Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS100070_0110
Title	Real-world evaluation of efficacy and safety with **AV**elumab (BAVENCIO®) + Axitinib (**IN**LYTA®) in patients with Advanced Renal-Cell Carcin**O**ma (RCC) in multiple EU cou**N**tries
Study Phase	Not applicable
Investigational Medicinal Product(s)	Avelumab injection, Axitinib tablet
Clinical Study Protocol Version	01 April 2021 / Version 1.0
Integrated Analysis Plan Author	**Coordinating Author** [redacted] Merck [redacted] **Function** / **Author(s) / Data Analyst(s)** [redacted]
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Integrated Analysis Plan Reviewers	**Function** / **Name** [redacted] Biostatistics Lead, Merck Regional Medical Director, Merck Medical Launch Lead, Merck Medical Manager, Merck Merck Safety Lead [redacted]

Approval Page

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Approval of the IAP will be collected via eSignature using Wingspan. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CM	Concomitant Medication
COVID-19	Coronavrus Disease 2019
CR	Complete Response
CSR	Clinical Study Report
DCR	Disease Control Rate
DI	Dose Intensity
DoR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
ePRO	Electronic Patient-Reported Outcomes
HRQoL	Health-Related Quality of Life
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
IMDC	International Metastatic RCC Database Consortium
IPD	Important Protocol Deviation
irAE	Immune-Related Adverse Event
IRR	Infusion Related Reaction
KM	Kaplan-Meier
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MSKCC	Memorial Sloan–Kettering Cancer Center
mTOR	Mammalian Target of Rapamycin
n	Number of participants with non-missing values
NA	Not Applicable
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
NE	Not Evaluable
nmiss	Number of participants with missing values
BOR	Best Overall Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-L1	Programmed Death Ligand 1
PFS	Progression-Free Survival
PFS2	Progression-Free Survival 2
PR	Partial Response
PS	Performance Score
PT	Preferred Term
Q1	25th Percentile
Q3	75th Percentile
RCC	Renal-Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Stable Disease
SOC	System Organ Class
STD	Standard Deviation
T2LT	Time to Second-Line Therapy
TEAE	Treatment-Emergent Adverse Events
TKI	Tyrosine Kinase Inhibitors
TNM	Tumor, Node, Metastasis
UNK	Unknown
VEGF	Vascular Endothelial Growth Factor
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
0.1	02JUL2021		Not applicable, first draft
0.2	20AUG2021		• Added Merck Safety Lead reviewer and updated Merck Biostatistician Lead • COVID-19 summaries clarified • ePRO windowing details added • On-treatment period definition updated including a 30 days window • Extended list of subsequent treatment to be described separately • Exposure derivation updated for Avelumab and inclusion of exposure in cycles. Treatment summaries derivation updated accordingly • Infusion related reaction events included in safety analysis • ORR and DCR analysis updated as "up to" month 24 • Subgroup list extended including the derivation of tumor stage • Weight over time analysis removed, listing only. Also listing only will be provided for physical examination.
1.0	24NOV2021		• Added rules to identify confirmed best response for secondary endpoint. Documented response will be used as primary [redacted] • COVID-19 summary also described separately (disposition, protocol deviation) • MedDRA version in use at the time of IAP development included • [redacted] • Included DoR censoring rules. • Included potential further analysis on other relevant adverse events section • Updated appendix to remove safety analysis and including secondary endpoints limited to 12 Months • Changed tool for e-signature and safety responsible • Removed one of IQVIA SBR as leaving IQVIA.

4 Purpose of the Integrated Analysis Plan

The purpose of this integrated analysis plan (IAP) is to document technical and detailed specifications for the primary endpoint and final analysis of data collected for protocol MS100070_0110. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is prepared in compliance with International Conference on Harmonization (ICH) E9 and describes analyses planned in the study protocol Section 9.7 (Data Analysis) and any protocol amendment.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To determine overall survival (OS) rate at 12 months after the index date (Baseline visit)	**Endpoint:** Percentage of patients who are still alive at 12 months after the index date.	14.1
Secondary		
To determine OS rate at 24 months after the index date	**Endpoint:** Percentage of patients who are still alive at 24 months after the index date.	14.2
To assess duration of OS	**Endpoint:** Time interval from the index date to the date of death from any cause.	14.2
To evaluate objective response rate (ORR) and disease control rate (DCR) up to 24 months after the index date	**Endpoints:** • Percentage of patients with complete response (CR) or partial response (PR), as best overall response (BOR) up to 24 months after the index date according to the investigator assessment. • Percentage of patients with CR, PR, or stable disease (SD), as BOR up to 24 months after the index date according to the investigator assessment. BOR will be derived as documented BOR considering the order CR>PR>SD>Progressive Disease (PD). [redacted]	14.2
To assess duration of response (DoR)	**Endpoint:** for patients with BOR of CR or PR only, is the time interval from the first CR or PR criteria met, whichever was reported earlier, until the date of documented overall disease progression. BOR will be derived as documented BOR [redacted]	14.2

Objectives	Endpoints (Outcome Measures)	IAP section
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	**Endpoints:** • Time interval from the index date to the date of disease progression or death from any cause, whichever comes first. • Time interval from the index date to the date of disease progression on second-line treatment or death from any cause, whichever comes first.	14.2
To assess the health-related quality of life (HRQoL)	**Endpoint:** National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (NCCN-FACT FKSI-19) at the index date and at every 6 weeks thereafter, until the end of treatment (EOT) or end of 24 months of study follow-up period, whichever occurs first.	16.3
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 (ie, end of the study) follow-up from the index date, whichever occurs first	**Endpoint:** 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 (ie, end of the study) follow-up from the index date, whichever occurs first.	15.1.1
To assess time to therapy discontinuation due to AE ≥ Grade 3	**Endpoint:** Duration of Avelumab plus Axitinib therapy among patients who discontinued the study drugs due to all-cause AEs ≥ Grade 3.	15.1.2
To assess therapy modifications due to AE related to Avelumab plus Axitinib therapy and management of AE related to Avelumab plus Axitinib therapy	**Endpoint:** Percentage of patients with therapy modifications due to AE related to Avelumab plus Axitinib therapy (eg, therapy interruptions and reductions of infusion rate for Avelumab, therapy interruptions, and dose reductions for Axitinib).	15.1
To determine percentage of patients receiving later-line therapy and frequency distribution of later-line therapy regimes among patients progressing on Avelumab plus Axitinib	**Endpoint:** 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.	15.1
To assess time to second-line therapy initiation (T2LT)	**Endpoint:** Time interval from Avelumab plus Axitinib therapy discontinuation to the initiation of second-line therapy.	14.2
To assess patient-reported potential signs and symptoms of immune-related AEs	**Endpoint:** Frequency of patient-reported signs and symptoms of potential immune-related AEs. Immune-related AEs may include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction.	15.2.3

6 Overview of Planned Analyses

This study will have the primary analysis assessed as soon as all evaluable patients complete 12 months of follow-up from the index date and the final analysis after database lock. No interim analyses are planned during the study.

