Non-Interventional Study Protocol

Study Protocol Number	MS100070_0110
Title	Real-world evaluation of efficacy and safety with **AV**elumab (BAVENCIO®) + Axitinib (**I**NLYTA®) in patients with Advanced Renal-Cell Carcin**O**ma (RCC) in multiple EU cou**N**tries
Protocol Version Identifier	4.0
Protocol Date / Version	24 April 2023 / Version 4.0
Replaces Version	21 December 2022 / Version 3.0
Active Substance	L01XC31: Avelumab, Axitinib
Medicinal Product	Avelumab injection, Axitinib tablet
Sponsor	Merck Healthcare Germany GmbH an affiliate of Merck KGaA, Darmstadt, Germany Waldstraße 3, 64331 Weiterstadt Germany
Research Question and Objectives	The aim of this study is to expand knowledge on the effectiveness of Avelumab 800 mg intravenous infusion flat-dose treatment in combination with Axitinib 5 mg orally twice per day as the first-line therapy in patients with advanced renal-cell carcinoma (RCC) in addition to the safety and tolerability under routine conditions of daily clinical practice. Primary objective: • To determine overall survival (OS) rate at 12 months after the index date (baseline visit) Secondary objectives: • To determine OS rate at 24 months after the index date • To assess duration of OS • To evaluate objective response rate (ORR) and disease control rate (DCR) up to 24 months after the index date • To assess duration of response (DoR) • To assess duration of progression-free survival (PFS) on Avelumab plus Axitinib therapy and progression-

free survival 2 (PFS2) on Avelumab plus Axitinib therapy followed by the second-line treatment

- To assess health-related quality of life (HRQoL) using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (NCCN-FACT FKSI-19) at the index date and at every third cycle of Avelumab treatment (intervals of about 6 weeks) thereafter, until the end of treatment or end of 24 months of study follow-up period, whichever occurs first
- To analyze the nature, severity, duration, frequency, and timing of adverse events (AEs) that occurred from the index date up to 90 days post discontinuation of Avelumab plus Axitinib or completion of the 24 months (i.e., end of the study) follow-up from the index date, whichever occurs first
- To assess time to therapy discontinuation due to AE ≥ Grade 3
- To assess therapy modifications due to AE related to Avelumab plus Axitinib therapy and management of AE related to Avelumab plus Axitinib therapy
- To determine percentage of patients receiving later-line therapy and frequency distribution of later-line therapy regimes among patients progressing on Avelumab plus Axitinib
- To assess time to second-line therapy initiation
- To assess patient-reported potential signs and symptoms of immune-related AEs

Countries of Study European countries

Author

1 Table of Contents

2 List of Abbreviations

ADL	activities of daily living
AE	adverse event
AR	adverse reaction
ATC	anatomical therapeutic chemical
CI	confidence interval
CR	complete response
CTCAE	common terminology criteria for adverse events
DCR	disease control rate
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ePRO	electronic patient-reported outcomes
FWB	functional and well-being
GPP	good pharmaco-epidemiology practices
GPS	Global Patient Safety
HA	Health Authorities
HR	hazard ratio
HRQoL	health-related quality of life
IAP	Integrated Analysis Plan
ICF	informed consent form
IEC	independent ethics committee
IMDC	International Metastatic RCC Database Consortium
IME	important medical event
IRB	institutional review board
KPS	Karnofsky performance status
MedDRA	medical dictionary for regulatory activities
MSKCC	Memorial Sloan–Kettering Cancer Center
NCCN-FACT FKSI-19	National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index 19
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD1	programmed cell death protein 1

PD-L1	programmed death ligand 1
PFS	progression-free survival
PFS2	progression-free survival 2
PR	partial response
PT	preferred term
RCC	renal-cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SAR	serious adverse reaction
SAS	statistical analysis system
SD	stable disease
SmPC	summary of product characteristics
SOC	system organ class
TNM	tumor, node, metastasis
TRAE	treatment-related adverse events
VEGF	vascular endothelial growth factor
WHO-DD	World Health Organization Drug Dictionary

3 Responsible Parties

Responsible Parties	Contact Details
Coordinating Investigator	[redacted]

3.1 Responsibilities of the Investigator

The investigator is responsible for the conduct of the study at his/her site. He/she will ensure that the study is performed in accordance with the protocol and will ensure the quality and integrity of data, following all applicable international and national guidelines.

This non-interventional study will not interfere with treatment prescription by investigators. Accordingly, the investigator will decide in advance the best therapeutic strategy for each patient according to current practice, regardless of the potential participation of this patient in the study. Subsequently, if the prescribed treatment is in line with the study protocol, the investigator will consider the possibility of including the patient in the study.

The investigator is responsible for recording of all adverse events (AEs) and reporting of adverse reactions (ARs) and/or laboratory abnormalities, as specified in Section 11.

4 Abstract

Title	Real-world evaluation of efficacy and safety with **AV**elumab (BAVENCIO®) + Axitinib (**I**NLYTA®) in patients with Advanced Renal-Cell Carcin**O**ma (RCC) in multiple EU cou**N**tries **AVION** 24 April 2023 / Version 4.0
Rationale and Background	Approval of Avelumab plus Axitinib and other combined therapies by European Medicines Agency (EMA) in 2019 triggered a paradigm shift in the management of treatment-naïve patients with advanced renal-cell carcinoma (RCC). However, available data for Avelumab plus Axitinib therapy in advanced RCC are derived primarily from clinical development programs and thus, these data may not reflect the current clinical practice. Particularly, the extent of benefit in terms of improved clinical and patient-reported outcomes, therapy tolerability, and management of toxicities in patients with advanced RCC treated with Avelumab plus Axitinib therapy under routine clinical conditions remain unknown. There is an urgent need to address this knowledge gap.
Research Question and Objectives	The aim of this study is to expand knowledge on the effectiveness of Avelumab 800 mg intravenous infusion flat-dose treatment in combination with Axitinib 5 mg orally twice per day as the first-line therapy in patients with advanced RCC in addition to the safety and tolerability under routine conditions of daily clinical practice. **Primary objective**: • To determine overall survival (OS) rate at 12 months after the index date (baseline visit) **Secondary objectives**: • To determine OS rate at 24 months after the index date • To assess duration of OS • To evaluate objective response rate (ORR) and disease control rate (DCR) up to 24 months after the index date • To assess duration of response (DoR) • To assess duration of progression-free survival (PFS) on Avelumab plus Axitinib therapy and progression-free survival 2 (PFS2) on Avelumab plus Axitinib therapy followed by the second-line treatment

	• To assess health-related quality of life (HRQoL) using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (NCCN-FACT FKSI-19) at the index date and at every third cycle of Avelumab treatment (intervals of about 6 weeks) thereafter, until the end of treatment or end of 24 months of study follow-up period, whichever occurs first • To analyze the nature, severity, duration, frequency, and timing of adverse events (AEs) that occurred from the index date up to 90 days post discontinuation of Avelumab plus Axitinib or completion of the 24 months (i.e., end of the study) follow-up from the index date, whichever occurs first • To assess time to therapy discontinuation due to AE ≥ Grade 3 • To assess therapy modifications due to AE related to Avelumab plus Axitinib therapy and management of AE related to Avelumab plus Axitinib therapy • To determine percentage of patients receiving later-line therapy and frequency distribution of later-line therapy regimes among patients progressing on Avelumab plus Axitinib • To assess time to second-line therapy initiation • To assess patient-reported potential signs and symptoms of immune-related AEs
Study Design	This study is a prospective, international, single-arm, observational real-world study in patients with advanced RCC. This multicenter study will be conducted in various European countries. Patients, who are currently receiving Avelumab (800 mg intravenously every 2 weeks) plus Axitinib (5 mg orally twice per day) in accordance with the terms of the marketing authorization for the first-line therapy, will be selected. Patient assignment to Avelumab plus Axitinib therapy should be decided in advance by the treating physician and fall within current clinical practice prior to study enrollment. The index date (baseline visit) is defined as the first administration date, after informed consent, of Avelumab plus Axitinib therapy to patients with advanced RCC. Patients will be recruited over a period of approximately 24 months and will be followed up for 24 months from the index date, irrespective of whether they continue or discontinue the study treatment. Study visits will be scheduled according to routine clinical practice in terms of visit frequency and types of performed treatments and assessments.
Population	**Inclusion criteria:** • Adult patient, age ≥ 18 years

	• Patient with the Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2 • Patient with a histologically confirmed diagnosis of RCC with any histological origin • Patient with a locally advanced/metastatic disease (i.e., newly diagnosed Stage IV RCC per American Joint Committee on Cancer) or has recurrent disease • Patient has received 1 or 2 cycles of Avelumab plus Axitinib treatment as a first-line therapy according to the approved Summary of Product Characteristics (SmPC) • Patient willing to sign the written informed consent form (ICF) to participate in this study **Exclusion criteria:** • Patient with contraindications for Avelumab or Axitinib according to the approved SmPC • Patient who has participated in any interventional clinical trial of a drug or device within 28 days prior to the start of Avelumab plus Axitinib

Outcomes	**Primary outcome**:
	• OS rate at 12 months after the index date
	  • Percentage of patients who are still alive at 12 months after the index date
	Key secondary outcomes:
	• OS rate at 24 months after the index date
	  • Percentage of patients who are still alive at 24 months after the index date
	• OS
	  • Time interval from the index date to the date of death from any cause
	• ORR up to 24 months after the index date
	  • Percentage of patients with complete response (CR) or partial response (PR), as best overall response up to 24 months after the index date according to the investigator assessment
	• DCR up to 24 months after the index date
	  • Percentage of patients with CR, PR, or stable disease (SD), as best overall response up to 24 months after the index date according to the investigator assessment

