NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	**Clinical outcomes and therapy management among patients with advanced Renal Cell Carcinoma (aRCC) receiving systemic first-line (1L) anti-cancer treatment under daily routine in Germany: Retrospective Chart Review (RENALISTIC study).**
Protocol number	A4061099
Protocol version identifier	1.0
Date	19-August-2022

Active substance	• **L01EX Other protein kinase inhibitors**
	  ○ L01EX01: sunitinib
	• **L01EK Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors**
	  ○ L01EK01: axitinib
	• **L01XC: Monoclonal antibodies**
	  ○ L01XC31: avelumab

Medicinal product	• **Sunitinib (Sutent®)** • **Axitinib (Inlyta®)** • **Avelumab (Bavencio®)**
Research question and objectives	• How is the effectiveness, defined as measurement of beneficial effects under "real world" clinical settings, (e.g. progression-free survival, overall survival and best response) of Tyrosine Kinase Inhibitors (TKI) and/or Immune-Checkpoint-Inhibitors (ICI) as 1L in patients with aRCC?

	• How are patients with aRCC treated in 1L under daily care conditions in Germany in general and in accordance to medical specialities (urology and medical oncology) and treatment settings (hospitals vs office-based practices)? • Are all patients assigned to individual risk ratings under standard daily care conditions according to a scale developed by the International Metastatic RCC Database Consortium (IMDC) before start of a 1L? • How are patients treated in 1L in different risk rating groups and how is the adherence to national/international guidelines? • What kind of previous and subsequent therapies are administered before and after 1L? • How often are evaluations for PD-L1 expression performed before start of 1L and how many patients are positive (TPS ≥1%) or negative? • How long are patients treated with TKI + ICI and ICI + ICI in 1L in general and in relation to specific therapies like avelumab + axitinib? • How frequent are dose modifications and early discontinuations and what are the reasons? • Are there differences in the handling of modifications among medical specialities? To answer these questions the following objectives are derived: **Primary Objective(s):** • Progression-free survival (PFS) for 1L therapies, expressed as median and as rates at

	timepoints of 6, 9, 12 and 18 months after start of 1L **Secondary Objectives:** • Overall survival (OS) of 1L therapies, expressed as median and rates at timepoints of 12 and 18 months after start of 1L therapy • Best response in 1L overall and in dependence of administered drug regimen • Progression-free survival of 1L therapies in dependence of specific drug regimen • Pre- and post-treatments (i.e. surgery, radiotherapy, medicinal therapies) before/after TKI + ICI and ICI + ICI in 1L • Duration of response (DoR) in 1L overall and in dependence of administered drug regimen (TKI + ICI or ICI + ICI) • Frequency of dose modifications and temporary/permanent discontinuations of 1L therapies and their reasons • Proportions of modifications by dose reduction compared to skipping single applications Effectiveness (PFS, OS and best response) of administered 1L therapies under real world conditions by medical speciality (urology, medical oncology) and setting (practice, hospital)
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Management
AR	Adverse Reaction
aRCC	Advanced Renal Cell Carcinoma
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften = Working party of scientic medicial societies
CR	Complete response
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computer tomography
DCF	Data clarification form
DGHO	Deutsche Gesellschaft fur Hämatologie und Onkologie = German Society for Hematology and Oncology
DoR	Duration of response
eCRF	Electronic Case Report Form
EU	European Union
FU	Follow-Up
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practices
ICD-10	International Classification of Disease 10.revision
ICI	Immune-Checkpoint-Inhibitors
IEC	Independent Ethics Committee

ICMJE	International Committee of Medical Journal Editors
IFN	Interferon
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic resonance imaging
NA	Not applicable
ND	Not done
NIS	Non-Interventional Study
OP	Operation
ORR	Objective response rate
OS	Overall survival
PASS	Post-authorization safety study
PD	Progressive disease
PD-L1	Programmed death ligand-1
PFS	Progression-free survival
PI	Product information
PI	Principle investigator
PR	Partial response
RCC	Renal Cell Carcinoma
RKI	Robert-Koch-Institute
RR	Response rate
SAE	Severe adverse event

SAP	Statistical Analysis Plan
SAR	Severe adverse reaction
SD	Stable disease
TKI	Tyrosine Kinase Inhibitor
TPS	Tumor Propotion Score
TTNT	Time-to-next-therapy
TTP	Time-to-progression
YRR	Your Reporting Responsibility
1L	First-line therapy
2L	Second-line therapy

3. RESPONSIBLE PARTIES

Responsible Parties	Contact details
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Country Coordinating Investigators

Not applicable.