Primary and final analyses identified in the study protocol and this IAP will be performed after the last participant has completed the 12 months of follow-up from the index date and after the last participant has completed the study respectively. Planned analyses will be performed when all the applicable study data will be entered in the electronic case report form (eCRF), all applicable data queries will be resolved, and the database will be locked.

Statistical analyses will be performed based on analysis datasets derived from eCRF data.

A Data Review Meeting will be held prior to the database lock, using a pre-database lock transfer. IAP must be approved before database lock.

6.1 Primary Analysis

This analysis will be the main analysis and will include disposition, demographic characteristics, medical and disease history, baseline characteristics, medications and procedures along with summary of exposure, primary and secondary endpoints (limited to the first 12 Months of observation and customized titles and footnotes), summary of safety profile. The detailed list of outputs is reported in Appendices section.

Primary analysis will be performed after the last participant has completed the 12 months of follow-up from the index date with all applicable study data in-house and related queries resolved, and the database is locked for the analysis.

6.2 Final Analysis

This analysis will include full set of the analyses and will be performed after the last participant has completed the study with all study data in-house, all data queries resolved, and the database is locked.

7 Changes to the Planned Analyses in the Clinical Study Protocol

With reference to ORR and DCR endpoints, evaluated at 24 months, current IAP will refer the endpoints intended as “up to” 24 months.

8 Analysis Sets and subgroups

8.1 Definition of Analysis Sets

All subjects who signed the informed consent will be included in Screened Analysis Set.

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 Set.

8.2 Subgroup definition and parameterization

Subgroup analyses will be performed on primary and some secondary effectiveness endpoints (OS, DCR, PFS, and PFS2 at 24 months). All subgroup analyses will be exploratory, no adjustment for multiplicity will be performed.

For the definition of subgroup level data, data will be taken, as documented in the eCRF. The category "missing" will not be included in any subgroup analysis.

In case of low number of participants within a category (< 20 participants, which is about 5% of the sample size), categories will be pooled when meaningful, merging the groups having the lower number of observation when the original number of groups is greater than 2.

The following subgroups will be defined:

Eastern Cooperative Oncology Group (ECOG) performance score (PS)

- ECOG PS 0 or 1 (reference level)
- ECOG PS > 1

International Metastatic RCC Database Consortium (IMDC) risk

- Low (reference level)
- Intermediate
- High

Memorial Sloan–Kettering Cancer Center (MSKCC) risk

- Low (reference level)
- Intermediate
- High

Renal-cell carcinoma (RCC) histopathology

- Clear cell (reference level)
- Sarcomatoid
- Other

Programmed death ligand 1 (PD-L1) status

- Negative (reference level)
- Positive

Age

- Age < 65 years (reference level)

- Age 65-75 years
- Age > 75 years

Concomitant autoimmune disease

- No (reference level)
- Yes

Prior nephrectomy

- No (reference level)
- Yes

Presence of bone metastases

- No (reference level)
- Yes

Presence of lymph nodes metastases

- No (reference level)
- Yes

Tumor stage at diagnosis

- I (reference level)
- II
- III
- IV

Sites country

- Germany (reference level)
- Greece
- Belgium
- Sweden
- Russia

9 General Specifications for Data Analyses

This section describes any general specifications not included in subsequent sections.

The “start date” for this study is the index date as the first administration date, after informed consent, of Avelumab plus Axitinib therapy to patients with advanced RCC.

Continuous variables will be summarized using descriptive statistics, i.e. the number of participants with non-missing values (n), the number of participants with missing values (nmiss), mean, standard deviation (STD), median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum. If there are no missing values, nmiss should be indicated by a 0. Mean, median, Q1, Q3, minimum and maximum will be reported with the same number of decimal places as collected in raw data while STD will be reported with one extra decimal place.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of participants of the analysis set. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

If confidence intervals (CIs) are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

Time to event data will be summarized descriptively as continuous data and using Kaplan-Meier (KM) analysis. Data summarization will include, when appropriate:

- Plot of KM curve with number at risk
- KM estimates with CI at fixed timepoints (eg, every 6 months) (with number at risk/ failed)
- Median times with CI, and Q1 and Q3.

To provide overall estimates of treatment effects, data will be pooled across sites. The "site" factor will not be considered in statistical models or for subgroup analyses due to the high number of participating sites in contrast to the anticipated small number of participants treated at each site.

All analyses will be performed using Statistical Analysis System (SAS)® Software version 9.4 or higher.

9.1 Data handling after cut-off date

By its nature, data after cut-off may be incomplete and subject to further change and will not be used for summary statistics, statistical analyses, listings, or imputations. A detailed list of data cut-off rules for raw data will be described in a separate document, "Data Cut-Off Specification for RAW Data" that will be provided before the primary analysis datasets delivery.

9.2 Definition of baseline and change from baseline

Baseline is defined as the non-missing assessment reported at index date (Baseline visit).

Absolute and percent changes from baseline are defined as

absolute change = visit value – baseline value

percent change = 100 * (visit value – baseline value) / baseline value

9.3 Study day / study treatment day

Day 1 is the index date, the day before is Day -1 (no Day 0 is defined). Study day / Study treatment day is defined relative to Day 1.

9.4 Definition of duration and 'time since' variables

Durations in days will be calculated by the difference of start and stop date + 1 if not otherwise specified.

The time since an event (eg, time since first diagnosis) will be calculated as reference date minus date of event.

9.5 Conversion factors

The following conversion factors will be used to convert days into months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

9.6 Date of last contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off using the latest complete date prior to or at the data cut-off date among the following:

- All participant assessment dates (visit date, dates of assessment for vital signs, disease assessment as per imaging, NCCN-FACT FKSI-19)
- AE start and end dates
- Study drugs start and end dates
- Date of discontinuation on the Avelumab and/or Axitinib Termination or Study Termination eCRF pages (do not use if reason for discontinuation is lost to follow-up).

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.

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

9.7 Time window

As this is a non-interventional study, study assessments are part of the standard of care and related data will be collected during the visits in line with the sites as per routine practice at the discretion of the treating physician. Therefore, the timing of the visits is an approximation.

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.

Apart from Screening, Baseline visit (index date) and HRQoL, analysis visits will be derived considering a 3 months (± 45 days [as intermediate timepoint between 2 consecutive visits]) frequency and will be calculated using study day as showed in table below.

