistent staging methods prior to introduction of a consensus staging system for MCC by the American Joint Commission on Cancer (AJCC) in 2010, which has since been adopted worldwide (Edge 2010). A recent analysis of prognostic factors resulted in proposed revisions (8th Edition) to the AJCC staging for MCC to improve the clinical and pathological staging consistent with AJCC criteria for other tumors and to update staging of unknown primary disease given the reported improved survival outcome for these patients (Harms 2016) as per the following:

- Stage I includes patients with a primary tumor size ≤ 2 cm, no regional lymph node metastasis or distant metastasis
- Stage II includes those with a primary tumor size of > 2 cm, which are further classified as IIA and IIB and includes tumors where the primary tumor invades fascia, muscle, cartilage or bone; both IIA and IIB have no regional lymph node metastasis or distant metastasis
- Stage III includes those with primary tumor of any size from no primary to primary tumor invades fascia, muscle, cartilage or bone, and also clinically detected regional lymph nodes, or in-transit metastasis (local). Stage III is further classified as A or B based on nodal evaluation, whereas IIIA includes occult nodal disease identified by pathology and clinically detected nodal disease with unknown primary; and IIIB combines clinically detected nodal disease with known primary, or in-transit disease without regional nodal disease (N2) or in transit metastases with regional nodal disease (new N3)
- Stage IV includes any distant metastasis regardless of primary tumor or nodal status; there are no further subgroups for Stage IV.

Indication: Advanced Renal Cell Carcinoma

Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

RCC is the most common (90-95%) form of kidney cancer and arises from the renal epithelium. There are 5 histologic RCC subtypes currently recognized: clear cell RCC (which accounts for approximately 70-80%), papillary, chromophobe, collecting duct, and unclassified RCC (Choueiri 2013).

4 RCC predisposing genes have been identified – MET protooncogene, von Hippel Lindau (VHL) tumor suppressor gene, fumarate hydratase tumor suppressor gene, and Birt Hogg Dubé tumor suppressor gene. Patients with VHL disease have a >70% risk of developing clear cell RCC (Frantzen 2012). This hereditary form of RCC is caused by germline mutations in the VHL tumor suppressor gene on chromosome 3p. In addition, a high proportion of sporadic, noninherited clear cell RCC involves somatic VHL gene mutations or methylation (Linehan 2004). VHL gene mutations lead to loss of function of the VHL protein, accumulation of hypoxia inducible transcription factors (e.g. hypoxia inducible factor 1-alpha and hypoxia inducible factor 2-alpha), which translocate to the nucleus and increase transcription of angiogenesis factors (such as vascular endothelial growth factor [VEGF] and platelet derived growth factor [PDGF]), which induce tumorigenesis (Ljungberg 2011). Clear cell RCC is a highly vascular tumor with high expression of VEGF, VEGF receptor, and PDGF receptor (Finley 2011).

Staging in RCC is crucial for clinical decision-making and prognostication. AJCC staging criteria have been revised periodically to reflect the prognostic categories, based upon the size and anatomical extent of cancer. RCC, especially clear cell type, has a penchant for intravenous growth. Level of antegrade intravenous extension is associated with decreased overall survival. In addition to antegrade spread of tumor into the major veins (Taneja 2018), RCC tumors may grow in a retrograde fashion into the proximal tributaries of the renal vein, especially when the main renal vein is occluded by tumor. This can lead to growth of cortical nodules in non-contiguous areas, separate from the original tumor (retrograde venous invasion). This intravenous spread may represent retrograde venous invasion or multifocality of separate smaller tumors (Taneja 2018).

Indication: Locally Advanced or Metastatic Urothelial Carcinoma

Bavencio is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with platinum-based induction chemotherapy.

UC is a disease involving multiple histologies and primary tumor locations. UC comprises carcinomas arising along the entire urothelial tract. UC, also known as transitional cell carcinoma, is the most common histologic subtype of bladder cancer (BC) accounting for ~90% cases, with 7-81% (depending on tissue sampling technique) of patients with UC exhibiting numerous histologic subtypes (Chalasani 2009; Morales 2011). The term ‘advanced bladder cancer’ is most often used to refer to T4/Stage IV muscle invasive BC or any stage of BC with distant or nodal metastases.

Papillary transitional cell tumors dominate, while non-papillary transitional cell carcinoma of the bladder has an orphan disease designation (Orpha number 209989) with a prevalence of 37.0/100,000 in Europe (Orphanet Report Series 2020). UC may be papillary (exophytic or outward projecting) or non-papillary (endophytic or flat), invasive or non-invasive. Non-papillary tumors appear as flat ulcerations surrounded by raised infiltrating borders or fungating necrotic masses (Rouprêt 2018). UC is graded on a scale of 0-III based on the degree of cytologic and architectural abnormalities to indicate the spread of the cancer to lymph nodes (NCCN Bladder Cancer Guideline 2019a).

Data on BC histologies beyond UC are lacking due to their relative rarity, although one review reports comparative rates as follows: pure squamous cell carcinoma occurs in approximately 3% of patients with BC; primary adenocarcinoma occurs in 1.4% of BC; and small cell carcinoma occurs in approximately 1% of BC (Chalasani 2009).

Incidence and Prevalence: MCC

In Europe, MCC is a rare skin tumor accounting for less than 1% of all cutaneous malignancies (Orphanet 2007). According to Orphanet, the reference portal for information on rare diseases and orphan drugs in Europe, the prevalence of cutaneous neuroendocrine carcinoma (synonym for MCC) can be estimated at 4.0 per 100,000 (Orphanet 2016). A study reporting on rare tumor cases diagnosed in 27 European countries (RARECARE) estimated the incidence of MCC between 1995 and 2002 to be 1.3 per 1,000,000 person-years, with the highest incidence observed in patients of > 65 years of age (van der Zwan 2013).

In Germany, the incidence of MCC has remained relatively stable between 1998 and 2010 (0.1 per 100,000 and 0.3 per 100,000 person-years, respectively in women; 0.2 per 100,000 and 0.4 per 100,000 person-years, respectively in men) (Eisemann 2014). In Denmark, a study in 153 patients with MCC identified in the Danish Cancer Registry showed that MCC incidence rates increased by 5.4-fold in the period from 1986 (0.05 cases per 100,000 person-years) to 2003 (0.27 cases per 100,000 person-years) (Lyhne 2011). In another study in 185 Danish patients diagnosed with MCC between 1978 and 2006, the incidence of MCC in Denmark between 1995 and 2006 was stable at 0.22 cases per 100,000 person-years (Kaae 2010). In Eastern France, the standardized incidence rate (SIR) of MCC which was standardized to the age-distribution of the world standard population, from 1980 to 2004 was 0.13 per 100,000 person-years (95% confidence interval [CI]: 0.08; 0.18) (Riou-Gotta 2009). In England, the age-standardized incidence rate for MCC increased from 0.1 per 100,000 person-years in 1998 to 0.2 cases per 100,000 person-years in 2008; this was still a small proportion of the incidence rate for all rare skin cancer in England in 2008 (0.9 per 100,000 person-years) (Public Health England 2010). In Sweden, the incidence of MCC increased in both sun-exposed and sun-covered patients between 1990 and 2005 and was estimated at 0.42 per 100,000 person-years for men and 0.33 per 100,000 person-years for women for that time period (Hussain 2010). Similarly, in the Netherlands, the age-standardized incidence of MCC roughly doubled from 1.7 per million in 1993-1997 to 3.5 per million in 2003-2007 (Reichgelt 2011). Conversely in Finland, the incidence rate of MCC has remained stable since 1989 (Kukko 2012).

Table 1 provides an overview of the reported incidence rate of MCC in Europe, the United States (US), Australia, and New Zealand. Based on cancer statistics of the Surveillance, Epidemiology

and End Results (SEER) program, the incidence of MCC in the US increased significantly from 0.22 per 100,000 in 1986 to 0.79 per 100,000 in 2011 (Fitzgerald 2015).

The incidence rate of MCC in Australia is about twice as high compared to New Zealand and despite age-standardization to different standard populations, there is a trend toward higher incidence rates compared to the estimates in the European Union (EU) and US. Youlden (2014) and colleagues reported an MCC incidence of 1.6 per 100,000 in Queensland between 1993 and 2010 with a higher incidence rate in men than in women (2.5 per 100,000 vs 0.9 per 100,000). In a study of 215 cases of MCC reported in Western Australia between 1993 and 2007, the age-standardized incidence rates were higher in men than in women (1.0 per 100,000 vs 0.63 per 100,000) (Girschik 2011). Similarly in New Zealand, Robertson (2015) and colleagues reported an age-standardized incidence rate of 0.88 per 100,000 between 2002 and 2011, with men having a higher age-standardized incidence rate than women (1.05 vs 0.74 per 100,000).

Table 1 MCC Incidence Rate in Europe, United States, Australia and New Zealand

Country/Region	Estimated Age-standardized Incidence Rate per 100,000 Person-Years (Reference)
Europe	0.13 (1995 to 2002) (van der Zwan 2013)
Denmark	0.22 (1995 to 2006) (Kaae 2010)
Eastern France	0.13 (1980 to 2004) (Riou-Gotta 2009)
England	0.2 (1998 to 2008) (Public Health England 2010)
Finland	0.19 (men) and 0.2 (women) (1989 to 2008) (Kukko 2012)
Germany	0.2-0.4 (men) and 0.1-0.3 (women) (1998 to 2010) (Eisemann 2014)
Sweden	0.42 (men) and 0.33 (women) (1990 to 2005) (Hussain 2010)
The Netherlands	0.35 (2003 to 2007) (Reichgelt 2011)
United States	0.79 (2011) (Fitzgerald 2015)
Australia	1.6 (1993 to2010) (Youlden 2014)
New Zealand	0.88 (2002 to2011) (Robertson 2015)

MCC=merkel cell carcinoma

Estimated incidence rates in the various publications were reported as age-standardized rate according to country- or region-specific standard populations with differences in the corresponding age distribution. Direct comparisons over countries should thus be made with caution. In general, standardization to a more elderly population lead to lower age-standardized incidence rates.

Incidence and Prevalence: RCC

RCC is the most common kidney cancer and constitutes about 3% of all malignant tumors in adults (Gupta 2008). It is difficult to obtain global population-based estimates of RCC incidence and mortality because data from various regions are typically presented for all kidney and renal pelvis cancers combined (Cho 2011). However, given that RCC comprises 90-95% of all kidney and renal pelvis cancer cases, (Znaor 2015) estimates reported for all kidney cancer can be used to approximate those for RCC. According to GLOBOCAN 2018 data, an estimated 403,262 cases of kidney cancer are diagnosed worldwide each year (Bray 2018), which would amount to roughly 362,900-383,000 new cases of RCC annually (secondary calculation). GLOBOCAN 2012 data indicate that during 2003-2007, for both sexes the age-adjusted incidence rates of RCC in Europe were lowest in Bulgaria (6.7 per 100,000 men and 3.0 per 100,000 women) and highest in the Czech Republic (22.2 per 100,000 men and 9.9 per 100,000 women) (Ferlay 2015). Extrapolating the proportion of all kidney and renal pelvis cancers that are RCC (90-95%) (Znaor 2015) (to the projected number of kidney and renal pelvis cancer cases that will be diagnosed in the US in 2018 [65,340 cases] [SEER 2018]) yields a rough estimate of the annual RCC incidence in the US that ranges from 59,000-62,000 cases (secondary calculation).

Incidence rates specific to metastatic renal cell carcinoma (mRCC) are also lacking but can be derived from overall RCC incidence estimates by applying the proportion of cases that present with metastatic disease at diagnosis. Similar to the method published by Gupta (2008) and colleagues, mRCC incidence estimates have been calculated using 2012 IARC GLOBOCAN RCC incidence rates and applying that 25 -30% (mean 27.5%) of all new patients with RCC, have been reported to present with metastatic disease. Table 2 contains country and sex-specific incidence rates for mRCC (based on Gupta 2008).

Table 2 Country and Sex-Specific Incidence Rates for mRCC

Region	Country	Estimated Age-adjusted Incidence Rate of mRCC in 2012 (per 100,000 Persons)		Estimated Total Number of Incident mRCC Cases in 2012
		Males	Females	
North/Central America	Canada	3.3	1.9	1,534
	Mexico	1.3	0.7	1,059
	United States	4.4	2.3	16,011
Europe	Belgium	3.3	1.6	485
	Denmark	2.7	1.3	207
	Finland	2.6	1.8	243
	France	3.9	1.6	3,031
	Germany	3.9	2.1	5,119
	Italy	3.6	1.3	3,108
	Portugal	2.0	0.8	276
	Spain	3.1	1.3	1,780
	Sweden	2.2	1.3	309
	United Kingdom	3.0	1.6	2,671
	European Union-28	3.4	1.6	23,434

Region	Country	Estimated Age-adjusted Incidence Rate of mRCC in 2012 (per 100,000 Persons)		Estimated Total Number of Incident mRCC Cases in 2012
		Males	Females	
Australia and Asia	Australia	3.5	1.7	963
	Japan	2.1	0.8	4,628
	Korea (Republic of)	3.2	1.3	1,554
	Singapore	2.0	0.9	110
South America	Argentina	3.2	1.4	1,119
	Brazil	1.1	0.6	1,720

mRCC=metastatic renal cell carcinoma

Incidence and prevalence: Urothelial Carcinoma

Incidence and prevalence data for UC are presented for BC, as UC represents more than 90% of BC (Chalasani 2009). According to the latest GLOBOCAN data, in 2018 BC was the 10th most common cancer worldwide in men and women (GLOBOCAN 2018a). There were 549,393 new cases of bladder cancer in 2018 worldwide. Overall, the incidences in both sexes were higher in Asia (198,753), followed by Europe (197,105), North America (91,689), Latin America and Caribbean (29,098), Africa (28,954) and Oceania (3,794). Statistics for age-standardized (world) incidence rates showed that in Europe, this was 11.3/100,000 (20.2/100,000 males and 4.3/100,000 females), with the number of new BC cases in males and females ranging from 86 in Iceland (5.7% of 35 ranked cancers in Iceland) to 35,738 in Germany (5.9% of 35 ranked cancers in Germany) (GLOBOCAN 2018b; GLOBOCAN 2018c; GLOBOCAN 2018d). Similarly, a much higher age-standardized (world) incidence rate was reported for men (424,082 cases, 9.6/100,000) than women (125,311 cases, 2.4/100,000) worldwide (GLOBOCAN 2018a).

Results from an analysis of the British Association of Urological Surgeons Urological Tumour Registry data revealed that 69,712 cases of BC were registered between 1999 and 2008 in the United Kingdom (UK), with a median incidence of 6,969 new registrations each year over this period (Boustead 2014). According to the GLOBOCAN 2018 statistics, BC was ranked as the 9th most common cancer with 12,218 cases observed in both men and women in the UK (GLOBOCAN 2018e). Additionally, results for the age-standardized (world) incidence rates in 2018 were reported as 10.8/100,000 in males and 3.6/100,000 females in the UK.

In the US, according to recent data, there was an estimated incidence of 76,960 new cases of BC in 2016 (Siegel 2016). The number of patients diagnosed with metastatic BC in the US appears to be increasing over time; according to US cancer statistics provided by the SEER program, there were 4,195 and 7,629 patients diagnosed with metastatic BC between 1991-2000 and 2001-2010, respectively (Shah 2015). This may reflect increased diagnosis for more severe disease presentations as opposed to an absolute increase in the occurrence of metastatic BC; however, it may also indicate an unmet need for earlier diagnosis and treatment of BC to avoid patients presenting with advanced disease. Another study of patients with metastatic BC (n=9,357) in the US SEER database reported that the incidence of metastases at presentation remained static over the past 2 decades to 2012 (6.05% and 6.34%, respectively) (Koll 2012). In 2018, 82,501 new cases of BC were observed in the US; the age -standardized (world) incidence rate was 12.0/100,000 in both males and females, and per gender this was reported as 20.0/100,000 in males and 5.2/100,000 in females (GLOBOCAN 2018f).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease: MCC

MCC is primarily a disease of the elderly with a median age at diagnosis ranging from 76 to 78 years (Kaae 2010; Kukko 2012; Lemos 2010; Reichgelt 2011). MCC generally affects men more often than women (Andea 2008; Allen 2005; Agelli 2003). In the US, between 1986 and 2001, the highest age-specific incidence was in the elderly (4.28 per 100,000 in the > 85 years age group) (Hodgson 2005). Similarly, among 1,034 MCC patients in the US between 1973 and 1999, the incidence of primary MCC increased gradually with advancing age, from the ages of 50 to 65 years, then progressively from 65 years onwards (Agelli 2003). In this study, men had a higher incidence rate compared with women in all ethnic groups studied (0.34 per 100,000 vs 0.17 per 100,000) (Agelli 2003). In a study of 3,870 MCC cases identified in the SEER database between 1973 and 2006, 4% were 49 years or younger, 24.4% were aged 50 years to 69 years, while most patients were aged 70 and above (71.6%) (Albores-Saavedra 2010). Additionally, in this study the incidence rate of MCC was higher in men compared with women (0.41 per 100,000 vs 0.18 per 100,000, respectively) (Albores-Saavedra 2010). Similar results, with the majority aged 75 and above (58.4%), were reported from an analysis of 10,020 MCC cases from 1986 to 2004 in the US National Cancer Database (NCDB) (Lemos 2010).

As reported in the literature, MCC is exceedingly rare in children (Albores-Saavedra 2010; Lemos 2010; van der Zwan 2013; Kaae 2010; Kukko 2012) and has only been described in a few case reports (Schmid 1992; Kacker 1992; Köksal 2009; Gherardi 1990; Marzban 2011; Dunker 1988).

MCC predominantly affects the white population according to available evidence. Albores-Saavedra (2010) and colleagues found that 95% of cases (N= 3,870) diagnosed during the interval of 1973 to 2006 arose in the white population, and similarly Lemos (2010) and colleagues reported 90.8% of MCC in the white population.

MCC has been associated with autoimmune conditions and immunosuppression from organ transplantation and human immunodeficiency virus (HIV) infection, suggesting that impaired immunity may be a predisposing factor for tumor development (Kempf 2013; Engels 2002; Lanoy 2009; Lanoy 2010a; Lanoy 2010b). A population-based case-control study in elderly US adults based on data from 44,613 skin cancer cases and 178,452 controls showed that the most frequent autoimmune condition among elderly patients with skin cancer was rheumatoid arthritis (2.29%), which, due to therapeutic immunosuppression, was associated with an increased risk of developing MCC (odds ratio [OR] 1.39 [95% CI : 1.10;1.74]) (Lanoy 2010b). In a similar case-control study in 29,926 skin cancer cases and 119,704 controls in an elderly population in the US, solid organ transplantation was also associated with increased risk of MCC (OR 4.95 [95% CI: 2.62;9.34]) (Lanoy 2010a). A study linking data from US population-based acquired immunodeficiency syndrome (AIDS) and cancer registries including 497,142 HIV-positive individuals found that from 60 months prior to and 60 months after AIDS onset, HIV-positive patients had an increased risk of MCC compared with the general population (Lanoy 2009).

Previous Merkel cell polyomavirus (MCPyV) infection in patients has been associated with an increased risk for future MCC. MCPyV is present in approximately 80% of patients with MCC, with an incidence as high as 97% in samples assessed using polymerase chain reaction methodology (Feng 2008; Santos-Juanes 2015; Rodig 2012). The virus integrates into deoxyribonucleic acid (DNA) to drive expression of MCPyV large T antigens, promotes tumor proliferation, and disrupts immune responses (Feng 2008; Bhatia 2011). In viral-negative tumors, a mutational burden signature associated with ultraviolet (UV)-light exposure appears to be important for oncogenesis, leading to increased expression of neoantigens, heightened immunogenicity, and likely increased immune evasion by the tumor (Wong 2015; Goh 2016; Harms 2015). In a study conducted in Sweden assessing 22 cases of MCC, the risk of developing MCC was increased in patients with high levels of MCPyV antibodies (OR 4.4 [95% CI : 1.3;17.4]) and MCPyV neutralizing activity (OR 5.3 [95% CI : 1.3;32.3]) (Faust 2014).

Additional risk factors for MCC include advancing age, fair skin, previous malignancies, and UV light exposure (Hodgson 2005; Agelli 2003; Koljonen 2009a). Patients diagnosed with chronic lymphocytic leukemia (CLL) have a substantially increased risk of developing MCC, likely due to the prolonged immunosuppression caused by their chronic underlying disease (Koljonen 2009b). In a study of 1,034 patients with MCC reported by SEER in the US between 1986 and 1999, the age-adjusted incidence of primary MCC among white patients correlated significantly with the ultraviolet B (UVB) radiation indexes of the geographic areas analyzed. The highest age-adjusted MCC incidence in this study was observed at the geographic location with the highest UVB index; Hawaii (incidence 0.29 per 100,000 person-years; UVB index 265) (Agelli 2003). Immunosuppression, occurring in relation to HIV infection, certain hematologic malignancies, and solid-organ transplantation, correlates with an elevated risk for MCC (Paulson 2013).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease: RCC

An approximately 2-fold difference in RCC incidence between males and females has been reported from the EU (15.8 vs 7.1 per 100,000) (Karim-Kos 2008). In the mRCC incidence estimates (based on GLOBOCAN data) provided above, incidence in males is twice the incidence in females on average. The recently updated guidelines on RCC from the European Association of Urology note a 1.5-fold increase in RCC incidence in males as compared with females, with greatest incidence seen in patients aged 60-70 years (Ljungberg 2014). For mRCC, an analysis of 11,182 patients registered in the US SEER database found that 65% were male, almost 69% of patients were over 60 years of age, and 85.5% of patients were white (Hellenthal 2009).

In the US, RCC incidence is higher among African Americans than among whites (Hofmann 2013). African American males have the highest RCC incidence in the US (17.5 per 100,000), while Asian American males and females have the lowest (7.7 and 3.6 per 100,000). A lower risk of RCC among Asians has been seen both in Asia and the US (Ljunberg 2011).

In addition to increasing age and male sex, recently published reviews of the epidemiology of RCC suggest that smoking, obesity, and hypertension are established risk factors for RCC, while diet, and occupational exposures to specific carcinogens may also contribute to its etiology; a minor proportion of RCC is attributed to rare genetic factors (Ljungberg 2011; Navai 2012).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease: UC

The majority of cases of bladder cancer (BC) occur in people aged over 60 years and about 70% of the patients are aged 65 years and above at diagnosis (Bellmunt 2014a). According to the US Centers for Disease Control and Prevention, men are about 3 times as likely as women to develop BC, and Caucasians have a higher rate of BC than people of other races and ethnicities (Mahdavifar 2016; Burger 2013). From the 1999-2014 US Cancer Statistics Incidence and Mortality Webbased Report white men had the highest rates of incident BC (36.4 per 100,000 men), followed by black men (19.0), Hispanic men (18.6), American Indian/Alaska Native men (14.8), and Asian/Pacific Islander men (14.0). Among women, white women also had the highest rates of incident BC (9.0 per 100,000 women), followed by black women (6.4), Hispanic women (4.8), Asian/Pacific Islander women (3.7), and American Indian/Alaska Native women (3.4) (GLOBOCAN 2012). Black race has been reported to be associated with advanced stage at initial presentation and reduced survival (5-year disease specific survival: whites, 82.8%; blacks, 70.2%; Hispanics, 80.7%; Asian/Pacific Islanders, 81.9%) (Yee 2011).

The main risk factors for the development of BC are behavioral and/or environmental; tobacco smoking is the most important causative agent accounting for 50-65% of male and 20-30% of female cases of BC (Witjes 2017). Smokers have a 2- to 4-fold increased risk of BC compared with nonsmokers, and the risk increases with increasing intensity and duration of smoking (Kirkali 2005). Tobacco contains aromatic amines and polycyclic aromatic hydrocarbons known to exert a carcinogenic effect on the entire urinary system when excreted (Burger 2013). Smoking cessation decreases only partially the risk of BC; about 40% after 1-4 years or 60% after 25 years of stopping (Freedman 2011). In relation to other behavioral factors, in addition to smoking, UC is strongly associated with increased dietary fat intake (Steineck 1990; Wingo 1999).

Environmental risk factors include occupational exposures to chemicals such as aromatic amines and other carcinogens (Klotz 2015), with generally long latency periods, and to a lesser extent ionizing radiation or pharmaceutical agents (Burger 2013; Witjes 2017). About 20% of BC are estimated to be related to exposures in industrial areas of paint, dye, metal and petroleum products (Burger 2013). Exposure to environmental pollutants such as arsenic in drinking water has also been associated with the risk of BC (Burger 2013).

Although BC is 3 to 4 times more common in men, women often present with more advanced disease and have worse overall survival (OS) (Liu 2015). These differences have been traditionally attributed to different smoking rates, but it is not known if hormonal status may also play a role (Burger 2013). In a large prospective cohort study, postmenopausal status was associated with an increase in BC risk, even after adjustment for smoking status. This result suggests that the differences in estrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of BC (McGrath 2006). The reasons for higher mortality rates are unclear, but recurrence, progression, and survival outcomes have been reported to be unfavorable in women compared to men (Burger 2013).

Family history of bladder cancer is associated with ~ 2-fold increased risk, suggesting shared genetic and potential environmental contribution to its etiology (Murta-Nascimento 2007). Metanalyses of established candidate genes and genome-wide association studies have identified 11 loci that harbor bladder cancer susceptibility alleles: 1p13.3 (GSTM1), 2q37.1

(UGT1A cluster), 3q28 (TP63), 4p16.3 (TMEM129 and TACC3-FGFR3), 5p15.33 (TERT--LPTM1L), 8p22 (NAT2), 8q24.21, 8q24.3 (PSCA), 18q12.3 (SLC14A1), 19q12 (CCNE1) and 22q13.1 (CBX6, APOBEC3A) but the role of genetic susceptibility is not yet fully understood (Figueroa 2014).

The main existing treatment options: MCC

Currently in Europe, there are no other approved therapies for patients with MCC. There is no consensus on the most effective treatment strategy for MCC (Aldabagh 2014; NCCN 2016). The choice of treatment depends on many factors, which include (Ramahi 2013):

- Stage of the tumor, particularly with respect to nodal involvement
- Location of the tumor
- Comorbidities and performance status of the patient

Surgery is the primary treatment option for patients with centrally localized MCC, with radiation therapy considered for inoperable cases of MCC as well as for post-surgical adjuvant therapy (NCCN 2016). Chemotherapy is normally reserved for metastatic MCC (mMCC; Stage IV) or as palliative therapy. Commonly used regimens include cisplatin ± etoposide, carboplatin ± etoposide, and topotecan. No studies have directly evaluated the efficacy of one regimen over another (NCCN 2016).