4. ABSTRACT

Title	**Clinical outcomes and therapy management among patients with advanced Renal Cell Carcinoma (aRCC) receiving systemic first-line (1L) anti-cancer treatment under daily routine in Germany: Retrospective Chart Review (RENALISTIC study).**
Rationale and background	In Germany RCC is a rare cancer type with around 15.000 new diagnoses per year and an incidence of 15.7 per 100.000 for men and 7.5 per 100.000 for women (Robert Koch Institute, 2020). Regarding new incidences per year RCC is the 10th most common cancer type in women and 9th most common type in men, whereas the rate of mortality per year due to RCC was lower, 13th position in women with 1,8% and 13th position in men with 2,5% of all cancer-associated deaths (Robert Koch Institute, 2020). Most of the newly diagnosed patients were amendable for radical surgery, but 4.000 – 5.000 patients per year will start a new systemic therapy due to their advanced or metastatic disease. Around 70-80% of the new RCC are diagnosed at an early stage and could be treated by partial or radical surgical resections in a curative intention. At present no neoadjuvant or adjuvant setting is established, but new data with TKIs and/or ICIs could be expected in the next few years. A part of patients with locally aRCC are not suitable for curative treatment by surgery. These patients would be treated like patients with metastatic diseases with systemic therapies under palliative intention. Guidelines of the German Cancer Society (S3-Leitlinie Nierenkarzinom, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), Nov 2021) and of the German Society for Hematology and Oncology (DGHO 2022) recommend for these patients combinations of ICI + TKI as the preferred 1L therapies for all risk groups. For patients with intermediate and poor risk, a combination of nivolumab plus ipilimumab could be considered as an alternative treatment approach. In patients ineligible for ICI and a low risk rating bevacizumab + INF, pazopanib, sunitinib or tivozanib, with an intermediate risk rating cabozantinib, pazopanib, sunitinib or tivozanib and with a high risk rating cabozantinib or sunitinib are recommended. During the treatment with combinations ICI (pembrolizumab or avelumab) + TKI higher rates of modifications and discontinuations of one or both drugs were seen in the pivotal studies. During the therapy with pembrolizumab + axitinib adverse events (AEs) of any cause led to permanent discontinuation of either drug in 30.5%, discontinuation of

	both drugs in 10.7%, interruption of either drug in 69.9%, and dose reduction of axitinib in 20.3% of the patients in 1st line RCC of any risk (Rini TI et al, 2019). During the treatment with avelumab + axitinib 42% of the patients had at least one reduction in the dose of axitinib due to AEs and in 8% of the patients AEs led to a discontinuation of both avelumab and axitinib (Motzer R et al, 2019). Based on this, an important objective of this study is to gain more insights how widespread the existing national guidelines are followed for the 1L treatments in this patient population. Additional objectives are to describe the frequencies of dose modifications and temporary/permanent discontinuations as well as the proportions of modifications by dose reductions in connection with drug combination of ICI + TKI and ICI + ICI in the standard care setting of urologists and hematologists in practices and hospitals in Germany.
Research questions and objectives	• How is the effectiveness, defined as measurement of beneficial effects under "real world" clinical settings, (e.g. progression-free survival, overall survival and best response) of TKI and/or ICI as 1L in patients with aRCC? • How are patients with aRCC treated in 1L under daily care conditions in Germany in general and in accordance to medical specialities (urology and medical oncology) and treatment settings (hospitals vs office-based practices)? • Are all patients assigned to individual risk ratings under standard daily care conditions according to a scale developed by the IMDC before start of a 1L? • How are patients treated in 1L in different risk rating groups and how is the adherence to national/international guidelines? • What kind of previous and subsequent therapies are administered before and after 1L? • How often are evaluations for PD-L1 expression performed before start of 1L and how many patients are positive (TPS ≥1%) or negative? • How long are patients treated with TKI + ICI and ICI + ICI in 1L in general and in relation to specific therapies like avelumab + axitinib? • How frequent are dose modifications and early discontinuations and what are the reasons?

	• Are there differences in the handling of modifications among medical disciplines? To answer these questions the following objectives are derived: **Primary Objective(s):** • Progression-free survival (PFS) for 1L therapies, expressed as median and as rates at timepoints of 6, 9, 12 and 18 months after start of 1L **Secondary Objectives:** • Overall survival (OS) of 1L therapies, expressed as median and rates at timepoints of 12 and 18 months after start of 1L therapy • Best response in 1L overall and in dependence of administered drug regimen • Progression-free survival of 1L therapies in dependence of specific drug regimen • Pre- and post-treatments (i.e. surgery, radiotherapy, medicinal therapies) before/after TKI + ICI and ICI + ICI in 1L • Duration of response (DoR) in 1L overall and in dependence of administered drug regimen (TKI + ICI or ICI + ICI) • Frequency of dose modifications and temporary/permanent discontinuations of 1L therapies and their reasons • Proportions of modifications by dose reduction compared to cancelling single applications • Effectiveness (PFS, OS and best response) of administered 1L therapies under real world conditions by medical specialty (urology, medical oncology) and setting (practice, hospital)
Study Design	This is a retrospective, non-interventional, observational, multicenter, Medical Chart Review project in patients with aRCC, who received a systemic 1L therapy between 01 January 2020 – 31 December 2021 under daily routine conditions in hospitals or practices in Germany. At timepoint of enrollment of patients, all decisions for specific treatment regimen or investigations were already made under discretion of the physicians and in accordance to the routine clinical practice. The study should describe and analyze in part 1 and part 2 for the the treatment situation from adult patients with aRCC in 1L as well as the clinical