Visit Name	Derivation
Screening	Screening [a]
Baseline	Index date/W0 (Baseline visit) [a]
3 Months	45 days [b] ≤ STUDY DAY ≤ 135 days
6 Months	136 days ≤ STUDY DAY ≤ 225 days
9 Months	226 days ≤ STUDY DAY ≤ 315 days
12 Months	316 days ≤ STUDY DAY ≤ 410 days
15 Months	411 days ≤STUDY DAY ≤ 495 days
18 Months	496 days ≤ STUDY DAY ≤ 585 days
21 Months	586 days ≤ STUDY DAY ≤ 675 days
24 Months	676 days ≤ STUDY DAY ≤ 765 days

[a] Screening and Baseline visits will not be remapped as they are the starting of the observation. Both will be assigned as per eCRF visit

[b] In case a follow-up visit will occur in period between Baseline visit and 44 days after the index date, analysis visit settings will be discussed to identify the best mapping.

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 6 weeks thereafter, until the EOT or end of 24 months of study follow-up period, whichever occurs first. For the ePRO collected during the study all the data in a time window of ± 14 days from the expected visit day will be used.

ePRO Assessment	Derivation
Baseline	Index date/W0 (Baseline visit) [a]
6 Weeks	28 < STUDY DAY ≤ 56
12 Weeks	70 ≤ STUDY DAY ≤ 98
18 Weeks	112 ≤ STUDY DAY ≤ 140
24 Weeks	154 ≤ STUDY DAY ≤ 182
30 Weeks	196 ≤STUDY DAY ≤ 224
36 Weeks	238 ≤ STUDY DAY ≤ 266
42 Weeks	280 ≤ STUDY DAY ≤ 308
48 Weeks	322 ≤ STUDY DAY ≤ 350
54 Weeks	364 ≤ STUDY DAY ≤ 392
60 Weeks	406 ≤ STUDY DAY ≤ 434
66 Weeks	448 ≤ STUDY DAY ≤ 476
72 Weeks	490 ≤ STUDY DAY ≤ 518
78 Weeks	454 ≤ STUDY DAY ≤ 482
84 Weeks	574 ≤ STUDY DAY ≤ 602
90 Weeks	616 ≤ STUDY DAY ≤ 644
96 Weeks	658 ≤ STUDY DAY ≤ 686
102 Weeks	700 ≤ STUDY DAY ≤ 728
104 Weeks	714 ≤ STUDY DAY ≤ 742

[a] Baseline visit will not be remapped as they are the starting of the observation and will be assigned as per eCRF visit.

For the last 2 assessments, in case of overlapping window, analysis visit will be assigned sequentially based on ePRO completion date. ePRO completed out of window will not be included in the analysis as timepoint, might bias the comparison of patients data. Out of windows data will only be listed.

9.8 Definition of on-treatment period

The on-treatment period is defined as the time from the index date to the last administration day of study treatment + 30 days, or the cut-off date or death or the start day of subsequent anti-cancer drug therapy -1, whichever occurs first.

9.9 Imputation of missing data

Unless otherwise specified all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings, imputed values will be presented, and imputed information will be flagged.

Treatment dates are not expected to be incomplete. Specific rules for classification of AEs and concomitant medications (CMs) for analysis purpose are presented below.

Missing statistics, eg, when they cannot be calculated, should be presented as "nd". For example, if n=1, the measure of variability (STD) cannot be computed and should be presented as "nd".

Cancer history	Incomplete dates for cancer history (initial cancer diagnosis date and date of documented, locally advanced, inoperable or metastatic disease diagnosis) will be imputed as follows: • If the day is missing, it will be imputed to the 15th day of the month. • If both day and month are missing and the year is prior to the year of the index date, the month and day will be imputed as July 1st. • If both day and month are missing and the year is same as the year of the index date, the month and day will be imputed as January 1st. • If the date is completely missing, no imputation will be performed.
Adverse events	Incomplete AE dates will be imputed as follows: • If the AE onset date is missing completely, then the onset date will be replaced by the index date. • If only the day part of the AE onset date is missing, but the month and year are equal to the index date, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and the index date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015. If the end date or resolution date indicates that the AE has stopped before the index date, this date will be used for imputation instead of the index date.

	• If both the day and month of the AE onset date are missing but the onset year is equal to the index date, then the onset date will be replaced by the index date. For example, if AE onset date is --/---/2014, and the index date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014. • In all other cases the missing onset day or missing onset month will be replaced by 1. • Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date. • In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off this date will not be imputed and the outcome of the event will be "Not recovered/not resolved" (i.e. ongoing).
Previous and concomitant medication	Incomplete prior/concomitant medication start and stop dates will be imputed as follows: • If the medication start date is missing completely, then the medication start date will be replaced by the index date. • If the day of medication start date is missing, but the month and year are equal to the index date, then the medication start date will be replaced by the index date. For example, if the medication start date is --/JAN/2015, and the index date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015. • If both the day and month of medication start date are missing but the start year is equal to the index date, then the medication start date will be replaced by the index date. For example, if the medication start date is --/---/2014, and the index date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014. • In all other cases the missing medication day or missing medication month will be replaced by 1. Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date. • In all other cases the incomplete medication stop date will not be imputed. In case an imputed medication start date is later than the medication stop date, it will be replaced by the medication stop date.

Table 1 Stopping rules for medication/procedure end dates

End date of medication/procedure			Stopping rule
Day	**Month**	**Year**	
Unknown (UNK)	UNK	UNK	After index date (ongoing)
UNK	UNK	< Index date (year)	Before index date
UNK	UNK	>= Index date (year)	After index date
UNK	< Index date (month and year)		Before index date
UNK	>= Index date (month and year)		After index date
< Index date (complete date)			Before index date
>= Index date (complete date)			After index date

UNK = Unknown

Table 2 Rules to define previous and/or concomitant medications

Start date of medication/procedure			Stopping rule (see Table 1)	Medication/procedure
Day	Month	Year		
UNK	UNK	UNK	Before index date	Previous
UNK	UNK	UNK	After index date	Previous and concomitant
UNK	UNK	<= Index date (year)	Before index date	Previous
UNK	UNK	<= Index date (year)	After index date	Previous and concomitant
UNK	UNK	> Index date (year) and <= Treatment end [+ 30] days (year)	After index date	Concomitant
UNK	<= Index date (month and year)		Before index date	Previous
UNK	<= Index date (month and year)		After index date	Previous and concomitant
UNK	> Index date (month and year) and <= last Avelumab/Axitinib (whichever comes later) [+ 30] days (month and year)		After index date	Concomitant
<= Index date (date)			Before index date	Previous
<= Index date (date)			After index date	Previous and concomitant
> Index date (date) and <= last Avelumab/Axitinib (whichever comes later) [+ 30] days (date)			After index date	Concomitant

UNK = Unknown

Dates of study treatment	• No imputation will be done for start date (index date will be present for all patients). End date of study treatments: • In case the last date of study drugs is missing or incomplete the date of last administration of study drugs will be taken from the treatment termination eCRF pages.