	• DoR
	  • DoR is defined as the time from the first CR or PR criteria met, whichever was reported earlier, until the date of documented overall disease progression
	• PFS
	  • Time interval from the index date to the date of disease progression or death from any cause, whichever comes first
	• PFS2
	  • Time interval from the index date to the date of disease progression on second-line treatment or death from any cause, whichever comes first
	• HRQoL using the NCCN-FACT FKSI-19 at the index date and at every third cycle of Avelumab treatment (intervals of about 6 weeks) thereafter until the end of treatment or end of 24 months of study follow-up period, whichever occurs first
	• Frequency and nature of all-cause AEs according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) that occurred from the index date up to 90 days post discontinuation of Avelumab plus Axitinib or completion of the 24 months (i.e., end of the study) follow-up from the index date, whichever occurs first
	• Duration of Avelumab plus Axitinib therapy among patients who discontinued the study drugs due to all-cause AEs ≥ Grade 3
	• Percentage of patients with therapy modifications due to AE related to Avelumab plus Axitinib therapy
	• Frequency and type of medical intervention or medications used for the management of AE related to Avelumab plus Axitinib therapy
	• Percentage of patients receiving later-line therapy and frequency distribution of later-line therapy regimes among patients progressing on Avelumab plus Axitinib including the names of medications of monotherapy/combination treatment used in second-line and third-line therapy
	• Time to second-line therapy initiation
	• Frequency of patient-reported potential signs and symptoms of immune-related AEs

Variables	In addition to the outcomes data, data will be collected on: • Patient demographics (year of birth, gender) • Physical examination and vital signs

	• Body weight • Concomitant diseases (e.g., autoimmune disease, cardiovascular disease, hypertension, renal failure, and liver disease) • Concomitant medications including the use of corticosteroids, anticoagulants, and antibiotics • Cancer history (age at diagnosis, tumor, node, metastasis (TNM) stage, location of metastases, received nephrectomy, other prior cancer therapies and procedures, and expression of the programmed death ligand 1 [PD-L1]) • ECOG performance status • Memorial Sloan–Kettering Cancer Center (MSKCC) risk group • International Metastatic RCC Database Consortium (IMDC) risk group
Data Sources	Medical records collected during routine clinical care will be used as data source. Data relevant for the study (baseline and prospective data) will be documented in the electronic case report form (eCRF) by the investigator or designated study site personnel. Patient-reported HRQoL data will be automatically captured by eCRF from electronic patient-reported outcomes (ePRO). In exceptional cases, when paper questionnaires for patient-reported HRQoL data will be completed, those signed and dated paper questionnaires will be considered as source documents.
Study Size	[redacted] In total, approximately 100 patients will be selected from approximately 30 sites in different European countries.
Data Analysis	All eligible patients, who provided written informed consent and received 1 or 2 cycles of Avelumab plus Axitinib treatment as a first-line therapy prior to informed consent, will be included in the analysis. All planned analyses will be descriptive, no formal statistical comparisons will be performed. **Primary analysis**: • OS rate (percentage of patients who are alive) at 12 months after the index date with the 95% CI **Secondary analysis**:

	• OS rate (percentage of patients who are alive) at 24 months after the index date with the 95% CI
	• OS will be estimated by the Kaplan-Meier method
	• Summary of absolute and relative frequencies of ORR and DCR up to 24 months after the index date together with the 95% CI
	• DoR, PFS, and PFS2 at 24 months after the index date will be estimated by the Kaplan-Meier method
	• There will be subgroup analyses for the primary outcome and selected secondary outcomes (OS, PFS, and PFS2 at 24 months and DCR up to 24 months) based on:
	  • ECOG performance status/IMDC risk group/MSKCC risk group
	  • RCC histopathology (clear cell, sarcomatoid, others)
	  • PD-L1 (±) status
	  • Age group (< 65, 65-75, and > 75 years)
	  • Concomitant autoimmune disease (yes, no)
	  • Prior nephrectomy (yes, no)
	• No interim analyses are planned, but the primary outcome will be analyzed as soon as all evaluable patients complete 12 months of follow-up from the index date
	• The scores (total and subscales) of the HRQoL at the index date and at every third cycle of Avelumab treatment (intervals of about 6 weeks) will be summarized using descriptive statistics for continuous variables. Possible trend in HRQoL will be also analyzed by repeated measure analysis
	• Safety analysis will be performed on AEs incidence tables, presented by MedDRA SOC and PT, and the number and percentage of patients experiencing an event
	• Exposure among the patients who discontinued the study drug due to all-cause AEs ≥ Grade 3 will be summarized as per appropriate statistics
	• Percentage of patients with therapy modifications due to related AEs and frequency and type of medical intervention or medications used for the management of related AE will be presented
	• Time to onset and duration of AEs, time to Avelumab plus Axitinib discontinuation, and time to second-line therapy after study treatment discontinuation will be summarized by descriptive statistics for continuous variables

	• Percentage of patients receiving later-line therapy (e.g., second-line therapy, third-line therapy) and frequency distribution of later-line therapy regimes among patients progressing on Avelumab plus Axitinib will be presented
Milestones	Start of data collection: July 2021 Primary analysis: September 2024 End of data collection: May 2025 Final report of study results: August 2025

5 Amendments and Updates

Amendment # 1: 13 May 2022

Sections modified	Updates	Reason(s)
Throughout	**Protocol Lead:** [redacted]	1. Administrative
Cover Page	Sponsor's address was updated	1. Administrative
Throughout	Time point to evaluate objective response rate (ORR) and disease control rate (DCR) was updated from 'at 24 months' to 'up to 24 months'.	1. To remain consistent with the respective description in the IAP.
Abstract – 'Data Sources' section **9.4 Data Source**	Clarification regarding paper questionnaires for patient-reported HRQoL data as source documents was provided.	1. To provide clarity on source documents pertaining to paper questionnaires when used.
9.2.4 Frequency of Assessments	Clarification regarding paper questionnaires for patient-reported HRQoL data was provided.	1. To provide clarity on use of paper questionnaires in addition to ePRO.
9.7 Data Analysis	Integrated Analysis Plan (IAP) replaced Statistical Analysis Plan (SAP)	1. Change in document name.
Abstract – 'Data Analysis' section **9.7.1 Analysis Sets**	Definition for the eligible patients for the analysis was updated.	1. To remain consistent with the definition of the eligible patients mentioned in the IAP.
11.4 Recording of Adverse Events	All SARs/ARs due to Avelumab as well as Axitinib will be collected in the study database.	1. To provide more clarity on recording of SARs/ARs due to Avelumab as well as Axitinib.
11.5 Safety Data Collection for Reporting	**AE/SAE Observed in Association with Disease Progression** Progression of the disease / disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) does not need to be reported as an (S)AE, unless the subject´s general condition is more severe than expected for the subject´s condition and / or unless the outcome is fatal within the AE reporting period, as defined in Section 11.4.	1. To provide more clarity on AE/SAE observed in association with disease progression.

11.6 Regulatory Reporting to the Health Authorities	Merck, as the marketing authorization holder of Avelumab, is only required to report SARs/ARs due to Avelumab to the Health Authorities.	1. To provide more clarity on reporting of SARs/ARs due to Avelumab to the Health Authorities.
14.1 Signature Pages and Responsible Persons for the Study	**Sponsor Responsible Persons Not Named on the Cover Page** Function/title, Institution, and Address were updated.	1. Administrative

Amendment # 2: 21 December 2022

Sections modified	Updates	Reason(s)
Section 4; **Section 9.1.1;** **Section 9.5;** **Figure 1**	Reduction of sample size from 400 to 250	1. Due to the change of disease landscape there is low probability that the study will be able to enroll 400 patients within the study period. 2. Investigators indicated that they will not be able to recruit the target number. 3. Multiple closure of multiple sites, including several sites in Russia, exacerbates likelihood to recruit original target sample size.
Section 4; **Section 9.5**	Updated precision estimate	1. Due to sample size reduction precision was recalculated
Throughout the document	Clarification on the wording for the frequency of visits	1. The wording in current protocol version is not clear, thus the wording is updated to avoid misunderstanding and to align with the Clinical Trial Agreement (CTA) and real-world practice.
Section 4; **Section 9.1.1**	Clarification on the wording for the duration of recruitment period	1. Planned recruitment should end March 2025, however, as the recruitment is competitive it may end sooner once 250 patients are enrolled

Throughout the document	The version number and date were updated	1. Changes in protocol as outlined above required protocol amendment
Section 4; Section 6	Planned dates updated.	1. Related to the potential reduction of the recruitment period. Last Patient In changed so Last Patient Out changed as well impacting dates for milestones.
Section 11.4; Section 11.5; Section 11.6	Collection and reporting of AEs and ARs depending on their relation to each product were clearly defined	1. All AE should be collected into Study Database, whereas only AR (serious and non-serious) related to Avelumab should be reported to Merck for entry into Safety Database and for regulatory reporting. 2. The only SAR/AR related to Axitinib that need reporting to Merck are those that are also related to Avelumab.