While cytotoxic chemotherapy had been the dominant mode of treatment for metastatic disease, it is rarely curative and is associated with significant toxicity. Side effects, such as myelosuppression (including neutropenic fever), nausea/vomiting, fatigue, and hair loss are common, with therapy-related death occurring in up to 16% of patients aged 65 years or older (Voog 1999).

Table 3 gives an overview of treatment, patient, and disease characteristics of patients with distant mMCC from a review of case reports in the literature. The most commonly used regimens were carboplatin with etoposide (8 cases in first-line and 1 in second-line), followed by cisplatin with etoposide (6 cases in first-line and 1 case in second-line). Moreover, 3 patients were treated with doxorubicin-based regimens (2 cases as first-line and 1 case as fourth-line palliative therapy) and 1 patient each was treated with idelalisib in first-line (Shiver 2015), prednisone in first-line and pazopanib in third-line (Davids 2009; Friedlaender 2002).

Table 3 Summary of Treatment, Patient and Disease Characteristics of Case Reports for Patients with Distant Metastases of MCC

(Author, Year)	Regimen Dosing	Line of Therapy	Age (Years)	Gender	Primary Site	Site of Metastases
(Orlova 2012)	CDDP + EPEG + Sandostatin LAR	1L	46	F	Left thigh	Inguinal adenopathy Para-aortal adenopathy
(Grenader 2011)	CBDCA/ EPEG	1L	87	F	Nasal region	• Left submandibular lymph node • Bilateral pleural effusions • Lymphangitic spread • Massive mediastinal, axillary and retroperitoneal lymphadenopathy.
(Shah 2012)	CBDCA + EPEG	1L	60	M*	Eyelid	• Liver • Bone • Nodes
	TS-1	2L				
(Davids 2009)	CBDCA +EPEG	1L	69	F	Right scalp	• Lungs • Right ear
	Tegafur + OXO + S1	2L				
	Pazopanib	3L				
	ADM	4L				
(Chang 2005)	Intrathecal MTX+ IFF (single dose)	1L	45	M**	Left temporal skin	• Cavernous sinuses bilaterally • Left trigeminal cistern • Internal acoustic meatus with cochlear involvement and cranial nerves V, VII, and VIII
(Cusick 2004)	Chemotherapy	1L	52	F	Left breast	• Liver • Bone
(Friedlaender 2002)	Prednisone	1L	46	M	Cervical Region	• Skull • Right acromion • Several ribs • Left sacroiliac joint
(Calza 2002)	Liposomal ADM	1L	51	M	Right gluteus	• Liver • Inguinal, pelvic and lumboaortic lymphadenopathy
(Waldmann 2000)	CDDP + ADM+ EPEG + BLM	1L	51	M**	Chest	• Right shoulder • Liver • Kidney • Pancreas
	High dose-PEI regimen (IFF + CBDCA + EPEG) + ABSCT	2L	-	-	-	-

(Author, Year)	Regimen Dosing	Line of Therapy	Age (Years)	Gender	Primary Site	Site of Metastases
(Gaba 2012)	CDDP + EPEG	1L	64	M	Left shoulder	• Right level V cervical lymphadenopathy • Left level I axillary lymphadenopathy • Mediastinal lymphadenopathy • Mesenteric lymphadenopathy
(Wang 2014)	CBDCA + EPEG	1L	76	M	Left neck	• Coronary sinus • Lymph node adjacent to pancreas
(Noell 2014)	CBDCA + EPEG	1L	61	M	Retroperitoneal mass obstructing ureter	• Right leg • Thigh • Foot • Lower extremity • Abdomen • Chest
	dFdC + TMZ	2L				
(Slovacek 2012)	LNT	1L	70	F	Right elbow	• Right arm • Right side of the neck • Chest wall
	LNT + EVR	2L	-	-	-	-
(Biver-Dalle 2011)	**Pt. 1)** CBDCA + EPEG	1L	84	M	Right shoulder	• Axillary lymph node • Subcutaneous
	Pt. 1) IFN-α-2b + NSAIDs + ADPs	2L				
	Pt. 2) IFN-α-2b + NSAIDs + ADPs	1L	81	F	Right upper quadrant, right groin	• Pancreas • Lung • Mediastinal lymph nodes • Hilar lymph nodes
(Santos-Juanes 2015)	Chemotherapy	1L	52	M	Right thigh	• Stomach
(Shiver 2015)	Idelalisib	1L	86	F**	Right temple	• Liver
(Barkdull 2004)	CBDCA + EPEG	1L	55	M	Right frontal region	• Nodule over sternum
(Yamana 2004)	CDDP	1L	50	F	Right cheek	• Left lobe of the thyroid • Interarterial septum • Right atrium
	CDDP + EPEG	2L				
(Tanemura 2012)	CBDCA + EPEG	1L	60	F	Right leg	• Duodenum

(Author, Year)	Regimen Dosing	Line of Therapy	Age (Years)	Gender	Primary Site	Site of Metastases
(Krejci 2010)	ADM + CTX	1L	61	M**	Right gluteal region	• Pancreatic head • Lymph nodes in the right groin • Inguinal • Pelvis • Multiple foci in the bone

ABSCT=autologous blood stem cell transplantation, ADM=doxorubicin, ADP=anti-depressant, BLM=bleomycin, CBDCA=carboplatin, CDDP=cisplatin, CTX=cyclophosphamide, dFdC=gemcitabine, EPEG=etoposide, EVR=everolimus, F=female, IFF=ifosfamide, IFN-α=interferon-alpha, LNT=lantreotide, M=male, MCC=merkel cell carcinoma, MTX=methotrexate, NSAID=nonsteroidal anti-inflammatory drug, OXO=5-chloro-2,4- dihydroxypyridine, S1=oxonic acid, TMZ=temozolomide, 1L=first-line, 2L=second-line, 3L=third-line, 4L=fourth-line

*Asian

**White/Caucasian

Currently, knowledge on the use of chemotherapy in advanced/metastatic MCC is inadequate to definitively assess whether any chemotherapeutic regimens improve either relapse-free or OS in patients with MCC, and thus their routine use in MCC cannot be recommended (NCCN 2016). The National Comprehensive Cancer Network (NCCN) guidelines for MCC indicate that for chemotherapy "…the literature does provide evidence that MCC is chemosensitive, although the responses are not durable…" (NCCN 2016). Similarly, the recent EU guidelines (Lebbe 2015) describe chemotherapy responses as being "of short duration with a median OS rate of 9 months and high toxicity in elderly patients." Only 5 cohort studies evaluated interventions for patients with distant mMCC (Iyer 2016; Satpute 2014; Sharma 1991; Tai 2000; Voog 1999). The interventions assessed included a combination of platinum-based chemotherapy, cyclophosphamide, vincristine, etoposide, or topotecan. Objective response rates (ORRs) in both the first-line and second-line setting ranged from 23% to 61% (complete response: 3%-37%; partial response: 20%-40%; stable disease: 3%-15%) (Iyer 2016; Satpute 2014; Sharma 1991; Tai 2000; Voog 1999). Although initial responses to chemotherapy were reported in most patients, the DOR was short (3-4 months) (Iyer 2016; Satpute 2014). Response rates were lower in the second-line setting (23%) compared with the first-line setting (53%-57%) (Iyer 2016; Voog 1999). Median OS was reported in 2 of the 5 studies (9-9.5 months) (Iyer 2016; Voog 1999), with 1 study also reporting median progression-free survival (PFS) (3.1 months) (Iyer 2016).

Consistent with the findings in the literature, an internally conducted observational real-world study conducted in the US and Europe found poor duration of response for second-line or later chemotherapy among immunocompetent patients with distant mMCC (ORR in US study – 28.6% and EU study – 10.3%; median duration of response (DOR), US study – 1.7 months and EU study – 1.9 months) (Cowey 2016; Becker 2019).

This highlights the need for novel agents that improve the prognosis of patients with MCC. Antitumor activity of an anti-programmed death 1 (PD-1) antibody has been recently reported in a small Phase 2 study of 26 patients with Stage IIIb/IV MCC who were treated in a first-line setting. Among the 25 patients with at least 1 evaluation during treatment, the ORR was 56% (95% CI: 35;76), DOR varied from 2.2 to 9.7 months and the PFS rate at 6 months was 67% (Nghiem 2016). Given the higher ORR and longer DOR reported with this anti-PD-1 therapy compared with chemotherapy results reported to date, these findings support the rationale for use

of anti-programmed death ligand 1 (PD-L1)/PD-1 agents and the need to further evaluate the therapeutic benefit of this class of agents for treatment of mMCC.

The main existing treatment options: RCC

First-line therapies for advanced renal cell carcinoma (aRCC) include the multi-targeted tyrosine kinase inhibitors (TKIs) cabozantinib, pazopanib and sunitinib; the anti-VEGF monoclonal antibody bevacizumab in combination with interferon-alpha; and the mammalian target of rapamycin (mTOR) pathway inhibitor temsirolimus (Choueiri 2017; Kidney Cancer News 2018). More recently, the anti-PD-1 agent nivolumab in combination with ipilimumab (an anti–cytotoxic T-lymphocyte–associated antigen 4 antibody) has been approved in the US for the first-line treatment of patients with aRCC in the intermediate and poor risk groups (Motzer 2018a). The pivotal studies supporting the approved first-line therapies for aRCC are summarized in Table 4. Second-line or later therapies include the TKIs axitinib, cabozantinib, and sorafenib; the mTOR inhibitor everolimus alone or in combination with the TKI lenvatinib; and nivolumab (Choueiri 2017).

Table 4 Clinical Trials of Approved First-line Treatments for aRCC

Treatment Comparison	Study	Primary Endpoint	Median PFS (95% CI)	PFS HR values (95% CI)
Bevacizumab + IFN-α (N=327) vs placebo + IFN-α (N=322) (Escudier 2007)	A randomized, double-blind, Phase 3 study of bevacizumab + IFN-α vs placebo + IFN-α in patients with mRCC	OS [a]	10.2 months (NR) vs 5.4 months (NR)	0.63 (0.52;0.75)
Sunitinib (N=375) vs IFN-α (N=375) (Motzer 2007)	An international, multicenter, randomized, Phase 3 trial of sunitinib vs IFN-α as first-line treatment of mRCC	PFS	11 months (10;12) vs 5 months (4;6) [b]	0.42 (0.32;0.54)
Temsirolimus (N=209) vs IFN-α (N=207) (Hudes 2007)	A randomized, open-label, Phase 3, three-arm, study of IFN-α, temsirolimus, and the combination of IFN-α and temsirolimus in first-line poor-prognosis patients with aRCC	OS [e]	5.5 months (3.9;7.0) vs 3.1 months (2.2;3.8) [b, c]	0.66 (0.53;0.81)
Pazopanib (N=290) vs Placebo (N=145) (Sternberg 2010)	A randomized, double-blind, placebo-controlled Phase 3 study evaluating efficacy and safety of pazopanib monotherapy in treatment-naive and cytokine-pretreated patients with aRCC	PFS	11.1 months (NR) vs 2.8 months (NR) [b]	0.40 (0.27;0.60)
Cabozantinib (N=79) vs sunitinib (N=78) (Choueri 2018)	A randomized Phase 2 multicenter trial to evaluate cabozantinib compared with sunitinib as first-line therapy in patients with mRCC	PFS	8.6 months (6.8;14.0) vs 5.3 months (3.04;8.2) [b, c]	0.48 (0.31;0.74)

Treatment Comparison	Study	Primary Endpoint	Median PFS (95% CI)	PFS HR values (95% CI)
Nivolumab + ipilimumab (N=425) vs Sunitinib (N=422) (Motzer 2018a)	A phase 3, randomized, open-label study of nivolumab combined with ipilimumab vs sunitinib monotherapy in patients with previously untreated mRCC	PFS [f]	11.6 months (8.7, 15.5) vs 8.4 months (7.0;10.8) [b, c]	0.82 (0.64;1.05) [d]

aRCC=advanced renal cell carcinoma, CI=confidence interval, HR=hazard ratio, IFN-α=interferon-alpha, mRCC=metastatic renal cell carcinoma, NR=not reported, ORR=objective response rate, OS=overall survival, PFS=progression-free survival, RCC=renal cell carcinoma

a OS data was not mature, PFS was used for regulatory submission

b Specified as independently assessed PFS

c Intermediate- and poor-risk patients

d 99.1% CI

e As compared with interferon alone, treatment with temsirolimus alone was associated with an HR for death of 0.73; 95% CI: 0.58;0.92; p=0.008. Median survival was 7.3 months in the interferon group, 10.9 months in the temsirolimus group.

f ORR and OS were co-primary endpoints.

Although many patients who receive currently approved TKI therapies show an initial clinical benefit, durable and complete responses in patients with newly diagnosed or recurrent aRCC are uncommon and most patients will eventually develop progressive disease (Minguet 2015; Powles 2011). The median OS of patients with aRCC is approximately 26 months with first-line VEGF inhibitors (Rodriguez-Vida 2017). A number of important clinically derived prognostic criteria are combined in the Heng (Heng 2009) and Memorial Sloan-Kettering Cancer Center criteria (Motzer 2002). In clinical trials they are commonly used to describe the study population and in a recent trial showed their predictive value (Motzer 2018a). Prognosis is influenced by the extent of disease at diagnosis: in the presence of distant metastases, 5-year survival and 10-year survival rates are 10% and < 5%, respectively (Ng 2008).

In 2016, nivolumab, a human anti PD-1 monoclonal antibody, was approved as second-line therapy for aRCC based on the OS benefit reported in the Phase 3 CheckMate 025 trial (Motzer 2015). The lack of durable responses with TKI therapies and lack of PFS benefit for the anti-PD-1 alone led to the further investigation of the combination of these therapies with 2 different mechanisms of action for the treatment of aRCC. When nivolumab was combined with a multi-targeted TKI (sunitinib or pazopanib) in the Phase 1 setting, it demonstrated more pronounced anti-tumor response in previously untreated patients with aRCC than the TKIs alone (Amin 2014). However, the combination treatments were not developed further because of concerns about renal and hepatic toxicity (Amin 2014).

The combination of nivolumab and ipilimumab has been recently approved in the US for the first-line treatment of patients with aRCC in the intermediate and poor risk groups, based on the results of the randomized Phase 3 CheckMate-214 trial (Motzer 2018a). However, the difference in PFS did not reach statistical significance. Furthermore, best overall response for 20% of the patients in the intermediate and poor risk groups was progressive disease (Motzer 2018a). In patients with favorable prognostic risk factors, there was no benefit in ORR, PFS, or OS over standard of care and the exploratory efficacy analysis showed a hazard ratio (HR) for OS in favor of sunitinib (1.45 [99.8% CI: 0.51;4.12], p = 0.27). The ORR was 29% (95% CI: 21;38) with

nivolumab plus ipilimumab versus 52% (95% CI: 43;61) with sunitinib ($p < 0.001$), and the median PFS was 15.3 months (95% CI: 9.7;20.3) versus 25.1 months (95% CI: 20.9; not estimable) (HR for PFS = 2.18 [99.1% CI: 1.29;3.68], $p < 0.001$), both favoring sunitinib (Motzer 2018a).

The results of the randomized, Phase 3, IMmotion 151 study, comparing the combination of atezolizumab with bevacizumab (an anti–PD-L1 with an anti-VEGF antibody) versus sunitinib for treatment naive patients with aRCC with PD-L1 positive tumors showed an improvement in PFS (26% reduction in the likelihood of disease progression or death [95% CI: 0.57;0.96], $p = 0.02$]) as assessed by the Investigator for the combination over sunitinib, but there was no PFS benefit observed for the combination when assessed by the Independent Radiology Committee. OS data were not mature at the time of reporting (Motzer 2018b). An improvement was also shown for the secondary endpoint of PFS (in patients irrespective of PD-L1 status) as assessed by the Investigator (17% reduction in the likelihood of disease progression associated with the combination therapy [95% CI: 0.70;0.97], $p = 0.02$) (Motzer 2018b). In addition, 19% of all randomized patients had a confirmed best overall response of progressive disease as assessed by the Investigator (Motzer 2018b). Increased efficacy in patients with PD-L1-positive tumors versus all patients irrespective of PD-L1 expression status of their tumor was observed in both the CheckMate-214 and IMmotion 151 trials (Motzer 2018a; Motzer 2018b).

Overall, the emerging data on new combination therapies with checkpoint inhibitors suggest improved antitumor activity compared with the current approved therapies for treatment-naïve patients with aRCC combined with a tolerable and manageable safety profile particularly in the subgroups of patients with intermediate and poor risk disease or patients with PD-L1-positive tumors. Recent data also seems to suggest that PD-L1 expression within the tumor might play a role in terms of a higher efficacy of anti-PD-1/PD-L1 therapies and their combinations in patients with PD-L1-positive tumors (Motzer 2015; McDermott 2017; McDermott 2018).

The main existing treatment options: UC

First-line Therapy

Combination chemotherapy with platinum-based regimens is the standard of care for locally advanced or metastatic BC. Patients with advanced, unresectable and metastatic BC receive cisplatin-containing combination chemotherapy with gemcitabine and cisplatin (GC) or methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) as standard first-line therapy due to favorable response and survival rates. However, durable and complete responses following first-line chemotherapy in patients with advanced UC are uncommon. Patients unfit for cisplatin-based chemotherapy may be palliated with a carboplatin-based regimen or single-agent taxane or gemcitabine. Selected patients with locally advanced disease may be candidates for cystectomy and lymph node dissection or definitive radiotherapy following systemic therapy. Palliative radiotherapy may be used to reduce symptoms such as pain or bleeding (Bellmunt 2014a).

Von der Maase (2000) and colleagues conducted a multicenter randomized controlled trial of GC versus MVAC in advanced or metastatic BC reported that cisplatin, taxanes, and gemcitabine for first-line treatment led to ORRs in the range of 40-50%; however, the performance status and comorbidities of this typically older patient population resulted in up to 50% of patients being

ineligible to receive standard of care cisplatin-based combination therapies due to the risk of substantial associated toxicities (von der Maase 2000). Based on the intent-to treat analysis, the ORR was 44.5% for all patients with measurable disease receiving GC versus 38.1% in the MVAC cohort; OS was similar in both cohorts (HR 1.04 [95% CI: 0.82;1.32], p = 0.75). Similarly, another study by von der Maase (2005) indicated that despite high initial response rates with first-line chemotherapy, most patients' disease often progressed within a median of 10-11 months; median OS is 14-15 months, and 5-year survival is only 13-15%. Additionally, the study reported a median OS of 14.0 months, median PFS of 7.7 months and 5-year PFS rate at 9.8% in patients receiving GC.

Furthermore, pembrolizumab and atezolizumab are also recommended for first-line treatment of UC in patients with high levels of PD-L1 (EMA 2018). Atezolizumab's use as a monotherapy in patients who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression ≥ 5% is based on the IMvigor210 single arm trial of previously untreated UC patients who are ineligible for cisplatin therapy and in UC patients previously treated with chemotherapy (Atezolizumab Summary of Product Characteristics [SmPC] 2020). The results showed that the confirmed ORRs per Independent Review Assessed–RECIST (Response Evaluation Criteria in Solid Tumors) v1.1 were 21.9% (95% CI: 9.3;40.0) in patients with PD-L1 expression ≥ 5%, 18.8% (95% CI: 10.9;29.0) in patients with PD-L1 expression ≥ 1%, and 19.3% (95% CI: 12.7;27.6) in all comers. The median DOR was not reached in any PD-L1 expression subgroup or in all comers. OS was not mature with an event patient ratio of approximately 40%. Median OS for all patient subgroups (PD-L1 expression ≥ 5 % and ≥ 1 %) and in all comers was 10.6 months. Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic UC in adults who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a combined positive score ≥ 10 (Pembrolizumab SmPC 2020). Results are drawn from the KEYNOTE-361, an open-label clinical study of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy as first-line treatment in subjects with advanced or metastatic UC, with preliminary data showing a reduced survival with pembrolizumab monotherapy in patients whose tumors express PD-L1 with a combined positive score < 10 compared with standard chemotherapy.

Second-line therapy

Second-line therapy in the metastatic setting is variable but a systematic approach, through clinical guidelines, to the management and treatment of BC is available (NCCN Bladder Cancer Guideline 2019b). Early phase clinical studies of single chemotherapy agents and chemotherapy combinations (excluding platinum-containing chemotherapies) evaluated in the second-line setting have been associated with low response rates (0-8.6%), short median PFS (1.5-3.0 months), and short OS (4.6-6.9 months) (Ortmann 2013). Furthermore, these regimens are associated with significant toxicities. Severe neutropenia and fatigue are common with taxanes, with increased toxicity when used in combination with gemcitabine. Re-challenge with platinum-containing combinations is also associated with substantial toxicity, e.g. 10% febrile neutropenia and 3% drug-related deaths with paclitaxel and carboplatin and 69% Grade 3/4 toxicity and 9% drug-related deaths with accelerated methotrexate, vinblastine, doxorubicin and cisplatin (Ortmann 2013). The cytotoxic agent vinflunine (Javlor®) is approved in Europe in the second-line setting based upon a randomized Phase 3 trial. Response rates were < 10%, with no complete responses, and the survival advantage with vinflunine over best supportive care was

2 months. The median DOR, PFS, and OS were 7.4 months, 3.0 months, and 6.9 months, respectively (Bellmunt 2009). Vinflunine was associated with Grade 3/4 neutropenia in 50% of patients and febrile neutropenia in 6%, while severe fatigue and constipation were reported in 19.3% and 16.1% of patients, respectively.

Recent published data on the use of checkpoint inhibitors in metastatic UC show encouraging clinical activity in patients with advanced disease, suggesting a paradigm shift in the treatment of UC (Rosenberg 2016; Galsky 2016; Balar 2016). There is a strong rationale for considering immunotherapy in patients with advanced UC. Over the past 40 years, progress evaluating immunotherapy for BC has been slow. Subsequently, the PD-1/PD-L1 pathway has emerged as an important biological pathway in UC (Plimack 2014; Powles 2014; Bellmunt 2014b). Atezolizumab (Tecentriq®) is an Fc-engineered, humanized immunoglobulin G1 (IgG1) anti-PD-L1 monoclonal antibody that has since been approved in the EU as a monotherapy for the treatment of adult patients with locally advanced or metastatic UC after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression ≥ 5 (Atezolizumab European Public Assessment Report [EPAR] 2017). Results from the Phase 3, open-label, multicenter, randomized study (IMvigor211) of 931 patients with UC treated with either atezolizumab or chemotherapy showed that the investigator-assessed median PFS was 2.1 months and 4.0 months in the atezolizumab and chemotherapy arms, respectively. Additionally, investigator-assessed ORR was 13.4% for patients in both study arms. Overall, IMvigor211 did not meet its primary endpoint of OS and therefore, all results, including PFS and ORR, were considered exploratory and thus not statistically significant (Atezolizumab EPAR 2017). Pembrolizumab (Keytruda) as monotherapy is indicated for the treatment of locally advanced or metastatic UC in adults who have received prior platinum-containing chemotherapy (Pembrolizumab EPAR 2019). Results from the pembrolizumab key trial KEYNOTE-045, a multicenter, randomized, controlled study for the treatment of locally advanced or metastatic UC in patients with disease progression on or after platinum-containing chemotherapy showed a median OS of 10.1 months in patients receiving pembrolizumab compared to 7.3 months in the chemotherapy arm. The median PFS was observed at 2.1 and 3.3 months in pembrolizumab and chemotherapy arms, respectively. Additionally, the ORR was 21% in patients treated with pembrolizumab and 11% in those receiving chemotherapy (Pembrolizumab EPAR 2019).

Natural history of the indicated condition in the untreated population, including mortality and morbidity: MCC

MCC is an aggressive neuroendocrine skin cancer with a high disease-associated mortality (Lemos 2010). MCC presents as a firm, painless, rapidly enlarging, red-violet cutaneous tumor nodule that is typically dome-shaped (Heath 2008; Smith 2012). MCC nodules are more frequently located in sun-exposed areas of the head and neck or upper extremities (Heath 2008; Smith 2012; Hussain 2010; Medina-Franco 2001). Heath (2008) and colleagues developed the asymptomatic/lack of tenderness, expanding rapidly, immunosuppression, older than 50 years, and location on an UV-exposed site (AEIOU) acronym to define the clinical features associated with MCC: asymptomatic/lack of tenderness, expanding rapidly, immunosuppression, older than 50 years, and location on an UV-exposed site (Heath 2008).

As is the case for all cancers, the stage of MCC is a good predictor of survival (Andea 2008; Stetsenko 2013; Lemos 2010; Santamaria-Barria 2013). In a study of 156 patients with MCC, patients with Stage III and Stage IV disease were more likely to die from MCC compared with patients with Stage I tumors (OR 2.68 [95% CI: 1.12;6.41] and OR 33.66 [95% CI: 10.35;109.43]) (Andea 2008). In a US study in 128 patients with MCC, advanced disease stage was associated with an increased risk of MCC-specific mortality (Stage III vs Stage I: HR4.92 [95% CI: 2.0;12.0] and Stage IV vs Stage I: HR 13.7 [95% CI: 4.3;44.0]) (Stetsenko 2013). In a study assessing MCC disease records in a single US institution between 1980 and 2010, among 161 patients with MCC, 9% of patients presented with metastatic disease, and the 5-year MCC-specific survival rate in this group of patients was 0% (Santamaria-Barria 2013). In another US study, based on data from the NCDB between 1986 and 2004, among 5,823 patients with MCC, the 5-year relative survival (per the 7th Edition AJCC staging) was lower in patients with Stage IIIB and Stage IV MCC (26% and 18%, respectively), compared with Stage I (60%-79%) and Stage II (47%-58%) MCC (see Table 5) (Lemos 2010). A recent report in distant metastatic disease based on 784 patients reported a 5-year survival rate of 13.5% (95% CI: 11.0;16.3) (Harms 2016).

Table 5 Relative Survival of Patients With MCC by Stage at Presentation (N=2,856) Based on 7th Edition AJCC Staging

Stage	5-Year Relative Survival, %
IA	79
IB	60
IIA	58
IIB	49
IIC	47
IIIA	42
IIIB	26
IV	18

Source: Lemos 2010.

AJCC=American Joint Committee on Cancer, MCC=Merkel cell carcinoma

Among 1,034 patients with first primary MCC reported by the SEER in the US between 1973 and 1999, the 5-year observed survival rate was 45%. When stratified by stage, the 5-year relative survival rate was 75% for localized MCC (Stage I-II), 59% for regional MCC (Stage III), and 25% for distant MCC (Stage IV) (Agelli 2003). Similarly, SEER tumor registry data in US patients with MCC from 1986 to 2011 showed that survival decreased as the disease progressed in stage; the 5-year disease-specific survival rate was 78% for Stages I-II , 54% for Stage III, and 30% for Stage IV disease (Fitzgerald 2015). In a study assessing MCC-related mortality in 185 patients diagnosed with MCC in Denmark between 1978 and 2006, in the first year after MCC diagnosis, 22% of patients with localized disease died compared with 54% of patients with non-localized disease; by 5 years after diagnosis, the proportions of patients who had died increased to 55% and 84%, respectively (Kaae 2010).