	• If the last date of study drugs is completely missing and there is no EOT eCRF page and no death date the participant should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date. • If the last date of study drugs is completely or partially missing and there is EITHER an EOT eCRF page or a death date available (within the cut-off date) then imputed last dose date is: = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date) = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date) = min (EOT date, death date), for all other cases
Death date	For survival analyses partially missing death dates will be imputed as follows: If only the day is missing, the death date will be imputed to the maximum of the (non-imputed) day after the date of last contact and the 15th day of the month. Otherwise it will not be imputed.
Tumor assessments	Tumor assessment must be completed with day, month and year. If measurement date for an evaluation have no day recorded, the 1st of the month is used. If the month is not completed, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.
Dates of subsequent anti-cancer therapy	Incomplete dates for start date of subsequent anti-cancer therapy (drug therapy, radiation, other) will be imputed as follows: • If only day is missing, it will be imputed as the last day of the month unless the end date of subsequent anti-cancer therapy is before that date. In that case, the incomplete anti-cancer therapy start date will be imputed as the end date of the anti-cancer therapy.

	• If both day and month are missing, no imputation will be performed. Incomplete subsequent anti-cancer therapy stop dates will not be imputed.

9.10 Scoring of HRQoL data

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 sub-scores 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.

9.11 Further subsections

Not applicable.

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study treatment/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

This section describes how participant disposition, study and study treatment discontinuations will be summarized.

The number and percentage of participants in each of the below disposition categories will be presented:

- Total number of participants screened (i.e. participants who gave informed consent)
- Number of participants who did not continue beyond screening, overall and grouped by the main reason (using the reasons as collected in the categories of the eCRF Study Entry Form: Subject did not meet all eligibility criteria, Withdrawal by subject, Other). The corresponding percentage will be calculated using the number of screened participants as a denominator.

For the following categories, the corresponding percentage will be calculated with respect to the number of enrolled participants:

- Number of participants who completed each treatment of the combination (considering the information collected through the eCRF Treatment Termination Form)
- Number of participants who discontinued each treatment of the combination, overall and grouped by main reason (with reason collected through the eCRF Treatment Termination Form). The percentages for the reasons will be calculated using the number of participants who discontinued each treatment of the combination as denominator
- Number of participants ongoing with reference to each treatment of the combination at the data cut (considering the information collected through the eCRF Treatment Termination Form)
- Number of participants who completed the study (considering the information collected through the eCRF Study Termination Form)
- Number of participants who discontinued the study, overall and grouped by main reason (with reason collected through the eCRF Study Termination Form). The percentages for the reasons will be calculated using the number of participants who discontinued the study as denominator
- Number of participants ongoing with reference to the study at the data cut (considering the information collected through the eCRF Study Termination Form)

For the participants discontinuing the study a listing with the following variables will be presented:

- Patient number
- Index date
- Last Avelumab and last Axitinib administration date
- Status at the EOT(Completed/ Permanently discontinued)
- Study discontinuation Date
- Primary reason for study discontinuation
- If Withdrawal by subject, specify
- If Other, specify.

Primary reason for study discontinuation will include Coronavirus disease 2019 (COVID-19) as possible reason evaluating the AEs description or the additional specification reported in study discontinuation form when “Adverse Events” or “Other” reasons will be selected.

For the participants permanently discontinuing the treatment a listing with the following variables will be presented:

- Patient ID

- Index start date
- Last Avelumab and last Axitinib administration date
- Primary reason for treatment termination
- If Withdrawal by subject, specify
- If Other, specify.

Primary reason for study treatment discontinuation will include COVID-19 as possible reason evaluating the AEs description or the additional specification reported in Avelumab and/or Axitinib discontinuation form when "Adverse Events" or "Other" reasons will be selected.

A separate disposition table with focus on COVID-19 impact will be presented including the following descriptive statistics:

- Participants potentially affected by COVID-19
- Total COVID-19 related protocol deviations (important and minor)
- Participants with at least one COVID-19 related protocol deviation (important and minor)
- Participants who discontinued any study treatment for reasons related to COVID-19
- Participants who discontinued the study for reasons related to COVID-19
- Participants with AEs related to COVID-19
- Participants with cause of death related to COVID-19

A subject potentially affected by COVID-19 will be defined as subject who started treatment after the start of the COVID-19 pandemic, or subject who started treatment prior to start of the COVID-19 pandemic and is still ongoing after the start of the pandemic. The start of COVID-19 pandemic is defined as the earliest date of either: (1) the date of the first death attributed to COVID-19 in the patient's country, according to the published data by European Centre for Disease Prevention and Control on 26th June 2020 or (2) 11th March 2020 (when the WHO declared COVID-19 pandemic).

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

IPDs include:

- Participants enrolled on the study who did not satisfy enrolment criteria
- Participants that develop withdrawal criteria whilst on the study but are not withdrawn
- Participants that receive an incorrect dose
- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data
- Any other protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

IPDs will be identified for all participants by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

Clinically IPDs are a subset of IPDs that could impact the key objectives of the study and that would lead to the exclusion of a patient from an analysis set (see Section 8.1 Definition of Analysis Sets).

Clinically IPDs may be identified during the course of the study but will not require amendments to this IAP.

IPDs will be summarized for:

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion

A frequency table for IPDs, organized according to whether the protocol deviation is a pre-/post inclusion deviation, as well as a listing of IPD, will be provided based on the analysis set.

Protocol deviations attributed to the impact of COVID-19 pandemic will be labeled accordingly. Both important and non-IPDs attributable to the COVID-19 pandemic will be included and summarized.
A listing including protocol deviation impacted by COVID-19 will be also provided.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

A frequency table organized according to reason for exclusion from the analysis set, as well as a listing, will be provided.

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based on analysis set overall.

11.1 Demographics and Baseline Characteristics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Screening/Baseline Visit eCRF pages.

- The following characteristics will be included:
  - Sex: male, female, other
  - Age (years)
  - Age categories: < 65 years, 65-75 years and >75 years
  - Baseline Systolic blood pressure and diastolic blood pressure (millimeters of mercury)
  - Baseline Pulse (beats per minute).
  - Baseline Weight (kilogram)

Specifications for computation:

- Age [years]: *(year of given informed consent - year of birth).*
- To convert weight collected in pounds to kilogram, the conversion factor 0.45359237 will be used.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using MedDRA version 24.0 or higher, PT as event category and SOC body term as Body System category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

11.3 Other Baseline Characteristics

Information on disease and disease related characteristics collected at baseline will be summarized.

Summary statistics will be presented for:

- Site of primary tumor (including sub-sites)
- Location of metastases
- Age at diagnosis (years)
- Time from initial diagnosis to documented, locally advanced, inoperable or metastatic disease diagnosis (years)
- Histopathological classification (clear cell, sarcomatoid, other)
- Tumor, node, metastasis (TNM) status at initial diagnosis and tumor staging derived as described in table below:

Stage	TNM
I	T1, N0, M0
II	T2, N0, M0
III	T3, N0, M0 or T1 to T3, N1, M0
IV	T4, any N, M0 or T4, any N, M1

The following additional categories are not listed in the table above:

- T0: There is no evidence of a primary tumor.
- NX: Nearby lymph nodes cannot be assessed due to lack of information.