	outcomes and handling of intolerabilities from combination therapies in 1L under daily routine in general and in relation to specific therapies. Only data from medical records for running therapies between 01 January 2020 - 31 December 2021 will be captured under conditions of full anonymization. Based on the full anonymization a written informed consent by the patients or an advice by participating doctors an Independent Ethical Committee (IEC) regarding accordance with professional law should not be necessary.
Population	**Inclusion criteria for part 1 and 2:** • Patients aged ≥18 years old • Patients with histologically/cytologically confirmed renal cell carcinoma (International Classification of Disease 10.revision (ICD)-10 C64) • Full medical information regarding all treatments before, during and after 1L should be available. **Specific inclusion criteria <u>only for Part 1</u>:** • Patients with locally advanced or metastatic disease and a start of any systemic 1L therapy against RCC between 01 January 2020 and 31 December 2021 **Specific inclusion criteria <u>only for Part 2</u>:** • Patients with locally advanced or metastatic disease, who were treated with a combination of ICI + TKI or ICI + ICI as 1st line therapy against RCC and who had a completion of this therapy between 01 January 2020 - 31 December 2021 with a follow-up period of at least 3 months after completion of the 1L. **Exclusion criteria for part 1 <u>and</u> 2:** • Patients participating in an interventional clinical study within 30 days before start of 1L.
Outcomes	The following clinical outcomes are of relevance in the study and should be answered regarding the research questions: **<u>Primary Outcome</u>** o Progression-free survival in 1L in median and at defined timepoints after start **<u>Secondary outcomes</u>**

	○ Overall survival rates from start of 1L therapy, expressed as median and at pre-defined timepoints ○ Proportions of different therapy protocols used in 1L ○ Best responses to 1L therapies ○ Duration of response to 1L therapies ○ Time-to-progression to 1L therapies ○ Time-to-next-therapy to 1L therapies ○ Frequency of modifications and discontinuations in 1L ○ Reasons for modifications and discontinuations in 1L ○ Treatment continuation after modifications and discontinuations in 1L (for all therapies and in relation to specific protocols like axitinib + avelumab or nivolumab + ipilimumab) **Other Outcomes** ○ Distribution of 1L therapy by age, gender and risk rating ○ Distribution of 1L therapy and frequency of modifications/discontinuations by medical speciality and institution
Variables	For the evaluations of the mentioned clinical outcomes the following parameters will be captured: **Part 1:** ○ Demographic data (age, gender, weight, body surface) ○ Date of first diagnosis ○ Stage and risk rating (IMDC) at first diagnosis and at start of 1L ○ Assessments and results of PD-L1 expression ○ Non-medicinal pre-treatments (primary operation (OP), cytoreductive nephrectomy, radiotherapy) ○ Medicinal pre-treatments (adjuvant, neoadjuvant) ○ Location of administration and performing medical discipline ○ Administered drugs / protocols in 1L ○ If applicable: Reason for ineligibility of ICI ○ Dates of administrations for i.v. drugs in 1L ○ Duration of 1L treatment ○ Dosages per administration ○ Dose modifications or drug administration cancelling or interim / permanent discontinuations of single drugs / complete therapy in 1L ○ Reasons for modfications, cancelling of single administrations and discontinuations in 1L ○ Supportive drugs prescribed during 1L ○ Date of first response and best response to 1L incl. date and mode of assessment

	o Assessment of first and best response in 1L o Date of tumor progression o Reasons for end of 1L o Subsequent therapies (2L and higher) with drugs/protocol and dates for start / end o Concomitant diseases and therapeutic medications **Part 2:** If patients will qualify for part 1 and part 2 (completion of 1L and follow-up of at least 3 months after completion), the documented data from part 1 will be transferred to part 2 automatically, so that only additional parameters must be filled in. If patients are newly documented in part 2, all of the parameters have to be documented. o Demographic data (age, gender, weight, body surface) o Date of first diagnosis o Stage and risk rating (IMDC) at first diagnosis and at start of 1L o Assessments and results of PD-L1 expression as TPS o Non-medicinal pre-treatments (primary OP, cytoreductive nephrectomy, radiotherapy) o Medicinal pre-treatments (adjuvant, neoadjuvant) o Location of administration and performing medical discipline o Administered drugs / protocols in 1L o If applicable: Reason for ineligibility of ICI o Dates of administrations for i.v. drugs in 1L o Dosages per administration o Dose modifications or drug administration cancelling or interim /permanent discontinuations of single drugs / complete therapy in 1L o Reasons for modfications, cancelling of single administrations and discontinuations in 1L o Supportive drugs prescribed during 1L o Date of first response and best response in 1L incl. mode of assessment o Assessment of first and best response in 1L o Date of tumor progression o Reasons for end of 1L o Subsequent therapies (2L and higher) with drugs/protocol and dates for start / end o Concomitant diseases and therapeutic medications