Male sex and advanced age have been shown to influence the prognosis of patients with MCC (Chen 2015; Smith 2012). Multivariate analyses among 4,815 patients with MCC recorded in the NCDB from 1998 to 2011 showed that age of at least 75 years was independently associated with

decreased OS (HR 2.83 [95% CI: 1.82;4.41]) (Chen 2015). A study of 2,104 patients with head and neck MCC demonstrated that male sex was an independent prognostic factor for decreased disease-specific survival (Smith 2012).

Potential prognosis factors of MCC include CD8+ lymphocyte infiltration, vitamin D deficiency, and immunosuppression (Paulson 2014; Samimi 2014; Asgari 2014; Paulson 2013). In a study of 137 patients with MCC who were diagnosed in the US between 1995 and 2009, increased intratumoral CD8+ lymphocyte infiltration was significantly associated with improved MCC-specific survival in a multivariate competing risk-regression analysis (HR 0.5 [95% CI: 0.3;0.9]) (Paulson 2014). Vitamin D deficiency has also been associated with poor prognosis in MCC. In a cohort of 89 patients with MCC in France, vitamin D deficiency correlated with a greater tumor size at diagnosis and recurrence of metastasis (HR 2.89 [95% CI: 1.03;8.13]) (Samimi 2014). In a retrospective study of 218 patients with MCC in the US identified between 1995 and 2009, immunosuppression was associated with higher MCC-specific mortality (HR 4.9 [95% CI: 1.7;14.4]) (Asgari 2014). Similarly, a study of 471 patients with MCC in the US demonstrated that immunosuppressed patients with MCC had significantly worse MCC-specific survival compared with patients who were not immunosuppressed. Immune suppression in this study was found to be a significant independent predictor of worse MCC-specific survival (HR 3.8 [95% CI: 2.2;6.4]) (Paulson 2013).

Unknown primary status has recently been recognized as a prognostic feature of survival and the staging for MCC is currently undergoing revision by the NCCN such that Stage IIIA will include the previous IIIB with “unknown primary” tumor status (Harms 2016). The survival benefit may be associated with improved early immune surveillance (Harms 2016).

Natural history of the indicated condition in the untreated population, including mortality and morbidity: RCC

RCC has an early asymptomatic course, resulting in 25-30% of patients with RCC presenting with metastatic disease at diagnosis (Gupta 2008). Additionally, another 20% of patients with RCC who have undergone nephrectomy will relapse and develop mRCC (Athar 2008). Systemic therapy is given to patients with advanced disease (relapsed or Stage IV at diagnosis- aRCC) that is not amenable to complete resection. Furthermore, traditional cancer treatments such as radiation therapy and chemotherapy are not effective in RCC. Newer systemic therapies are now given to patients with aRCC that is not amenable to complete resection.

With respect to prognosis, more than 25% of RCC patients present with advanced or metastatic disease at the time of first diagnosis (Rossi 2018). In a Danish cohort of 1,008 advanced (Stage III or IV) clear cell RCC patients (median [interquartile range] age in years: 67.0 [59.3-73.8]; 32.8% female) who were diagnosed from 2013-2016, 295 (29.3%) had radiation therapy, 479 (47.5%) had chemotherapy, and 690 (68.5%) underwent at least 1 therapeutic surgical procedure. With respect to the disease outcome, as of the most recent follow-up (through 2017) 497 patients have died, resulting in a mortality rate of 26.1 per 100 person-years since the date of diagnosis with advanced RCC; their median survival time was 31.9 months (95% CI: 29.0;40.4). Among the subset of 920 cohort members who initiated RCC treatment (therapeutic surgery, chemotherapy, immunotherapy, or radiation therapy), the median survival time from the date of treatment initiation was 35.5 months (95% CI: 30.6;47.9) (Pfizer Data on File 2018).

The mortality burden of aRCC is significant. While 5-year survival can be up to 90.3% for patients with localized kidney and renal pelvis cancer, it is roughly 12% among patients with aRCC (Howlader 2012) and can be significantly lower in sub populations of untreated patients, e.g. as low as 2.3% in patients without cytoreductive nephrectomy (Zini 2009).

Natural history of the indicated condition in the untreated population, including mortality and morbidity: UC

UC can occur in the renal pelvis, urachus, ureter or bladder. Symptoms of BC include hematuria, changes in urination, such as frequent urination, pain or burning during urination and anuria, while other symptoms including lower back pain on one side, loss of appetite and weight loss, fatigue or weakness, swelling in the feet and bone pain have been associated with more advanced BC (American Cancer Society 2018). Approximately 5% of patients with BC present with metastatic disease (N1-3 or M1) and 25% of BC are muscle invasive (T2-T4); furthermore, approximately 50% of patients with muscle invasive BC will develop distant metastases (Babjuk 2008; Boustead 2014; Milowsky 2016).

An estimated 199,922 deaths (~74% men) due to BC occurred in 2018 worldwide (GLOBOCAN 2018a). Crude mortality rates (per 100,000) are higher among countries in high income regions than low -income areas (7.3 vs 0.97), highest in Europe (overall 8.7) and North America (5.6), Oceania (4.4), Asia (1.9), Latin America and Caribbean (1.8), and lowest in Africa (1.3) (GLOBOCAN 2018g).

The American Cancer Society, based on collated data from the National Center for Health Statistics, projected 16,390 deaths from BC in the US in 2016 (11,879 deaths in men and 4,570 deaths in women) (Siegel 2016). Despite assumed advances in treatment over time, US SEER data have indicated that overall, 6-month relative survival in patients with metastatic BC pooled across all ages, races, and both sexes has decreased significantly ($p < 0.01$) over time from $67.8 \pm 0.7\%$ in 1991-2000 to $64.7 \pm 0.5\%$ in 2001-2010. Similarly, pooled 12-month relative survival also decreased significantly ($p < 0.01$) from $49.6 \pm 0.7\%$ in 1991-2000 to $45.7 \pm 0.6\%$ in 2001-2010 (Shah 2015).

In a comprehensive analysis of data extracted from 2000-2012 from 9 databases (from France, Italy, Germany, the Netherlands, Austria, Norway, Ireland, Finland, and UK) accompanied by a systematic review of all types of advanced and metastatic tumors, marked differences were observed in population-based survival across Europe. One-year relative-survival rates for Stage IV BC ranged from 24-56%; 5-year relative-survival rates for Stage III bladder cancer ranged from 20-45%. This broad variation in survival was attributed to methodological issues with the analysis and the databases used (data collected over wide time periods and used inconsistent disease-stage definitions, for example) but other factors also contributed, such as variation in clinical practice, histological type, age, method of death ascertainment and co-morbidities (Moulard 2012).

Important co-morbidities: MCC

Although co-morbidities in patients with MCC or mMCC are not well-known due to the rarity of the disease and scarcity of literature, it is known that MCC is a disease of the elderly, where one can expect a higher frequency of co-morbidities (Desch 2013).

One important co-morbidity found in patients with MCC is HIV infection, as the course of MCC in patients with HIV/AIDS can be aggressive and associated with poor survival. The prevalence of HIV in patients with MCC overall is not well-described, however several large epidemiologic studies on patients with HIV/AIDS have identified an increased risk of MCC in these patients (Lanoy 2009; Engels 2002). Patients with MCC presenting with HIV diagnosis can be expected to receive concomitant treatment for HIV. Izikson (2011) and colleagues investigated 14 patients with HIV-MCC, of which 3 patients were from a tertiary care specialty hospital and 11 other patients previously described in the literature. Eleven of these patients were treated for their HIV with highly active antiretroviral therapy (HAART). 5 of these patients began antiretroviral therapy after their diagnosis of MCC (Izikson 2011). The use of HAART improves survival of HIV-infected patients; however, the effect of HAART on MCC development and behavior in patients with HIV/AIDS is not known. There are case reports describing sustained remission of mMCC in HIV-positive patients with HAART and interleukin (IL)-2 treatment (Burack 2003; Brugnaro 2011).

Immunosuppression due to HIV infection or organ transplantation is common in patients with MCC. Heath and colleagues identified 195 patients with MCC from 3 US medical centers, and in these patients, profound immunosuppression was noted in 7.8%; HIV was present in 3 patients, CLL in 8 patients, and solid organ transplant in 4 patients (Heath 2008). In transplant patients, they observed more advanced disease at time of presentation in the immunosuppressed group; 10 of the 15 (67%) immunocompromised patients presented with either nodal or distant metastatic disease as compared to 42% in the immunocompetent group. However, the difference was not statistically significant (Heath 2008). In an MCC population one might expect also to find autoimmune disease (Hemminki 2012; Lanoy 2010a; Sahi 2010).

Patients diagnosed with MCC are overall also at risk of developing second cancers (Bzhalava 2011; Tadmor 2012; Saxena 2014). Based on data from national cancer registries in Denmark, Norway and Sweden, there were significantly increased standardized incidence ratios for non-melanoma skin cancers (SIR 6.63 [95% CI: 4.55;9.67]), melanoma of the skin (SIR 3.58 [95% CI: 1.49;8.60]) and laryngeal cancer (SIR 9.51 [95% CI: 2.38;38.04]) in patients with MCC; these cancers occurred at least 1 year after MCC diagnosis (Bzhalava 2011). Similarly, a meta-analysis of 5 population-based cohort studies published between 1999 and 2014 showed an overall increased risk for second malignancies due to MCC (SIR 1.52 [95% CI: 1.10;2.11]), and in particular a significant increase in risk for malignant melanoma (SIR 3.09 [95% CI: 2.02;4.73]) compared with all common second malignancies among the studies (Saxena 2014). In addition, hematologic malignancies have been reported in patients with MCC, the most frequent types being CLL/small lymphocytic lymphoma, and non-Hodgkin lymphoma (Tadmor 2012).

The presence or absence of MCPyV infection in patients with MCC may be predictive of clinical outcomes (Shantha 2015). A study in 282 patients with MCC found that 81% of patients were MCPyV-positive and 19% were MCPyV-negative. Patients with MCPyV-negative tumors had significantly decreased PFS and poorer disease-specific survival compared with patients who had MCPyV-positive tumors (Shantha 2015). A study in 143 patients with MCC diagnosed between 1998 and 2014 in France found that low baseline titers (< 10 ,000) of serum antibodies against the major MCPyV capsid protein were significantly and independently associated with increased risk of recurrence (HR 2.71 [95% CI : 1.13;6.53]) and death (HR 3.74 [95% CI: 1.53;9.18]) compared with high titers at baseline (> 10,000) (Samimi 2016). In the same study, antibodies against MCPyV oncoproteins (T antigens) were more frequently detected in patients with recurrence or

progression at 12 months and 24 months after diagnosis compared with patients in remission (Samimi 2016).

There is limited information about concomitant medications for patients with MCC or in general. The NCCN clinical guidelines for MCC state that management of patients with metastatic disease should always include best supportive care and refer to the NCCN guidelines for palliative care in addition to the consideration of surgery, chemotherapy, or radiotherapy (NCCN MCC Guideline 2016). In terms of symptoms, management of pain, dyspnea, anorexia/cachexia, nausea and vomiting, constipation, diarrhea, malignant bowel obstruction, fatigue, sleep/wake disturbances, delirium and psychological distress are described by NCCN as fundamental in palliative care of patients (NCCN Palliative Care Guideline 2016). Common concomitant medications for symptom management in patients with mMCC as per the NCCN palliative guideline is described in Table 6. In addition to symptoms management, as the MCC population is mainly elderly, and immunosuppression often presents in patients, a higher amount of concomitant medications can be expected, compared to a younger patient population.

Table 6 Concomitant Medications in the Target Population (mMCC, RCC and UC)

Symptoms	Treatment	NCCN Palliative Care Guideline 2016
Pain	In general, cancer pain is treated with opioids. Pain associated with inflammation: NSAIDS or corticosteroids. Bone pain: NSAID, analgesic, bone-modifying agents. Diffuse: hormonal therapy, chemotherapy, corticosteroids or radioisotopes. Nerve pain: corticosteroids, antidepressant, anticonvulsant, topical agents, Painful lesions likely to respond to antineoplastic regimens: radiation, hormones, chemotherapy (NCCN 2016). WHO recommendations for palliative care of cancer patients include prompt administration of drugs according to a 3-step cancer pain ladder approach, which entails administering drugs in the following order: Step 1: Pain persistent or increasing: non-opioids (aspirin and paracetamol); Step 2: Pain persisting or increasing: mild opioids (codeine); Step 3: Moderate to severe pain: strong opioids such as morphine, with or without non-opioids until the patient is free of pain. To calm fears and anxiety, additional drugs – "adjuvants" – is recommended (WHO 2016)	Palliative sedation can be considered for refractory pain. For pain management the NCCN Guidelines for adult cancer pain are recommended (NCCN Adult Cancer Pain Guideline 2016).
Dyspnea	Opioids with or without benzodiazepines. Morphine has undergone most extensive investigation for dyspnea, but fentanyl and oxycodone have been suggested to treat dyspnea also. For excessive secretions: scopolamine, atropine, hyoscyamine and glycopyrrolate	Benzodiazepines can be used for dyspnea if associated with anxiety, however the beneficial effect on dyspnea in patients with advanced cancer is small.
Anorexia/ cachexia	Metoclopramide, megestrol acetate, dexamethasone, olanzapine	Combination therapy approach may yield better outcomes in patients with cancer cachexia

Symptoms	Treatment	NCCN Palliative Care Guideline 2016
Nausea and vomiting	Gastritis or gastroesophageal reflux: Proton pump inhibitors and histamine-2 receptor antagonists Gastric outlet obstruction: corticosteroids Non-specific nausea and vomiting: dopamine antagonists, benzodiazepines Persistent nausea: adding 5HT3 receptor antagonists, anti-cholinergic agents, antihistamines, corticosteroids, antiemetics, antipsychotics, or cannabinoids	Palliative sedation can be considered as last resort.
Constipation	Stimulating laxatives, bisacodryl, glycerine suppositories. For persistent constipation also rectal bisacodryl, oral polyethylene glycol, lactulose, magnesium hydroxide or magnesium citrate For gastroparesis: addition of prokinetic agent	For opioid -induced constipation there are additional NCCN guidelines.
Diarrhea	The National Cancer Institute Common Toxicity Criteria are typically used for measuring diarrhea, and it is recommended that patients are screened to determine the grade of diarrhea. For patients with years, years to months, or months to weeks of estimated life expectancy with Grade 1 or 2 diarrhea recommendations include hydration and electrolyte replacement (intravenous fluids if appropriate), antidiarrheal medications and a bland (bananas, rice, applesauce and toast [BRAT]) diet. For Grade 2 diarrhea: anticholinergic agents can be considered. Infection induced: antibiotics. Persistent diarrhea: morphine concentrate. In addition to fluid replacement, antidiarrheal therapy and anticholergenics, octreotide can be considered.	Persistent Grade 2, 3 or 4 should receive inpatient treatment.
Malignant bowel obstruction	Opioids, antiemetics, corticosteroids. When no longer possible to maintain gut function: somatostatin analogs and/or anticholinergics.	Surgery is primary treatment, however advanced cancer patients are often unfit for surgery.
Fatigue/ weakness/ asthenia	Methylphenidate or modafinil suggested.	Data on these medications not conclusive
Sleep-wake disturbances	Restless legs syndrome: ropinirole, pramipexole with pregabalin or carbidopa-levodopa. Refractory insomnia: benzodiazepine lorazepam, non-benzodiazepine zolpidem, antipsychotics: i.e. chlorpromazine, quetiapine, olanzapine, sedating antidepressants: i.e. trazodone and mirtazapine For refractory daytime sedation: central nervous system stimulants methylphenidate or dextroamphetamine, or modafinil. Caffeine and dextroamphetamine additional options.	The majority of advanced cancer patients suffer from sleep disturbances. Benzodiazepines are not recommended for older patients or patients with cognitive impairment

Symptoms	Treatment	NCCN Palliative Care Guideline 2016
Delirium	Moderate delirium: oral haloperidol, risperidone, olanzapine, quetiapine. Fumarate not indicated in the elderly there could be an increased risk of mortality with their use. Severe delirium: antipsychotic, neuroleptic drugs. A benzodiazepine may be added for agitation refractory to high doses of neuroleptics. Opioid dose reduction or rotation can be considered also.	Delirium inducing medications i.e. steroids, anticholinergics should be reduced as much as possible. Benzodiazepines should not be used for initial treatment if patients are not already using them. Palliative sedation may be considered for refractory delirium in dying patients.

mMCC=metastatic Merkel cell carcinoma, NCCN=National Comprehensive Cancer Network, NSAID=nonsteroidal anti-inflammatory drug, RCC=renal cell carcinoma, UC=urothelial carcinoma, WHO=World Health Organization

Important Co-morbidities: RCC

No data on the prevalence of medical co-morbidities in the population of patients with aRCC were identified. The table below (Table 7) summarizes the data on co-morbidities among patients with any RCC. Specific search terms were "metastatic renal cell carcinoma" or "mRCC" or "RCC" or "renal cell carcinoma" or "renal cancer" or "kidney cancer" and "comorbid" or "comorbidity" or "anaemia" or "decreased haemoglobin" or "cardiovascular" or "diabetes" or "hypertension" or "high blood pressure" or "hypothyroidism" or "thyroid function" or "thyroid."

Table 7 Co-morbidity in the RCC Patient Population

Important Co-morbidity in the RCC Population	Prevalence, Mortality and Co-prescribed Medicinal Products
Anemia	Prevalence Anaemia is common in RCC patients. In a study of 760 RCC cases (70% localized, 30% metastatic) undergoing nephrectomy between 1989 and 2001 at a single US institution, anaemia (defined as preoperative haematocrit less than 40% in men and less than 36% in women) was present in 52.1% of the subjects (Kim 2003). In a small study of 39 patients diagnosed with RCC between 1987 and 1995 in a single UK hospital, anaemia was present in 46% of the cases (Doherty 1999). In a recent study of 968 patients with metastatic RCC from 13 international centers, 56% had a baseline haemoglobin concentration that was less than the lower limit of normal (Heng 2013). Mortality Anaemia is associated with shorter survival times and increased risk of mortality in patients. Based on a comprehensive literature review by Caro (2001) and colleagues, patients with RCC who have anaemia have a mortality rate that is 1.9-fold higher than those without anaemia. Co-prescribed medications Anaemia can be effectively treated with erythropoietin.
Cardiovascular disease	Prevalence

Important Co-morbidity in the RCC Population	Prevalence, Mortality and Co-prescribed Medicinal Products
	In a large population-based study that included 1,259 patients aged 50 years or older who were diagnosed with kidney cancer (includes RCC and renal pelvis carcinoma) in 1995-2002 in southern Netherlands, the prevalence of heart and vascular disease varied by age from 14% to 39% in males and from 6% to 27% in females (Janssen-Heijnen 2005). Of the 368 RCC patients in a Danish population-based case-control study conducted in 1989-1991, 11.7% had a history of angina pectoris, 7.1% had a prior myocardial infarction, and 3.5% had a history of stroke (Mellemgaard 1994). In a recent study of 8,633 Danish residents with RCC, 6.1% had a prior myocardial infarction, 5.2% had congestive heart failure, and 8.4% had cerebrovascular disease (Smith 2014). Mortality No data on cardiovascular mortality are available for the RCC patient population. Co-prescribed medications Medications that may be prescribed for coronary heart disease patients include beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, diuretics, nitrates, and statins.
Diabetes	Prevalence In a Danish population-based case-control study conducted in 1989-1991, 6.3% of the 368 RCC patients had a history of diabetes (Mellemgaard 1994). In a large population-based study that included 1,259 patients aged 50 years or older who were diagnosed with kidney cancer (includes RCC and renal pelvis carcinoma) from 1995 to 2002 in southern Netherlands, the prevalence of diabetes varied by age from 8% to 21% (Janssen-Heijnen 2005). In a recent study of 8633 Danish residents with RCC, 2.6-6.2% had a history of diabetes (Smith 2014). In a study of 1,761 Italian patients with RCC, 8.9% had a prior diabetes diagnosis (Antonelli 2013). Mortality In a study of 1,604 Italian patients with non-metastatic RCC (152 with prior diagnosis of diabetes), diabetes was not significantly associated with RCC or non-RCC related mortality (Antonelli 2013). Co-prescribed medications Most commonly, patients with diabetes are treated with oral antihyperglycemics, insulin, HMG -CoA (3-hydroxy-3-methylglutaryl-coenzym A) reductase inhibitors (statins), antiplatelets, and antihypertensives.
Hypertension	Prevalence Studies suggest that a significant proportion of patients with RCC have a history of arterial hypertension and that blood pressure returns to normal or decreases following nephrectomy (Stojanovic 2009). The reported estimates of hypertension prevalence in RCC population vary from ~ 29% to 79% (Doherty 1999; Mellemgaard 1994; Stojanovic 2009; Wong 2001; Steffens 1992). Mortality No data on hypertension-associated mortality are available for RCC patient population. Co-prescribed medications Medications that may be prescribed for hypertensive patients include alpha blockers, ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, central alpha agonists, diuretics, and renin inhibitors.
Thyroid disorders	Prevalence

Important Co-morbidity in the RCC Population	Prevalence, Mortality and Co-prescribed Medicinal Products
	Literature suggests that history of thyroid disorders is common in RCC patients. For instance, in an epidemiological study of 247 women diagnosed with RCC in a single US cancer center between 1981 and 1985, 19% had a prior history of thyroid disorders, including hypothyroidism, nodular thyroid, goiter, hyperthyroidism, and carcinoma of the thyroid (Rosenberg 1990). In a Danish population-based case-control study of RCC risk factors, a history of thyroid disorders was present in 6.5% of 368 histologically verified RCC cases (Mellemgaard 1994). Mortality No data on mortality in association with thyroid disorders in RCC patients are available. Co-prescribed medications Thyroid-hormone supplements may be used to treat thyroid disorders. Standard treatment for hypothyroidism involves daily use of the synthetic thyroid hormone levothyroxine.

RCC=renal cell carcinoma

In addition, similar to the mMCC population, common concomitant medications for symptom management in patients with RCC as per the NCCN palliative guideline are described in Table 6.

Important Co-morbidities: UC

UC, like MCC, is primarily a disease of the elderly and therefore co-morbidities are common. In addition, UC is strongly associated with smoking and increased dietary fat intake (Steineck 1990; Wingo 1999). These factors predispose to other medical conditions, including cardiovascular, cerebrovascular, and pulmonary disease, and therefore it is not surprising that patients with UC often have significant co-morbidities (Yusuf 2005).

The presence of co-morbidities, in particular kidney dysfunction, may limit treatment options and affect outcomes in older patients with UC. Approximately 50% of patients with UC are not eligible for cisplatin-based chemotherapy (due to impaired renal function [creatinine clearance < 60 mL/min], poor performance status [Eastern Cooperative Oncology Group (ECOG) > 1] or co-morbidity) (Morales 2011; Nogue-Aliguer 2003). A retrospective analysis of Phase 2/3 trials in metastatic UC reported that patients ≥ 70 years old had a significantly lower baseline calculated creatinine clearance than younger patients (57 vs 73 mL/min, p < 0.0001) (Bamias 2013).

Similar to the mMCC population, common concomitant medications for symptom management in patients with UC as per the NCCN palliative guideline are described in Table 6.

Part II: Module SII: Non-clinical Part of the Safety Specification

The key safety findings from the non-clinical program and their relevance to clinical use in humans are presented in Table 8.

Table 8 Key Safety Findings from Non-clinical Studies and Relevance to Human Usage

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
Acute and repeat-dose toxicity The results of a 4-week repeat-dose study in CD-1 mice (mortalities at all dose levels within 30 minutes after the third administration) are fully supportive of a mouse anti-human antibody response caused by the repeated administration of a human protein in mice, the mechanism of which is highly likely to be anaphylaxis (immunoglobulin E / immunoglobulin G mediated).	The hypersensitivity reactions due to mouse anti-human antibody are not relevant to human. The immunogenicity incidence against fully human monoclonal antibody in rodents is not predictive of incidence in humans.
Small increases in AST/ALT were observed in a few cynomolgus monkeys treated with avelumab and C-reactive protein was statistically higher in female monkeys at the highest dose of 140 mg/kg of avelumab in the 13-week study although the increase was minor and considered without toxicological relevance. There was no evidence macroscopically or histopathologically of any form of liver injury, there were no adverse clinical observations and there was no evidence of adverse immune-mediated hepatic events in any of the monkey studies.	The results observed in Cynomolgus monkeys reveal no special hazard for humans with regard to hepatic safety.
Perivascular mononuclear cell cuffing was observed in the brain and spinal cord of monkeys treated with avelumab at > 20 mg/kg for 13 weeks. Although there was no clear dose-response relationship, it cannot be excluded that this finding was related to avelumab treatment.	A potential relevance to humans cannot be excluded. Encephalitis is included in the clinical safety specification under the important potential risk Other immune-mediated events'.
Reproductive toxicity Avelumab has been shown to bind to male and female reproductive organs in tissue cross-reactivity studies. Disruption of programmed death 1 / programmed death ligand 1 communication has been reported to significantly increase the risk of fetal loss during pregnancy and neonatal death. An impact on embryofetal development in the context of avelumab treatment cannot be excluded.	Due to its mechanism of action, avelumab may increase the risk of abortion and stillbirth if administered during pregnancy.
General and Safety Pharmacology In both the intravenous repeat-dose toxicity studies (4 and 13 week), heart rate, electrocardiogram, arterial blood pressure, respiratory rate, central nervous system parameters and body temperature were unaffected by treatment with avelumab at the highest dose level of 140 mg/kg.	No risks identified.
Other toxicity studies Initial CRAs in human and cynomolgus monkey whole blood and PBMCs revealed little to no release of pro-inflammatory cytokines in most samples. After the observation of infusion-related reactions in the clinical setting, CRAs with phyto-hemagglutinin pre-stimulated PBMCs from healthy human volunteers were conducted which demonstrated evidence of modest cytokine release indicating a potential for infusion-related reactions.	The risk of Infusion-related reactions is currently being characterized in ongoing clinical trials.