- TNM status at study entry
- Prior nephrectomy (Yes/No)
- Expression of PD-L1 (Positive/Negative)
- MSKCC risk group (0 - low, 1 or 2 - intermediate, ≥ 3 - high)
- IMDC risk group (0 - low, 1 or 2 - intermediate, ≥ 3 - high)
- ECOG PS (0, 1, 2, 3, 4, 5).

11.4 Prior Anti-cancer Therapy

The prior anti-cancer therapies are collected under the "Prior Anti-Cancer Drug Therapies", "Prior Radiotherapy" and "Prior Anti-Cancer Surgeries" eCRF pages.

The number and percentage of participants in each of the following anti-cancer therapy categories will be tabulated:

- Participants with at least one prior anti-cancer drug therapy
- Participants with at least one prior anti-cancer surgery
- Participants with at least one prior anti-cancer radiotherapy.

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of participants with the following:

- Prior anti-cancer drug therapy regimens: missing / 1 / 2 / 3 / ≥4
- Prior anti-cancer drug therapy regimens: drug class and PT
- Type of prior anti-cancer drug therapy
- Intent of Therapy: Neo-Adjuvant / Adjuvant / Metastatic or Locally advanced
- Prior anti-cancer drug therapy line number: missing / 1 / 2 / 3 / ≥4
- Prior anti-cancer drug therapy duration

- Best response to last prior treatment: CR / PR / SD / PD / not evaluable (NE) / UNK / not applicable (NA). Best response is derived from the last treatment regimen.

The prior anti-cancer drug therapy will be summarized based on the number and percentage of participants by the Anatomical therapeutic chemical (ATC) 2nd level and PT as given from the World Health Organization Drug Dictionary (WHO-DD) March 2021 version or higher. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Prior anti-cancer surgeries will be summarized as follows based on the number and percentage of participants with the following:

- Prior anti-cancer surgery location
- Curative intent (Yes/No)
- Surgery outcome to last prior surgery: No residual tumor after resection (R0), Tumor/metastases not resected completely with microscopic residual lesions (R1), Tumor/metastases not resected completely with macroscopic residual lesions (R2), Metastases not resected (NR), Other. Surgery outcome is derived from the last surgery.

Surgeries will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

Prior anti-cancer radiotherapy will be summarized as follows based on the number and percentage of participants with the following:

- Prior anti-cancer radiotherapy location
- Intent of Therapy: Neo-Adjuvant / Adjuvant / Metastatic or Locally advanced
- Prior anti-cancer radiotherapy duration
- Prior anti-cancer radiotherapy total dose
- Prior anti-cancer radiotherapy number of fractions
- Best response to last prior radiotherapy: CR / PR / SD / PD / NE / UNK / NA. Best response is derived from the last radiotherapy.

The listings of prior anti-cancer treatments and procedures will also be provided as follows. These will include the participant identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of prior anti-cancer drugs therapies
- Listing of prior anti-cancer surgeries
- Listing of prior anti-cancer radiotherapy

12 Previous or Concomitant Medications/Procedures

The following analyses will be performed based on the analysis set overall.

Concomitant treatments are medications, other than study treatment, which are taken by participants any time during the on-treatment period, see Section 9.8.

Previous medications are medications, other than study treatment and pre-medications for study treatments, which started before first administration of study treatments.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date.

Concomitant and previous treatment each will be summarized by number and percentage of participants from the "Previous and Concomitant medication and/or Therapies" eCRF. AATC 2nd level and PT will be tabulated as given from the WHO-DD March 2021 version or higher. If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted by decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have an ATC classification level 2 coded term, it will be summarized under "Unavailable ATC classification" category. Each participant will only be counted once, even if he/she received the same medication at different times.

Subsequent anti-cancer therapy

Anti-cancer therapy after end of study treatment will be summarized according to the respective eCRF page. Treatments will be categorized by means of coding and medical review. The same approach as for CMs will be applied based on ATC level 2 and PT.

Number and percentage of participants with any anti-cancer post study treatment and by type [(immunotherapy, targeted therapy, chemotherapy, radiotherapy, other)] will be presented.

Number and percentage of participants treated with targeted therapies, monoclonal antibodies and other protein kinase inhibitors as post study treatment (based upon ATC coding) will be presented including PT separately for:

- Anti-vascular endothelial growth factor (VEGFR, ATC code L01EK)
- Tyrosine kinase inhibitors (TKIs, ATC code L01EB)
- Mammalian target of rapamycin (mTOR, ATC code L01EG)
- Monoclonal antibodies (ATC code L01EX)
- Other protein kinase inhibitors (ATC code L01XC).

Summary statistics will be created for intent of therapy (Neo-Adjuvant / Adjuvant / Metastatic or Locally advanced), line number, duration, and best response across all post study treatments. For

participants who received more than one anti-cancer therapy after treatment discontinuation, the BOR among all anti-cancer therapies will be summarized.

13 Study Treatment: Compliance and Exposure

The following analyses will be performed based on the analysis set for Avelumab and Axitinib by visit.

All dosing calculations and summaries will be based on "Avelumab Administration" and "Axitinib Administration" eCRFs pages.

No imputation of missing start dates of study treatments will be done.

In case the last date of study drugs is incomplete the date of last study drugs administration will be taken from the EOT page. A dose is regarded to be administered if the actual dose received is > 0.

Exposure duration and cumulative dose for each treatment of the combination will be summarized after being derived in days respectively as difference between last treatment date–index date +1, for Axitinib (days unit) and (last treatment date – index date +14) for Avelumab and the sum of the actual doses of study drugs received overall. For Avelumab, duration will also be expressed in terms of cycles and derived as (last treatment date – index date +14)/14 considering each cycle duration of 2 weeks.

The summary of treatment exposure will include the following information:

- Exposure duration (days/cycles)
- Cumulative dose (milligrams)
- Overall actual dose intensity (DI) will be derived as overall actual cumulative dose (mg) / exposure duration (cycles or days for Avelumab or Axitinib respectively)
- Avelumab relative DI will be derived as 100 × [overall actual DI] / [intended DI] = 100 × [overall actual DI] / [overall planned cumulative dose (mg) /exposure duration (cycles)]
- Axitinib relative DI will be derived as 100 × [overall actual DI] / [intended DI] = 100 × [overall actual DI] / [overall planned cumulative dose (mg)/ exposure duration (days)]

Percentage of patients with at least one dose adjustment over the study will be presented for each treatment of the combination descriptively along with frequency of adjustments (Dose adjusted, No dose) and detailed reasons (AEs, Missed dose [applicable for No dose only], Other).

14 Efficacy Analyses

The following analyses will be performed based on the analysis set.

14.1 Primary Endpoint: Overall Survival Rate at 12 Months

14.1.1 Primary Objective: Derivation and Analysis of the Primary Endpoint: Overall Survival Rate at 12 Months

Endpoint Derivation

OS Rate at 12 months	OS rate is defined as the percentage of patients who are alive at 12 months after the index date. OS rate will be presented along with 95% CI. Percentage of patients alive at the time of outcome assessment (12 months) will be calculated as per the KM approach.