Amendment # 3: 24 April 2023

Sections modified	Updates	Reason(s)
Section 4 ; Section 9.1.1; Section 9.5; Figure 1	Reduction of sample size from 250 to 100 and updated precision estimate	1. Due to the change of disease landscape there is low probability that the study will be able to enroll 250 patients within the study period. 2. Investigators indicated that they will not be able to recruit the target number. 3. Multiple closure of multiple sites, including several sites in Russia, increases likelihood that the original target sample size cannot be reached. [redacted]

Abstract – 'Milestones'	Planned dates updated.	1. Recruitment period was reduced due to sample size reduction, impacting subsequent dates for milestones.
1.1 Collection and Recording of Adverse Events ; 11.5 Safety Data Reporting; 11.6 Regulatory Submission to the Health Authorities;	Safety and regulatory submission updated	1. There is a newly approved safety section for non-interventional study protocol, as a result these sections were updated to align with the new safety section. 2. Direct transmission of non-serious adverse reaction to Global Patient Safety clarified.

6 Milestones

Milestone	**Planned date**
Start of data collection	July 2021
Primary analysis	September 2024
End of data collection	May 2025
Final report of study results	August 2025

7 Rationale and Background

Kidney cancer, including renal-cell carcinoma (RCC) accounts for 3.5% of all new cancer cases and for 2.8% of all cancer deaths in Europe (Ferlay 2018). RCC represents approximately 90% of all kidney malignancies, affecting men more frequently than women (Ferlay 2018, Ljungberg 2019). Since the early stage of RCC is often asymptomatic, most patients are diagnosed at an advanced stage of the disease when prognosis is poor.

Tyrosine kinase inhibitors, immune checkpoint inhibitors, and immunotherapy are the mainstay treatments in advanced and metastatic RCC. Until recently, Sunitinib, an inhibitor of vascular endothelial growth factor (VEGF) receptor, was a standard-of-care, first-line treatment for patients with advanced RCC. However, in the last years, several phase III trials demonstrated superior efficacy of combined therapies involving immune checkpoint inhibitors over Sunitinib monotherapy.

The CheckMate 214 study (NCT02231749) showed that therapy with Nivolumab (anti-programmed cell death protein 1 [PD1] antibody) and Ipilimumab (anti-cytotoxic T-lymphocyte–associated antigen 4 [CTLA4] antibody) resulted in a longer median progression-free survival (PFS) (11.6 months, 95% confidence interval [CI]: 8.7-15.5) compared with Sunitinib (8.4 months, 95% CI: 7.0-10.8). The hazard ratio (HR) for disease progression or death was 0.82 (99.1% CI: 0.64-1.05; p = 0.03). The objective response rate (ORR) was 42% (95% CI: 37%-47%) with Nivolumab plus Ipilimumab vs 27% (95% CI: 22%-31%) with Sunitinib (p < 0.001). The median overall survival (OS) was not reached in Nivolumab plus Ipilimumab group (95% CI: 28.2 to not estimable) vs 26.0 months (95% CI: 22.1 to not estimable) in Sunitinib group (HR for death, 0.63, p < 0.001) (Motzer 2018).

Similarly, in the KEYNOTE-426 study (NCT02853331), Pembrolizumab (anti-PD1 antibody) combined with Axitinib (VEGF receptor inhibitor) increased median PFS to 15.1 months (95% CI: 12.6-17.7) compared to 11.1 months (95% CI: 8.7-12.5) in the Sunitinib group. The HR for disease progression or death was 0.69 (95% CI: 0.57-0.84; p < 0.001). The ORR was 59.3% (95% CI: 54.5%-63.9%) in the Pembrolizumab plus Axitinib arm and 35.7% (95% CI: 31.1%-40.4%) in the Sunitinib arm (p < 0.001). The OS rate at 1 year in the Pembrolizumab plus Axitinib group was 89.9% vs 78.3% in the Sunitinib group (HR: 0.53, 95% CI: 0.38-0.74; p < 0.0001) (Rini 2019a).

The JAVELIN Renal 101 study (NCT02684006) evaluated the combination Avelumab (anti-programmed death ligand 1 [PD-L1] antibody) and Axitinib (VEGF receptor inhibitor). In the overall population, patients receiving Avelumab plus Axitinib achieved longer median PFS (13.8 months, 95% CI: 11.1 to not estimable) than those treated with Sunitinib (8.4 months, 95% CI: 6.9-11.1). The HR for disease progression or death was 0.69 (95% CI: 0.56-0.84; p < 0.001). Furthermore, Avelumab plus Axitinib therapy increased ORR to 51.4% (95% CI: 46.6%-56.1%) compared to 25.7% (95% CI: 21.7%-30.0%) with Sunitinib therapy. Among the patients with PD-L1-positive tumors, PFS and ORR were similar to those observed in the overall population. The OS data were immature at the time of that analysis (Motzer 2019).

The updated efficacy data from the JAVELIN Renal 101 study (NCT02684006) showed that after a follow-up of 13 months, PFS was significantly longer in the Avelumab plus Axitinib arm than in the Sunitinib arm as follow: (i) PD-L1+ population – HR: 0.62, 95% CI: 0.490-0.777, one-sided $p < 0.0001$, median: 13.8 months, 95% CI: 10.1-20.7 versus 7.0 months, 95% CI: 5.7-9.6; and (ii) overall population – HR: 0.69, 95% CI: 0.574-0.825, one-sided $p < 0.0001$, median: 13.3 months, 95% CI: 11.1-15.3 versus 8.0 months, 95% CI: 6.7-9.8. The OS data were immature: (i) PD-L1+ population – HR: 0.828, 95% CI: 0.596-1.151, one-sided $p = 0.1301$; and (ii) overall population – HR: 0.796, 95% CI: 0.616-1.027, one-sided $p = 0.0392$ (Choueiri 2020).

Importantly, these clinical trials demonstrated that increased efficacy offered by these treatments was paralleled by acceptable safety profile. Treatment-related adverse events (TRAEs) ≥ Grade 3 occurred in 46% of patients treated with Nivolumab plus Ipilimumab, 62.9% of patients treated with Pembrolizumab plus Axitinib and in 56.7% of patients treated with Avelumab plus Axitinib compared to 55.4% to 63.0% of patients receiving Sunitinib. TRAEs ≥ Grade 3 occurred in ≥ 10% of patients were increased lipase levels among patients receiving Nivolumab plus Ipilimumab (10.0%), hypertension, and increased alanine aminotransferase levels in patients treated with Pembrolizumab plus Axitinib (22.1% and 13.3%, respectively), and hypertension in patients treated with Avelumab plus Axitinib (25.6%). Death due to toxicity of trial treatment was documented in 1.5% of patients treated with Nivolumab plus Ipilimumab, 0.9% of patients receiving Pembrolizumab plus Axitinib and 0.7% of patients treated with Avelumab plus Axitinib. About 22%, 10.7%, and 7.6% of patients treated with Nivolumab plus Ipilimumab, Pembrolizumab plus Axitinib, and Avelumab plus Axitinib, respectively, discontinued both study drugs due to TRAEs (Rini 2019b).

Furthermore, therapy modifications were frequent across the studies. For instance, delays in administration of Nivolumab and Ipilimumab occurred in 58% and 27% of patients, respectively (Motzer 2018), while 69.9% of patients had interruption of either Pembrolizumab or Axitinib (Rini 2019a). Axitinib dose was reduced in 20.3% of patients co-treated with Pembrolizumab and in 42.2% of patients co-treated with Avelumab (Rini 2019a, Motzer 2019). High doses of glucocorticoids for management of immune-related adverse events (AEs) were required by 35% of patients on Nivolumab plus Ipilimumab and only by 11.1% of patients on Avelumab plus Axitinib therapy (Motzer 2018, Motzer 2019). Among patients treated with Avelumab plus Axitinib, 38.2% had any grade pre-specified immune-related AEs, which were most frequently immune-related thyroid disorders (24.7% of patients) (Motzer 2019). In 9.0% of patients, these immune-related AEs were of ≥ Grade 3 (Motzer 2019).

Safety of Avelumab plus Axitinib was also investigated in an open-label, dose-finding phase 1b study JAVELIN Renal 100 (NCT02493751). About 58% of enrolled treatment-naïve advanced RCC patients experienced ≥ Grade 3 TRAEs, which were most frequently hypertension (29.0%) and increased concentrations of alanine aminotransferase, amylase, and lipase, and palmar-plantar erythrodysesthesia syndrome in 7.0% of patients each. About 2.0% of patients died due to treatment-related autoimmune myocarditis (Choueiri 2018).

In general, the safety profile of combined Avelumab plus Axitinib therapy is in line with that of single agents. Recently, phase 1 JAVELIN Solid Tumor study (NCT01772004) provided further safety data for first-line Avelumab monotherapy in metastatic RCC. In this study, 12.9% of

patients had a ≥ Grade 3 TRAE, which was most frequently increased lipase levels (Vaishampayan 2019). About 3.2% of patients had serious TRAEs (colitis and hyperthermia). TRAEs led to drug discontinuation in 4.8% of patients (anaphylactic reaction, aspartate aminotransferase increase, and nephritis). Infusion-related reactions occurred in 35.5% of patients and 29.0% had immune-related AEs with thyroid disorders and immune-related rash documented in ≥ 10.0% of patients. Axitinib was compared against Sorafenib in phase III study in previously untreated metastatic RCC patients. Most frequent all-cause AEs ≥ Grade 3 in Axitinib arm were hypertension, asthenia, diarrhea, weight decrease, palmar-plantar erythrodysesthesia, and fatigue (Hutson 2013). About 5.0% of patients had serious TRAEs, including diarrhea, atrial flutter, cardiac arrest, myocardial infarction, gastric ulcer, gastrointestinal hemorrhage, melena, nausea, rectal hemorrhage, vomiting, retroperitoneal hematoma, asthenia, mucosal inflammation, dehydration, decreased appetite, aortoduodenal fistula, and hypertensive crisis. Compared to other VEGF receptor inhibitors, Axitinib causes less hepatic and hematologic toxicity and thus, it is considered a better partner for combined treatments with other anti-cancer agents such as Avelumab.