Data Sources	Source documents (paper or electronic medical charts) are those, in which patient data of daily care are recorded and documented in individual patient files. The data to be collected in the study will be obtained via a specific programmed eCRF. The data in the eCRF should be consistent with the relevant source documents. Medical records should contain demographic data, medical data, treatments and diagnostic documentations according to common practice. The documentation will be performed under full anonymization, so that a re-identification of single patients will not be possible. Based on this anonymization, queries for explanations or changes of data could not be submitted by the data management. All documented variables will be checked by data manager and/or medical lead of GermanOncology in relation to implausibility, inaccuracies or missing data. If implausibility or inaccuracies or missing data of single patients will be of great relevance for analyses, the data management and/or medical lead have the right to reject patients. For such rejected patients no payment will be triggered.
Study Size	Based on public data the population of patients with aRCC and an indication for a 1L therapy is around n = 4.500 - 5.000 patients per year (Robert Koch Institute 2020). In the period of 01 January 2020 – 31 December 2021, which is the main period of interest in the study for completing or starting 1L therapies, the total population of patients with aRCC would be around n = 9.000 - 10.000 patients. To estimate the needed number of patients in the study to reach adequate representation across Germany, the following common formula is used $$n = \frac{z^2\,\pi(1-\pi)N}{z^2\,\pi(1-\pi) + E^2(N-1)}$$ N = population of patients with aRCC and indication for 1L = 10.000 patients in 24 months Π = 0,5 (consensus, if attribute is unknown before study) E = margin of error = 5% = 0,05 Z = 1,96 (for confidence interval of 95%) Based on these assumptions (PFS of 1L therapies included in guidelines was 8.4 – 15.1 months in clinical studies) the number of patients needed for representative statement regarding the primary objective (= PFS rates at defined time points under real world conditions) is at least n = 370. With a buffer of around 10% the sample size in the study should be n = 400 patients with aRCC and 1L therapies in the period from 01 January 2020 – 31 December 2021. Based on published data for PFS it could be

	assumed for part 2, that also the number of patients with combination therapies in part 2 (n = 300) will grant a representative statement to all research questions. Based on information of urological and oncological experts as well as own data of the GermanOncology *[1] network (see below), the following assumptions could be set: • Number of patients with new 1L in urological practices (per practice 1- 3 urologists) = 4 - 6 per year o Number of patients with new 1L in period of 24 months = 8 - 12 • Number of patients with new 1L in oncological practices (per practice 2- 4 oncologists) = 4 - 6 per year o Number of patients with new 1L in period of 24 months = 8 – 12 • Number of patients with new 1L in hospitals with urological focus = 8 - 12 per year o Number of patients with new 1L in period of 24 months = 16 – 24 • Proportion of 1L therapies in urological and oncological practices: 50% : 50% • Proportion of patients treated with 1L in practices and hospitals (as most of therapies are oral therapies): 65% : 35% Based on the assumptions the needed number of sites are at least: • Number of urological practices: 15 • Number of oncological practices: 15 • Number of hospitals with urological focus: 10 • Total number of sites across Germany: 40 *[1] GermanOncology operates a permanent network of 25 oncological practices across Germany, is collecting longitudinal RWE data about several tumor entities since 2012 and is able to analyze data from more than 25.000 patients with around 25 different tumor entities
Data Analysis	The following clinical outcomes will be measured: **Primary outcome:** o ***PFS in 1L:*** ▪ described as median and rates of patients without disease progression or death for any cause at defined timepoints (6, 9, 12 and 18 months) after start of 1L therapy. **Secondary outcomes**: o ***OS in 1L***

	▪ Defined as median and rates of patients alive at pre-defined timepoints (12 and 18 months) after start of 1L therapy. o ***Proportion of different drug regimen in 1L*** ▪ Defined as percentages of therapy protocols used as 1L therapy. o ***Best response rate (RR) in 1L*** ▪ Defined as best response (complete response (CR) / partial response (PR) / stable disease (SD) / progressive disease (PD) / not done (ND)) recorded from the start of the therapy until disease progression/recurrence based on investigator´s assessment. A confirmation of response is not required. o ***Duration of Response (DoR) in 1L*** ▪ Defined as time from documentation of first disease response to disease progression. o ***Time to progression (TTP) in 1L*** ▪ Defined as time from start of therapy until objective disease progression without including deaths. o ***Time to next treatment (TTNT) in 1L*** ▪ Defined as time from last drug administered to initiation of next therapy. o ***Dose modifications and discontinuations in 1L*** ▪ Defined of number of patients with at least 1 dose modification (reduction of dose or cancelling of administration) or with an interim/permanent discontinuation of one or all drugs of a therapy. o ***Handling after dose modification or discontinuations in 1L*** ▪ Defined as continuation of therapies after dose modifications or temporary/permanent discontinuation of single drugs. The clinical outcomes will be analyzed for the total group of all patients and for following subgroups: o Age: < 70 years vs. ≥70 years o Gender: male vs. female o Risk rating: favorable (low) vs. intermediate vs poor (high) risk o Medical disciplines: urology vs. medical oncology o Institutions: practices vs. hospitals
Milestones	**Planned milestones:** • Start of data collection: 1 October 2022 • Interim analysis (expected): 31 October 2022 • End of data collection: 30 January 2023 • Final study report: 15 April 2023

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Tab.1: Milestones of the study

Milestone	Planned date
Completion of feasibility assessment	31 January 2022
Start of data collection	1 October 2022
End of data collection	30 January 2023
Interim report 1 (after enrollment of 10% in Part 1 and 2)	31 October 2022
Final study report	15 April 2023

7. RATIONALE AND BACKGROUND

In clinical trials, patients are treated strictly according to a study protocol and show sometimes different risk factors, fewer comorbidities or a lower age than patients under standard care conditions. However, there is limited larger data collections on current therapy behavior in the 1L of patients with RCC, who are treated under standard care conditions in Germany.