[redacted]

[redacted] (collected in "[redacted]" eCRF page) [redacted]

14.1.3 Supplementary Analyses of the Primary Endpoint Overall Survival Rate at 12 Months

Not applicable.

14.1.4 Subgroup Analyses of the Primary Endpoint Overall Survival Rate at 12 Months

The subgroup analyses will be performed on the primary endpoint based on the analysis set for all subgroup levels defined in Section 8.2 "Subgroup definition and parametrization". All the subgroup analyses are exploratory and will be performed unstratified.

No adjustment for multiplicity will be performed. In the case of a low number of participants within a category of the analysis set, the categories will be pooled when meaningful (see Section 8.2).

14.2 Further Endpoints

Endpoint Derivations

OS Rate at 24 months	**OS rate** is defined as the percentage of patients who are alive at 24 months after the index date. OS rate will be presented along with 95% CI.

<table>
<tr><td></td><td>Percentage of patients alive at the time of outcome assessment (24 months) will be calculated as per the KM approach.</td></tr>
<tr><td>OS</td><td>
OS is defined as the time from index date to the date of death due to any cause. OS for participants without death prior to cut-off will be censored at date of last contact. OS in months is calculated as follows:

OS (months) = [date of death or censoring– index date +1]/30.4375

Note: If death events occurring after cut-off are to be taken into account, the table below may be used for OS. Nevertheless, this will not be the standard process.

OS will be estimated by the KM 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.

Analyses of overall survival time

Table 3 Date of event / censoring definition for OS analysis
<table>
<tr><th colspan="2">Survival tatus</th><th>Source</th><th>Outcome</th><th>Date of event/censoring</th></tr>
<tr><td rowspan="2">Died</td><td>Before and on cut-off date</td><td>Death eCRF</td><td>Event</td><td>Date of death</td></tr>
<tr><td>After cut-off date</td><td>Death eCRF</td><td>Censored</td><td>Date of cut-off</td></tr>
<tr><td rowspan="2">Alive (no date of death)</td><td>Alive after cut-off date</td><td>Follow-up eCRF</td><td>Censored</td><td>Date of cut-off</td></tr>
<tr><td>Otherwise</td><td>Date of last contact, see Section 9.6</td><td>Censored</td><td>Date of last contact</td></tr>
<tr><td rowspan="2">Other</td><td>Study end for consent withdrawn</td><td>Study Termination at Log</td><td>Censored</td><td>Completion/Discontinuation Date</td></tr>
<tr><td>Study end for lost to follow-up</td><td>Study Termination at Log</td><td>Censored</td><td>Completion/Discontinuation Date</td></tr>
</table>
</td></tr>
<tr><td>PFS</td><td>PFS time is defined as the time from index date to the date of the first documentation of objective PD or death due to any cause, whichever occurs first. The tumor response will be determined according to Response Evaluation Criteria in Solid Tumours (RECIST) v 1.1 and assessed by the investigator.

PFS time (in months) = (Date of PD or death – index date + 1)/ 30.4375 (months)</td></tr>
</table>

PFS data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death) or start a subsequent anti-cancer therapy prior to an event. Participants who do not have any post-baseline tumor assessments will be censored on the start date.

The last adequate tumor assessment is defined as the last tumor assessment result that is not "NE" or "NA".

The censoring and event date options to be considered for the PFS analysis is presented in below table.

PFS will be estimated by the KM 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.

Table 4 Outcome and event dates for PFS

Scenario	Date of event/censoring	Outcome
PD or death before subsequent anti-cancer therapy	Date of PD or death	Event
PD or death after subsequent anti-cancer therapy	Date of last adequate tumor assessment [a] documenting no PD before subsequent anti-cancer therapy is given	Censored
No PD/Death	Date of last adequate tumor assessment [a] documenting no PD before subsequent anti-cancer therapy is given	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
Study end for consent withdrawn without PD or death	Date of last adequate tumor assessment [a] documenting no PD before subsequent anti-cancer therapy is given	Censored

	Study end for lost to follow-up without PD or death | Date of last adequate tumor assessment [a] documenting no PD before subsequent anti-cancer therapy is given | Censored [a] If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from the index date; if the criteria were met the censoring will be on the index date.
PFS2	**PFS2** time is defined as the time from the index date to the date of disease progression on second-line treatment or death from any cause, whichever comes first. The tumor response will be determined according to RECIST v 1.1 and assessed by the investigator. PFS2 time (in months) = (Date of PD or death after second-line treatment start – index date + 1)/ 30.4375 (months). PFS2 data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death) or start a further subsequent anti-cancer therapy prior to an event. Participants who do not have any post-baseline tumor assessments will be censored on the start date. The last adequate tumor assessment is defined as the last tumor assessment result that is not "NE" or "NA". The censoring and event date options to be considered for the PFS2 analysis are presented in below table. PFS2 will be estimated by the KM 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. **Table 5 Outcome and event dates for PFS2** **Scenario** | **Date of event/censoring** | **Outcome** PD or death after further subsequent anti-cancer therapy | Date of PD or death | Event PD before further subsequent anti-cancer therapy | Date of last adequate tumor assessment [a] documenting no PD after further subsequent anti-cancer therapy is given | Censored

	No PD/Death	Date of last adequate tumor assessment [a] documenting no PD after further subsequent anti-cancer therapy is given	Censored
	Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
	Study end for consent withdrawn without PD or death	Date of last adequate tumor assessment [a] documenting no PD after subsequent anti-cancer therapy is given	Censored
	Study end for lost to follow-up without PD or death	Date of last adequate tumor assessment [a] documenting no PD after subsequent anti-cancer therapy is given	Censored
	[a] If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from the index date; if the criteria were met the censoring will be on the index date.		
ORR	The **ORR** will be calculated along with the two-sided 95% CI using the Clopper-Pearson method. In addition, the frequency (number and percentage) of participants with BOR of CR, PR, SD, PD and NE will be tabulated. Investigator response will be used to determine the BOR up to 24 months derived as per documented BOR considering the order CR>PR>SD>PD. [redacted]		
DCR	**DCR** is defined as proportion of participants with BOR of CR, PR, SD and will be calculated along with the two-sided 95% CI using the Clopper-Pearson method. Investigator response will be used to determine the BOR up to 24 months derived as per documented BOR considering the order CR>PR>SD>PD. [redacted]		
DoR	**DoR** is defined, for participants with BOR CR or PR only, as the time interval from the first CR or PR criteria met, whichever was reported earlier, until the date of documented overall disease progression. BOR will be derived as documented BOR. [redacted] If a participant has not had the event, DoR is censored at the date of last adequate tumor assessment.		

DoR (months) = [date of event or censoring–date of first CR or PR +1]/30.4375

DoR will be estimated by the KM 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.