Approval of Avelumab plus Axitinib and other combined therapies by the European Medicines Agency (EMA) in 2019 triggered a paradigm shift in the management of treatment-naïve patients with advanced RCC (BAVENCIO® Summary of Product Characteristics (SmPC), KEYTRUDA® SmPC, OPDIVO® SmPC). Nevertheless, available data for Avelumab plus Axitinib therapy in patients with advanced RCC are derived primarily from clinical development programs and thus, they may not fully reflect the current clinical practice. Particularly, the extent of benefit in terms of improved clinical and patient-reported outcomes, therapy tolerability, and management of toxicities in patients with advanced RCC treated with Avelumab plus Axitinib under routine clinical conditions remain unknown. Therefore, evidence on the real-world efficacy (i.e., effectiveness) and safety of Avelumab in combination with Axitinib therapy in advanced RCC is urgently needed to address this knowledge gap and can help bolster the value of using Avelumab plus Axitinib in first-line therapy in patients with advanced RCC.

8 Research Question and Objectives

The aim of this study is to expand knowledge on the effectiveness of Avelumab 800 mg intravenous infusion flat-dose treatment in combination with Axitinib 5 mg orally twice per day as the first-line therapy in patients with advanced RCC in addition to safety and tolerability under routine conditions of daily clinical practice.

8.1 Primary Objective

- To determine OS rate at 12 months after the index date (baseline visit)

8.2 Secondary Objectives

- To determine OS rate at 24 months after the index date
- To assess duration of OS
- To evaluate ORR and disease control rate (DCR) up to 24 months after the index date
- To assess duration of response (DoR)

- To assess duration of PFS on Avelumab plus Axitinib therapy and progression-free survival 2 (PFS2) on Avelumab plus Axitinib therapy followed by the second-line treatment
- To assess the health-related quality of life (HRQoL) using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (NCCN-FACT FKSI-19) at the index date and at every third cycle of Avelumab treatment (intervals of about 6 weeks) thereafter, until the end of treatment or end of 24 months of study follow-up period, whichever occurs first
- To analyze the nature, severity, duration, frequency, and timing of AEs that occurred from the index date up to 90 days post discontinuation of Avelumab plus Axitinib or completion of the 24 months (i.e., end of the study) follow-up from the index date, whichever occurs first
- To assess time to therapy discontinuation due to AE ≥ Grade 3
- To assess therapy modifications due to AE related to Avelumab plus Axitinib therapy and management of AE related to Avelumab plus Axitinib therapy
- To determine percentage of patients receiving later-line therapy and frequency distribution of later-line therapy regimes among patients progressing on Avelumab plus Axitinib
- To assess time to second-line therapy initiation
- To assess patient-reported potential signs and symptoms of immune-related AEs

9 Research Methods

9.1 Study Design

9.1.1 Design Overview

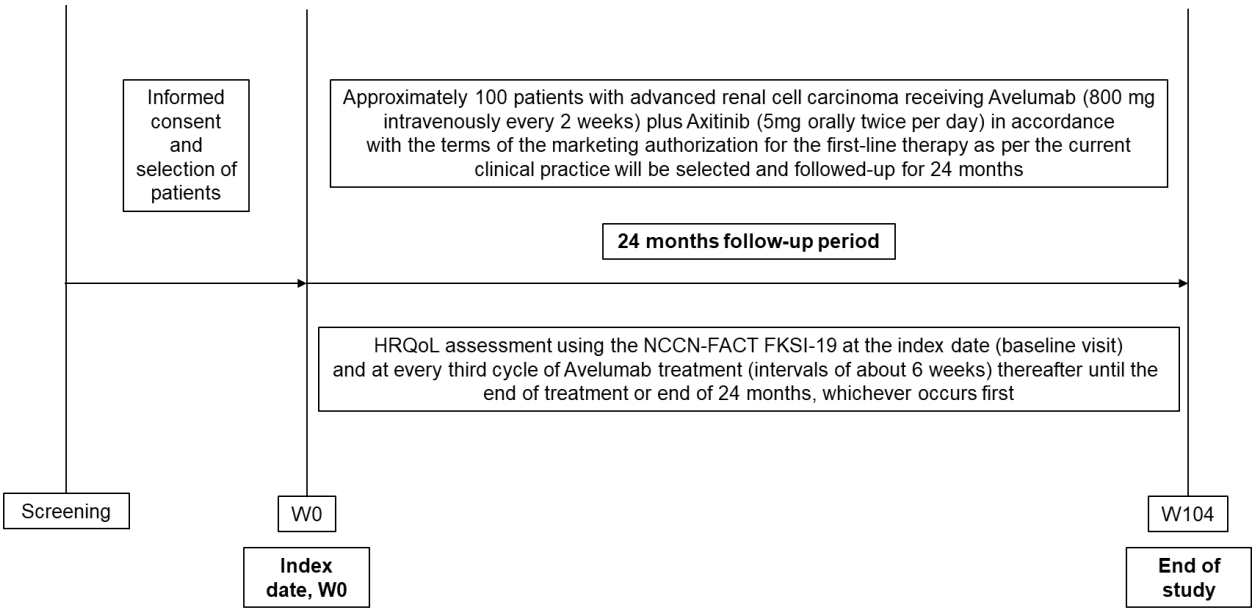
This study is a prospective, international, single-arm, observational real-world study in patients with advanced RCC. This multicenter study will be conducted at approximately 30 centers in various European countries. A total of approximately 100 patients, who are currently receiving Avelumab (800 mg intravenously every 2 weeks) plus Axitinib (5 mg orally twice per day) in accordance with the terms of the marketing authorization for the first-line therapy, will be selected. Patient assignment to Avelumab plus Axitinib therapy should be decided in advance by the treating physician and fall within current clinical practice prior to study enrollment. There will not be any study-specific interventions in this study. The study size is further described in Section 9.5.

The index date (baseline visit) is defined as the first administration date, after informed consent, of Avelumab plus Axitinib therapy to patients with advanced RCC. Patients will be recruited over a period of approximately 24 months and will be followed up for 24 months from the index date, irrespective of whether they continue or discontinue the study treatment. There will be a safety follow-up at 90 days post discontinuation of Avelumab plus Axitinib therapy.

Study visits will be scheduled according to routine clinical practice in terms of visit frequency and types of performed treatments and assessments. Due to the observational nature of this study, planned assessments will be recorded as part of routine clinical practice, in line with the approved SmPC and as clinically indicated.

Figure 1 below provides a schematic overview of the study design.

Figure 1 . Overview of the Study Design



W=Week, HRQoL=Health-related quality of life, NCCN-FACT FKSI-19=National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index 19

9.1.2 Outcomes

9.1.2.1 Primary

The primary effectiveness outcome is:

- OS rate at 12 months after the index date
  - Percentage of patients who are still alive at 12 months after the index date

9.1.2.2 Secondary

Secondary effectiveness outcomes:

- OS rate at 24 months after the index date
  - Percentage of patients who are still alive at 24 months after the index date
- OS
  - Time interval from the index date to the date of death from any cause
- ORR up to 24 months after the index date
  - Percentage of patients with complete response (CR) or partial response (PR), as best overall response up to 24 months after the index date according to the investigator assessment

- DCR up to 24 months after the index date
  - Percentage of patients with CR, PR, or stable disease (SD), as best overall response up to 24 months after the index date according to the investigator assessment
- DoR
  - DoR is defined as the time from the first CR or PR criteria met, whichever was reported earlier, until the date of documented overall disease progression

Note: CR, PR, SD, progressive disease (PD) will be defined as per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer 2009)

Progression-free survival:

- PFS
  - Time interval from the index date to the date of disease progression or death from any cause, whichever comes first
- PFS2
  - Time interval from the index date to the date of disease progression on second-line treatment or death from any cause, whichever comes first

Patient-reported outcomes:

- HRQoL using the NCCN-FACT FKSI-19 at the index date and at every third cycle of Avelumab treatment (intervals of about 6 weeks) thereafter until the end of treatment or end of 24 months of study follow-up, whichever occurs first
  - The NCCN-FACT FKSI-19 is a 19-item self-reported questionnaire that captures symptom severity and interference in activity and general health perceptions (Rothrock 2013, Rao 2009)
  - The NCCN-FACT FKSI-19 covers 4 subscales of the FKSI:
    1. DRS-P, disease-related symptoms subscale–physical
    2. DRS-E, disease-related symptoms subscale–emotional
    3. TSE, treatment side effects subscale
    4. Functional and well-being (FWB), function and well-being subscale (Rao 2009)
  - Each of the items is scored on a five-point scale from zero (not at all) to 4 (very much).