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CRA=cytokine release assay, PBMC=peripheral blood mononuclear cell

In conclusion the main toxicities observed in the non-clinical development program that have relevance for use in humans are:

Important identified risks:

- None

Important potential risks:

- Infusion-related reactions (IRRs; severe IRRs were classified as an important identified risk based on clinical experience)
- Embryofetal toxicity
- CNS toxicity (encephalitis)

Part II: Module SIII: Clinical Trial Exposure

Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), B9991001 - Pooled Safety Set

The integrated safety analyses supporting this Risk Management Plan (RMP) include pooled data from subjects who were administered at least 1 dose (partial or complete) of avelumab 10 mg/kg every 2 weeks (Q2W) in Studies EMR100070-003 (Part A) and EMR100070-001 as of the clinical database cut-off date (09 Jun 2016) and from subjects with locally advanced or metastatic UC administered at least 1 dose (partial or complete) of avelumab 10 mg/kg Q2W as maintenance therapy following first-line systemic therapy with a platinum-based regimen in Study B9991001 as of the clinical database cut-off (21 Oct 2019).

Avelumab in Combination with Axitinib in RCC

Clinical trial exposure data pertaining to the RCC population (N=488) includes subjects who were administered at least 1 dose (partial or complete) of avelumab 10 mg/kg Q2W in combination with at least 1 dose of axitinib 5 mg twice a day (BID) in clinical trials B9991002 (N=54) as of 03 Apr 2018 and B9991003 (N=434) as of 20 Jun 2018. Of note, 1 subject in Study B9991002 received only axitinib treatment and therefore is not included in the avelumab clinical trial exposure data for the RCC population.

Avelumab Single-Agent

Study EMR100070-003 (Part A)

Study EMR100070-003 (Part A) was a multicenter, international, single-arm, open label, Phase 2 study that evaluated the efficacy and safety of 10 mg/kg avelumab administered by intravenous infusion Q2W in 88 subjects with mMCC whose disease had progressed after at least 1 prior chemotherapy regimen.

Study EMR100070-001

Study EMR100070-001 is a, Phase 1, open-label, dose-escalation study with consecutive parallel group expansion in multiple solid tumor indications to investigate the safety, tolerability, pharmacokinetics (PK), and biological and clinical activity of avelumab. This study has 2 phases, a dose escalation phase (receiving an avelumab dose of 1, 3, 10, or 20 mg/kg) and treatment expansion phase (receiving avelumab doses of 10 mg/kg Q2W). In the dose expansion phase, subjects receive treatment with avelumab until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the study or study drug was fulfilled. As of 09 Jun 2016, 53 subjects were included in the dose-escalation phase and exposed to doses up to 20 mg/kg avelumab.

Pooled data (dose escalation and expansion phase) from all subjects from Study EMR100070-001 treated with 10 mg/kg avelumab Q2W in the study (N=1,650) are included in the integrated safety analysis and presented in this RMP. These include data from subjects across multiple tumor types and across various lines of therapy: adrenocortical carcinoma (N=50), colorectal cancer (N=21), castrate-resistant prostate cancer (N=18), gastric and gastroesophageal cancer (N=252), ovarian cancer (N=228), UC (N=249), head and neck cancer (N=153), metastatic breast cancer (N=168), melanoma (N=51), mesothelioma (N=53), non-small cell lung cancer (N=340), RCC (N=52), and unknown (N=15).

Study B9991001 (Javelin Bladder 100)

Study B9991001, is a Phase 3, randomized, multi-center, open-label study conducted in 700 patients with unresectable, locally advanced or metastatic UC whose disease has not progressed with first-line platinum-based induction chemotherapy. Patients were randomized (1:1) to receive either avelumab 10 mg/kg intravenous infusion Q2W plus best supportive care (BSC) or BSC alone.

BSC could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), etc. BSC did not include any active anti-tumor therapy, however local radiotherapy of isolated lesions with palliative intent was acceptable.

Avelumab in Combination with Axitinib in RCC

Study B9991002 (Javelin Renal 100)

Study B9991002 is a Phase 1b, open-label, multicenter, multiple-dose study of the combination of avelumab with axitinib in treatment-naïve patients with aRCC. This study included a dose-finding phase followed by a dose-expansion phase.

The axitinib starting dose was 5 mg per os (PO) BID and the dose for avelumab was 10 mg/kg iv Q2W.

Study B9991003 (Javelin Renal 101)

Study B9991003 is a Phase 3, multinational, multicenter, randomized (1:1), open-label, parallel 2-arm study in which treatment naïve patients with aRCC were randomized to receive 1 of the following study treatments:

- Arm A: avelumab 10 mg/kg iv Q2W in combination with axitinib 5 mg PO BID
- Arm B: sunitinib 50 mg PO once daily on schedule 4/2 (4 weeks on treatment followed by 2 weeks off)

Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), B9991001 - Pooled Safety Set

Clinical trial exposure data for subjects treated with avelumab 10 mg/kg Q2W (single-agent avelumab) in clinical trials EMR100070-001 (N=1,650; data cut-off 09 Jun 2016), EMR100070-003 (Part A, N=88; data cut-off 09 Jun 2016), B9991001 (N=344; data cut-off 21 Oct 2019), and for the Pooled Safety Set (N=2,082) are presented in Table 9 to Table 13. The clinical trial exposure analyses include clinical exposure by time, gender, age group (years), and racial origin. Table 9 summarizes the duration of exposure to avelumab in the clinical trials EMR100070-001, EMR100070-003 (Part A), B9991001, and in the Pooled Safety Set, respectively. Overall, the mean number of weeks on treatment was 23.0 (range: 2 to 159.9 weeks).

Table 9 Summary of Drug Exposure (Single Agent Avelumab) - Safety Analysis Set (EMR100070-001, EMR100070-003 [Part A], B9991001, and Pooled Safety Set)

Characteristic	Statistics	EMR100070-001 Avelumab (N=1,650)	EMR100070-003 Avelumab (N=88)	B9991001 Avelumab (N=344)	Total Avelumab (N=2,082)
Treatment duration (weeks) [1]	Mean ± SD	19.5 ± 20.5	26.8 ± 23.6	38.7 ± 33.7	23.0 ± 24.4
	Median	12.0	17.0	24.9	12.6
	Q1; Q3	6.0; 24.0	7.4; 45.9	13.2; 57.9	6.1; 30.0
	Min; max	2.0; 137.9	2.0; 90.1	2.0; 159.9	2.0; 159.9

Source: RMP data output Table 12.10.1 Cut-off dates: 09 Jun 2016 for EMR100070-001 and EMR100070-003 (Part A); 21 Oct 2019 for B9991001.

Max=maximum, min=minimum, Q1=quartile 1, Q3=quartile 3, SD=standard deviation

[1] Duration of avelumab treatment is defined as Duration (weeks) = (last dose date of avelumab - first dose date of avelumab + 14) / 7.

Table 10 presents exposure to avelumab by dose in the supporting clinical trials EMR100070-001, EMR100070-003 (Part A), B9991001, and in the Pooled Safety Set, respectively.

Table 10 Extent of Exposure by Dose (Single -Agent Avelumab) - Safety Analysis Set (EMR100070-001, EMR100070-003 [Part A], B9991001, and Pooled Safety Set)

Characteristic	Dose	EMR100070-001 Avelumab N (%)	EMR100070-003 Avelumab N (%)	B9991001 Avelumab N (%)	Total Avelumab N (%)
Number of subjects treated	-	1,650*	88	344	2,082
Person-time exposure per 100 years	-	6.18	0.45	2.55	9.18
Number of subjects (%)	10.0 mg/kg	1,650 (100.0)	88 (100.0)	344 (100.0)	2,082 (100)

Source: RMP data output Table 12.11.1 Cut-off dates: 09 Jun 2016 for EMR100070-001 and EMR100070-003 (Part A); 21 Oct 2019 for B9991001.

*Patients treated in the expansion phase of Study EMR100070-001 and patients treated in Study EMR100070-003 (Part A).

Table 11 presents the duration of exposure to avelumab over time in the supporting clinical trials EMR100070-001, EMR100070-003 (Part A), B9991001, and in the Pooled Safety Set. Overall, 1,036 patients were treated for more than 3 months, 574 patients were treated for more than 6 months, 392 patients for more than 9 months, 220 patients for more than 1 year, 103 patients for more than 1.5 years, 41 patients for more than 2 years, and 5 patients were treated for more than 2.5 years.

Table 11 Duration of Exposure (Single -Agent Avelumab) - Safety Analysis Set (EMR100070-001, EMR100070-003 [Part A], B9991001, and Pooled Safety Set)

Characteristic	Statistics	EMR100070-001 Avelumab N (%)	EMR100070-003 Avelumab N (%)	B9991001 Avelumab N (%)	Total Avelumab N (%)
Number of subjects treated		1,650	88	344	2,082
Person-time exposure per 100 years [1]		6.18	0.45	2.55	9.18
Duration of treatment, n (%) [2]	> 0 Months	1,650 (100.0)	88 (100.0)	344 (100.0)	2,082 (100.0)
	> 1 Months	1,406 (85.2)	77 (87.5)	325 (94.5)	1,808 (86.8)
	> 2 Months	1,059 (64.2)	60 (68.2)	296 (86.0)	1,415 (68.0)
	> 3 Months	731 (44.3)	47 (53.4)	258 (75.0)	1,036 (49.8)
	> 6 Months	376 (22.8)	35 (39.8)	163 (47.4)	574 (27.6)
	> 9 Months	234 (14.2)	31 (35.2)	127 (36.9)	392 (18.8)
	> 12 Months	111 (6.7)	12 (13.6)	97 (28.2)	220 (10.6)
	> 18 Months	52 (3.2)	4 (4.5)	47 (13.7)	103 (4.9)
	> 24 Months	17 (1.0)	0 (0.0)	24 (7.0)	41 (2.0)

Characteristic	Statistics	EMR100070-001 Avelumab N (%)	EMR100070-003 Avelumab N (%)	B9991001 Avelumab N (%)	Total Avelumab N (%)
	> 30 Months	2 (0.1)	0 (0.0)	3 (0.9)	5 (0.2)

Source: RMP data output Table 12.11.1 Cut-off dates: 09 Jun 2016 for EMR100070-001 and EMR100070-003 (Part A); 21 Oct 2019 for B9991001.

[1] Person exposure-100 years = Sum of duration of exposure (in days) to avelumab for all patients / (100*365.25).

[2] The denominator to calculate percentages is N.

Table 12 presents the extent of exposure to avelumab by age group (years) and gender in the supporting clinical trials EMR100070-001, EMR100070-003 (Part A), B9991001 and in the Pooled Safety Set, respectively. Overall, more patients below the age of 65 years were treated with avelumab (n=1,058) compared to patients older than 65 years (n=1,024). Overall and in the age group older than 65 years, more male patients (n=1,159; ≥ 65 years: n=633) have been treated with avelumab compared to female patients (n=923; ≥ 65 years: n=391). However, across age groups below the age of 65 years more female subjects (n=532) have been treated with avelumab compared to male subjects (n=526).

Table 12 **Extent of Exposure by Age Group (Years) and Gender (Single Agent Avelumab) - Safety Analysis Set (EMR100070-001, EMR100070-003 [Part A], B9991001, and Pooled Safety Set)**

Characteristic	Statistics	EMR100070-001 Avelumab (N=1,650)	EMR100070-003 Avelumab (N=88)	B9991001 Avelumab (N=344)	Total Avelumab (N=1,738)
Number of subjects treated, n (%) [1]	Male	834 (50.5)	65 (73.9)	260 (75.6)	1,159 (55.7)
	Female	816 (49.5)	23 (26.1)	84 (24.4)	923 (44.3)
	Subjects Age < 65	907 (55.0)	22 (25.0)	129 (37.5)	1,058 (50.8)
	Subjects Age 65-<75	498 (30.2)	35 (39.8)	130 (37.8)	663 (31.8)
	Subjects Age 75-<85	221 (13.4)	28 (31.8)	80 (23.3)	329 (15.8)
	Subjects Age ≥ 85	24 (1.5)	3 (3.4)	5 (1.5)	32 (1.5)
	Male: Age < 65	419 (25.4)	16 (18.2)	91 (26.5)	526 (25.3)
	Male: Age 65-<75	282 (17.1)	25 (28.4)	102 (29.7)	409 (19.6)
	Male: Age 75-<85	119 (7.2)	22 (25.0)	64 (18.6)	205 (9.8)
	Male: Age ≥ 85	14 (0.8)	2 (2.3)	3 (0.9)	19 (0.9)
	Female: Age < 65	488 (29.6)	6 (6.8)	38 (11.0)	532 (25.6)
	Female: Age 65-< 75	216 (13.1)	10 (11.4)	28 (8.1)	254 (12.2)
	Female: Age 75-<85	102 (6.2)	6 (6.8)	16 (4.7)	124 (6.0)
	Female: Age ≥ 85	10 (0.6)	1 (1.1)	2 (0.6)	13 (0.6)
Person-time exposure per 100 years [2]	Male	3.27	0.33	1.95	5.55
	Female	2.91	0.12	0.60	3.63
	Subjects Age < 65	3.09	0.12	0.89	4.10
	Subjects Age 65-< 75	2.13	0.16	1.03	3.31
	Subjects Age 75-< 85	0.88	0.15	0.60	1.63
	Subjects Age ≥ 85	0.09	0.02	0.03	0.14
	Male: Age < 65	1.51	0.09	0.62	2.23
	Male: Age 65-< 75	1.22	0.11	0.79	2.12
	Male: Age 75-< 85	0.48	0.12	0.51	1.11
	Male: Age ≥ 85	0.05	0.01	0.03	0.09
	Female: Age < 65	1.58	0.03	0.27	1.87
	Female: Age 65-< 75	0.91	0.04	0.24	1.19
	Female: Age 75-< 85	0.40	0.04	0.08	0.52
	Female: Age ≥ 85	0.03	0.01	0.00	0.05

Source: RMP data output Table 12.12.1. Cut-off dates: 09 Jun 2016 for EMR100070-001 and EMR100070-003 (Part A); 21 Oct 2019 for B9991001.

[1] The denominator to calculate percentages is N.

[2] Person exposure-100 years = Sum of duration of exposure (in days) to avelumab for all patients / (100*365.25).

Table 13 summarizes the extent of exposure to avelumab by racial origin in the supporting clinical trials EMR100070-001, EMR100070-003 (Part A), B9991001, and in the Pooled Safety Set, respectively. The majority of patients treated with avelumab have been White (n=1,585), followed by Asian (n=228) and Other (n=168).

Table 13 Extent of Exposure by Racial Origin (Single -Agent Avelumab) - Safety Analysis Set (EMR100070-001, EMR100070-003 [Part A], B9991001, and Pooled Safety Set)

Characteristic	Statistics	EMR100070-001 Avelumab (N=1,650)	EMR100070-003 Avelumab (N=88)	B9991001 Avelumab (N=344)	Total Avelumab (N=2,082)
Number of subjects treated, n (%) [1]	Black or African American	87 (5.3)	0 (0.0)	2 (0.6)	89 (4.3)
	American Indian or Alaska Native	5 (0.3)	0 (0.0)	0 (0.0)	5 (0.2)
	Asian	151 (9.2)	3 (3.4)	74 (21.5)	228 (11.0)
	Native Hawaiian or Other Pacific Islander	4 (0.2)	0 (0.0)	0 (0.0)	4 (0.2)
	White	1,275 (77.3)	81 (92.0)	229 (66.6)	1,585 (76.1)
	Other	128 (7.8)	1 (1.1)	39 (11.3)	168 (8.1)
	Missing	0 (0.0)	3 (3.4)	0 (0.0)	3 (0.1)
Person-time exposure per 100 years [2]	Black or African American	0.30	ND	0.00	0.30
	American Indian or Alaska Native	0.01	ND	ND	0.01
	Asian	0.45	0.02	0.60	1.08
	Native Hawaiian or Other Pacific Islander	0.03	ND	ND	0.03
	White	4.95	0.42	1.66	7.02
	Other	0.44	0.00	0.29	0.73
	Missing	ND	0.02	ND	0.02

Source: RMP data output Table 12.12.2. Cut-off dates: 09 Jun 2016 for EMR100070-001 and EMR100070-003 (Part A); 21 Oct 2019 for B9991001.

ND=not done (0 patients in the category).

1 The denominator to calculate percentages is N.

2 Person exposure-100 years = Sum of duration of exposure (in days) to avelumab for all patients / (100*365.25).

Avelumab in Combination with Axitinib in RCC

Clinical trial exposure data for subjects with RCC (N=488) who were administered at least 1 dose (partial or complete) of avelumab 10 mg/kg Q2W in trials studying avelumab in combination with axitinib 5 mg BID (B9991002 (N=54) as of 03 Apr 2018 and B9991003 (N=434) as of 20 Jun 2018) are presented in Table 14. The clinical trial exposure data are presented separately and pooled for clinical trials B9991002 and B991003 by time, age and gender, and racial origin.

Table 14 summarizes the duration of exposure to avelumab in patients who received at least 1 dose of avelumab in trials of avelumab in combination with axitinib.

Table 14 Summary of Drug Exposure (Avelumab Administered in Trials of Avelumab in Combination With Axitinib) - RCC (B9991002, B9991003)

	B9991002 + B9991003 Avelumab + Axitinib (N=489)	B9991002 Avelumab + Axitinib (N=55)	B9991003 Avelumab + Axitinib (N=434)
Duration of treatment (weeks)[1]			
N	488	54	434
Mean (SD)	41.9 (27.03)	55.4 (40.55)	40.2 (24.39)
Q1	22.0	14.0	23.0
Median	37.9	45.1	37.2
Q3	58.0	95.7	56.0
Range	(2.0, 126.0)	(2.0, 126.0)	(2.0, 110.0)
Person exposure-100 yrs[2]	3.92	0.57	3.35

Source: Supplemental Biologics License Application RCC Table 14.4.1.1.1. Cut-off dates: 20 Jun 2018 for B9991003; 03 Apr 2018 for B9991002.

N=the number of subjects in the safety analysis set within each treatment group, n=the number of subjects who have received at least 1 dose of avelumab, Q1=quartile 1, Q3=quartile 3, RCC=renal cell carcinoma, SD=standard deviation

[1] Duration of avelumab treatment is defined as Duration (weeks) = (last dose date of avelumab - first dose date of avelumab + 14) / 7.

[2] Person exposure-100 years = Sum of duration of exposure (in days) to avelumab for all patients / (100*365.25).

Table 15 presents the duration of exposure to avelumab in patients treated with avelumab in combination with axitinib over time.

Table 15 Duration of Exposure (Avelumab Administered in Trials of Avelumab in Combination With Axitinib) - RCC (B9991002, B9991003)

	B9991002 + B9991003 Avelumab + Axitinib (N=488)	B9991002 Avelumab + Axitinib (N=54)	B9991003 Avelumab + Axitinib (N=434)
Person-time exposure per 100 years[1]	3.92	0.57	3.35
Duration of treatment, n (%)[2]			
> 0 Months	488 (100.0)	54 (100.0)	434 (100.0)
> 1 Months	459 (94.1)	51 (94.4)	408 (94.0)
> 2 Months	429 (87.9)	46 (85.2)	383 (88.2)
> 3 Months	404 (82.8)	42 (77.8)	362 (83.4)
> 6 Months	341 (69.9)	36 (66.7)	305 (70.3)
> 9 Months	237 (48.6)	30 (55.6)	207 (47.7)
> 12 Months	152 (31.1)	25 (46.3)	127 (29.3)
> 18 Months	63 (12.9)	22 (40.7)	41 (9.4)
> 24 Months	8 (1.6)	7 (13.0)	1 (0.2)

Source: Supplemental Biologics License Application RCC Table 14.4.1.1.11. Cut-off dates: 20 Jun 2018 for B9991003; 03 Apr 2018 for B9991002.

N=the number of subjects in the safety analysis set within each treatment group, n=the number of subjects who have received at least 1 dose of avelumab, RCC=renal cell carcinoma.

[1] Person exposure-100 years = Sum of duration of exposure (in days) to avelumab for all patients / (100*365.25).

[2] The denominator to calculate percentages is N.

Table 16 presents the extent of exposure to avelumab in patients treated with avelumab in combination with axitinib by age group and gender.

Table 16 Extent of Exposure by Age Group (Years) and Gender (Avelumab Administered in Trials of Avelumab in Combination With Axitinib) - RCC (B9991002, B9991003)

	B9991002 + B9991003 Avelumab + Axitinib (N=488)	B9991002 Avelumab + Axitinib (N=54)	B9991003 Avelumab + Axitinib (N=434)
Number of subjects treated, n (%)[1]			
Male	350 (71.7)	41 (75.9)	309 (71.2)
Female	138 (28.3)	13 (24.1)	125 (28.8)
Age			
Age < 65	305 (62.5)	37 (68.5)	268 (61.8)
Age 65-<75	147 (30.1)	14 (25.9)	133 (30.6)
Age 75-< 85	36 (7.4)	3 (5.6)	33 (7.6)
Age ≥ 85	0 (0.0)	0 (0.0)	0 (0.0)
Gender			-
Male: Age < 65	226 (46.3)	30 (55.6)	196 (45.2)
Male: Age 65-< 75	97 (19.9)	9 (16.7)	88 (20.3)
Male: Age 75-< 85	27 (5.5)	2 (3.7)	25 (5.8)
Male: Age ≥ 85	0 (0.0)	0 (0.0)	0 (0.0)
Female: Age < 65	79 (16.2)	7 (13.0)	72 (16.6)
Female: Age 65-<75	50 (10.2)	5 (9.3)	45 (10.4)
Female: Age 75-< 85	9 (1.8)	1 (1.9)	8 (1.8)
Female: Age ≥ 85	0 (0.0)	0 (0.0)	0 (0.0)
Exposure			
Person exposure-100 years[2]			
Male	2.86	0.43	2.43
Female	1.06	0.14	0.92
Age			
Age < 65	2.56	0.42	2.14
Age 65-<75	1.11	0.13	0.99
Age 75-< 85	0.24	0.02	0.22
Age ≥ 85	ND	ND	ND
Gender			
Male: Age < 65	1.91	0.34	1.57
Male: Age 65-< 75	0.75	0.07	0.68
Male: Age 75-< 85	0.20	0.02	0.18
Male: Age ≥ 85	ND	ND	ND
Female: Age < 65	0.65	0.08	0.57

	B9991002 + B9991003 Avelumab + Axitinib (N=488)	B9991002 Avelumab + Axitinib (N=54)	B9991003 Avelumab + Axitinib (N=434)
Female: Age 65-< 75	0.36	0.06	0.30
Female: Age 75-< 85	0.04	<0.01	0.04
Female: Age ≥ 85	ND	ND	ND

Source: Supplemental Biologics License Application RCC Table 14.4.1.1.12. Cut-off dates: 20 Jun 2018 for B9991003; 03 Apr 2018 for B9991002.

N= the number of subjects in the safety analysis set within each treatment group, n= the number of subjects who have received at least 1 dose of avelumab, ND= not done (0 patients in the category), RCC=renal cell carcinoma.

[1] The denominator to calculate percentages is N.

[2] Person exposure-100 years = Sum of duration of exposure (in days) to avelumab for all patients / (100*365.25).

Table 17 summarizes the extent of exposure to avelumab in patients treated with avelumab in combination with axitinib by racial origin.

Table 17 Extent of Exposure by Racial Origin (Avelumab Administered in Trials of Avelumab in Combination With Axitinib) - RCC (B9991002, B9991003)

	B9991002 + B9991003 Avelumab + Axitinib (N=488)	B9991002 Avelumab + Axitinib (N=54)	B9991003 Avelumab + Axitinib (N=434)
Number of subjects treated, n (%)[1]			
Black or African American	13 (2.7)	3 (5.6)	10 (2.3)
American Indian or Alaska Native	4 (0.8)	0 (0.0)	4 (0.9)
Asian	74 (15.2)	6 (11.1)	68 (15.7)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	370 (75.8)	43 (79.6)	327 (75.3)
Other	10 (2.0)	1 (1.9)	9 (2.1)
Missing	17 (3.5)	1 (1.9)	16 (3.7)
Exposure			
Person exposure-100 years[2]			
Black or African American	0.08	0.02	0.06
American Indian or Alaska Native	0.02	ND	0.02
Asian	0.69	0.10	0.59
Native Hawaiian or Other Pacific Islander	ND	ND	ND
White	2.98	0.45	2.52
Other	0.06	<0.01	0.06
Missing	0.09	<0.01	0.09

Source: Supplemental Biologics License Application RCC Table 14.4.1.1.13. Cut-off dates: 20 Jun 2018 for B9991003; 03 Apr 2018 for B9991002.

N=the number of subjects in the safety analysis set within each treatment group, n=the number of subjects who have received at least 1 dose of avelumab; ND= not done (0 patients in the category), RCC=renal cell carcinoma.

[1] The denominator to calculate percentages is N.

[2] Person exposure-100 years = Sum of duration of exposure (in days) to avelumab for all patients / (100*365.25).

Part II: Module SIV: Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Concurrent treatment with a non-permitted drug (immunosuppressive drugs, vaccine therapies for the prevention of infectious disease, growth factors, bisphosphonate treatment)

Reason for exclusion: Avoid factors that may confound understanding of the efficacy and safety profile of avelumab in a clinical trial.

Is it considered to be included as missing information? No

Rationale: In clinical practice patients treated with avelumab may be treated with concomitant therapies. Avelumab is primarily metabolized through catabolic pathways and therefore it is not expected that avelumab will have pharmacokinetic drug-drug interactions (DDIs) with other medicinal products. There are no contraindications or warnings concerning concomitant use with other medicinal products as there are no known safety concerns for use of avelumab in patients co-administered other medicines, although patients administered vaccines may be at increased risk of immune-mediated events (see below). There are extensive warnings and guidance in the avelumab SmPC concerning the risk of immune-mediated adverse reactions and the treatment to be administered based on the severity of reactions should they occur.

Prior therapy with any antibody/drug targeting T-cell coregulatory proteins (immune checkpoint inhibitors) such as anti-PD-1, anti-PD-L1, or anticytotoxic T lymphocyte antigen-4 antibody

Reason for exclusion: Avoid factors that may confound understanding of the efficacy and safety profile of avelumab in a clinical trial.

Is it considered to be included as missing information? No

Rationale: In clinical practice patients treated with avelumab may have previously received checkpoint inhibitors either in clinical trials or in clinical practice. Patients administered immune checkpoint inhibitors may experience immune-mediated adverse reactions. There are extensive warnings and guidance in the avelumab SmPC concerning the risk of immune-mediated adverse reactions and the treatment to be administered based on the severity of reactions should they occur.

Concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy, immune therapy, or cytokine therapy)

Reason for exclusion: Avoid factors that may confound understanding of the efficacy and safety profile of avelumab in a clinical trial.