Table 6 Outcome and event dates for DoR

Scenario	Date of event/censoring	Outcome
PD before subsequent anti-cancer therapy	Date of PD	Event
PD after subsequent anti-cancer therapy	Date of last adequate tumor assessment [a] documenting no PD before subsequent anti-cancer therapy is given	Censored
No PD/Death	Date of last adequate tumor assessment [a] documenting no PD/Death before subsequent anti-cancer therapy is given	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
Study end for consent withdrawn without PD	Date of last adequate tumor assessment [a] documenting no PD before subsequent anti-cancer therapy is given	Censored
Study end for lost to follow-up without PD	Date of last adequate tumor assessment [a] documenting no PD before subsequent anti-cancer therapy is given	Censored

[a] If there are no adequate post-baseline assessments prior to the PD, then the time without adequate assessment should be measured from the index date; if the criteria were met the censoring will be on the index date.

T2LT

T2LT is defined as the time from the last dose of Avelumab plus Axitinib to the start date of second-line treatment for RCC.

	T2LT time (in months) = (Second-line treatment start date – last dose of Avelumab plus Axitinib + 1)/ 30.4375 (months) T2LT will be summarized by descriptive statistics for continuous variables.

The subgroup analyses will be performed on selected secondary endpoints (OS, DCR, PFS, and PFS2) based on the analysis set for all subgroup levels defined in Section 8.2 "Subgroup definition and parametrization". All the subgroup analyses are exploratory and will be performed unstratified.

No adjustment for multiplicity will be performed. In the case of a low number of participants within a category of the analysis set, the categories will be pooled when meaningful (see Section 8.2).

15 Safety Analyses

This section includes specifications for summarizing safety endpoints that are common across clinical studies such as AEs, laboratory tests and vital signs.

Safety analyses will be done on the analysis set.

15.1 Adverse Events

Treatment-emergent adverse events (TEAEs): those AEs with onset dates occurring within the on-treatment period as defined in Section 9.8.

TEAEs related to study treatment are those events with relationship missing, unknown or related.

Immune-related adverse events (irAE) are identified according to eCRF AE form ("Is this an immune-related event" selected as Yes).

Infusion related reaction (IRR) are identified as per the following table:

Infusion related reactions	**Reactions:** considered when onset is on the day of study drugs infusion (during or after the infusion) or the day after the study drugs infusion (irrespective of resolution date): • IRR • Drug hypersensitivity • Hypersensitivity • Type I hypersensitivity • Anaphylactic reaction **Signs and Symptoms:** occurring on the day of study drugs infusion (during or after the infusion) and resolved on the day of onset or the next day: • Pyrexia • Chills • Flushing • Hypotension • Dyspnea • Wheezing • Back pain • Abdominal pain • Urticaria

All analyses described in Section 15.1 will be based on TEAEs if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not).

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the TEAE in the category of interest, primary SOC and PT in decreasing frequency.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

15.1.1 All Adverse Events

The following tables will be presented:

- Overview of TEAEs, summarizing number (%) of patients with any:
    - TEAEs
    - Related TEAEs (overall and to Avelumab or Axitinib)
    - Serious TEAEs
    - Related (overall and to Avelumab or Axitinib) serious TEAEs
    - National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 5.0) TEAEs Grade ≥ 3
    - Related (overall and to Avelumab or Axitinib) NCI-CTCAE TEAEs Grade ≥ 3
    - TEAEs leading to death
    - Related (overall and to Avelumab or Axitinib) TEAEs leading to death
- Overview of TEAEs leading to discontinuation
- Summary of TEAEs by SOC and PT
- Summary of serious TEAEs by SOC and PT
- Summary of related (overall and to Avelumab or Axitinib) TEAEs by SOC and PT
- Summary of NCI-CTCAE (version 5.0) TEAEs Grade ≥ 3 by SOC and PT
- Summary of TEAEs leading to death by SOC and PT
- Summary of serious related (overall and to Avelumab or Axitinib) TEAEs by SOC and PT
- Summary of serious NCI-CTCAE (version 5.0) TEAEs Grade ≥ 3 by SOC and PT
- Summary of serious TEAEs leading to death by SOC and PT
- Summary of related (overall and to Avelumab or Axitinib) TEAEs NCI-CTCAE (version 5.0) Grade ≥ 3 by SOC and PT
- Summary of related (overall and to Avelumab or Axitinib) TEAEs leading to death by SOC and PT

- Summary of TEAEs NCI-CTCAE (version 5.0) Grade ≥ 3 leading to death by SOC and PT
- Summary of potential signs and symptoms of immune-related TEAEs.

Exposure (exposure duration [days and cycles when applicable] and cumulative dose [milligrams]) among the patients who discontinued the study drugs due to all-cause TEAEs Grade ≥ 3 will be summarized as per appropriate statistics.

Percentage of patients with therapy modifications due to AEs related to Avelumab and/or Axitinib (eg, 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 (eg, use of corticosteroids, immunosuppressants, or hormonal therapy) will be presented.

Percentage of patients receiving later-line therapy (eg, second-line therapy, third-line therapy) and frequency distribution of later-line therapy treatments 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 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).

15.1.2 Adverse Events Leading to Discontinuation of Study Treatment

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to temporary/permanent discontinuation of each treatment of the combination or to the combination itself:

- TEAEs leading to discontinuation of Avelumab only by SOC and PT
- TEAEs leading to discontinuation of Axitinib only by SOC and PT
- TEAEs leading to discontinuation of Avelumab + Axitinib by SOC and PT
- Serious TEAEs leading to discontinuation of Avelumab only by SOC and PT
- Serious TEAEs leading to discontinuation of Axitinib only by SOC and PT
- Serious TEAEs leading to discontinuation of Avelumab + Axitinib by SOC and PT
- Avelumab related TEAEs leading to discontinuation of Avelumab only by SOC and PT
- Axitinib related TEAEs leading to discontinuation of Axitinib only by SOC and PT
- Related TEAEs leading to discontinuation of Avelumab + Axitinib by SOC and PT

- TEAEs (NCI-CTCAE [version 5.0]) Grade ≥ 3 leading to discontinuation of Avelumab only by SOC and PT
- TEAEs (NCI-CTCAE [version 5.0]) Grade ≥ 3 leading to discontinuation of Axitinib only by SOC and PT
- TEAEs (NCI-CTCAE [version 5.0]) Grade ≥ 3 leading to discontinuation of Avelumab + Axitinib by SOC and PT.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

The following summaries for the deaths will be reported in a table:

- Number and percentages of deaths
- Number and percentages of deaths due to COVID-19 (identified based on specification collected when reason for death corresponds to "Event unrelated to study treatment")
- Number and percentages for each primary reason of death (percentage calculated using the number of deaths as denominator):
    - Progressive disease and/or disease related condition
    - Event unrelated to study treatment
    - Event related to Avelumab
    - Event related to Axitinib
    - Unknown.