Safety and tolerability:

- Frequency and nature of all-cause AEs according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) that occurred from the index date up to 90 days post discontinuation of Avelumab plus Axitinib or completion of the 24 months (i.e., end of the study) follow-up from the index date, whichever occurs first
- Frequency of all-cause AEs by maximum Common Terminology Criteria for Adverse Events (CTCAE) grade that occurred from the index date up to 90 days post discontinuation of

Avelumab plus Axitinib or completion of the 24 months (i.e., end of the study) follow-up from the index date, whichever occurs first

- Frequency of all-cause AE ≥ Grade 3 leading to discontinuation of Avelumab plus Axitinib summarized by MedDRA SOC and PT
- Duration of Avelumab plus Axitinib therapy among patients who discontinued the study drug due to all-cause AEs ≥ Grade 3
- Time to onset of all-cause AEs defined as the time interval from the index date to the onset of AE
- Duration of all-cause AEs defined as the time interval between the onset and resolution of AE
- Outcome of all-cause AEs: resolved, resolving, not resolved, resolved with sequelae, fatal, unknown
- Percentage of patients with therapy modifications due to AE related to Avelumab plus Axitinib therapy (e.g., therapy interruptions and reductions of infusion rate for Avelumab, therapy interruptions, and dose reductions for Axitinib)
- Frequency and type of medical intervention or medications used for the management of AE related to Avelumab plus Axitinib therapy (e.g., use of corticosteroids, antihypertensive therapy, treatment for thyroid dysfunction, measures to decrease hemoglobin, and hematocrit)
- Percentage of patients receiving later-line therapy and frequency distribution of later-line therapy regimes among patients progressing on Avelumab plus Axitinib including the names of medications of monotherapy/combination treatment used in second-line and third-line therapy
- Time to second-line therapy initiation is defined as the time from Avelumab plus Axitinib therapy discontinuation to the initiation of second-line therapy
- Frequency of patient-reported potential signs and symptoms of immune-related AEs (the investigator or the treating physician will explain signs and symptoms of potential immune-related AEs to patients; immune-related AEs may include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction etc.) (BAVENCIO, SmPC)

9.2 Setting

9.2.1 Study Population

The study population will be identified according to the below inclusion and exclusion criteria. For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Adult patient, age ≥ 18 years
2. Patient with the Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2 (Oken 1982)
3. Patient with a histologically confirmed diagnosis of RCC with any histological origin

4. Patient with a locally advanced/metastatic disease (i.e., newly diagnosed Stage IV RCC per American Joint Committee on Cancer) or has recurrent disease
5. Patient has received 1 or 2 cycles of Avelumab plus Axitinib treatment as a first-line therapy according to the approved SmPC
6. Patient willing to sign the written informed consent form (ICF) to participate in this study

Patients are not eligible for this study if they fulfill any of the following exclusion criteria:

1. Patient with contraindications for Avelumab or Axitinib according to the approved SmPC
2. Patient who has participated in any interventional clinical trial of a drug or device within 28 days prior to the start of Avelumab plus Axitinib

9.2.2 Definition of Study Cohorts and Description of Treatments

This is a single cohort study enrolling patients with advanced RCC, who are currently receiving Avelumab plus Axitinib in accordance with the terms of the marketing authorization for the first-line therapy. Patient assignment to Avelumab plus Axitinib therapy should have been decided in advance by the treating physician and fall within current clinical practice and prior to study enrollment.

According to the approved SmPC, the recommended dose of Avelumab is 800 mg administered intravenously over 60 minutes every 2 weeks in combination with Axitinib 5 mg orally taken twice per day (12 hours apart) with or without food until disease progression or unacceptable toxicity.

9.2.3 Observation Period

Each patient will be followed up from the date the ICF is signed until lost to follow-up, withdrawal of consent, death, or the end of the data collection period, whichever comes first. Patients will be followed up for 24 months from the index date, irrespective of whether they continue or discontinue the study treatment.

9.2.4 Frequency of Assessments

The Table 1 provides the Schedule of Assessments for this study. Patients who sign the ICF and meet all eligibility criteria during the screening will be enrolled in this study. The baseline visit will be at the index date, which is defined as the first administration date, after informed consent, of Avelumab plus Axitinib therapy to patients with advanced RCC. Baseline data will be collected at the index date. The screening visit and the baseline visit may or may not be on the same day.

Patients will attend the sites (hospitals) as per routine clinical practice at the discretion of the treating physician. Therefore, the timing of the visits may vary. Results from physical examinations, vital signs, and body weight will be collected upon availability. Data on treatment response will also be collected upon availability. Patients will be asked to provide HRQoL data using the NCCN-FACT FKSI-19 questionnaires available as electronic patient-reported outcomes (ePRO) questionnaires at the index date and at every third cycle of Avelumab treatment (intervals of about 6 weeks) thereafter, until the end of treatment or end of 24 months of study follow-up period, whichever occurs first. Patients can fill out HRQoL data (ePRO questionnaires) either at their homes or at sites (hospitals) during their scheduled visits as per their convenience. In

exceptional cases, the questionnaires on patient-reported HRQoL data can be completed on paper and transferred into electronic case report form (eCRF) afterwards.

Table 1. Schedule of Assessments

Assessment	Screening visit	W0 (Index date/ Baseline visit)	Follow-up visits (between W0 to W104) as per routine clinical practice	W104 (end of study)
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Demographics (year of birth, gender)		X		
Physical examination/ vital signs[a]		X		
Body weight[a]		X	X	X
Concomitant diseases[b]		X		
Concomitant medications[c]		X	X	X
Cancer history[d]		X		
ECOG performance status		X		
MSKCC risk group[e]		X		
IMDC risk group[f]		X		
HRQoL using the NCCN-FACT FKSI-19 questionnaire[g]		X	X	X
Safety assessment	X	X	X	X
Avelumab plus Axitinib therapy[h]		X	X	X
Second-line treatment (if Avelumab plus Axitinib discontinued)			X	X
Third-line treatment (if second-line treatment discontinued)			X	X
Treatment response[i]			X	X
Treatment for AE related to Avelumab plus Axitinib therapy[j]		X	X	X

AE=Adverse event, ECOG=Eastern Cooperative Oncology Group, HRQoL=health-related quality of life, IMDC= International Metastatic RCC Database Consortium, MSKCC=Memorial Sloan–Kettering Cancer Center, NCCN-FACT FKSI-19=National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index 19, W=Week

[a] Results from physical examinations, vital signs, and body weight will be collected upon availability. Physical examination includes an examination of major body systems. Vital signs include blood pressure (systolic and diastolic) and pulse rate.

[b] Information on concomitant diseases such as autoimmune disease, cardiovascular disease, hypertension, renal failure, and liver disease.

[c] Information on concomitant medications such as the use of corticosteroids, anticoagulants, and antibiotics.

[d] Information on cancer history: age at diagnosis, tumor, node, metastasis (TNM) stage, location of metastases, received nephrectomy, other prior cancer therapies and procedures, expression of the programmed death ligand 1 (PD-L1).

[e] The MSKCC risk score is based on 5 independent risk factors: low Karnofsky performance status (KPS), low hemoglobin level, high serum lactate dehydrogenase, high corrected serum calcium level, and time from diagnosis to the initiation of systemic therapy of less than 1 year (Heng 2013). The MSKCC risk score categorizes patients into 3 risk groups: 0 (low risk), 1 or 2 (intermediate risk), and ≥ 3 (high risk).

[f] The IMDC risk score is based on data of patients with metastatic RCC treated with targeted therapies and includes 6 risk factors: low KPS, low hemoglobin level, high neutrophil count, high platelet count, high corrected serum calcium level, and time from diagnosis to the initiation of systemic therapy of less than 1 year (Heng 2013). The IMDC risk score categorizes patients into 3 risk groups: 0 (low risk), 1 or 2 (intermediate risk), and ≥ 3 (high risk).

[g] All patients will be asked to fill HRQoL data available as ePRO questionnaires at the index date and at every third cycle of Avelumab treatment (intervals of about 6 weeks) thereafter, until the end of treatment or end of 24 months of study follow-up period, whichever occurs first.

[h] Avelumab plus Axitinib therapy: data on dose at regular follow-up visits, therapy modifications (change in dose) due to AE, temporary interruption, and treatment discontinuation will be collected upon availability.

[i] Treatment response includes data on complete response, partial response, stable disease, or progressive disease defined as per RECIST version 1.1. Data on treatment response will be collected upon availability.

[j] Information on treatment used for the management of AE related to Avelumab plus Axitinib therapy such as use of corticosteroids, antihypertensive therapy, treatment for thyroid dysfunction, measures to decrease hemoglobin, and hematocrit.

9.2.5 Withdrawal from the Study

Patients are free to withdraw from the study at any time without giving their reasons. Patients who discontinue treatment will continue to be followed up until end of the study, as per Schedule of Assessments (Table 1), regardless of treatment status.

A patient is considered lost to follow-up after 2 documented failed attempts to reach out to the patient. If a patient is lost to follow-up, adequate effort must be made by study center personnel to contact the patient and determine the reason for discontinuation. The measures taken to follow-up on the patient must be documented. If a patient withdraws before completion of study procedures (as described in the Schedule of Assessments in Table 1), the reason for withdrawal shall be documented in source documents and in the eCRF.

9.3 Variables

In addition to the outcomes data, data will be collected on:

- Demographic data at baseline visit: year of birth, gender
- Physical examination and vital signs at baseline visit
- Body weight at baseline visit and follow-up visits
- Concomitant diseases (e.g., autoimmune disease, cardiovascular disease, hypertension, renal failure, and liver disease) at baseline visit
- Concomitant medications including the use of corticosteroids, anticoagulants, and antibiotics at baseline visit and follow-up visits
- Cancer history (age at diagnosis, tumor, node, metastasis (TNM) stage, location of metastases, received nephrectomy, other prior cancer therapies and procedures, and expression of the PD-L1) at baseline visit
- ECOG performance status at baseline visit
- Memorial Sloan–Kettering Cancer Center (MSKCC) risk group at baseline visit (Heng 2013)
- International Metastatic RCC Database Consortium (IMDC) risk group at baseline visit (Heng 2013)

Derived and transformed data needed for the analysis are described in Section 9.7.2.