Is it considered to be included as missing information? No

Rationale: In clinical practice patients treated with avelumab may also be treated with concurrent anticancer therapy. There are no known safety concerns for use of avelumab in this population. Unlike other anticancer therapies avelumab, as an IgG1 monoclonal antibody directed against PD-L1, blocks the interaction between PD-L1 and the PD-1 and B7.1 receptor. Avelumab is primarily metabolized through catabolic pathways and therefore it is not expected that avelumab will have pharmacokinetic DDIs with other medicinal products.

Major surgery for any reason within 4 weeks

Reason for exclusion: Avoid factors that may confound understanding of the efficacy and safety profile of avelumab in a clinical trial.

Is it considered to be included as missing information? No

Rationale: Patients who recently have undergone major surgery could benefit from avelumab therapy. There are no known safety concerns for use of avelumab in this population. There are extensive warnings concerning the risks of avelumab in the SmPC that also apply to this population.

Concurrent systemic therapy with steroids or other immunosuppressive agents, or use of any investigational drug within 28 days before the start of trial treatment

Reason for exclusion: Avoid factors that may confound understanding of the efficacy and safety profile of avelumab in a clinical trial.

Is it considered to be included as missing information? No

Rationale: There are no contraindications or warnings concerning concomitant use with other medicinal products. Avelumab is primarily metabolized through catabolic pathways, therefore, it is not expected that avelumab will have pharmacokinetic DDIs with other medicinal products. Safety and efficacy in immune compromised patients is recognized as an area of missing information and is being further investigated in a non-interventional cohort registry study to assess characteristics and management of patients with MCC in Germany (Part III.2).

Subjects with active central nervous system metastases. Subjects with a history of treated CNS metastases who fully recovered from treatment, demonstrated no progression for at least 2 months, and did not require continued steroid therapy were eligible.

Reason for exclusion: The activity of avelumab in untreated CNS metastases has not been established.

Is it considered to be included as missing information? No

Rationale: The safety and efficacy of avelumab in patients with active CNS metastases have not been established. There are no known safety concerns in this population. The SmPC highlights that this population was excluded from clinical trials.

Previous malignant disease (other than disease under study) within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ. In B9991002 and B9991003, exceptions also included carcinoma in situ of the breast or low grade (Gleason 6 or below) prostate cancer with no plans for treatment.

Reason for exclusion: Avoid factors that may confound understanding of the efficacy of avelumab in a clinical trial.

Is it considered to be included as missing information? No

Rationale: The safety and efficacy of avelumab in patients with a history of other malignancies within the last 5 years have not been established. The SmPC highlights that this population was excluded from clinical trials. There are no known safety concerns in this population. The efficacy and safety of avelumab in other cancer indications is currently being investigated (Annex 6).

Prior organ transplantation, including allogeneic stem-cell transplantation

Reason for exclusion: The experience with immune checkpoint inhibitors in subjects with prior organ transplantation remains limited (Lipson 2016). Patients were excluded based on the theoretical concern of graft rejection.

Is it considered to be included as missing information? No

Rationale: The current evidence of safety in patients with a medical history of organ transplant is insufficient to conclude that the safety profile in this patient population differs from the safety profile in the general population. The SmPC highlights that this population was excluded from clinical trials. There is a warning concerning the risks of avelumab in the SmPC that also apply to this population.

Known history of testing positive for HIV or known AIDS or any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection

Reason for exclusion: The impact of immune checkpoint inhibitors on HIV or hepatitis B or hepatitis C remains unknown. Patients were excluded based on the fact that chronic infections are known to induce T-cell exhaustion and the theoretical concern that avelumab could cause an inflammatory reaction against those pathogens by reinvigorating the antipathogen immune response.

Is it considered to be included as missing information? Yes

Active or history of any autoimmune disease (except for subjects with vitiligo type 1 diabetes mellitus, psoriasis, hypothyroidism and hyperthyroidism) or immunodeficiencies that required treatment with systemic immunosuppressive drug

Reason for exclusion: Avoid factors that may confound understanding of the safety profile.

Is it considered to be included as missing information? No

Rationale:

The safety concern 'safety in patients with autoimmune disease' previously classified as missing information was removed from the list of safety concerns and added as a risk factor for immune-mediated adverse events (important identified risks). The rationale for this is that there is a strong biologic plausibility that pre-existing AID exacerbates the risk of immune-mediated adverse reactions (including flares of the pre-existing AID) regardless of the specific ICI product. The causal association between avelumab and immune-mediated adverse reactions is established and the underlying mechanisms, applicable to the class of ICIs, is well described, generally involving the activation of T-cells. Therefore, in the view of available data on immune-related adverse reactions in patients with pre-existing autoimmune disease from the literature, and in view of a plausible mechanism of action, a causal relationship between avelumab and an increased risk of immune-related adverse reaction in patients with pre-existing autoimmune disease is at least a reasonable possibility (Cai 2022, Cortellini 2019, Haanen 2023, Xie 2020, Tang 2022, Tison 2022).

Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE v 4.0]), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partly controlled asthma)

Reason for exclusion: Avoid factors that may confound understanding of the safety profile needed for subsequent drug development and use.

Is it considered to be included as missing information? No

Rationale: Patients who are known to be hypersensitive should not receive avelumab in clinical practice. As avelumab treatment is initiated and supervised by a physician experienced in the treatment of cancer it is likely that there would be treatment available should severe hypersensitivity occur in clinical practice.

Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v 4.0; however, sensory neuropathy Grade ≤ 2 is acceptable

Reason for exclusion: Avoid factors that may confound the understanding of the safety profile.

Is it considered to be included as missing information? No

Rationale: Persisting toxicity is not a reason for withholding avelumab should the patient require treatment. It is not anticipated that there will be many patients with persisting toxicity exposed to avelumab. There are extensive warnings concerning the risks of avelumab in the SmPC that also apply to this population.

Pregnancy

Reason for exclusion: Avoid potential harm to the unborn fetus.

Is it considered to be included as missing information? No

Rationale: Use during pregnancy is not expected to be substantial as avelumab may cause fetal harm when administered to a pregnant woman. Avelumab has the potential to be transmitted from the mother to the developing fetus and may increase the risk of developing immune-mediated disorders or altering the normal immune response.

In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of avelumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.

The SmPC recommends that women of childbearing potential should be advised to avoid becoming pregnant while receiving avelumab and should use effective contraception during treatment with avelumab and for at least 1 month after the last dose of avelumab. Embryofetal toxicity is an important potential risk, and the safety concern will be monitored in clinical use.

Lactation

Reason for exclusion: Avoid potential harm to the breast-fed neonate.

Is it considered to be included as missing information? No

Rationale: It is unknown whether avelumab is excreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded.

The SmPC recommends that women should be advised not to breast feed during treatment and for at least 1 month after the last dose due to the potential for serious adverse reactions in breast fed infants.

Known alcohol or drug abuse

Reason for exclusion: Avoid factors that may confound understanding of efficacy or safety profile.

Is it considered to be included as missing information? No

Rationale: The safety and efficacy of avelumab in patients with known alcohol or drug abuse have not been established. There are no known safety concerns for use of avelumab in this population. Use of avelumab in this population is not expected to be substantial.

Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident / stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious cardiac arrhythmia requiring medication

Reason for exclusion: Avoid factors that may confound understanding of efficacy or safety profile.

Is it considered to be included as missing information? No

Rationale: The safety and efficacy of avelumab in patients with clinically significant cardiovascular disease have not been established. There are no known safety concerns in this population and the risks of avelumab in this population are not expected to differ from patients without clinically significant cardiovascular disease.

All other significant diseases (for example, inflammatory bowel disease), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment

Reason for exclusion: Avoid factors that may confound understanding of efficacy or safety profile.

Is it considered to be included as missing information? No

Rationale: The safety and efficacy of avelumab in patients with other significant diseases have not been established. There are no known safety concerns in this population and the risks of avelumab in this population are not expected to differ from other patients without other significant diseases.

Non-oncology vaccine therapies for prevention of infectious disease (for example, seasonal flu vaccine, human papilloma virus vaccine) within 4 weeks of trial drug administration. Vaccination while on trial is also prohibited except for administration of inactivated vaccines (for example, inactivated seasonal influenza vaccine)

Reason for exclusion: Avoid factors that may confound understanding of efficacy or safety profile needed for subsequent drug development and use.

Is it considered to be included as missing information? No

Rationale: In clinical practice it is expected that some patients will receive non-oncology vaccine therapies for prevention of infectious disease, and it is possible that patients treated with avelumab may be at an increased risk for immune-mediated adverse reactions after receiving the seasonal influenza vaccination. There are extensive warnings and guidance in the avelumab SmPC concerning the risk of immune-mediated adverse reactions and the treatment to be administered based on the severity of reactions should they occur.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

Safety data are available for 2,082 subjects in the clinical program (as defined in the Pooled Safety Set) treated with avelumab as a single agent. This sample size allows the detection of very common, common and uncommon adverse reactions. In the Pooled Safety Set (N=2,082) 220 patients were treated for > 1 year, 103 patients > 1.5 years, 41 patients > 2 years, and 5 patients > 2.5 years in the clinical program (Table 11).

In the Pooled aRCC population (n=488) treated with avelumab in combination with axitinib, 152 subjects were treated for > 1 year, and 8 patients were treated for > 2 years (Table 15). Avelumab is not known to accumulate.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 18 Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	**Patients with hepatic impairment:** For participation in clinical trials EMR100070-001 and EMR100070-003, subjects were required to have an adequate hepatic function defined by a total bilirubin level ≤ 1.5 × ULN range and AST and ALT levels ≤ 2.5 × ULN. In the Pooled Safety Set, 116 of 2,082 subjects (5.6%) had impaired liver function (defined as AST or ALT > 1.5 × ULN); (refer to RMP data output Table 12.10.1). **Patients with renal impairment:** For participation in clinical trials EMR100070-001 and EMR100070-003, subjects were required to have adequate renal function defined by an estimated creatinine clearance > 50 mL/min according to the Cockcroft-Gault formula. In the Pooled Safety Set, a total of 578 of 2,082 subjects (27.8%) had an estimated creatinine clearance of < 60 mL/min/1.73 m^2; (refer to RMP data output Table 12.10.1). **Patients with cardiovascular impairment** Patients with clinically significant cardiovascular disease: cerebral vascular accident / stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious cardiac arrhythmia requiring medication were excluded from clinical trial participation (Section SIV.1). **Immunocompromised patients** The safety and efficacy of avelumab in immune compromised patients is limited in the clinical trials. The non-interventional cohort registry study to assess characteristics and management of patients with Merkel cell carcinoma in Germany (Study MS100070-0031) will provide further information concerning the efficacy and safety of avelumab in this population (Part III.2). **Patients with a disease severity different from inclusion criteria in clinical trials** Avelumab is being studied in subjects with advanced metastatic disease. The safety population has a heavy burden of disease with extensive visceral organ involvement and often multiple prior lines of therapy.
Population with relevant different ethnic origin	Avelumab is being studied in subjects with cancer worldwide from all racial origins. No major differences were observed when adverse events were analyzed by the subjects' racial origin. There are currently no data indicating that specific ethnic backgrounds may impact the clinical safety of avelumab.
Subpopulations carrying relevant genetic polymorphisms	No information is available regarding the effects of avelumab in sub-populations carrying known and relevant genetic polymorphisms.

Type of Special Population	Exposure
Other If applicable, other special population under-represented in clinical trials which are relevant for the targeted indication if the safety profile is expected to be different to the general population.	The populations excluded from clinical trial participation are presented in Section SIV.1. Sections 4.4 and 5.1 of the Summary of Product Characteristics inform HCPs which patients with certain conditions were excluded from clinical trials including patients with active or history of central nervous system metastasis; active or a history of autoimmune disease; a history of other malignancies within the last 5 years; organ transplant; conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C.

ALT=alanine aminotransferase, AST=aspartate aminotransferase, HCP=healthcare professional, RMP=Risk Management Plan, ULN=upper limit of normal

Part II: Module SV: Post-authorization Experience

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

Estimated post-authorization exposure data of avelumab/Bavencio were generated using the following model:

Unit volumes were based on ex-factory sales and were the basis for allocating usage by geography and by time period.

Average duration of treatment and dosing regimens for patients by indication were based on the pivotal trial data adjusted for real world experience.

Exposure by indication was based on secondary data sources of real-world use.

Calculations of 'treated patients' by region/indication were based on dividing sold unit volume by the average delivered dose per patient for that region/indication.

When estimating the cumulative patient exposure in the post-marketing setting, sales data until 31 Mar 2024 were used. Up to 31 Mar 2024, avelumab/Bavencio was commercially available as a single formulation (20 mg/mL solution for infusion, 10 mL vial).

The provision of post-authorization exposure data stratified by age group and gender is not possible due to privacy protection regulations.

SV.1.2 Exposure

Up to 31 Mar 2024, approximately CCI patients have been treated with avelumab/ Bavencio in the post-marketing setting.

Cumulative post-marketing exposure is summarized by indication and region in Table 19.

Table 19 Estimated Cumulative Patient Exposure From Post-marketing Experience With Avelumab/Bavencio by Indication and Region

Indication	Region							Total Patients	Contribution by Indication
	US	Canada	Europe	MEAR	Japan	APAC excluding Japan	LATAM		
MCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UC	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCC	[redacted]	[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (patients)	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**100%**

APAC=Asia Pacific, LATAM=Latin America, MCC=merkel cell carcinoma, MEAR=Middle East, Africa, Russia, RCC=renal cell carcinoma, UC=urothelial carcinoma, US=United Sates.

Estimates are based on cumulative sales data through 31 Mar 2024.

a Total patient for MCC includes CCI patients from a global MCC compassionate use program.

b For UC and RCC, the data from region Europe include CCI UC patients and CCI RCC patients from the Early Access to Medicines Scheme (EAMS) programs in the UK.

Part II: Module SVI: Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Based on the mode of action, the potential of avelumab for misuse for illegal purposes is regarded as low.

Potential for transmission of infectious agents

The potential for transmission of infectious agents is considered to be low (refer to Module SVII.1).

Part II: Module SVII: Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Table 20 presents the summary of safety concerns for the initial marketing authorization application in MCC (EU RMP, Version 1.6 [Procedure number: EMEA/H/C/004338/0000]).

Table 20 Summary of Safety Concerns for the Initial Marketing Authorization Application in MCC

Summary of safety concerns	
Important identified risks	• Immune-related pneumonitis • Immune-related hepatitis • Immune-related colitis • Immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders) • Other immune-related events (myositis, myocarditis, Guillain-Barre Syndrome, uveitis) • Immune-related nephritis and renal dysfunction • Severe infusion-related reactions (Grade ≥ 3)
Important potential risks	• Other immune-related events (encephalitis, myasthenic syndrome, pancreatitis) • Severe cutaneous reactions • Immunogenicity • Embryofetal toxicity
Missing information	Safety in patients • With Autoimmune disease • With HIV, Hepatitis B or C infections • With Organ transplants • During lactation • Long-term treatment • Safety and efficacy in immune compromised patients

HIV=human immunodeficiency virus

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Based on cumulative review in the periodic benefit-risk evaluation report covering the reporting period of 23 Mar 2022 to 22 Mar 2023, the signal of sclerosing cholangitis was initially refuted. This signal was subsequently confirmed as an important identified risk based on follow-up information received for ICSR.

In response to the Australian Health Authority (Therapeutic Goods Administration [TGA]) request to update the PIs for immune checkpoint inhibitors (ICIs), including avelumab, to adequately communicate the risks of musculoskeletal rheumatic irAEs, arthritis (including immune-mediated arthritis), polymyalgia rheumatica and Sjogren's syndrome were confirmed as important identified risks after internal assessment of these topics.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Safety data for avelumab are presented for the trials EMR100070-003 (Part A; N=88), EMR100070-001 in various solid tumor indications (N=1,650), and B9991001 for locally advanced or metastatic UC (N=344) in a pooled fashion referenced as the Pooled Safety Set (N=2,082).

The safety data for the Pooled Safety Set (N=2,082) are presented with data cut-off dates of 09 Jun 2016 for EMR100070-001 and EMR100070-003 (Part A), and 21 Oct 2019 for B9991001. Toxicity of AEs was graded per NCI-CTCAE v4.0 for EMR100070-003 (Part A) and EMR100070-001 and per NCI-CTCAE v4.03 for B9991001.

Safety data from subjects with RCC who were treated with avelumab 10 mg/kg Q2W in combination with axitinib 5 mg BID in the clinical trials B9991002 and B9991003 are included to characterize the safety profile of avelumab in combination with axitinib in this population. The safety data for subjects with RCC are pooled and referenced as the Pooled aRCC Population (N=489) with a data cut-off of 03 Apr 2018 for Study B9991002 (N=55) and a data cut-off 20 Jun 2018 for Study B9991003 (N=434). Of note, the Pooled aRCC Population includes 1 subject in Study B9991002 who received only axitinib treatment.

Toxicity of AEs was graded per NCI -CTCAE v4.03 for the RCC studies B9991002 and B9991003.

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Immune-mediated adverse reactions	
Potential mechanisms:	Avelumab binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on T cells, which can lead to decreases in self-tolerance and immune-mediated effects.
Evidence source(s) and strength of evidence:	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was evaluated in the clinical trials B9991002 and B9991003 in patients with aRCC (489 patients). Evaluation of post-marketing sources and completed randomized clinical studies EMR100070-004, EMR10007-005, EMR10007-007, EMR10007-008, B9991001, B9991003, B9991009, B9991010, and B9991016 for other immune-mediated adverse reactions of sclerosing cholangitis, polymyalgia rheumatica, and Sjogren's syndrome.
Characterization of the risk:	**<u>Pneumonitis</u>**

Important Identified Risk: Immune-mediated adverse reactions	
	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set Across clinical studies, 1.3% (28/2,082) of patients developed immune-mediated pneumonitis, of these patients there was 1 (less than 0.1%) patient with a fatal outcome, 1 (less than 0.1%) patient with Grade 4, 6 (0.3%) patients with Grade 3, 16 (0.8%) patients with Grade 2 and 4 (0.2%) patients with Grade 1 immune-mediated pneumonitis. Serious AEs were reported in 12 (0.6%) patients. The median time to onset of immune-mediated pneumonitis was 10.9 weeks (range: 0.4 to 60.1 weeks). The median duration was 57 days (range: 4 to 148 days). Avelumab was discontinued in 0.4% (9/2,082) of patients due to immune-mediated pneumonitis. All 28 patients with immune-mediated pneumonitis were treated with corticosteroids and 21 (75%) of the 28 patients were treated with high-dose corticosteroids for a median of 9 days (range: 1 day to 69 days). Immune-mediated pneumonitis resolved in 18 (64.3%) of the 28 patients at the time of data cut-off. Avelumab in Combination with Axitinib in RCC Immune-mediated pneumonitis was observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials, 0.6% (3/489) of patients developed immune-mediated pneumonitis, including 1 (0.2%) patient with a Grade 2 event and 2 (0.4%) patients with Grade 1 events. There were no Grade 3 or 4 events or events with a fatal outcome. No serious events were reported. The median time to onset of immune-mediated pneumonitis was 15.9 weeks (range: 11.9 to 37.3 weeks). The median duration was 78 days (range: 23 to 240 days). All 3 patients were treated with high-dose corticosteroids for a median of 100 days (range: 21 to 678 days). Immune-mediated pneumonitis did not lead to discontinuation of avelumab in any patient. Immune-mediated pneumonitis resolved in 2 patients and was ongoing in 1 patient at the time of data cut -off.
	Hepatitis Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 – Pooled Safety Set Across clinical studies, 1.0% (21/2,082) of patients developed immune-mediated hepatitis. Of these patients, there were 2 (0.1%) patients with a fatal outcome,no patients with Grade 4, 16 (0.8%) patients with Grade 3, 2 patients (0.1%) with Grade 2 and 1 (less than 0.1%) patient with Grade 1 immune-mediated hepatitis. Serious AEs were reported in 9 (0.4%) patients. The median time to onset of immune-mediated hepatitis was 14.3 weeks (range: 1.3 to 64.1 weeks). The median duration was 77 days (range: 1 day to more than 224 days). Avelumab was discontinued in 0.6% (13/2,082) of patients due to immune-mediated hepatitis. All 21 patients with immune-mediated hepatitis were treated with corticosteroids and 20 (95.2%) of the 21 patients received high-dose corticosteroids for a median of 17 days (range: 1 to 126 days). Immune-mediated hepatitis resolved in 12 (57.1%) of the 21 patients at the time of data cut-off. Avelumab in Combination with Axitinib in RCC Immune-mediated hepatitis was observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials, 6.3% (31/489) of patients developed immune-mediated hepatitis, including 3 (0.6%) patients with Grade 4 events, 18 (3.7%) patients with Grade 3 events, , 8 (1.6%) patients with Grade 2 events and 2 (0.4%)

Important Identified Risk: Immune-mediated adverse reactions	
	patients with Grade 1 immune-mediated hepatitis. There were no events with a fatal outcome. Serious AEs were reported in 10 (2.0%) patients. The median time to onset of immune-mediated hepatitis was 10.1 weeks (range: 2.1 to 63.1 weeks). The median duration was 15 days (range: 2 to 270 days). Avelumab was discontinued in 4.7% (23/489) of patients due to immune-mediated hepatitis. All 31 patients with immune-mediated hepatitis were treated including 30 (96.8%) patients treated with corticosteroids and 1 patient treated with a nonsteroidal immunosuppressant. 28 (90.3%) of the 31 patients treated received high -dose corticosteroids for a median of 16.5 days (range: 1 day to 309 days). Immune-mediated hepatitis resolved in 27 (87.1%) of the 31 patients at the time of data cut-off.
	Colitis <u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), B9991001 – Pooled Safety Set</u> Across clinical studies, 1.5% (31/2,082) of patients developed immune-mediated colitis. Of these patients, there were 10 (0.5%) patients with Grade 3, 15 (0.7%) patients with Grade 2 and 6 (0.3%) patients with Grade 1 immune-mediated colitis. There were no Grade 4 events or events with a fatal outcome. Serious AEs were reported in 11 (0.5%) patients. The median time to onset of immune-mediated colitis was 8.9 weeks (range: 0.3 to 49.9 weeks). The median duration was 41 days (range: 1 day to more than 425 days). Avelumab was discontinued in 0.5% (11/2,082) of patients due to immune-mediated colitis. All 31 patients with immune-mediated colitis were treated with corticosteroids and 19 (61.3%) of the 31 patients received high-dose corticosteroids for a median of 19 days (range: 1 day to 69 days). Immune-mediated colitis resolved in 22 (71%) of 31 patients at the time of data cut-off. <u>Avelumab in Combination with Axitinib in RCC</u> Immune-mediated colitis was observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials, 2.7% (13/489) of patients developed immune-mediated colitis, including 9 (1.8%) patients with Grade 3 events and 4 (0.8%) patients with Grade 2 events. There were no Grade 1, Grade 4 events or events with a fatal outcome. Serious AEs were reported in 5 (1.0%) patients. The median time to onset of immune-mediated colitis was 22.3 weeks (range: 2.3 to 61.0 weeks). The median duration was 11.5 days (range: 1 to 274 + days). Avelumab was discontinued in 0.4% (2/489) of patients due to immune-mediated colitis. All 13 patients with immune-mediated colitis were treated with corticosteroids and 12 of the 13 patients received high-dose corticosteroids for a median of 16 days (range: 5 to 141 days). Immune-mediated colitis resolved in 10 patients and was ongoing in 3 patients at the time of data cut-off.
	Pancreatitis <u>Avelumab Single-Agent. EMR100070-001, EMR100070-003 (Part A), and B9991001 – Pooled Safety Set</u> Across clinical studies, 0.1% (2/2,082) of patients developed immune-mediated pancreatitis. There was 1 (less than 0.1%) patient with a Grade 3 event and 1 (less than 0.1%) patient with a Grade 2 event. Serious AEs were reported in 1 (less than 0.1%) patient. The median time to onset of immune-mediated pancreatitis was 6.6 weeks (range: 6.0 to 7.1 weeks). The median duration was not estimable (range: 7 to more than 78 days). Avelumab was discontinued in both patients (0.1%) due to immune-mediated pancreatitis. Both patients with immune-mediated pancreatitis were treated with

Important Identified Risk: Immune-mediated adverse reactions	
	corticosteroids and 1 (50%) of the 2 patients was treated with high dose corticosteroids for 2 days. Immune-mediated pancreatitis resolved in 1 (50%) of the 2 patients at the time of data cut-off. Avelumab in Combination with Axitinib in RCC Immune-mediated pancreatitis was observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials, 0.6% (3/489) of patients experienced immune-mediated pancreatitis, including 2 (0.4%) patients who experienced a fatal event (including 1 fatal event occurring post data cut-off) and 1 (0.2%) patient with a Grade 4 event. There were no Grade 1, 2 or 3 events reported. Serious AEs were reported in 3 (0.6%) patients. The median time to onset of immune-mediated pancreatitis was 14 weeks (range: 11 to 16.9 weeks). Avelumab was discontinued in all patients due to immune-mediated pancreatitis and all patients were treated with high-dose corticosteroids. Immune-mediated pancreatitis resolved in 1 patient and as noted, was fatal in 1 patient at the time of data cut -off and in another patient after the data cut-off.
	Myocarditis Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 – Pooled Safety Set Within the Pooled Safety Set, no cases of immune-mediated myocarditis were observed. In patients treated with avelumab as monotherapy, immune-mediated myocarditis occurred in less than 1% (5/4,000) of patients across clinical trials in multiple tumor types. 1 event of immune-mediated myocarditis was reported as autoimmune disorder in the 20 mg/kg cohort of the dose-escalation phase of Study EMR100070-001. Avelumab in Combination with Axitinib in RCC Immune-mediated myocarditis was observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials, 3 (0.6%) patients experienced immune-mediated myocarditis including 1 (0.2%) patient with a Grade 3 event and 2 (0.4%) patients with fatal events. Serious AEs were reported in 3 (0.6%) patients. The median time to onset of immune-mediated myocarditis was 4.1 weeks (range: 3.9 to 4.1 weeks). The median duration was not estimable (range: 1 + to 169 + days). Avelumab was discontinued in all 3 patients due to immune-mediated myocarditis. 2 (66.7%) of the 3 patients with immune-mediated myocarditis were treated with high-dose corticosteroids for a median of 299 days (range: 13 to 585 days). 1 patient did not receive any corticosteroids due to the fulminant course of the adverse reaction. The Grade 3 event of immune-mediated myocarditis was not resolved at the time of data cut-off.
	Endocrinopathies – Thyroid disorders Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 – Pooled Safety Set Across clinical studies, 6.7% (140/2,082) of patients developed immune-mediated thyroid disorders, of which 127 (6.1%) patients with hypothyroidism, 23 (1.1%) with hyperthyroidism, and 7 (0.3%) with thyroiditis. Of these patients there were 4 (0.2%) patients with Grade 3, 104 (5.0%) patients with Grade 2 and 32 (1.5%) patients with Grade 1 immune-mediated thyroid disorders. There were no Grade 4 events or events with a fatal outcome. Serious AEs were reported in 8 (0.4%) patients. The median time to onset of immune-mediated thyroid disorders was