The special interest of this retrospective Medical Chart Review project is to obtain in a Part 1 more precise data for the distribution of different 1L therapies of patients with aRCC, which have started within 01 January 2020 – 31 December 2021 and are representative for Germany. In Part 2 the effectiveness, sequences as well as the frequencies and handling of intolerabilities of combination therapies (ICI + TKI or ICI + ICI) in 1L aRCC will be analyzed by capturing data of patients, who completed a 1L in 01 January 2020 – 31 December 2021 with a follow up period of at least 3 months after completion. All data describe also the current therapy behavior and the resulting clinical effectiveness of the individual therapy protocols used in the 1L. These data allow the transferability of the results from clinical studies to standard care as well as the specific handling of intolerabilities. Particular emphasis is placed on analyses of this handling of intolerabilities during combination therapies with ICI + TKI or ICI + ICI. Information about current processes in decision findings regarding dose modifications or interruptions or interim / permanent discontinuations of one or both drugs can help to unify processes and to develop standard recommendations for daily care situations. Another point of the data analysis lies in the area of the medical disciplines and institutions that initiate and carry out 1L therapies for aRCC under standard care conditions. Questions about the different therapeutic behavior between urologists and medical oncologists, between practices and hospitals and between different regions in Germany are of particular relevance.

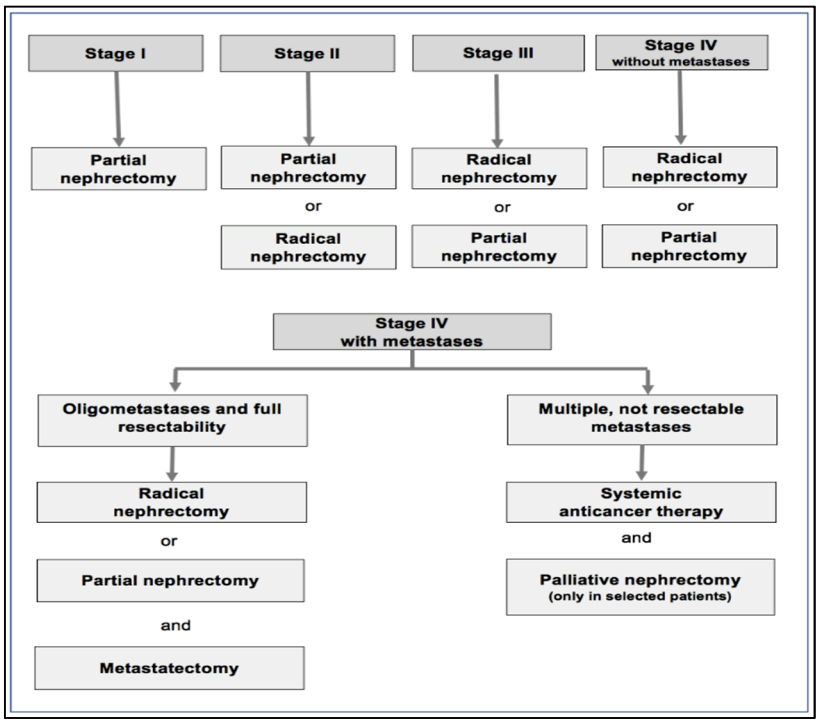
In conclusion, the rationale of this study is more clarity in the effectiveness of different 1L therapies, more clarity in the accordance of 1L therapies to national guidelines and more clarity in the handling of intolerabilities or other situations where dose modifications or discontinuation of treatment occurs

with combinations with ICI + TKI or ICI + ICI in the standard care settings of urologists and hematologists in practices and hospitals in Germany.

8. RESEARCH QUESTION AND OBJECTIVES

In Germany RCC is a rare cancer type with around 15.000 new diagnoses per year and an incidence of 15,7 per 100.000 for men and 7,5 per 100.000 for women (Robert Koch Institute, 2020). Regarding new incidences per year RCC is the 10th most common cancer type in women and 9th most common type in men, whereas the rate of mortality per year due to RCC was lower, 13th position in women with 1,8% and 13th position in men with 2,5% of all cancer-associated deaths (Robert Koch Institute, 2020). The mean age of onset in Germany is 72 years for women and 68 years for men. Risk factors for RCC are hereditary disease (ca. 5% of all cases with RCC) like von Hippel - Lindau – syndrome or Birt-Hogg-Dubé syndrome or acquired factors like obesity, chronic kidney failure, smoking or arterial hypertension, but also some professional exposition with halogenated hydrocarbons or long-term x-ray exposure (DGHO May 2022). Around 70-80% of the new RCC are diagnosed at an early stage and could be treated by partial or radical surgical resections in a curative intention. Most of the newly diagnosed patients were amendable for radical surgery, but 4.000 – 5.000 patients per year will start a new systemic therapy due to their advanced or metastatic disease. At present no neoadjuvant or adjuvant setting is established, but new data with TKIs and/or ICIs could be expected in the next few years. In stage I-IV (without metastases) the standard therapies are partial or radical nephrectomy (fig. 1).