9.4 Data Source

The data to be collected in the study will be obtained by means of an eCRF. The data in the eCRF should be consistent with the relevant source documents. Further details are provided in Section 9.6.

Data on patient demographics, concomitant diseases, concomitant medications, cancer history, ECOG performance status, MSKCC risk group, and IMDC risk group will be collected from the patient's medical records at the time of the baseline visit. The data collected from physical examinations, vital signs, body weight, treatment response, and AE reporting, upon availability, will be transcribed into the eCRF by the site staff. Patient-reported HRQoL data using the NCCN-FACT FKSI-19 questionnaires will be automatically captured by eCRF from ePRO questionnaires. In exceptional cases, when paper questionnaires for patient-reported HRQoL data will be completed, those signed and dated paper questionnaires will be considered as source documents.

9.5 Study Size

[redacted]

In total, approximately 100 patients will be selected from approximately 30 sites in different European countries.

9.6 Data Management

The main purpose of the eCRF is to obtain data required by the non-interventional study protocol in a complete, accurate, legible, and timely manner. The data in the eCRF should be consistent with the relevant source documents.

The investigator or designee is responsible for ensuring that the data collected in the course of this study is accurate and documented appropriately on all applicable forms. Data will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures (including serious adverse event [SAE]/ serious adverse reaction [SAR] reconciliation) and coding activities have been completed. PDF files of the eCRFs will be provided to the investigators at the completion of the study.

The eCRFs are essential study documents and must be suitable for regulatory inspections and submissions.

9.7 Data Analysis

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables will be described with the following measures of central tendency and dispersion: the number of patients, missing observations, mean, standard deviation, median, interquartile range, minimum,

and maximum. Frequency, percentage, and number of missing observations will be provided for categorical variables. Exact Clopper-Pearson 95% CIs will be included where appropriate. The Kaplan-Meier method will be used for the analysis of time to event objectives.

In general, descriptive statistics of quantitative parameters (results and change from baseline) will be provided for observed cases, that is, patients having non-missing assessments at a specific timepoint. Missing data count will be presented.

All AE verbatim terms and medical history terms will be recorded and coded using the MedDRA. All previous and concomitant medication being recorded will be coded using World Health Organization Drug Dictionary (WHO-DD).

Baseline data will be defined as the data collected at the index date.

Computations and generation of tables, listings, and data for figures will be performed using statistical analysis system (SAS)® version 9.4 or higher (SAS Institute, Cary, NC, USA).

The full analysis will be described in a written and approved Integrated Analysis Plan (IAP).

9.7.1 Analysis Sets

All eligible patients, who provided written informed consent and received 1 or 2 cycles of Avelumab plus Axitinib treatment as a first-line therapy prior to informed consent, will be included in the analysis. All planned analyses will be descriptive, no formal statistical comparisons will be performed.

9.7.2 Derived and Transformed Data

Primary and secondary effectiveness outcomes will be derived as per definition reported in Section 9.1.2.

For OS, PFS, PFS2 and DoR, the percentage of patients alive at the time of outcome assessment (12 or 24 months) will be calculated as per the Kaplan-Meier approach.

For PFS, PFS2 and DoR, a patient progressing after stopping current treatment and starting a new therapy will be censored at the latest tumor assessment showing no progression before changing therapy.

For safety, time to onset of AE will be calculated as difference in days between start date of AE and the index date +1, while duration of AE (applicable for resolved AEs only) will be calculated as difference in days between end date of AE and start date of AE +1.

Time to Avelumab plus Axitinib discontinuation will be derived as difference in days between last dose of Avelumab plus Axitinib and the index date +1 and time to second-line therapy after study treatment discontinuation will be calculated as difference in days between start date of second-line treatment and last dose of Avelumab plus Axitinib +1.

As per NCCN-FACT FKSI-19 scoring guidelines (version 2), the total HRQoL score (range 0-76) will be calculated as sum of single items scores multiplied by 19 and divided by the number of items completed. NCCN-FACT FKSI-19 will also cover 4 subscales: DRS-P (items from 1 to 11, range 0-48), DRS-E (item 12, range 0-4), TSE (items from 13 to 15, range 0-12) and FWB (items from 16 to 19, range 0-12). The higher the subscores or the total score, the better the HRQoL. The subscales will be evaluable, if at least 50% of respective items will be answered and will be calculated as sum of items included in the subscale, multiplied by the item included in the subscale, and divided by the item answered in the subscale. The FKSI-19 questionnaire as a whole will be evaluable, if all subscales will be evaluable and at least 80% of all items will be answered. Score of items 11 (C6), 12 (GF5), and from 16 to 19 (GF1, GF3 and GF7) will be reversed before calculating total and subscale scores.

Every effort will be made to capture all available data by:

- Ensuring that primary variables of interest are those that are routinely collected as part of routine clinical practice and are available via medical charts, physician, and/or patient/caregiver reporting, as appropriate
- Collecting only critical data elements (i.e., variables aligned with the study objectives) to minimize site/participant burden
- Training of sites and data abstractors regarding data collection; setting reporting windows around a target timepoint
- Checking for patterns of missingness and addressing any issues with targeted operational strategies

Full details on handling missing data, which are common in observational studies, will be described separately in the IAP. In general, missing data will not be imputed and data will be analyzed as they are recorded in the study eCRFs.

9.7.3 Statistical Methods

Patient demographics, medical and cancer history, MSKCC and IMDC risk group, and concomitant medications will be summarized with appropriate descriptive statistics in the analysis set overall.

Medications will be summarized according to the WHO-DD, considering the first digit of the Anatomical Therapeutic Chemical (ATC) classification system (anatomic category) and the first 3 digits of the ATC class (therapeutic category). Multiple occurrences of the same drug in the same patient will be counted only once in the tables.

Recorded medications will be classified into the following groups:

- Prior medications are those that the patient took and discontinued prior to the index date
- Concomitant medications are those that the patient continued or started on or after the index date

- Medications used for the management of AE related to Avelumab plus Axitinib therapy on or after the index date
- Medications used as second-line or third-line therapy after the index date

The exposure will be analyzed descriptively by means of summary of treatment duration in weeks or months, reasons for dose reduction or temporary interruption, number of patients with permanent discontinuation, and reason for permanent discontinuation.

- The primary analysis will include:
  - OS rate (percentage of patients who are alive) at 12 months after the index date with the 95% CI
- The secondary analysis will include:
  - OS rate (percentage of patients who are alive) at 24 months after the index date with the 95% CI
  - OS will be estimated by the Kaplan-Meier method. The percentage of censored patients will also be reported. Median event time will be reported, along with 25th and 75th percentiles
  - Summary of absolute and relative frequencies of ORR and DCR up to 24 months after the index date together with the 95% CI
  - DoR, PFS, and PFS2 at 24 months after the index date will be estimated by the Kaplan-Meier method. The percentage of censored patients will also be reported. Median event time will be reported, along with 25th and 75th percentiles. Percentage of patients experiencing event or being event-free at applicable timepoints will also be reported along with the corresponding two-sided 95% CIs
  - There will be subgroup analyses for the primary outcome and selected secondary outcomes (OS, PFS, and PFS2 at 24 months and DCR up to 24 months) based on:
    - ECOG performance status at baseline (0-1, > 1)
    - IMDC risk group (low, intermediate, high)
    - MSKCC risk group (low, intermediate, high)
    - RCC histopathology (clear cell, sarcomatoid, others)
    - PD-L1 (±) status
    - Age group (< 65, 65-75, and > 75 years)
    - Concomitant autoimmune disease (yes, no)
    - Prior nephrectomy (yes, no)

Further subgroup analysis will be defined in the IAP.

Safety analysis will be performed on AEs incidence tables, presented by MedDRA SOC and PT, and the number and percentage of patients experiencing an event. Multiple occurrences of the same event in the same patient will be counted only once in the tables.

Summaries of AEs will include:

- The overview of AEs, summarizing number (%) of patients with any:
  - AEs
  - SAEs
  - National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 5.0) AEs ≥ Grade 3
  - Related AEs
  - AEs leading to permanent treatment discontinuation
  - AEs leading to death
- Summary of AEs by SOC and PT
- Summary of SAEs by SOC and PT
- Summary of NCI-CTCAE (version 5.0) AEs ≥ Grade 3 by SOC and PT
- Summary of related AEs by SOC and PT
- Summary of related AEs (NCI-CTCAE [version 5.0]) ≥ Grade 3 by SOC and PT
- Summary of AEs leading to permanent treatment discontinuation by SOC and PT
- Summary of AEs (NCI-CTCAE [version 5.0]) ≥ Grade 3 leading to permanent treatment discontinuation by SOC and PT
- Summary of potential signs and symptoms of immune-related AEs
- Summary of AEs leading to death by SOC and PT

Exposure among the patients who discontinued the study drug due to all-cause AEs ≥ Grade 3 will be summarized as per appropriate statistics.