Important Identified Risk: Immune-mediated adverse reactions	
	12.1 weeks (range: 2.0 to 55.7 weeks). The median duration was not estimable (range: 3 to more than 839 days). Avelumab was discontinued in 0.2% (4/2,082) patients due to immune-mediated thyroid disorders. A total of 15 (10.7%) patients with immune-mediated thyroid disorders were treated with corticosteroids and 7 (5.0%) of the 140 patients were treated with high-dose corticosteroids for a median of 11 days (range: 1 to 67 days). All 127 (100%) patients with hypothyroidism were treated with thyroid preparations and 10 (43.5%) of the 23 patients with hyperthyroidism were treated with antithyroid preparations. Thyroid disorders resolved in 14 (10%) of the 140 patients at the time of data cut-off. <u>Avelumab in Combination with Axitinib in RCC</u> Immune-mediated thyroid disorders were observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials 24.7% (121/489) patients developed immune-mediated thyroid disorders, of which 111 (22.7%) patients with hypothyroidism, 17 (3.5%) with hyperthyroidism, and 7 (1.4%) with thyroiditis. Of these patients, there were 2 (0.4%) patients with Grade 3 events, 95 (19.4%) patients with Grade 2 events and 24 (4.9%) patients with Grade 1 events. There were no Grade 4 events or events with a fatal outcome. Serious AEs were reported in 2 (0.4%) patients. The median time to onset of immune-mediated thyroid disorders was 12.3 weeks (range: 3.6 to 84.1 weeks). The median duration was not estimable (range: 8 to 726+ days). Avelumab was discontinued in 0.2% (1/489) of patients due to an immune-mediated thyroid disorder. 120 (99.2%) patients with immune-mediated thyroid disorders were treated with thyroid preparations and 5 (4.1%) were treated with antithyroid preparations. Immune-mediated thyroid disorders resolved in 14 patients and were ongoing in 107 patients at the time of data cut-off.
	Endocrinopathies – Adrenal insufficiency <u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 – Pooled Safety Set</u> Across clinical studies, 0.5% (11/2,082) of patients developed immune-mediated adrenal insufficiency. Of these patients, there was 1 (less than 0.1%) patient with Grade 3, 8 (0.4%) patients with Grade 2 and 2 (0.1%) patients with Grade 1 immune-mediated adrenal insufficiency. There were no Grade 4 events or events with a fatal outcome. Serious AEs were reported in 3 (0.1%) patients. The median time to onset of immune-mediated adrenal insufficiency was 14.1 weeks (range: 0.1 to 32.9 weeks). The median duration was not estimable (range: 2 to more than 318 days). Avelumab was discontinued in 0.1% (2/2,082) of patients due to immune-mediated adrenal insufficiency. All 11 patients with immune-mediated adrenal insufficiency were treated with corticosteroids, 5 (45.5%) of the 11 patients received high-dose systemic corticosteroids for a median of 2 days (range: 1 day to 24 days). Immune-mediated adrenal insufficiency resolved in 3 (27.3%) of the 11 patients at the time of data cut-off. <u>Avelumab in Combination with Axitinib in RCC</u> Immune-mediated adrenal insufficiency was observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials, 1.8% (9/489) of patients developed immune-mediated adrenal insufficiency, including 2 (0.4%) patients with Grade 3 events and 7 (1.4%) patients with Grade 2 events. There were no Grade 1, and Grade 4

Important Identified Risk: Immune-mediated adverse reactions	
	events or events with a fatal outcome. Serious AEs were reported in 4 (0.8%) patients. The median time to onset of adrenal insufficiency was 24.1 weeks (range: 3.6 to 38 weeks). The median duration was 84 days (range: 3 to 471 + days). Immune-mediated adrenal insufficiency did not lead to discontinuation of avelumab in any patient. 8 (88.9%) patients with immune-mediated adrenal insufficiency were treated with corticosteroids and 2 of the 8 patients received high-dose corticosteroids for a median of 8 days (range: 5 to 11 days). Adrenal insufficiency was resolved in 4 patients and ongoing in 5 patients at the time of data cut-off.
	Endocrinopathies – Type 1 diabetes mellitus <u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 – Pooled Safety Set</u> Across clinical studies, type 1 diabetes mellitus without an alternative etiology was observed in 0.2% (5/2,082) of patients, of these patients all 5 (0.2%) patients had a Grade 3 events. Serious AEs were reported in 2 (0.1%) patients. The median time to onset of type 1 diabetes mellitus was 14.1 weeks (range: 0.1 to 81.1 weeks). The median duration was not estimable (range: 14 to more than 146 days). Avelumab was discontinued in 0.1% (2/2,082) of patients due to immune-mediated diabetes mellitus. All 5 patients with type 1 diabetes mellitus were treated with insulin. Type 1 diabetes mellitus resolved in 2 (40%) of the 5 patients at the time of data cut -off. <u>Avelumab in Combination with Axitinib in RCC</u> Type 1 diabetes mellitus without an alternative etiology was observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials, 1.0% (5/489) of patients developed type 1 diabetes mellitus without an alternative etiology, including 1 (0.2%) patient with a Grade 3 event, 3 (0.6%) patients with Grade 2 events and 1 (0.2%) patient with Grade 1 event. There were no Grade 4 events or events with a fatal outcome. Serious AEs were reported in 1 (0.2%) patient. The median time to onset of type 1 diabetes mellitus was 8.1 weeks (range: 4.6 to 31.9 weeks). Avelumab was discontinued in 0.2% (1/489) of patients due to type 1 diabetes mellitus. All 5 patients with type 1 diabetes mellitus were treated with insulin. Type 1 diabetes mellitus did not resolve in any of the patients at the time of data cut-off.
	Endocrinopathies – Pituitary disorders <u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 – Pooled Safety Set</u> A single event (Grade 2) of immune-mediated pituitary disorder was observed in a patient treated with avelumab in the clinical trials. The event occurred 70.3 weeks after the start of avelumab and avelumab was not discontinued due to the event. The patient was not treated with corticosteroids and at the time of data cut-off, the event was not resolved. No serious AEs were reported. <u>Avelumab in Combination with Axitinib in RCC</u> In the clinical trials B9991002 and B9991003, 1 (0.2%) patient developed Grade 2 hypophysitis. The event occurred 24.1 weeks after the start of avelumab and avelumab was not discontinued due to the event. The patient was treated with corticosteroids and, at the time of data cut-off, the event was not resolved. No serious AEs were reported.

Important Identified Risk: Immune-mediated adverse reactions	
	Nephritis and renal dysfunction Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 – Pooled Safety Set Across clinical studies, 0.3% (7/2,082) of patients developed immune-mediated nephritis, of these patients there was 1 (less than 0.1%) patient with Grade 3, 4 (0.2%) patients with Grade 2 and 2 (0.1%) patients with Grade 1 immune-mediated nephritis. There were no Grade 4 events or events with a fatal outcome. Serious AEs were reported in 4 (0.2%) patients. The median time to onset of immune-mediated nephritis was 10.4 weeks (range: 7.1 to 95.1 weeks). The median duration was 185 days (range: 9 to 185 days). Avelumab was discontinued in 0.2% (4/2,082) of patients due to immune-mediated nephritis. All 7 patients with immune-mediated nephritis were treated with corticosteroids and 6 (85.7%) of the 7 patients were treated with high-dose corticosteroids for a median of 17.5 days (range: 6 to 85 days). Immune-mediated nephritis resolved in 4 (57.1%) of the 7 patients at the time of data cut-off. Avelumab in Combination with Axitinib in RCC Immune-mediated nephritis was observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials, 2 (0.4%) patients developed immune-mediated nephritis. Both events were Grade 3. Serious AEs were reported in 2 (0.4%) patients. The median time to onset of immune-mediated nephritis was 5.4 weeks (range: 2.9 to 7.9 weeks). The median duration was 9 days (range: 4+ to 9 days). Avelumab was not discontinued due to events of immune-mediated nephritis. Both patients with immune-mediated nephritis were treated with high-dose corticosteroids for a median of 8 days (range: 3 to 13 days). Immune-mediated nephritis resolved in 1 patient and was ongoing in 1 patient at the time of data cut-off. Based on reported cases and the fact that immune-mediated nephritis and renal dysfunction has been described as an ADR for other drugs in the class, immune-mediated nephritis and renal dysfunction has been assessed as an important identified risk for avelumab.
Other immune mediated reactions	
	Source for other immune-mediated adverse reactions including myositis, Guillain-Barré syndrome, uveitis, and myasthenia gravis/myasthenic syndrome: pooled safety set, clinical trials of avelumab in combination with axitinib, and safety set across clinical trials in multiple tumour types. Across clinical trials in pooled safety set, immune-mediated myositis was observed in 0.5% (11/2,082) of patients (3 (0.1%) Grade 2, 4 (0.2%) Grade 3, and 3 (0.1%) Grade 4); Guillain-Barré syndrome was observed in 0.1% (2/2,082) of patients (Grade 3); immune-mediated uveitis was observed in 0.1% (2/2,082) patients (Grade 2) and no cases of immune-mediated myasthenia gravis/myasthenic syndrome were observed. Immune-mediated myasthenia gravis/myasthenic syndrome was observed in less than 1% (4/4,000) of patients across clinical trials in multiple tumour types and in 0.2% (1/489) of patients (fatal) treated with avelumab in combination with axitinib in RCC. Immune-mediated myositis, Guillain-Barrè syndrome and uveitis were not observed in studies of avelumab in combination with axitinib in RCC.

Important Identified Risk: Immune-mediated adverse reactions	
	Source for other immune-mediated adverse reactions including sclerosing cholangitis, polymyalgia rheumatica, Sjogren's syndrome and arthritis: clinical trial data, post-marketing experience and literature. Immune-mediated sclerosing cholangitis and polymyalgia rheumatica were not observed in completed randomized clinical trials and their frequency in the post marketing setting is 'Not known'. 3 AEs of immune-mediated Sjogren's syndrome were observed in completed randomized clinical trials with a frequency of 'Rare', no event was observed in studies of avelumab in combination with axitinib in RCC and frequency in this indication in the post marketing setting is 'Not known'. Immune-mediated arthritis was observed in clinical trials in the pooled safety set with frequency of 'Rare' and in studies of avelumab in combination with axitinib in RCC with frequency of 'Uncommon'.
Risk factors and risk groups:	No analysis of specific risk factors associated with immune-mediated adverse reactions has been performed. In patients with pre-existing autoimmune disease, data from observational studies suggest that the risk of immune-related adverse reactions following immune-checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.
Preventability:	The occurrence of immune-mediated adverse reactions cannot be entirely prevented. However, by early diagnosis and following recommended treatment guidelines serious complications may be prevented. Thus, patients should be monitored for signs and symptoms of suspected immune-mediated adverse reactions, ensuring adequate evaluation to confirm etiology or to rule out other causes. • Suspected pneumonitis should be confirmed with radiographic imaging. • Patients should be monitored for changes in liver function and symptoms of hepatitis. • For pancreatitis obtain gastroenterology consultation and laboratory investigations (including imaging) in symptomatic patients to ensure the initiation of appropriate measures at an early stage. • For myocarditis obtain cardiologic consultation and laboratory investigations in symptomatic patients to ensure the initiation of appropriate measures at an early stage. • Thyroid disorders can occur at any time during treatment and patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. • Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment. • Patients should be monitored for hyperglycemia or other signs and symptoms of diabetes. • For nephritis and renal dysfunction, patients should be monitored for elevated serum creatinine prior to and periodically during treatment. **Pneumonitis/Hepatits** Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper). Avelumab should be withheld for Grade 2 immune-mediated adverse reactions of pneumonitis and hepatitis until resolution, and permanently discontinued for • Grade ≥ 3 or recurrent Grade 2 immune-mediated pneumonitis, • Grade 3 or Grade 4 immune-mediated hepatitis,

Important Identified Risk: Immune-mediated adverse reactions	
	Pancreatitis/ Myocarditis: Corticosteroids should be administered for immune-mediated adverse reactions of pancreatitis and myocarditis (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper). If there is no improvement within 24 hours on corticosteroids for myocarditis, additional immunosuppression (e.g. mycophenolate, infliximab, anti-thymocyte globulin) should be considered. Avelumab should be withheld in the event of suspected immune-mediated adverse reactions of pancreatitis or myocarditis and permanently discontinued if immune-mediated pancreatitis or myocarditis is confirmed. **Colitis/Nephritis and renal dysfunction:** Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper). Avelumab should be withheld for Grade 2 or Grade 3 immune-mediated colitis until resolution, and permanently discontinued for Grade 4 or recurrent Grade 3 immune-mediated colitis. Avelumab should be withheld for Grade 2 or Grade 3 nephritis until resolution to Grade ≤ 1 and permanently discontinued for Grade 4 nephritis. **Adrenal insufficiency** Corticosteroids should be administered (1 to 2 mg/kg/day prednisone intravenously, or oral equivalent) for Grade ≥ 3 adrenal insufficiency followed by a taper until a dose of less than or equal to 10 mg/day has been reached. Avelumab should be withheld for Grade 3 or Grade 4 symptomatic adrenal insufficiency. **Thyroid disorder** Hypothyroidism should be managed with replacement therapy and hyperthyroidism with anti-thyroid medicinal product as needed. Avelumab should be withheld for Grade 3 or Grade 4 thyroid disorders. **Type I Diabetes** Treatment with insulin for type 1 diabetes mellitus should be initiated. In patients with Grade ≥ 3 hyperglycemia, avelumab should be withheld and anti-hyperglycemics should be administered. Treatment with avelumab should be resumed when metabolic control is achieved on insulin replacement therapy. **Pituitary disorders/Myositis/Guillain-Barré syndrome/Uveitis/ myasthenia gravis/myasthenic syndrome, sclerosing cholangitis, arthritis, polymyalgia rheumatica and Sjogren's syndrome:** Based on the severity of the immune-mediated adverse reactions of pituitary disorders, myositis, Guillain-Barré syndrome, uveitis, myasthenia gravis/myasthenic syndrome, sclerosing cholangitis, arthritis, polymyalgia rheumatica and Sjogren's syndrome avelumab should be withheld and corticosteroids administered. Avelumab should be resumed when those immune-mediated adverse reactions return to Grade 1 or less following corticosteroid taper. Avelumab should be permanently discontinued for any Grade 3 immune-mediated adverse reactions that recurs and for Grade 4 immune-mediated adverse reactions. The SmPC Section 4.4 as well as the patient educational material contain the information that the risk of immune-mediated adverse reactions in patients with pre-existing autoimmune disease may be increased as compared with the risk in patients without pre-existing AID. A warning is provided that avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population. Additional risk minimization measures are described in Part V, V.2

Important Identified Risk: Immune-mediated adverse reactions	
Impact on the risk-benefit balance of the product:	Immune-mediated adverse reactions of nephritis or renal dysfunction, Guillain-Barré syndrome, myasthenia gravis/myasthenic syndrome, pancreatitis, thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, and pituitary disorders could potentially be severe or life-threatening. Uveitis (including iritis) could potentially be severe or debilitating and myositis can lead to muscle weakness and decrease quality of life. Sclerosing cholangitis, arthritis, polymyalgia rheumatica, and Sjogren's syndrome could be severe. Immune-mediated adverse reactions of pneumonitis, hepatitis, colitis, myocarditis may be life-threatening or fatal in individual patients. Avelumab has shown to be effective in treating adult patients with mMCC including patients who have failed to improve following treatment with other chemotherapies. Avelumab has also been shown to be effective in treating adult patients with locally advanced or metastatic UC as first-line maintenance treatment. Overall, the benefit of avelumab for treating a life-threatening condition is considered to outweigh the risk of immune-mediated adverse reactions that can be managed in clinical practice through monitoring to prevent serious complications. Avelumab in combination with axitinib has shown to be effective in treating adult patients with RCC. Overall, the benefit of avelumab in combination with axitinib for treating a life-threatening condition is considered to outweigh the risk of immune-mediated adverse reactions that can be managed in clinical practice through monitoring to prevent serious complications. The risk of immune-mediated adverse reactions will be further characterized in patients exposed to avelumab in the ongoing clinical trials, but this is unlikely to impact the risk-benefit balance of avelumab.
Public health impact:	The potential impact of the immune-mediated adverse reactions on public health is considered to be low.

ADR=adverse drug reaction, AE=adverse event, AID=autoimmune disease, ALT=alanine aminotransferase, AST=aspartate aminotransferase, aRCC=advanced renal cell carcinoma, CI=confidence interval, EPAR=European public assessment report, imAE=immune-mediated adverse event, mMCC=metastatic merkel cell carcinoma, PD-1=programmed death 1, PD-L1=programmed death ligand 1, UC=urothelial carcinoma

Important Identified Risk: Severe infusion-related reactions (Grade ≥ 3)	
Potential mechanisms:	In the optimized cytokine release assay (phytohemagglutinin-stimulated peripheral blood mononuclear cells), mild and transient increases in IL-6, MCP-1 and TNF-α were observed at 48 hours after the avelumab infusion, however, the results were not conclusive of the underlying mechanism of the clinically observed IRRs.
Evidence source(s) and strength of evidence:	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients).
Characterization of the risk:	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set

Important Identified Risk: Severe infusion-related reactions (Grade ≥ 3)	
	IRRs, some of which were severe, occurred in patients receiving avelumab in clinical studies. Across clinical studies, 0.7% (15/2,082) of patients developed severe IRRs (Grade ≥ 3), of these 12 (0.6%) patients reported Grade 3 events and 3 (0.1%) reported Grade 4 events as worst severity. There were no events with a fatal outcome. Serious AEs were reported in 11 (0.5%) patients. The median time to onset of severe IRRs (Grade ≥ 3) was 0.14 weeks (range: 0.1 to 10.4 weeks). The median duration was 1 day (range: 1 to 3 days). Avelumab was discontinued in 0.6% (13/2082) of patients due to severe IRRs. Of the 15 patients with severe IRRs, 11 (73.3%) were treated with systemic corticosteroids. Severe IRRs resolved in all 15 (100%) of the patients at the time of data cut-off. <u>Avelumab in Combination with Axitinib in RCC</u> Severe IRRs (Grade ≥ 3) occurred in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials, 1.6% (8/489) of patients developed severe IRRs (Grade ≥ 3). All 8 events were Grade 3. Serious AEs were reported in 2 (0.4%) patients. The median time to onset of severe IRRs (Grade ≥ 3) was 7.5 days (range: 1 to 43 days) including 4 events that occurred at the time of the first avelumab administration, 3 events that occurred at the time of the second avelumab administration, and 1 event that occurred at the time of the fourth avelumab administration. Avelumab was permanently withdrawn due to 7 of the 8 events and no action was taken with avelumab due to 1 event. All 8 events resolved on the day of onset.
Risk factors and risk groups:	No analysis of specific risk factors associated with IRRs has been performed. There are no known risk factors for patients treated with avelumab developing IRRs.
Preventability:	Patients should be monitored for signs and symptoms of IRRs including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria. For Grade 3 or Grade 4 IRRs, the infusion should be stopped and avelumab should be permanently discontinued. For Grade 1 IRRs, the infusion rate should be slowed by 50% for the current infusion. For patients with Grade 2 IRRs, the infusion should be temporarily discontinued until Grade 1 or resolved, then the infusion should be restarted with a 50% slower infusion rate. In case of recurrence of a Grade 1 or Grade 2 IRR, the patient may continue to receive avelumab with close monitoring after appropriate infusion rate modification and premedication with paracetamol and antihistamine. Additional risk minimization measures are described in Part V, V.2.
Impact on the risk-benefit balance of the product:	IRRs can potentially be severe. Avelumab has shown to be effective in treating adult patients with mMCC including patients who have failed to improve following treatment with other chemotherapies. Avelumab has also been shown to be effective in treating adult patients with locally advanced or metastatic UC as first-line maintenance treatment. Overall, the benefit of avelumab for treating a life-threatening condition is considered to outweigh the risk of IRRs that can be managed in clinical practice. Avelumab in combination with axitinib has shown to be effective in treating adult patients with RCC. Overall, the benefit of avelumab treating a life-threatening condition is considered to outweigh the risk of IRRs that can be managed in clinical practice through monitoring to prevent serious complications. The risk of IRRs will be further characterized in patients exposed to avelumab in the ongoing clinical trials, but this is unlikely to impact the risk-benefit balance of avelumab.
Public health impact:	The potential impact on public health is considered to be low.

IL-6=interleukin 6, IRR=infusion-related reaction, MCP-1=monocyte chemoattractant protein-1, mMCC=metastatic merkel cell carcinoma, RCC=renal cell carcinoma TNF-α=tumor necrosis factor-alpha, UC=urothelial carcinoma

Important Potential Risk: Other immune-mediated events (encephalitis)	
Potential mechanisms:	Avelumab binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on T cells, which can lead to decreases in self-tolerance and immune-mediated effects.
Evidence source(s) and strength of evidence:	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients).
Characterization of the risk:	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set Within the Pooled Safety Set, no cases of immune-mediated encephalitis were received. Encephalitis was assessed as an important potential risk for avelumab based on the fact that it is considered a class effect described as an ADR for other drugs in the class. Avelumab in Combination with Axitinib in RCC No events of immune-mediated encephalitis were observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003.
Risk factors and risk groups:	No analysis of specific risk factors associated with immune-mediated encephalitis has been performed. There are no known risk factors for patients treated with avelumab developing immune-mediated encephalitis.
Preventability:	The occurrence of encephalitis cannot be entirely prevented. However, by early diagnosis and following recommended treatment guidelines serious complications may be prevented.
Impact on the risk-benefit balance of the product:	Encephalitis could potentially be severe or life-threatening. Avelumab has shown to be effective in treating adult patients with mMCC including patients who have failed to improve following treatment with other chemotherapies. Avelumab has also been shown to be effective in treating adult patients with locally advanced or metastatic UC as first-line maintenance treatment. Overall, the benefit of avelumab for treating a life-threatening condition is considered to outweigh the risk of encephalitis that can be managed in clinical practice through monitoring to prevent serious complications. Avelumab in combination with axitinib has shown to be effective in treating adult patients with RCC. Overall, the benefit of avelumab treating a life-threatening condition is considered to outweigh the risk of encephalitis that can be managed in clinical practice through monitoring to prevent serious complications. The risk of encephalitis will be further characterized in patients exposed to avelumab in the ongoing clinical trials but this is unlikely to impact the risk-benefit balance of avelumab.
Public health impact:	The potential impact on public health is considered to be low.

aRCC=advanced renal cell carcinoma, mMCC=metastatic merkel cell carcinoma, PD-1=programmed death 1, PD-L1=programmed death ligand 1, UC=urothelial carcinoma

Important Potential Risk: Severe cutaneous reactions	
Potential mechanisms:	Avelumab binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on T cells, which can lead to decreases in self-tolerance and immune-mediated effects.

Important Potential Risk: Severe cutaneous reactions	
Evidence source(s) and strength of evidence:	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients).
Characterization of the risk:	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set</u> Across clinical studies, 0.3% (6/2,082) of patients developed severe cutaneous reactions (immune-mediated rash). All 6 events were Grade 3. Serious AEs were reported in 1 (less than 0.1%) patient. The median time to onset of severe cutaneous reactions (immune-mediated rash) was 6.1 weeks (range: 1.9 to 79.6 weeks). The median duration was 68 days (range: 8 to more than 651 days). Avelumab was not discontinued in any of the 6 patients due to severe cutaneous reactions (immune-mediated rash). Of the 6 patients with severe cutaneous reactions (immune-mediated rash), 5 (83.3%) were treated with systemic corticosteroids and 3 (50%) of the 6 patients were treated with high dose systemic corticosteroids. 3 (50%) of the 6 patients were treated with topical corticosteroids. Severe cutaneous reactions (immune-mediated rash) resolved in 4 (66.7%) of the patients at the time of data cut-off. <u>Avelumab in Combination with Axitinib in RCC</u> Severe cutaneous reactions (immune-mediated rash) were observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. In these clinical trials, 0.8% (4/489) of patients developed a severe cutaneous reaction (immune-mediated rash). All 4 events were Grade 3. Serious AEs were reported in 1 (0.2%) patient. The median time to onset of severe cutaneous reactions (immune-mediated rash) was 7.4 weeks (range: 5.9 to 46.3 weeks). Avelumab was discontinued in 1 patient due to a severe cutaneous reaction (immune-mediated rash). Of the 4 patients with a severe cutaneous reaction (immune-mediated rash), 3 were treated with high-dose corticosteroids systemically and 1 was only treated with topical corticosteroids. In all 4 patients, the severe cutaneous reactions (immune-mediated rash) were resolved at the time of data cut off.
Risk factors and risk groups:	No analysis of specific risk factors associated with severe cutaneous reactions (immune-mediated rash) has been performed. There are no known risk factors for patients treated with avelumab developing severe cutaneous reactions.
Preventability:	The occurrence of severe cutaneous reactions (immune-mediated rash) cannot be entirely prevented. However, by early diagnosis and following recommended treatment guidelines serious complications may be prevented.

Important Potential Risk: Severe cutaneous reactions	
Impact on the risk-benefit balance of the product:	Severe cutaneous reactions (immune-mediated rash) can potentially be severe or life-threatening. Avelumab has shown to be effective in treating adult patients with mMCC including patients who have failed to improve following treatment with other chemotherapies. Avelumab has also been shown to be effective in treating adult patients with locally advanced or metastatic UC as first-line maintenance treatment. Overall, the benefit of avelumab for treating a life-threatening condition is considered to outweigh the risk of severe cutaneous reactions that can be managed in clinical practice through monitoring to prevent serious complications. Avelumab in combination with axitinib has shown to be effective in treating adult patients with RCC. Overall, the benefit of avelumab treating a life-threatening condition is considered to outweigh the risk of severe cutaneous reactions that can be managed in clinical practice through monitoring to prevent serious complications. The risk of severe cutaneous reactions (immune-mediated rash) will be further characterized in patients exposed to avelumab in the ongoing clinical trials but this is unlikely to impact the risk-benefit balance of avelumab.
Public health impact:	The potential impact on public health is considered to be low.

aRCC=advanced renal cell carcinoma, CI=confidence interval, mMCC=metastatic merkel cell carcinoma, PD-1=programmed death 1, PD-L1=programmed death ligand 1, UC=urothelial carcinoma

Important Potential Risk: Immunogenicity	
Potential mechanisms:	Administration of any monoclonal antibody has the potential for the formation of anti-drug antibodies (ADA).
Evidence source(s) and strength of evidence:	<u>Avelumab Single-Agent: EMR100070-001 and EMR100070-003 (Part A)</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), and a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients). <u>Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment</u> The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). <u>Avelumab in Combination with Axitinib in RCC</u> The safety of Avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients).
Characterization of the risk:	Treatment emergent anti-drug antibodies (ADA) were detected in 8.5% of MCC patients (study EMR107000-003, 8.9% for Part A and 8.2% for Part B), 19% of UC patients (study B9991001) and 16% of RCC patients (study B9991003). The majority of the ADA were of neutralising character. No evidence of ADA or neutralising antibodies (nAb) impact on pharmacokinetics, efficacy or safety was observed.
Risk factors and risk groups:	None identified.
Preventability:	No data are currently available on potential measures to prevent antibody formation in patients treated with avelumab.
Impact on the risk-benefit balance of the product:	The presence of nAb could theoretically impact avelumab efficacy. In addition, immunogenicity could potentially be associated with clinically significant adverse reactions. Based on data available, no evidence of ADA or nAb impact on pharmacokinetics, efficacy or safety was observed.