A listing with the following columns will be presented:

- Patient number
- Age (yrs.)/ Sex/ Weight (kilograms)
- First dose date, last dose date, dose in milligram or dose not administered for Avelumab and Axitinib
- Date of death
- Primary cause of death
- If event unrelated to study treatment, specify
- Fatal AE
- Period

- irAE or IRR flag

15.2.2 Serious Adverse Events

The following overall frequency tables will be prepared for serious AEs:

- Incidence of serious AEs by SOC and PT
- Incidence of related serious AEs by SOC and PT
- Incidence of serious NCI-CTCAE [version 5.0]) Grade ≥ 3 by SOC and PT
- Incidence of serious AEs leading to death by SOC and PT

The listings of serious adverse events (SAEs) will also be provided with the relevant information:

- Patient number
- Age (yrs.)/ Sex/ Weight (kilograms)
- Start date/ End date
- Seriousness criteria
- Is a TEAE? (Yes/No)
- Relationship with Avelumab (Not Related/ Related)
- Relationship with Axitinib (Not Related/ Related)

For the seriousness criteria report all that apply: Results in death, Is life-threatening, Requires/prolongs hospitalization, Persistent/significant disability/incapacity, Is a congenital anomaly/birth defect, Other medically important condition.

15.2.3 Other Significant Adverse Events

The frequency (number and percentage) of participants with each of the following will be presented for treatment-emergent irAEs, by treatment group:

- The overall summary of irAEs table will include the following categories:
    - All irAEs
    - Serious irAEs
    - irAEs, NCI-CTCAE [version 5.0]) ≥ Grade 3
    - irAEs leading to permanent treatment discontinuation
    - irAEs leading to death

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period. In case of irAEs percentage is more than 10% of events a summary by SOC and PT will be presented. In case of any irAE leading to death a separate summary by SOC and PT will be included.

The frequency (number and percentage) of participants with each of the following will be presented for treatment-emergent IRR, by treatment group:

- The overall summary of IRR table will include the following categories:
    - All IRR
    - Serious IRR
    - IRR, NCI-CTCAE [version 5.0]) ≥ Grade 3
    - IRR leading to permanent treatment discontinuation
    - IRR leading to death

In case of IRR percentage is more than 10% of events a summary by SOC and PT will be presented. In case of any IRR leading to death a separate summary by SOC and PT will be included.

15.3 Clinical Laboratory Evaluation

Not applicable.

15.4 Vital Signs

Vital signs including systolic blood pressure, diastolic blood pressure and pulse will be collected upon availability at baseline only (see Section 11.1) while body weight will be collected upon availability all over the study. Weight at Baseline will be summarized as described in Section 11.1 while weight collected after Baseline visit will only be listed along with demographic data.

15.5 Other Safety or Tolerability Evaluations

Physical Examinations will be collected upon availability at Baseline visit and will only be listed.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

Not applicable.

16.2 Pharmacodynamics

Not applicable.

16.3 Patient-Reported Outcome

The NCCN-FACT FKSI-19 scores (total and subscales described in Section 9.10) of the HRQoL at the index date and at every 6 weeks will be summarized using descriptive statistics for continuous variables.

Possible trend in HRQoL will be analyzed by repeated measure analysis. The repeated measure model will be handled with mixed effects models using PROC MIXED with an unstructured correlation matrix to model the within-patient errors, unless the model does not converge, in which case the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be checked. Parameters will be estimated using the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using the Kenward-Roger approximation by fitting values from post-baseline scheduled visits. This likelihood-based approach is tolerant of missing data if they are Missing at Random (MAR).

16.4 Further Other Endpoints

Not applicable.

17 References

Rothrock NE, Jensen SE, Beaumont JL, Abernethy AP, Jacobsen PB, Syrjala K, Cella D. Development and initial validation of the NCCN/FACT symptom index for advanced kidney cancer. Value Health. 2013 Jul-Aug;16(5):789-96.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

18 Appendices

List of outputs included in primary analysis.

Output Number	Output Title
Table 8.1.1.1	Subject Disposition Status
Table 8.1.1.3	Analysis Sets
Table 8.1.4.1	Demographics and Baseline Characteristics
Table 8.1.5.1	Medical History
Table 8.1.6.1	Disease History
Table 8.1.6.2	ECOG Performance Status
Table 8.1.7.1	Previous Medication
Table 8.1.7.3	Concomitant Medication
Table 8.1.7.2.1	Prior Anti-Cancer Drug Therapies
Table 8.1.7.2.2	Prior Anti-Cancer Drugs
Table 8.1.7.2.3	Prior Anti-Cancer Surgeries
Table 8.1.7.2.4	Prior Anti-Cancer Radiotherapies
Table 8.1.8.1.1	Duration of Therapy
Table 8.1.8.2	Cumulative Dose, Dose Intensity, Relative Dose Intensity
Table 8.1.8.4	Dose Reduction
Table 8.2.1.1	Primary analysis, Overall Survival Rate at 12 Months
Table 8.2.1.2	[redacted]
Table 8.2.1.3	Subgroups Analysis: Primary Analysis, Overall Survival Rate at 12 Months by Subgroups
Table 8.2.2.1.2	Overall Survival, Censoring/Event Status Limited to 12 Months of Observation
Figure 8.2.2.2	Overall Survival Limited to 12 Months of Observation

Table 8.2.2.4.1	Progression Free Survival
Table 8.2.2.4.2	Progression Free Survival, Censoring/Event Status
Table 8.2.2.7.1	Progression Free Survival to 2nd Line of Treatment
Table 8.2.2.7.2	Progression Free Survival to 2nd Line of Treatment, Censoring/Event Status
Table 8.2.2.10.1	Objective Response Rate and Disease Control Rate up to 12 Months
Table 8.2.2.10.2	[redacted]
Table 8.2.2.12.1	Duration of Response up to 12 Months
Table 8.2.2.12.2	[redacted]
Table 8.2.2.12.3	Duration of Response up to 12 Months, Censoring/Event Status
Table 8.2.2.13	Time to 2nd Line Treatment
Table 8.3.1.1	Overview of Treatment-Emergent Adverse Events
Table 8.3.1.2	Overview of TEAEs Leading to Discontinuation
Table 8.3.1.3	TEAEs by Primary System Organ Class (SOC) and Preferred Term (PT)
Table 8.3.1.7	Serious TEAEs by Primary System Organ Class (SOC) and Preferred Term (PT)
Table 8.3.1.8.1	Related TEAEs by Primary System Organ Class (SOC) and Preferred Term (PT)
Table 8.3.1.10	TEAEs leading to death by Primary System Organ Class (SOC) and Preferred Term (PT)
Table 8.3.1.23	Frequency of Medical Intervention or Medications Used for the Management of Related TEAEs

RECIST v 1.1 Best overall response with confirmation for CR and PR

Overall response at first timepoint	Overall response at subsequent timepoint	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

[a]If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

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