Percentage of patients with therapy modifications due to related AEs (e.g., therapy interruptions and reductions of infusion rate for Avelumab, therapy interruptions and dose reductions for Axitinib) and frequency and type of medical intervention or medications used for the management of related AEs (e.g., use of corticosteroids, antihypertensive therapy, treatment for thyroid dysfunction, and measures to decrease hemoglobin and hematocrit) will be presented.

Percentage of patients receiving later-line therapy (e.g., second-line therapy, third-line therapy) and frequency distribution of later-line therapy regimes among patients progressing on Avelumab plus Axitinib therapy will be presented.

Time to onset and duration of AEs, time to Avelumab plus Axitinib therapy discontinuation, and time to second-line therapy after study treatment discontinuation will be summarized by descriptive statistics for continuous variables.

Type of therapy for management of related AEs and type of second-line therapy and third-line therapy will be presented according to the WHO-DD, considering the first digit of the ATC classification system (anatomic category) and the first 3 digits of the ATC class (therapeutic category).

Descriptive statistics will also be provided on body weight over the course of the study.

The scores (total and subscales) of the HRQoL at the index date and at every third cycle of Avelumab treatment (intervals of about 6 weeks) will be summarized using descriptive statistics for continuous variables. Possible trend in HRQoL will be also analyzed by repeated measure analysis.

9.7.4 Sequence of Analyses

No interim analyses are planned, but the primary outcome will be analyzed as soon as all evaluable patients complete 12 months of follow-up from the index date. All other study outcomes will be analyzed after completing 24 months study follow-up for all enrolled patients.

9.8 Quality Control

Quality control activities will include verification of data and ensure the data collected in eCRF is accurate, valid, and in accordance with the study protocol. Only authorized staff will have access to the Electronic Data Capture (EDC) system via a secure website and will receive training regarding data entering in the eCRF.

9.9 Limitations of the Research Methods

[redacted]

Treatment response evaluated by RECIST (version 1.1) in real-world observational study may not be as accurate and timely as in a randomized controlled trial. However, the treating physicians will be requested to provide their best judgment on treatment response by evaluating results of patients' radiological investigations.

[redacted]

Despite these limitations, real-world observational data reflects routine clinical practice more closely compared to randomized controlled trials in terms of selection of heterogeneous patient populations and medical treatment they receive. Real-world observational data is essential to assess and improve clinical practice worldwide and complement results of randomized controlled trials. The HRQoL data collected in this study will provide a unique insight into the patient experience and self-assessed impact of the treatment in daily life.

9.10 Other Aspects

9.10.1 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, the protocol will be submitted together with its associated documents (e.g., ICF, subject information) to the responsible Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed by the investigator and a copy will be sent to the Sponsor.

The study must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the study, the protocol version, and the Subject Information and Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the protocol will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes.

9.10.2 Monitoring

A study Monitor will perform visits to the site at regular intervals. Monitoring visits will involve checking of eCRFs against original patient records and identification of any questions or problems related to study conduct or data collection. Investigators must therefore ensure that the study Monitor has access to relevant documents during monitoring visits, and that they and/or relevant site staff members are available to discuss any issues that may arise.

The study Monitor will send monitoring reports to the Sponsor.

9.10.3 Health Authorities

The protocol and any applicable documentation (Subject Information and Consent Form) will be submitted or notified to the National Health Authorities (HA) in accordance with the regulations of the country or countries involved in the study.

9.10.4 Quality Assurance

In compliance with regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, or IRB/IECs may conduct quality assurance audits/inspections at any time during or following a study. The investigator must agree to allow auditors/inspectors direct access to all study-related documents, including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors/inspectors in order to discuss findings and issues.

The protocol, each step of the data capture procedure, and the handling of the data, as well as the study report, may be subject to independent Clinical Quality Assurance. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.10.5 Archiving

The archive should be maintained for the period specified by local regulations, where applicable. All original patient files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations. In the absence of applicable regulations, the archive should be maintained for at least 5 years after the final study report or the first publication of study results, whichever comes later. In any case, the investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10 Protection of Human Subjects

10.1 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the study is his/her written informed consent. The subject's written informed consent to participate in the study must be given before any study-related activities are carried out.

Adequate information must therefore be given to the subject by the investigator before informed consent is obtained (a person designated by the investigator may give the information, if permitted by local regulations). A subject information sheet in the local language will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the investigator or his/her designee will inform the subject verbally of all pertinent aspects of the study *(the language used in doing so must be chosen so that the information can be fully and readily understood by laypersons)*. Depending on national regulations, a person other than the investigator may inform the subject and sign the ICF.

The ICF must be signed and personally dated by the subject and the investigator. The signed and dated declaration of informed consent will remain at the investigator's site and must be safely archived by the investigator. A copy of the signed and dated information and consent form should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be forwarded to each subject in the study. The investigator will explain the changes to the previous version.

10.2 Subject Identification and Privacy

A unique subject number will be assigned to each subject at screening. This number will serve as the subject's identifier in the study as well in the study database.

The investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by their assigned identification numbers. If subject names are included on copies of documents submitted to the Sponsor, the names (except for initials) must be obliterated and the assigned subject numbers be added to the documents.

The investigator should keep a separate log of subjects' identification numbers, names, addresses, telephone numbers, and hospital numbers (if applicable). Documents not for submission to the Sponsor, such as signed ICFs, should be maintained in strict confidence by the investigator.

Only authorized persons will have access to identifiable personal details, if required for data verification. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits, and Health Authority inspections will be kept strictly confidential. The investigator agrees to provide direct access to these documents to the Sponsor and to Health Authority representatives. The investigator is responsible for retrieving information from personal medical records.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

11 Management and Reporting of Adverse Events

11.1 Adverse Events

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal

laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Reaction (AR)

An AR is a response to a medicinal product which is noxious and unintended.

Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

ARs may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse, and medication errors.

Reports of Special Situations: Pregnancy, Overdose, Off-label use, Misuse, Medication Error or Occupational Exposure, Lack of Therapeutic Efficacy, and Others

- Use of a medicinal product during pregnancy or breastfeeding: reports where embryo, fetus, or child may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure)
- Reports of overdose, abuse, off-label use, misuse, medication error, or occupational exposure
- Lack of therapeutic efficacy
- Prescription error/dispensing error, (e.g., due to confusion of invented names of the medicinal products)
- Drug interaction
- Suspected transmission of an infectious agent via a medicinal product
- Product complaints, including falsified product or counterfeit

Reports of special situation with no associated AR will not be submitted to the authorities as individual case safety reports. They will be collected and considered in the study report or any interim reports, as applicable.

Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An SAE/SAR is any AE/AR as defined above, which also fulfills at least one of the seriousness criteria below:

- Results in death
- Is life-threatening[1)]
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered as medically important[2)]

[1)] Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

[2)] Medical and scientific judgment should be exercised in deciding whether other situations should be considered as serious reactions, such as important medical events (IMEs) that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require an intervention to prevent one of the other outcomes listed above. Such IMEs should be considered as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse. As a guidance, the IME terms list is intended to be used for assessment of suspected ARs (see EMA/207865/2017).

Any suspected transmission via a medicinal product of an infectious agent is also considered a SAR.

Events Not to be Considered as AEs

Medical conditions present and documented at study start, which do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and elective procedures and are NOT to be considered AEs.

11.2 Severity of Adverse Events

Investigators should assess the severity/intensity of any AE as follows:

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the subject is unable to carry out usual activities.

Investigators are required to grade the severity/intensity of each AE (including serious) recorded. In oncology indications, investigators will reference the NCI-CTCAE, current version 5.0 (publication date: 27 November 2017). This is a descriptive terminology with 5 Grades: Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-threatening) and Grade 5 (Death due to AE).

Note: *NCI-CTCAE Grade 4 or 5*

If events are graded in accordance to the NCI-CTCAE criteria, then all AEs with severity Grade 4 or 5 should be classified as serious. Exception: Asymptomatic Grade 4 laboratory abnormalities (e.g., Grade 4 anemia, Grade 4 neutropenia) may be considered non-serious, if not meeting any of the above seriousness criteria.

If the severity/intensity of a particular AE cannot be specifically graded by NCI-CTCAE, the investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his or her best medical judgment grading the AE according to the Qualitative Toxicity Scale below:

Grade 1 (mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 (moderate): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 (severe): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL. Significant impairment of functioning: the subject is unable to carry out usual activities.

Grade 4 (life-threatening): Life-threatening consequences; urgent intervention indicated.

Grade 5 (fatal): AE with fatal outcome

11.3 Causality Assessment

Investigators must assess the causal relationship between AEs and study drug (including any other non-medicinal product, radiation therapy, etc.) considering temporal relationship between the AE onset and study drug administration, safety profile of study drug (known ARs), the patient's condition (medical history, underlying disease), concomitant medication, and study procedures.

Related: Suspected to be reasonably related to any study medication.

Not related: Not suspected to be reasonably related to any study medication. A reasonable alternative explanation must be provided.

11.4 Collection and Recording of Adverse Events

The recording period for AEs begins when the subject is initially included in the study (date of signature of first informed consent) and continues to at least end of the mandatory safety-follow-up period (90 days post discontinuation of Avelumab plus Axitinib therapy or completion of the 24 months (i.e., end of the study) follow-up from the index date, whichever occurs first).

All safety data, as specified above, occurring during the study, must be documented by the investigator within 24 hours of awareness and recorded in the eCRF, including its description, seriousness, severity (grading), duration (onset and resolution dates), causal relationship, any other potential causal factors, actions taken with the study drug (e.g., dose reduction, withdrawal), required treatment, and outcome of the AE.