Important Potential Risk: Immunogenicity	
	Avelumab has shown to be effective in treating adult patients with mMCC including patients who have failed to improve following treatment with other chemotherapies. Avelumab has also been shown to be effective in treating adult patients with locally advanced or metastatic UC as first-line maintenance treatment. Overall, the benefit of avelumab for treating a life-threatening condition is considered to outweigh the risk of immunogenicity. The risk of immunogenicity will be further characterized in patients exposed to avelumab in the ongoing clinical trials, but this is unlikely to impact the risk-benefit balance of avelumab.
Public health impact:	The potential impact on public health is considered to be low.

ADA=anti-drug antibodies, aRCC=advanced renal cell carcinoma, IRR=infusion-related reaction, mMCC=metastatic merkel cell carcinoma, nAB=neutralizing antibody, PK=pharmacokinetics, TEAEs=treatment-emergent adverse events, UC=urothelial carcinoma

Important Potential Risk: Embryofetal toxicity	
Potential mechanisms:	In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Human IgG1 immunoglobulins are known to cross the placenta. Therefore, avelumab has the potential to be transmitted from the mother to the developing fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss.
Evidence source(s) and strength of evidence:	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients) and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the fetus throughout pregnancy. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk that administration of avelumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. <u>Avelumab in Combination with Axitinib in RCC</u> Embryofetal toxicity was not observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. There was 1 case of paternal exposure timing unspecified when the wife of a male patient in clinical trial B9991003 became pregnant while he was receiving avelumab in combination with axitinib. This event of exposure during pregnancy was not associated with an AE in the mother or fetus/child. A healthy baby was born at 36 weeks.
Characterization of the risk:	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set</u> Across clinical studies there were no cases of avelumab exposure during pregnancy. <u>Seriousness/outcomes:</u> Not applicable <u>Severity and nature of risk:</u> Administration of avelumab during pregnancy could cause fetal harm including increased rates of abortion or stillbirth. <u>Avelumab in Combination with Axitinib in RCC</u>

Important Potential Risk: Embryofetal toxicity	
	There was 1 case of paternal exposure timing unspecified as described the section above.
Risk factors and risk groups:	Pregnant women
Preventability:	Preventable through use of effective contraception during treatment with avelumab and for at least 1 month after the last dose of avelumab in women of childbearing potential.
Impact on the risk-benefit balance of the product:	Administration of avelumab during pregnancy may result in spontaneous abortion or stillbirth. Avelumab has shown to be effective in treating adult patients with mMCC including patients who have failed to improve following treatment with other chemotherapies. Avelumab has also been shown to be effective in treating adult patients with locally advanced or metastatic UC as first-line maintenance treatment. Overall, the benefit of avelumab for treating a life-threatening condition is considered to outweigh the risk of embryofetal toxicity that can be minimized in clinical practice through use of effective contraception during treatment with avelumab and for at least 1 month after the last dose of avelumab. Avelumab in combination with axitinib has shown to be effective in treating adult patients with RCC. Overall, the benefit of avelumab treating a life-threatening condition is considered to outweigh the risk of embryofetal toxicity that can be managed in clinical practice through use of effective contraception. The risk of embryofetal toxicity will be further characterized in patients exposed to avelumab in the ongoing clinical trials but this is unlikely to impact the risk-benefit balance of avelumab.
Public health impact:	The potential impact on public health is considered to be low.

IgG1= immunoglobulin G1, mMCC=metastatic merkel cell carcinoma, PD-1=programmed death 1, PD-L1=programmed death ligand 1, RCC= renal cell carcinoma, UC=urothelial carcinoma

SVII.3.2 Presentation of the Missing Information

Missing information: Safety in patients with HIV, hepatitis B or C infections	
Evidence source:	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated; however, patients with HIV, hepatitis B or C infections were excluded from these clinical trials. Avelumab in Combination with Axitinib in RCC The safety of avelumab was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients); however, patients with HIV, hepatitis B or C infections were excluded from these clinical trials.
Anticipated risk/consequence of the missing information:	There are no known safety concerns in patients with HIV, hepatitis B or C infections but efficacy and safety of avelumab are unknown in this population as patients with a history of active HIV or hepatitis B or C infections were excluded from the clinical trials. Further collection of data relating to the use of avelumab in patients with HIV, hepatitis B or C infections will be through collection and evaluation of spontaneous reports in the post-marketing setting (routine pharmacovigilance).

aRCC=advanced renal cell carcinoma, HIV=human immunodeficiency virus, mMCC=metastatic merkel cell carcinoma, UC=urothelial carcinoma

Missing information: Safety and efficacy in immune compromised patients	
Evidence source:	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with mMCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated however, immune compromised patients were excluded from these clinical trials. Avelumab in Combination with Axitinib in RCC The safety of avelumab was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients); however, immune compromised patients were excluded from these clinical trials.
Population in need of further characterization:	Further collection of data relating to the safety and efficacy of avelumab in immune compromised patients will be evaluated in a non-interventional cohort registry study to assess characteristics and management of patients with MCC in Germany (Study MS100070-0031) (Part III.2).

mMCC=metastatic merkel cell carcinoma, RCC=renal cell carcinoma, UC=urothelial carcinoma

Part II: Module SVIII: Summary of the Safety Concerns

Table 21 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Immune-mediated adverse reactions • Severe infusion-related reactions (Grade ≥ 3)
Important potential risks	• Other immune-mediated events (encephalitis) • Severe cutaneous reactions • Immunogenicity • Embryofetal toxicity
Missing information	• Safety in patients with HIV, hepatitis B or C infections • Safety and efficacy in immune compromised patients

HIV= human immunodeficiency virus

Part III: Pharmacovigilance Plan (including Post-authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

Not applicable

Other forms of routine pharmacovigilance activities for:

- Immune-mediated adverse reactions
- Severe infusion-related reactions (Grade ≥ 3)
- Other immune-mediated events (encephalitis)
- Severe cutaneous reactions
- Immunogenicity

Further monitoring and characterization of these safety concerns are occurring in patients exposed to avelumab in the ongoing clinical trials. As the studies were not initiated to specifically quantify these safety concerns, they are not considered additional pharmacovigilance activities.

Other forms of routine pharmacovigilance activities for safety concerns:

- Not applicable

The early access program (EAP) for patients with mMCC provided further data relating to the safety and efficacy of avelumab in immune compromised patients. Data from the EAP were published in 2020 (Walker 2020), and the program was subsequently closed in 2022. Although the results presented are limited by the nature of data reporting within the MCC EAP, they highlight that in a real-world setting, avelumab showed efficacy and safety consistent with results from the MCC trial EMR100070-003, Part A, despite including patients who would have been ineligible for the trial (e.g. those with ECOG Performance Status of 2 or 3, treated brain metastases, or immunosuppressive conditions including HIV infection). Durable responses were observed in both immune-competent and immunocompromised patients, and no new safety signals were identified in the EAP population with IRR, fever, fatigue, and rash among the most frequently occurring treatment-related AEs.

III.2 Additional Pharmacovigilance Activities

Post-authorization safety study (PASS) summary

Study short name and title:

Non-interventional cohort registry study to assess characteristics and management of patients with Merkel cell carcinoma in Germany (Study MS100070-0031)

Rationale and study objectives:

The study will evaluate the efficacy and safety of avelumab in immune compromised patients in addition to other objectives, by using real-world data. Within this context, the study aims to:

1) describe patient characteristics (including co-morbidities and concomitant medications),

2) estimate background rates of potential safety events (including immune -mediated events),

3) describe treatment patterns, and

4) characterize disease outcomes (effectiveness and safety).

Objectives related to effectiveness/ safety outcomes will also be assessed in the sub-group of immune compromised patients treated with avelumab, and an exploratory objective (due to expected limited sample size) will compare these outcomes in immune compromised patients with the ones in immune competent patients.

Study design:

A 5-year non-interventional (observational), multi-center cohort registry study in patients diagnosed with MCC in Germany. The design is an open cohort study design, with dynamic, renewed sampling, which means that each patient eligible at a study site and not yet included in the study will have the same probability to be included all along the inclusion period.

Patients will be included from study start until the end of second quarter of Year 4 and followed until the end of Year 5. This allows for a minimum follow-up of 6 months for each patient.

There is no assignment of a patient to a particular therapeutic strategy for this study. Patients will be recruited based on a diagnosis of MCC only.

Study population:

The study population comprises male and female patients with MCC in Germany. Patients' participation will be allowed irrespective of their MCC stage and their prior and/or current treatment situation. Patients currently participating and/or having participated in a clinical trial and/or the previous Arbeitsgemeinschaft Dermatologische Onkologie MCC registry will be approached at each study site to participate in ADOReg (German Skin Cancer Registry) and subsequently, in this study if they are able to consent.

Patients must fulfill the following inclusion criteria:

1) Diagnosis of MCC

2) Signed written informed consent to collect and process data in an anonymized manner by either the patient or legal guardian if age < 18 years

3) Signed written informed consent to collect and process tumor specimens in a pseudonymized manner.

Milestones:

Final protocol (amended v4.0): 03 Dec 2018

Registration in the EU PAS Register: within 2 months after final protocol: 20 Nov 2018

Independent Ethics Committee approval: 12 Mar 2019

Start of data collection: 29 Apr 2019

End of data collection: 5 years after start of the data collection (anticipated in Quarter 1 2024)

Interim reports: first annual progress update report in Mar 2020, and then yearly

Final study report: Quarter 4 2024

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 22 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Non-interventional cohort registry study to assess characteristics and management of patients with Merkel cell carcinoma in Germany (Study MS100070-0031) Ongoing	5-year open cohort study (based on primary data collection) of patients with Merkel cell carcinoma in Germany to 1) describe patient characteristics (including co-morbidities and concomitant medications), 2) estimate background rates of relevant comorbidities, 3) describe treatment patterns, 4) characterize disease outcomes (overall, per treatment and in immune compromised patients treated with avelumab), 5) describe safety events of interest (e.g. immune-mediated adverse drug reactions) overall and in immune compromised patients treated with avelumab Exploratory objectives: Compare safety and effectiveness profile of avelumab in immune compromised patients with immune competent patients	Safety in immune compromised patients in addition to gathering of other real-world data	Interim reports	Interim reports (first interim annual progress update report on Mar 2020 and following reports yearly)
			Final report	31 Dec 2024

Part IV: Plans for Post-Authorization Efficacy Studies

Not applicable

Part V: Risk Minimization Plan (Including Evaluation of the Effectiveness of Risk Minimization Activities)

V.1 Routine Risk Minimization Measures

Table 23 Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Immune-mediated adverse reactions	Routine risk communication: • SmPC Section 4.4 contains the information that the risk of immune-mediated adverse reactions in patients with pre-existing autoimmune disease may be increased as compared with the risk in patients without pre-existing AID. A warning is provided that avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population. • Immune mediated adverse reactions listed in SmPC Section 4.8. • Description of selected immune-mediated adverse reactions observed in clinical trials provided in SmPC Section 4.8 • Signs of immune-mediated adverse reactions listed as side effects in PL Section 4. Routine risk minimization activities recommending specific clinical measures to address the risk: • Guidance for withholding or discontinuing avelumab based on the severity of immune-mediated adverse reactions provided in SmPC Section 4.2 • Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advice based on severity included in SmPC Section 4.4 Warning for the patient to talk to their doctor if they develop immune mediated adverse reactions provided in PL Section 2 Guidance to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease which may increase the risk of immune-mediated adverse reactions provided in PL section 2 Other routine risk minimization measures beyond the Product Information: • Legal status: subject to restricted medical prescription
Severe infusion-related reactions (Grade ≥ 3)	Routine risk communication: • Description of the IRRs observed in clinical trials provided in SmPC Section 4.4 • Infusion-related reaction listed as an adverse reaction in SmPC Section 4.8 • Information that ADA positive patients may be at increased risk of IRRs provided in SmPC Section 4.8 • Signs of infusion related reactions listed as a side effect in PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Guidance to pre-medicate with an antihistamine and paracetamol prior to the first 4 infusions of avelumab to minimize the risk of an IRR provided in SmPC Section 4.2 • Guidance for withholding or discontinuing avelumab based on the severity of the IRR provided in SmPC Section 4.2 • Warning to monitor for signs and symptoms of IRRs and treatment advice based on severity included in SmPC Section 4.4 • Warning for the patient to talk to their doctor before receiving avelumab if they have IRRs provided in PL Section 2

Safety Concern	Routine Risk Minimization Activities
	• Information for the patient that they will receive paracetamol and an antihistamine before at least the first 4 treatments of avelumab to prevent possible side effects related to the infusion in PL Section 3 Other routine risk minimization measures beyond the Product Information: • Legal status: subject to restricted medical prescription
Other immune-mediated events (encephalitis)	Routine risk communication: • None Routine risk minimization activities recommending specific clinical measures to address the risk: • Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advice based on etiology, including withholding treatment and initiation of corticosteroids, included in SmPC Section 4.4 • Information that avelumab works on the immune system and may cause inflammation in parts of the body which may be serious and life-threatening requiring avelumab withdrawal or treatment provided in PL Section 4 Other routine risk minimization measures beyond the Product Information: • Legal status: subject to restricted medical prescription
Severe cutaneous reactions	Routine risk communication: • Severe cutaneous reactions listed as adverse reactions in SmPC Section 4.8 • Skin reactions listed as side effects in PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advice based on etiology, including withholding treatment and initiation of corticosteroids, included in SmPC Section 4.4 • Information that avelumab works on the immune system and may cause inflammation in parts of the body which may be serious and life-threatening requiring avelumab withdrawal or treatment provided in PL Section 4 Other routine risk minimization measures beyond the Product Information: • Legal status: subject to restricted medical prescription
Immunogenicity	Routine risk communication: • Information that treatment-emergent ADA were observed in clinical trials and that there was no evidence of ADA or nAb impact on pharmacokinetics, efficacy, and safety in SmPC Section 5.1 Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the Product Information: • Legal status: subject to restricted medical prescription
Embryofetal toxicity	Routine risk communication: • Information that there are no or limited data from the use of avelumab in pregnant women with reference to non-clinical data provided in SmPC Section 4.6

Safety Concern	Routine Risk Minimization Activities
	• Information that animal reproduction studies have not been conducted with avelumab but that blockade of programmed death ligand 1 signalling has been shown to disrupt tolerance to the fetus and to result in an increased fetal loss in murine models of pregnancy provided in SmPC Section 5.3 Routine risk minimization activities recommending specific clinical measures to address the risk: • Guidance for women of childbearing to avoid becoming pregnant and to use effective contraception during avelumab treatment and for at least 1 month after the last dose of avelumab in SmPC Section 4.6 • Guidance that avelumab is not recommended for use during pregnancy unless the clinical condition of the woman requires treatment with avelumab in SmPC Section 4.6 • Guidance for the patient to ask their doctor for advice before taking avelumab if they are pregnant, think they may be pregnant or are planning to have a baby in PL Section 2 • Warning for the patient not to use avelumab if they are pregnant unless their doctor specifically recommends it in PL Section 2 • Guidance for a woman who could become pregnant to use effective contraceptives while they are being treated with avelumab and for at least 1 month after their last dose in PL Section 2 Other routine risk minimization measures beyond the Product Information: • Legal status: subject to restricted medical prescription
Safety in patients with HIV, hepatitis B or C infections	Routine risk communication: • Information that patients with conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from clinical trials provided in SmPC Section 4.4. A warning is included that avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population • Information that patients with conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from Study EMR100070-003 and B9991001 provided in SmPC Section 5.1 Routine risk minimization activities recommending specific clinical measures to address the risk: • Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have HIV infection or acquired immune deficiency syndrome provided in PL Section 2 • Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have ever had chronic viral infection of the liver, including hepatitis B or hepatitis C provided in PL Section 2 Other routine risk minimization measures beyond the Product Information: • Legal status: subject to restricted medical prescription
Safety and efficacy in immune compromised patients	Routine risk communication: • Information that patients with active or a history of autoimmune disease, organ transplant, conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from clinical trials provided in SmPC Section 4.4. A warning is included that avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population

Safety Concern	Routine Risk Minimization Activities
	• Information that patients with active or a history of autoimmune disease, organ transplant, conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from Study EMR100070-003 and B9991001 provided in SmPC Section 5.1 Routine risk minimization activities recommending specific clinical measures to address the risk: • Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease provided in PL Section 2 Other routine risk minimization measures beyond the Product Information: • Legal status: subject to restricted medical prescription

ADA=antidrug antibody, ALT=alanine aminotransferase, AST=aspartate aminotransferase, HIV=human immunodeficiency virus, IRR=infusion-related rection, PL=package leaflet, SmPC=summary of product characteristics.

V.2 Additional Risk Minimization Measures

Additional Risk Minimization Measures

Patient Educational Material (EM) including

- Patient Card

Objectives:

Important risks covered by the EM:

- Immune-mediated adverse reactions
- Severe infusion-related reactions

The objective of the EM is to enhance the awareness of patients on the signs and symptoms relevant to the early recognition/identification of imAEs and IRRs.

Rationale for the additional risk minimization activity:

In order to minimize the risks of imAEs and IRRs, EM is being distributed to patients via relevant healthcare professionals (HCPs).

The EM includes information on the signs and symptoms of immune-mediated adverse reactions and IRRs, as well as guidance on the need for premedication and the importance of these events to prevent more severe complications. Details are included in Annex 6. The EM comprises of the patient card.

Target audience and planned distribution path:

The patient EM will be distributed to relevant HCPs as a package and patients will receive their materials through the HCP.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness of the EM is being measured via process indicators as follows:

Process indicator: Distribution metrics for the EM are being collected (confirmed distribution to and receipt by selected HCPs).

Removal of Additional Risk Minimization Activities

Patient Information Brochure was removed from the list of the additional risk Minimization Activities based on the recommendations of the PRAC included in PRAC AR under procedure number: EMEA/H/C/PSUSA/00010635/202303.

The PRAC rapporteur highlighted that the content and key elements of the patient information brochure and the patient card are very similar, the patient information brochure has no additional or more detailed information about the risks addressed, questioning the continued need for this educational material in addition to the patient card.

Therefore, the PRAC recommended an updated version of the key elements of the patient card (that covers all the relevant and important key elements to mitigate the important identified risk immune-related adverse reactions and infusion-related reactions) that can be used as a single document that replaces the currently available educational materials.

Since the package leaflet is not considered as an additional risk minimization measure, it is not part of the educational material. Hence, it was removed from the list of patient educational material. The educational material (patient card) is based on targeted communication with the aim to supplement the information in the SmPC and package leaflet. The patient card should increase the awareness of patients on the signs and symptoms relevant to the early recognition/identification of immune-mediated adverse reactions and infusion related reactions.

V.3 Summary of Risk Minimization Measures

Table 24 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-mediated adverse reactions	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of immune-mediated adverse reactions in SmPC Section 4.2* *Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advice based on severity included in SmPC Section 4.4.* *Warning about an increased risk of immune-mediated adverse reactions in patients with pre-existing autoimmune disease as compared with the risk in patients without pre-existing AID included in SmPC Section 4.4. Avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in these population.* *Immune mediated adverse reactions listed in SmPC section 4.8* *Description of selected immune-mediated adverse reactions observed in clinical trials in SmPC Section 4.8.* *Warning for the patient to talk to their doctor if they develop immune mediated adverse reactions provided in PL Section 2.* *Guidance to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease which may increase the risk of immune-mediated adverse reactions provided in PL Section 2* *Signs of Immune mediated adverse reactions listed as side effects in PL Section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-mediated adverse reactions in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Severe infusion-related reactions (Grade ≥ 3)	Routine risk minimization measures: *Guidance to pre-medicate with an antihistamine and paracetamol prior to the first 4 infusions of avelumab in SmPC Section 4.2*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Guidance for withholding or discontinuing avelumab based on the severity of IRRs in SmPC Section 4.2 *Description of IRRs observed in clinical trials in SmPC Section 4.4* *Warning to monitor for IRRs and treatment advice based on severity in SmPC Section 4.4* *SmPC Section 4.8* *Information that ADA positive patients may be at increased risk of IRRs in SmPC Section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have IRRs in PL Section 2* *Information for the patient that they will receive paracetamol and an antihistamine before at least the first 4 treatments of avelumab in PL Section 3* *PL Section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	*Further monitoring and characterization of severe IRRs in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Other immune-mediated events (encephalitis)	Routine risk minimization measures: *Warning to monitor for immune-mediated adverse reactions and treatment advice based on etiology in SmPC Section 4.4* *Information that avelumab works on the immune system and may cause inflammation which may be serious and life-threatening requiring avelumab withdrawal or treatment in PL Section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of other immune-mediated event encephalitis in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Severe cutaneous reactions	Routine risk minimization measures: *Warning to monitor for immune-mediated adverse reactions and treatment advice based on etiology in SmPC Section 4.4* *Severe cutaneous reactions listed as adverse reactions in SmPC Section 4.8* *Information that avelumab works on the immune system and may cause inflammation which may be serious and life-threatening requiring avelumab withdrawal or treatment in PL Section 4* *PL Section 4* *Legal status (prescription only medicine)* Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of severe cutaneous reactions in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	None	
Immunogenicity	Routine risk minimization measures: *Information that treatment-emergent ADA were observed in clinical trials and that there was no evidence of ADA or nAb impact on PK, efficacy, and safety in SmPC Section 5.1.* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of subjects developing ADA in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Embryofetal toxicity	Routine risk minimization measures: *Guidance for women of childbearing to avoid becoming pregnant and to use effective contraception during treatment and for at least 1 month after the last dose in SmPC Section 4.6* *Guidance that avelumab is not recommended for use during pregnancy unless the woman requires treatment in SmPC Section 4.6* *Information that there are no or limited data in pregnant women in SmPC Section 4.6* *Information that blockade of programmed death ligand 1 signaling has been shown to disrupt tolerance to the fetus and result in increased fetal loss in murine models of pregnancy in SmPC Section 5.3* *Guidance for the patient to seek advice before taking avelumab if they are pregnant, think they may be pregnant or are planning to have a baby in PL Section 2* *Warning for the patient not to use avelumab if they are pregnant unless their doctor specifically recommends it in PL Section 2* *Guidance for a woman to use effective contraceptives while they are being treated and for at least 1 month after their last dose in PL Section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Safety in patients with HIV, hepatitis B or C infections	Routine risk minimization measures: *Information that patients with conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from clinical trials in SmPC Section 4.4. A warning that avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population is included in SmPC Section 4.4.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Information that patients with conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from Study EMR100070-003 and B9991001 in SmPC Section 5.1. *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have HIV infection or acquired immune deficiency syndrome in PL Section 2* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have ever had chronic viral infection of the liver, including hepatitis B or hepatitis C in PL Section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*	
Safety and efficacy in immune compromised patients	Routine risk minimization measures: *Information that patients with active or a history of autoimmune disease, organ transplant, conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from clinical trials in SmPC Section 4.4. A warning that avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population is included in SmPC Section 4.4.* *Information that patients with active or a history of autoimmune disease, organ transplant, conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from Study EMR100070-003 and B9991001 in SmPC Section 5.1.* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease in PL Section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Non-interventional cohort study to assess characteristics and management of patients with Merkel cell carcinoma in Germany (Study MS100070-0031)*

ADA=antidrug antibody, HIV=human immunodeficiency virus, IRR=infusion-related reaction, PL=package Leaflet, SmPC=summary of product characteristics.

Part VI: Summary of the Risk Management Plan

Summary of the Risk Management Plan for Avelumab (Bavencio)

This is a summary of the Risk Management Plan (RMP) for Bavencio. The RMP details important risks of Bavencio, how these risks can be minimized, and how more information will be obtained about Bavencio's risks and uncertainties (missing information).

Bavencio's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) provide an essential information to HCPs and patients on how Bavencio should be used.

This summary of the RMP for Bavencio should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Bavencio's RMP.

I. The Medicine and What it is Used for

Bavencio is authorized as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC) and as first-line maintenance treatment for locally advanced or metastatic urothelial carcinoma (UC). In addition, Bavencio in combination with axitinib is approved for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC; see SmPC for the full indication). It contains avelumab as the active substance and it is given as an intravenous infusion.