Fig. 1: Guidelines for Renal Cell Carcinoma Stage I – IV (DGHO 2022 and German Cancer Society 2021)

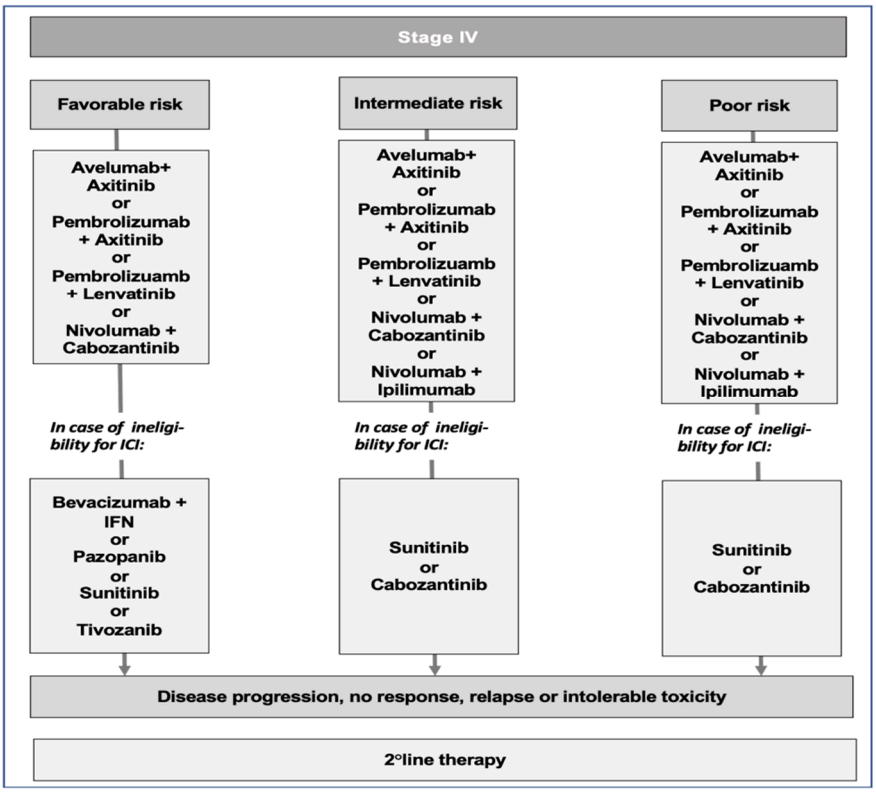


In Stage IV with few number of resectable metastases, the partial or radical nephrectomy should be supplemented by metastatectomy of all metastases. Patients in stage IV without option for full resection of all metastases, a systemic anticancer therapy is recommended (fig. 1). Additionally, in selected patients with stage IV, a cytoreductive/palliative nephrectomy should be considered.

A part of patients with locally aRCC are not suitable for curative treatment by surgery. These patients would be treated like patients with metastatic diseases with systemic therapies under palliative intention.

In the guideline of the German Cancer Society (S3-Leitlinie Nierenkarzinom, AWMF, Nov 2021) and of the German Society for Hematology and Oncology (DGHO, May 2022) for these patients combinations of pembrolizumab or avelumab with axitinib or pembrolizumab + lenvatinib or nivolumab + cabozantinib are recommended as the preferred first-line therapy for all risk groups (fig.2). As an alternative for patients with intermediate and high risk, the combination of nivolumab plus ipilimumab could be used. In patients ineligible for ICI and a low risk rating bevacizumab + INF, pazopanib, sunitinib or tivozanib, with an intermediate and poor risk rating cabozantinib and sunitinib are recommended.

Fig. 2: Guidelines for Treatment of Stage IV Renal Cell Carcinoma (DGHO May 2022 and German Cancer Society Nov 2021)



For subsequent therapies in case of progression, relapse, no response or intolerable toxicities the recommended first choices for 2L are nivolumab or cabozantinib or lenvatinib + everolimus. As alternatives or second choices, axitinib or sunitinib or everolimus or pazopanib or sorafenib are listed.

In the pivotal studies the effectiveness for the combinations of ICI + TKI wwa shown with PFS ranges of 15,1 – 23,9 months, with OS rates at 12 months of 89,9 – 91% and with objective response rate (ORR) ranges of 51,4 – 71% (Bini TI et al, 2019; Motzer R et al, 2019, Motzer R et al, 2021).

In pivotal studies, a higher rate of modifications and discontinuations of one or both drugs were seen for combinations of ICI (pembrolizumab or avelumab) + axitinib. During the therapy with pembrolizumab + axitinib AEs of any cause led to discontinuation of either drug in 30.5%, discontinuation of both drugs in 10.7%, interruption of either drug in 69.9%, and dose reduction of axitinib in 20.3% of the patients in 1L line RCC of any risk (Bini TI et al, 2019). During the treatment with avelumab + axitinib 42% of the patients had at least one reduction in the dose of axitinib due to AEs and in 8% of the patients AEs led to a discontinuation of both avelumab and axitinib (Motzer R et al, 2019). In the pembrolizumab-plus-lenvatinib group, AEs of any grade led to discontinuation of lenvatinib, pembrolizumab, or both drugs in 37.2% of patients (lenvatinib, 25.6%; pembrolizumab, 28.7%; both drugs, 13.4%), to dose reduction of lenvatinib in 68.8% of patients and to interruption of lenvatinib, pembrolizumab, or both drugs in 78.4% of patients (Motzer R et al, 2021). A comparable situation could be found for combination of Nivolumab + Ipilimumab as also for this combination dose delays were described in up to 58% and discontinuations in up to 22% (Motzer R et al, 2018).