Note: *Event term'Death', 'Disability' and 'Hospitalization'*

Death, disability, and hospitalization are considered outcomes in the context of safety reporting and not usually considered ARs/AEs. Therefore, the primary cause of death, disability, or hospitalization should be recorded and reported as an SAE/AR, and the outcome should be recorded in a separate data field. However, a term for the outcome will be selected if it is the only information reported or provides significant clinical information.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. “Fatal” will be recorded as the outcome of this respective event and not as a separate event. Only if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

All SAEs/AEs due to Avelumab as well as Axitinib will be collected in the study database.

Reports of Special Situations (see definition) are also to be recorded in the eCRF following the AE procedure, even if occurring without AE.

Pregnancy and Breastfeeding. Pregnancy or breastfeeding must be recorded in the eCRF and additionally be reported to the Sponsor immediately (within 24 hours of awareness) by using separate paper data collection forms for pregnancy, independent if an AE was reported or not. The outcome of the pregnancy should be followed up and reported to the Sponsor until delivery.

11.5 Safety Data Reporting

Safety Data Collection Forms:

The following safety data collection forms are used in this study:

- (Serious) Adverse Event Report Form
- Pregnancy Report Form
- Parent-Child/Fetus AE Report Form

Events Reported via the Safety Check Desk

The following events are reportable to the Safety Check Desk within 24 hours of awareness:

- All SARs related to Avelumab are to be reported to the Safety Check Desk. Also, the only SARs related to Axitinib that should be reported to Safety Check Desk are those which are also related to Avelumab.
- Pregnancy or lactation is to be reported by using the Pregnancy Report Form.
- All events that occur in a child/fetus of a pregnant woman who was exposed to the study drug are to be reported by using the Parent-Child/Fetus Report Form.
- Special situations (see definition) should be reported on the (Serious) Adverse Event Report Form by indicating whether serious or not.

Events Reported Directly to Global Patient Safety (GPS):

- All Non-Serious ARs related to Avelumab are to be reported to Global Patient Safety (GPS). Also, the only Non-Serious ARs related to Axitinib that should be reported to GPS are those which are also related to Avelumab. Non-Serious ARs are to be reported within 4 calendar days via the eCRF system or via paper (Serious) Adverse Event Report form (only if eCRF system/eCRF email notifications are not available).

Procedure for Safety Data Reporting (Completion and Forwarding):

For any new events that are serious, fatal, or related to a special situation, the investigator/healthcare professional must immediately (within 24 hours after becoming aware of the event) send a report using eCRF or respective paper Safety Data Collection Form to the Sponsor in English via the Safety Check Desk. For Non-Serious ARs, an electronic data transfer or a paper form (only in case electronic data transfer is not available) must be transmitted within 4 calendar days to the Sponsor, including the GPS.

The investigator must respond to any request by the Safety Check Desk for follow-up information, as noted above for initial report. The Safety Check Desk should forward the follow-up information within 24 hours to GPS, as noted above for initial reports. The Sponsor has to meet strict regulatory timelines associated with expedited safety reporting obligations.

Safety Check Desk:

- Email: OSM_Safety@merckgroup.com

Global Patient Safety:

- Email: GlobalDrugSafety@merckgroup.com
- Fax: +49 (0) 6151 72 6914

The data entered on the safety data collection forms must be consistent with the information recorded in the eCRF. If some data are missing, the form should be completed with the available data and a follow-up report will be sent as soon as possible. The minimum information to be included in the initial report is the following:

- Investigator name and contact details
- Subject identification (e.g., ID number, site number, gender, age/year of birth)Product (including lot/batch number)
- Description of SAE/AR/fatal case/special situation
    - Diagnosis of the event with its clinical course or, if a diagnosis is not available, a short description of signs/symptoms/clinical course
    - Date of onset
    - Seriousness criteria
    - Causality assessment
    - Date of report and reporter’s signature

The report should contain causality and seriousness information (for AEs) and must be signed off by the investigator.

When AE information is communicated via telephone, a written/EDC report must be sent immediately within 24 hours thereafter by fax or email. In such cases, the “clock start” for case reporting to Health Authorities is the date and time of the telephone communication.

AE/SAE Observed in Association with Disease Progression

Progression of the disease / disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) does not need to be reported as an (S)AE, unless the subject´s general condition is more severe than expected for the subject´s condition and / or unless the outcome is fatal within the AE reporting period, as defined in Section 11.4.

Exposure During Pregnancy

All pregnancies with an estimated conception date in the period from the date of informed consent signature (where applicable) until the last post-treatment safety visit, or as defined in the protocol, must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The investigator must notify the Sponsor in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting. The Sponsor must be notified about any pregnancy independent whether the pregnancy is associated with an AE or not.

Investigators must actively follow-up, document, and report to the Sponsor on the outcome of all these pregnancies and deliveries even if the subject is withdrawn from the study. If an abnormal outcome occurs, the respective safety data collection form (Pregnancy Report Form, Parent-Child/Fetus AE Report Form) is to be completed and sent to the Sponsor.

Procedure for Follow-up Information

The investigator must promptly respond to any request for follow-up information or questions from the Sponsor or delegate, as noted above for initial report. Such requests will be sent to the investigator via the Safety Check Desk. SAEs/ARs and special situations occurring during the study must be monitored and followed up by the investigator until stabilization or until the outcome is known, unless the subject has a fatal outcome or is lost to follow-up.

The investigator will ensure any necessary additional therapeutic measures and follow-up procedures are recorded and reported via a follow-up report form. For all serious cases/ARs/fatal cases, and special situations, missing information such as outcome, confounders, and causality are to be provided. In addition, follow-up information of non-serious adverse drug reactions may be required by the Sponsor for medical assessment. Reasonable attempts to obtain follow-up information must be made and documented.

Reporting of any new information on a previously reported event (follow-up) will follow the procedures and timelines of the original report.

The Safety Check Desk should forward the follow-up information within 24 hours to GPS, as noted above for initial reports. The Sponsor has to meet strict regulatory timelines associated with expedited safety reporting obligations.

11.6 Regulatory Submission to the Health Authorities

Expedited submissions of serious ARs and non-serious adverse drug reactions to HA is performed - for Merck's authorized medicinal products - by GPSaccording to applicable global and local requirements. Merck, as the marketing authorization holder of Avelumab, is only required to submit SARs/ARs due to Avelumab to the HAs of the participating countries, or in case of EU/EEA countries to the EMA only. SAR/AR due to Axitinib only will not be submitted to the authorities by Merck, unless they are also related to Avelumab.
In addition, the investigator will comply with any applicable local pharmacovigilance requirements to report appropriate safety data, to national pharmacovigilance systems (e.g., Yellow Card Scheme in UK), as required by country-specific reporting requirements. For non-Merck products the investigator is responsible to report safety information to regulatory authorities directly, where required per local regulations.

12 Plans for Disseminating and Communicating Study Results

12.1 Study Report

The completed study will be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings.

12.2 Publication

The first publication will be a publication of study design followed by a publication of the results of the analysis of the primary outcome(s), which will include data from all study sites. The third publication will be a publication of the results of all final analyses.

The investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by investigators or their representatives will require pre-submission review and approval by the Sponsor.

The Sponsor will not suppress or veto publications but maintains the right to delay publication in order to protect intellectual property rights.

13 References

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14 Appendices

14.1 Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title:	Real-world evaluation of efficacy and safety with **AV**elumab (BAVENCIO®) + Axitinib (**I**NLYTA®) in patients with Advanced Renal-Cell Carcin**O**ma (RCC) in multiple EU cou**N**tries
Study Protocol Date / Version:	24 April 2023 / Version 4.0

Protocol Lead Responsible for Designing the Non-Interventional Study:

I approve the design of the non-interventional study:

[redacted] _____

Signature Date of Signature

Name, academic degree: [redacted]

Function/title:

[redacted]

[redacted]

Telephone number: [redacted]

Fax number: Not Available

Email address: [redacted]

Signature Page – Coordinating Investigator

Study Title	Real-world evaluation of efficacy and safety with **AV**elumab (BAVENCIO®) + Axitinib (**I**NLYTA®) in patients with Advanced Renal-Cell Carcin**O**ma (RCC) in multiple EU cou**N**tries
Study Protocol Date / Version	24 April 2023 / Version 4.0

I approve the design of the non-interventional study and I understand and will conduct the study according to the study protocol, any approved protocol amendments, Good Pharmaco-epidemiology Practices (GPP) and all applicable Health Authority requirements and national laws.

[redacted] _____

Signature Date of Signature

Name, academic degree: [redacted]

Function/title: [redacted])

Institution: [redacted]

Address: [redacted]

Telephone number: [redacted]

Email address: [redacted]

Signature Page – Principal Investigator

Study Title	Real-world evaluation of efficacy and safety with **AV**elumab (BAVENCIO®) + Axitinib (**I**NLYTA®) in patients with Advanced Renal-Cell Carcin**O**ma (RCC) in multiple EU cou**N**tries
Study Protocol Date / Version	24 April 2023 / Version 4.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the study at this site and affirm that I understand and will conduct the study according to the study protocol, any approved protocol amendments, GPP and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of the study to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/title:

Institution:

Address:

Telephone number:

Fax number:

Email address:

Sponsor Responsible Persons Not Named on the Cover Page

Name, academic degree:	[redacted]
Function/title:	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Telephone number:	[redacted]
Fax number:	[redacted]
Email address:	[redacted]