Further information about the evaluation of Bavencio's benefits can be found in Bavencio's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004338/human_med_002157.jsp&mid=WC0b01ac058001d124

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Bavencio, together with measures to minimize such risks and the proposed studies for learning more about Bavencio's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine *Risk Minimization Measures.*

In the case of Bavencio, these measures are supplemented with *additional Risk Minimization Measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment - so that immediate action can be taken as necessary. These measures constitute *routine Pharmacovigilance Activities.*

If important information that may affect the safe use of Bavencio is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Bavencio are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Bavencio. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information	
Important identified risks	• Immune-mediated adverse reactions • Severe infusion-related reactions (Grade ≥ 3)
Important potential risks	• Other immune-mediated events (encephalitis) • Severe cutaneous reactions • Immunogenicity • Embryofetal toxicity
Missing information	• Safety in patients with HIV, hepatitis B or C infections • Safety and efficacy in immune compromised patients

HIV=human immunodeficiency virus

II.B Summary of Important Risks

Important identified risk: Immune-mediated adverse reactions	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), B9991001 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was evaluated in the clinical trials B9991002 and B9991003 in patients with advanced RCC (489 patients). Evaluation of post-marketing sources and completed randomized clinical trials EMR100070-004, EMR10007-005, EMR10007-007, EMR10007-008, B9991001, B9991003, B9991009, B9991010, and B9991016 for other immune-mediated adverse reactions of sclerosing cholangitis, polymyalgia rheumatica, and Sjogren's syndrome
Risk factors and risk groups	No analysis of specific risk factors associated with immune-mediated adverse reactions has been performed. In patients with pre-existing autoimmune disease, data from observational studies suggest that the risk of immune-related adverse reactions following immune-checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.
Risk minimization measures	Routine risk minimization measures *Guidance for withholding or discontinuing avelumab based on the severity of immune-mediated adverse reactions in SmPC Section 4.2.* *Warning to monitor for signs and symptoms of immune-mediated adverse reactions and treatment advise based on severity included in SmPC Section 4.4.* *Warning about an increased risk of immune-mediated adverse reactions in patients with pre-existing autoimmune disease as compared with the risk in patients without pre-existing AID included in SmPC Section 4.4.* *SmPC Section 4.8* *Description of selected immune-mediated adverse reactions observed in clinical trials provided in SmPC Section 4.8* *Warning for the patient to talk to their doctor if they develop immune mediated adverse reactions provided in PL Section 2* *PL Section 4* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease,* which may increase the risk of immune-mediated adverse reactions, *in PL Section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

Important identified risk:
Immune-mediated adverse reactions

AID=autoimmune disease, aRCC=advanced renal cell carcinoma, mMCC=metastatic merkel cell carcinoma, PD L-1=programmed death ligand 1, PL=package leaflet, SmPC=summary of product characteristics, UC=urothelial carcinoma

Important identified risk: Severe infusion-related reactions (Grade ≥ 3)	
Evidence for linking the risk to the medicine	<u>Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), B9991001 - Pooled Safety Set</u> The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients) and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. <u>Avelumab in Combination with Axitinib in RCC</u> The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with aRCC (489 patients).
Risk factors and risk groups	No analysis of specific risk factors associated with infusion-related reactions has been performed. There are no known risk factors for patients treated with avelumab developing infusion-related reactions.
Risk minimization measures	Routine risk minimization measures: *Guidance to pre-medicate with an antihistamine and paracetamol prior to the first 4 infusions of avelumab in SmPC Section 4.2* *Guidance for withholding or discontinuing avelumab based on the severity of infusion-related reactions in SmPC Section 4.2* *Description of infusion-related reactions observed in clinical trials in SmPC Section 4.4* *Warning to monitor for infusion-related reactions and treatment advice based on severity in SmPC Section 4.4* *SmPC Section 4.8* *Information that anti-drug antibody (ADA) positive patients may be at increased risk of infusion-related reactions in SmPC Section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have infusion-related reactions in PL Section 2* *Information for the patient that they will receive paracetamol and an antihistamine before at least the first 4 treatments of avelumab in PL Section 3* *PL Section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*

MCC=metastatic merkel cell carcinoma, PL=package leaflet, PD-L1=programmed death ligand 1, RCC= renal cell carcinoma, SmPC=summary of product characteristics

Important potential risk: Other immune-mediated events (encephalitis)	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), B9991001 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with advanced RCC (489 patients).
Risk factors and risk groups	No analysis of specific risk factors associated with immune-mediated encephalitis has been performed. There are no known risk factors for patients treated with avelumab developing immune-mediated encephalitis.
Risk minimization measures	Routine risk minimization measures: *Warning to monitor for immune-mediated adverse reactions and treatment advice based on etiology in SmPC Section 4.4* *Information that avelumab works on the immune system and may cause inflammation which may be serious and life-threatening requiring avelumab withdrawal or treatment in PL Section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: None

MCC=metastatic merkel cell carcinoma, PL=package leaflet, RCC= renal cell carcinoma, SmPC=summary of product characteristics

Important potential risk: Severe cutaneous reactions	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), B9991001 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with advanced RCC (489 patients).
Risk factors and risk groups	No analysis of specific risk factors associated with severe cutaneous reactions (immune-mediated rash) has been performed. There are no known risk factors for patients treated with avelumab developing severe cutaneous reactions.
Risk minimization measures	Routine risk minimization measures: *Warning to monitor for immune-mediated adverse reactions and treatment advice based on etiology in SmPC Section 4.4* *SmPC Section 4.8*

Important potential risk: Severe cutaneous reactions	
	Information that avelumab works on the immune system and may cause inflammation which may be serious and life-threatening requiring avelumab withdrawal or treatment in PL Section 4 *PL Section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*

MCC=metastatic merkel cell carcinoma, PL=package leaflet, RCC= renal cell carcinoma, SmPC=summary of product characteristics

Important potential risk: Immunogenicity	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001 and EMR100070-003 The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), and a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients). Avelumab Single-Agent: B9991001 - UC First-Line Maintenance Treatment The safety of avelumab was evaluated in the clinical trial B9991001 in patients with locally advanced or metastatic UC (344 patients). Avelumab in Combination with Axitinib in RCC The safety of avelumab in combination with axitinib was also evaluated in clinical trials B9991002 and B9991003 in patients with advanced RCC (489 patients).
Risk factors and risk groups	None identified
Risk minimization measures	Routine risk minimization measures: *Information that treatment-emergent ADA were observed in clinical trials and that there was no evidence of ADA or nAb impact on pharmacokinetics, efficacy and safety in SmPC Section 5.1.* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*

ADA=anti-drug antibodies, MCC=metastatic merkel cell carcinoma, nAB= neutralizing antibody, RCC= renal cell carcinoma, SmPC=summary of product characteristics, UC=urothelial carcinoma

Important potential risk: Embryofetal toxicity	
Evidence for linking the risk to the medicine	Avelumab Single-Agent: EMR100070-001, EMR100070-003 (Part A), and B9991001 - Pooled Safety Set The safety of avelumab was evaluated in clinical trial EMR100070-003 in patients with metastatic MCC (Part A; 88 patients), a large Phase 1 trial EMR100070-001 in patients with various solid tumors (1,650 patients), and clinical trial B9991001 in patients with locally advanced or metastatic UC as first-line maintenance treatment (344 patients). A total of 2,082 patients treated with avelumab were evaluated. The programmed death 1/programed death ligand 1 pathway is thought to be involved in maintaining tolerance to the fetus throughout pregnancy. Blockade of programed death ligand 1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk that administration of avelumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.

Important potential risk: Embryofetal toxicity	
	Avelumab in Combination with Axitinib in RCC Embryofetal toxicity was not observed in patients with RCC treated with avelumab in combination with axitinib in clinical trials B9991002 and B9991003. There was 1 case of paternal exposure timing unspecified when the wife of a male patient in clinical trial B9991003 became pregnant while he was receiving avelumab in combination with axitinib. This event of exposure during pregnancy was not associated with an adverse event in the mother or fetus/child. A healthy baby was born at 36 weeks.
Risk factors and risk groups	Pregnant women
Risk minimization measures	Routine risk minimization measures: *Guidance for women of childbearing to avoid becoming pregnant and to use effective contraception during treatment and for at least 1 month after the last dose in SmPC Section 4.6* *Guidance that avelumab is not recommended for use during pregnancy unless the woman requires treatment in SmPC Section 4.6* *Information that there are no or limited data in pregnant women in SmPC Section 4.6* *Information that blockade of programed death ligand 1 signaling has been shown to disrupt tolerance to the fetus and result in increased fetal loss in murine models of pregnancy in SmPC Section 5.3* *Guidance for the patient to seek advice before taking avelumab if they are pregnant, think they may be pregnant or are planning to have a baby in PL Section 2* *Warning for the patient not to use avelumab if they are pregnant unless their doctor specifically recommends it in PL Section 2* *Guidance for a woman to use effective contraceptives while they are being treated and for at least 1 month after their last dose in PL Section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*

MCC=metastatic merkel cell carcinoma, PL=package leaflet, RCC= renal cell carcinoma, SmPC=summary of product characteristics, UC=urothelial carcinoma

Missing information: Safety in patients with HIV, hepatitis B or C infections	
Risk minimization measures	Routine risk minimization measures: *Information that patients with conditions requiring therapeutic immune suppression or active infection with human immunodeficiency virus (HIV), or hepatitis B or C were excluded from clinical trials in SmPC Section 4.4. A warning is included that avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population.* *Information that patients with conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from Study EMR100070-003 and B9991001 in SmPC Section 5.1* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have HIV infection or acquired immunodeficiency syndrome (AIDS) in PL Section 2* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have ever had chronic viral infection of the liver, including hepatitis B or hepatitis C in PL Section 2* *Legal status (prescription only medicine)* Additional risk minimization measures:

	None

PL=package leaflet, SmPC=summary of product characteristics

Missing information: Safety and efficacy in immune compromised patients	
Risk minimization measures	Routine risk minimization measures: *Information that patients with active or a history of autoimmune disease, organ transplant, conditions requiring therapeutic immune suppression or active infection with human immunodeficiency virus (HIV), or hepatitis B or C were excluded from clinical trials in SmPC Section 4.4. A warning is included that avelumab should be used with caution after careful consideration of the potential benefit/risk on an individual basis in this population in SmPC Section 4.4.* *Information that patients with active or a history of autoimmune disease, organ transplant, conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from Study EMR100070-003 and B9991001 in SmPC Section 5.1* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease in PL Section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: Non-interventional cohort study to assess characteristics and management of patients with Merkel cell carcinoma in Germany (Study MS100070-0031) See Section II.C of this summary for an overview of the post-authorization development plan.

PL=package leaflet, SmPC=summary of product characteristics

II.C Post-Authorization Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligations.

II.C.2 Other Studies in the Post-Authorization Development Plan

Study short name: Non-interventional cohort registry study to assess characteristics and management of patients with Merkel cell carcinoma in Germany (Study MS100070-0031).

Rationale and study objectives:

The study will evaluate the efficacy and safety of avelumab in immune compromised patients in addition to other objectives, by using real-world data. Within this context, the study aims to:

1) describe patient characteristics (including co-morbidities and concomitant medications),

2) estimate background rates of potential safety events (including immune mediated events),

3) describe treatment patterns, and

4) characterize disease outcomes (effectiveness and safety).

Objectives related to effectiveness/ safety outcomes will also be assessed in the sub-group of immune compromised patients treated with avelumab, and an exploratory objective (due to expected limited sample size) will compare these outcomes in immune compromised patients with the ones in immune competent patients.

Part VII Annexes

Annex 1 CCI [redacted]

Annex 2 CCI [redacted]

Annex 3 CCI [redacted]

Annex 4 **Specific Adverse Drug Reaction Follow-up Forms**

Not applicable

Annex 5 CCI [redacted]

Not applicable

Annex 6 **Details of Proposed Additional Risk Minimization Activities**

Annex 7 **Other Supporting Data (including Referenced Material)**

Annex 8 CCI [redacted]

Signature Page for VV-PVG-049764 v1.0

Approval Task	Elke Sylvester Pharmacovigilance 13-Mar-2025 08:16:50 GMT+0000

Approval Task	PPD ovigilance 13-Mar-2025 14:53:47 GMT+0000

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Annex 2 CCI

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Annex 6 Details of Proposed Additional Risk Minimization Activities

Approved key message of the additional risk minimization measures

Prior to launch of Bavencio in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness of patients on the signs and symptoms relevant to the early recognition/identification of immune-mediated adverse reactions and infusion related reactions.

The MAH shall ensure that in each Member State where Bavencio is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Bavencio have access to/are provided with the Patient Card.

The Patient Card shall contain the following key messages:

- Brief introduction to avelumab (indication and purpose of this tool).
- Description of the main signs and symptoms of the immune-mediated adverse reactions and infusion related reactions, and the importance of notifying their treating physician immediately if symptoms occur, persist or worsen.
- Warning message for patients on the importance of consulting their doctor immediately in case they develop any of the listed signs and symptoms and on the importance of not attempting to treat themselves.
- Reminder to carry the Patient Card at all times and to show it to all healthcare professionals that may treat them.
- The card should also prompt to enter contact details of the physician who has prescribed avelumab and include a warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Bavencio.

Annex 7 Other Supporting Data (including Referenced Material)

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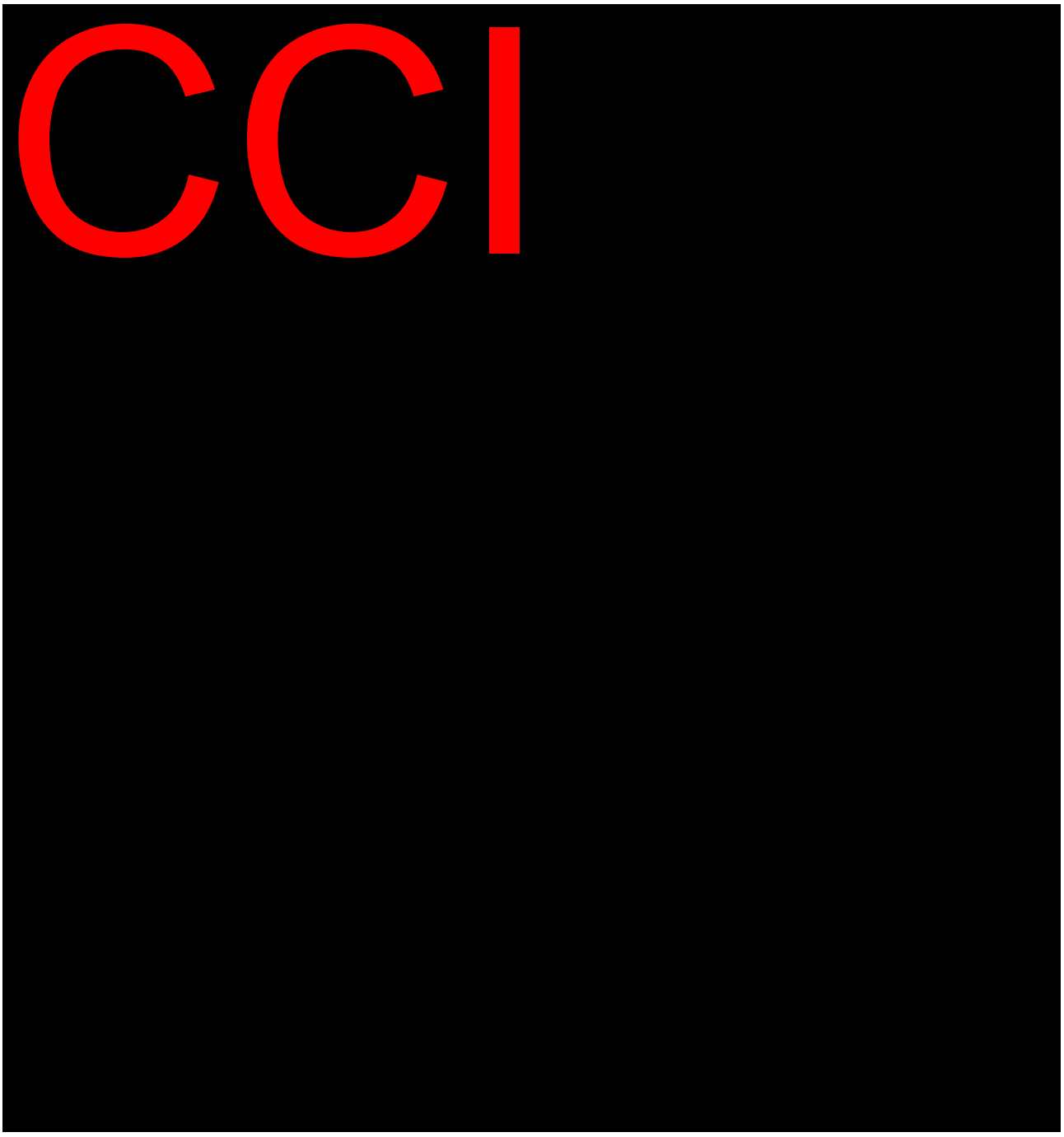
Annex 8 CCI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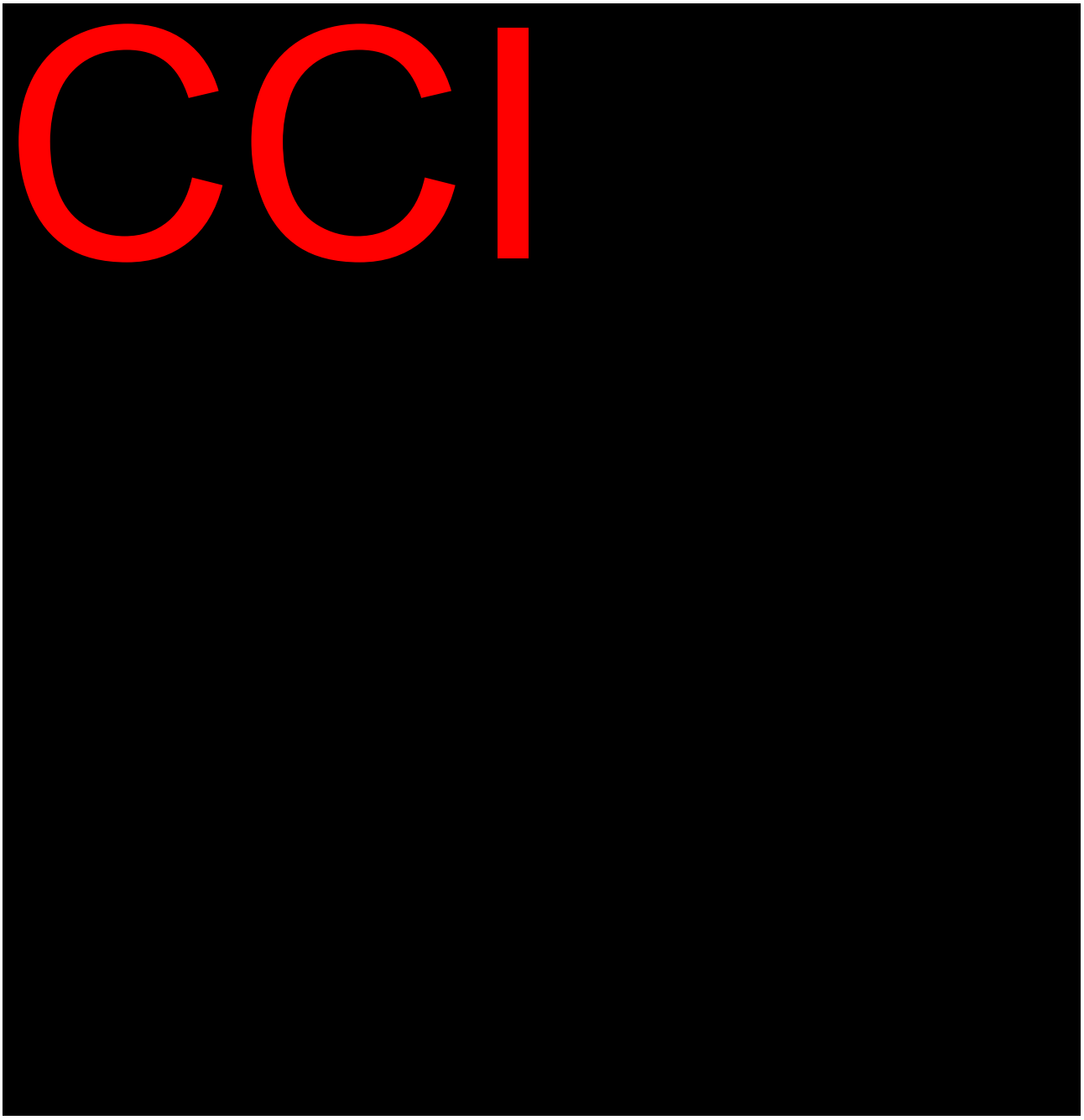
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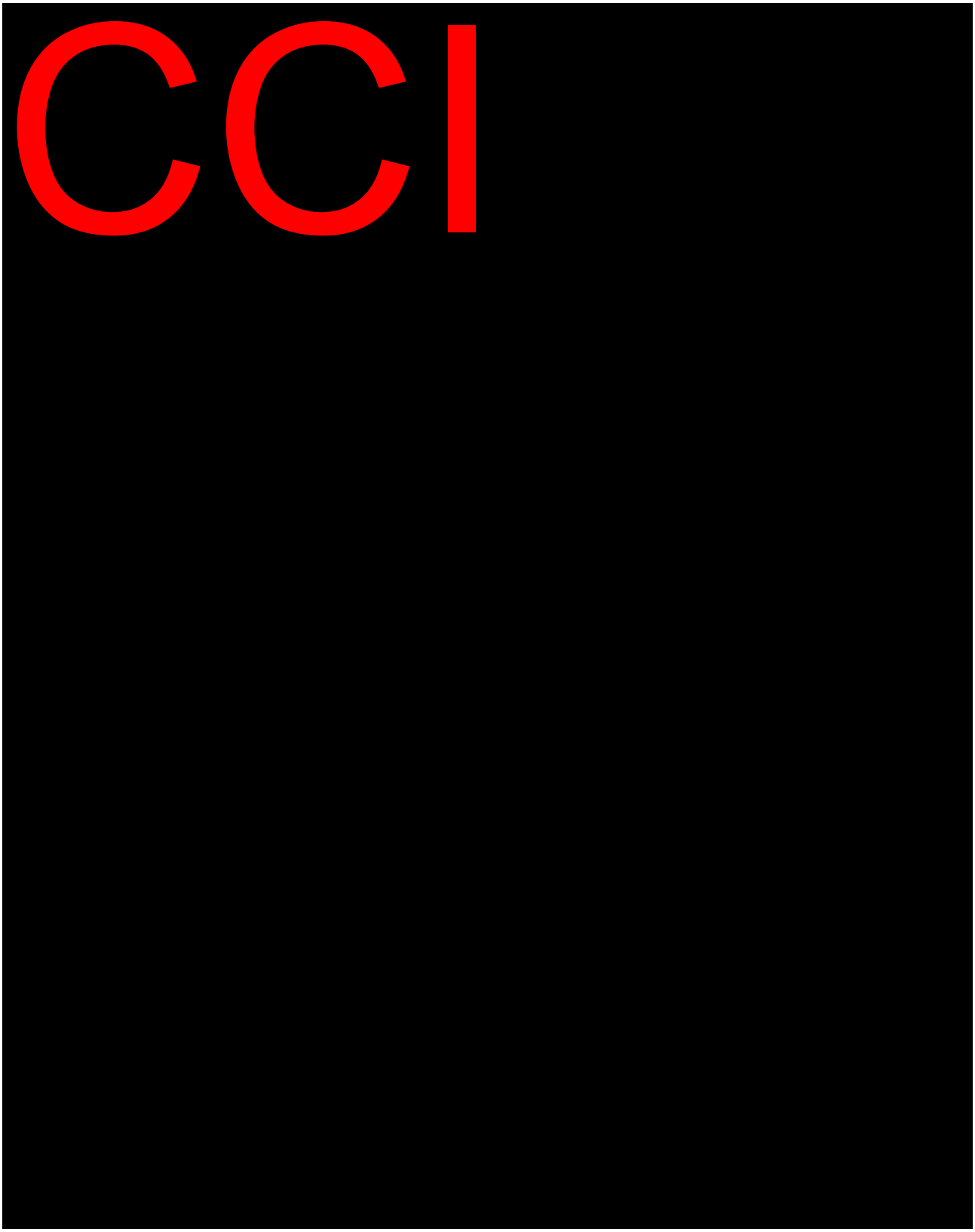
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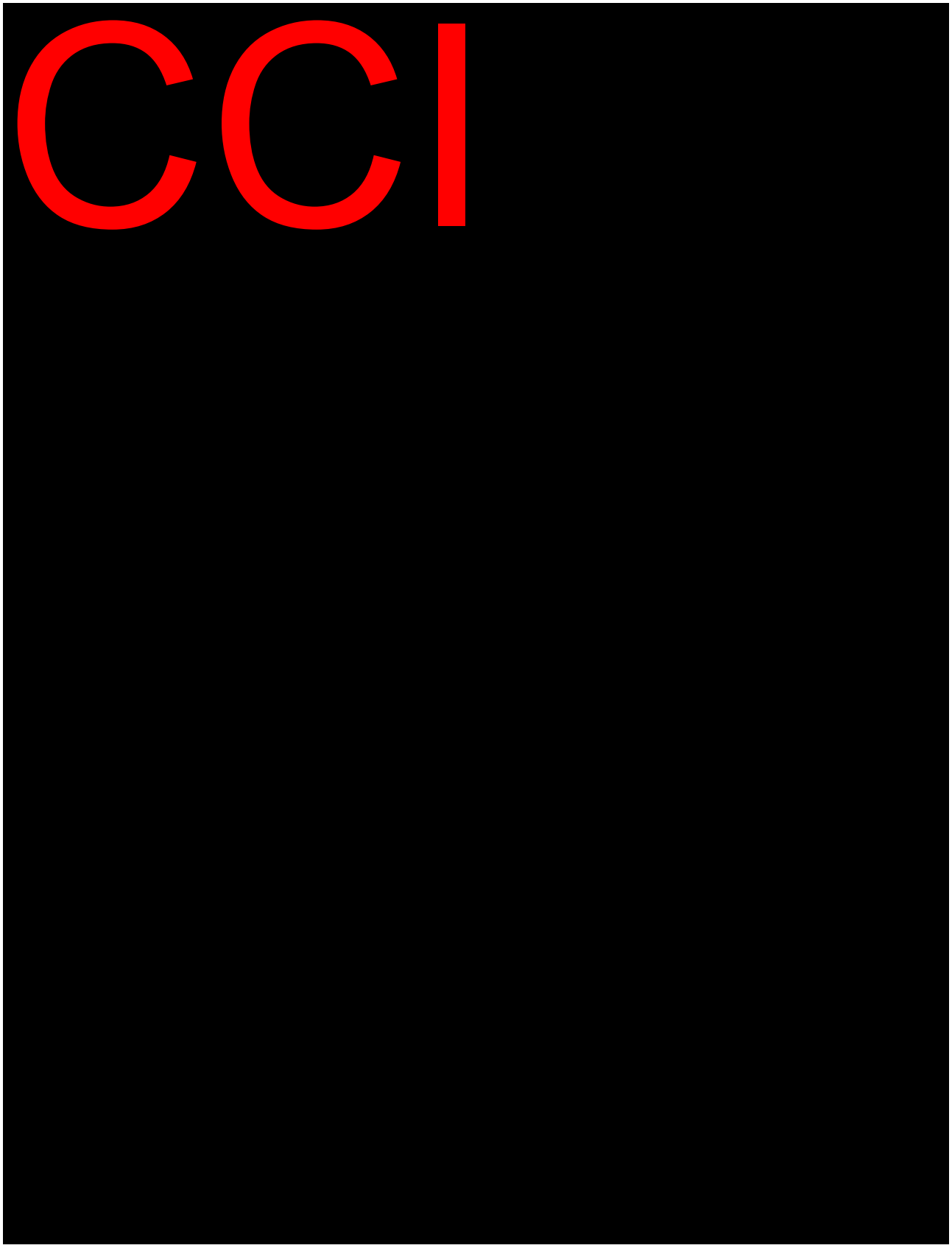
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