But the present handling of severe AEs in the standard care setting of combinations ICI + TKI or ICI + ICI in 1L RCC (e.g. dose reduction or interim discontinuation of axitinib or interim/permanent discontinuation of both drugs) seems to be unclear as no detailed data are available.

8.1. Primary Research Questions

Based on the above background, there are currently a number of unanswered questions for health services research:

- How is the effectiveness, defined as measurement of beneficial effects under “real world” clinical settings, (e.g. progression-free survival, overall survival and best response) of TKI and/or ICI as 1L in patients with aRCC?
- How are patients with aRCC treated in 1L under daily care conditions in Germany in general and in accordance to medical specialities (urology and medical oncology) and treatment settings (hospitals vs office-based practices)?
- Are all patients assigned to individual risk ratings under standard daily care conditions according to a scale developed by the IMDC before start of a 1L?
- How are patients treated in 1L in different risk rating groups and how is the adherence to national/international guidelines?
- What kind of previous and subsequent therapies are administered before and after 1L?
- How often are evaluations for PD-L1 expression performed before start of 1L and how many patients are positive (TPS ≥1%) or negative?

- How long are patients treated with TKI + ICI and ICI + ICI in 1L in general and in relation to specific therapies like avelumab + axitinib?
- How frequent are dose modifications and early discontinuations and what are the reasons?
- Are there differences in the handling of modifications among medical disciplines?

8.2. Study Objectives

To answer these questions the following objectives are derived:

Primary Objective(s):

- Progression-free survival (PFS) for 1L therapies, expressed as median and as rates at timepoints of 6, 9, 12 and 18 months after start of 1L

Secondary Objectives:

- Overall survival (OS) of 1L therapies, expressed as median and rates at timepoints of 12 and 18 months after start of 1L therapy
- Best response in 1L overall and in dependence of administered drug regimen
- Progression-free survival of 1L therapies in dependence of specific drug regimen
- Pre- and post-treatments (i.e. surgery, radiotherapy, medicinal therapies) before/after TKI + ICI and ICI + ICI in 1L
- Duration of response (DoR) in 1L overall and in dependence of administered drug regimen (TKI + ICI or ICI + ICI)
- Frequency of dose modifications and temporary/permanent discontinuations of 1L therapies and their reasons
- Proportions of modifications by dose reduction compared to cancelling single applications
- Effectiveness (PFS, OS and best response) of administered 1L therapies under real world conditions by medical specialty (urology, medical oncology) and setting (practice, hospital)

9. RESEARCH METHODS

The present 1L treatment of patients with aRCC in Germany is wide-ranging with several options like combinations of ICI + TKI, ICI + ICI or monotherapies with TKI alone. Some of these therapies are only recommended in specific risk situations or in cases of ineligibilities for ICI, but at present there is only limited information available about decisions in 1L aRCC. Additionally, a higher proportion of patients with combined therapies of ICI + TKI or ICI + ICI show intolerabilities with the necessary for dose modifications or interim / permanent discontinuations of one or both drugs, but the processes of decision finding between dose modifications, interruptions and discontinuation are also unclear, although these processes would be very important for the outcomes of the therapy. In contrast to study protocols with clear specifications for handling AEs, in standard daily care the decision processes seem to be in the discretion of every oncologist. But at present, no detailed information about these

processes in standard daily care are available. Such information is also important as these therapies could be administered under in- or out-patient´s settings and by urologists or medical oncologists. Study design

The general design of this data project is a sampling of data about patients with aRCC receiving a 1L therapy, with a start (part 1) or completion (part 2) in 01 January 2020 – 31 December 2021. Data will be documented retrospectively and under full anonymization by investigators or their designees in a specific eCRF. All analyses and reports will be performed under aggregation of data as secondary data reports.

9.1. Setting

This Medical Chart Review project will take place in Germany and especially in oncological and urological practices as well as in hospitals with urological/oncological departments and a high focus on systemic treatment for RCC.

It is planned to recruit up to n = 40 study sites with a distribution of 37.5% practices hematology-oncology, 37,5% practices urology and 25% hospitals with urological cancer focus. The number of study sites may increase if it becomes apparent that the number of patients to be recruited per site is lower than expected. The sites are addressed through direct contact by the project management of GermanOncology. As part of a feasibility process the potential case numbers and availability of study nurses or other documentation staff are also queried. All sites have to sign a service contract before start of study, in which rights and obligations as well as documentation fees are clearly defined.

9.1.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

Part 1 <u>and</u> 2:

- Patients aged ≥18 years old
- Patients with histologically/cytologically confirmed renal cell carcinoma (ICD-10 C64)
- Full medical information regarding all treatments before, during and after 1L should be available.

Specific inclusion criteria <u>only for Part 1</u>:

- Patients with locally advanced or metastatic disease and a start of any systemic 1L therapy against RCC between 01 January 2020 and 31 December 2021

Specific inclusion criteria <u>only for Part 2</u>:

- Patients with locally advanced or metastatic disease, who were treated with a combination of ICI + TKI or ICI + ICI as 1L therapy against RCC and who had a completion of this therapy between 01 January 2020 - 31 December 2021 with a follow-up period of at least 3 months after completion of the 1L.

9.1.2. Exclusion criteria

Exclusion criteria for part 1 and 2

Patients meeting the following criteria will not be included in the study:

- Patients participating in an interventional clinical study within 30 days before start of 1L

All sites are asked to document all of their patients with the fulfilled inclusion and not fulfilled exclusion criteria, starting with the earliest start (in part 1) and the longest follow-up period (in part 2), respectively. The patients should be treated with the systemic 1L therapy in the site and data should be available in the medical records of the sites. The enrollment will be competitively over all participating sites without a limitation for the single sites. In part 2 quotas for groups with ICI + TKI and ICI + ICI and with the specific therapy avelumab + axitinib or nivolumab + ipilimumab will be set up.

9.2. Variables

The following variables will be captured by a spefic eCRF and are needed for the analysis of all outcomes and for answering all research questions.

Tab. 2: List of all variables, role, data source and operational definitions

Variable	Role	Data source(s)	Operational definition
Age and gender	baseline characteristic	Medical Chart	Years; male/female
Weight and body surface	baseline characteristic	Medical Chart	kg, m^2
Date of first diagnosis	baseline tumor characteristic	Medical Chart	dd/mm/yyyy
Stage and risk rating (IMDC) at first diagnosis and at start of 1L	baseline tumor characteristic	Medical Chart	Favorable risk / intermediate risk / poor risk
Assessments and results of PD-L1 expression as TPS	baseline tumor characteristic	Medical Chart	y/n; 0-100%
Non-medicinal pre-treatments (primary OP, cytoreductive nephrectomy radiotherapy)	baseline tumor characteristic	Medical Chart	y/n; dd/mm/yyyy of OP; mode of OP; intention of OP (curative/palliative); period and dose of radiotherapy
Medicinal pre-treatments (adjuvant, neoadjuvant)	baseline tumor characteristic	Medical Chart	y/n; start/stop and used therapy protocol
Location of administration and performing medical discipline	Relevant for outcomes	Medical Chart	Urological practice; hematological practice; hospital with urological department; hospital with oncological department
Administered drugs / protocols in 1L	Relevant for outcomes	Medical Chart	administered therapy protocol
If applicable: Reason for ineligibility of ICI	Relevant for outcomes	Medical Chart	Concomitant disease; patient´s wish
Duration of 1L	Relevant for outcomes	Medical Chart	Start/stop of therapy or every cycle;

Dates of administrations for i.v. drugs in 1L	Relevant for outcomes	Medical Chart	Dates of every administration
Dosages per administration	Relevant for outcomes	Medical Chart	Dose of administered drugs per administration
Dose modifications or drug administration cancelling or interim/permanent discontinuations of single drugs / complete therapy in 1L	Relevant for outcomes	Medical Chart	Each for single/all drugs: Dose modification; cancelling single administration; temporare discontinuation; permanent discontinuation
Reasons for modifications, cancelling of single administrations and discontinuations in 1L	Relevant for outcomes	Medical Chart	Each for single/all drugs: intolerability; age; performance status; patient´s decision; other
Supportive drugs prescribed during 1L	Relevant for outcomes	Medical Chart	Administered supportive drugs in connection with cancer therapy
Date of first response and best response in 1L incl. date and mode of assessment	Relevant for outcomes	Medical Chart	dd/mm/yyy; CT/MRI/ultrasound/x-ray; clinical assessment; laboratory
Assessment of first and best response in 1L	Relevant for outcomes	Medical Chart	CR/PR/SD/PD/ND
Date of tumor progression	Relevant for outcomes	Medical Chart	dd/mm/yyyy
Reasons for end of 1L	Relevant for outcomes	Medical Chart	Progression; intolerability; decision oncologist; patient´s wish; death; deterioration performance
Subsequent therapies (Second-line therapy (2L) and higher) with drugs/protocol and dates for start / end	Relevant for outcomes	Medical Chart	y/n; used drugs/regime; start/stop
Concomitant diseases and therapeutic measures	Relevant for outcomes	Medical Chart	Detailed diagnosis; therapeutic measures OP/medicinal/none/other

9.3. Data sources

Source documents (paper or electronic medical charts) are those, in which patient data of daily care are recorded and documented in individual patient files. The data to be collected in the study will be obtained via a specific programmed eCRF. The data in the eCRF should be consistent with the relevant source documents. Medical records should contain demographic data, medical data, treatments and diagnostic documentations according to common practice. The documentation will be performed under full anonymization, so that a re-identification of single patients will not be possible. Based on this anonymization, queries for explanations or changes of data could not be submitted by the data

management. All documented variables will be checked by data manager and/or medical lead of GermanOncology in relation to implausibility, inaccuracies or missing data. If implausibility or inaccuracies or missing data of single patients will be of great relevance for analyses, the data management and/or medical lead have the right to reject patients. For such rejected patients no payment will be triggered.

9.4. Study size

Based on public data the population of patients with aRCC and an indication for a 1L therapy is around n = 4.500 - 5.000 patients per year (Robert Koch Institute 2020). In the period of 01 January 2020 – 31 December 2021, which is the main period of interest in the study for completing or starting 1L therapies, the total population of patients with aRCC would be around n = 9.000 - 10.000 patients. To estimate the needed number of patients in the study to reach adequate representation across Germany, the following common formula is used

$$n = \frac{z^2\,\pi(1-\pi)N}{z^2\,\pi(1-\pi) + E^2(N-1)}$$

N = population of patients with aRCC and indication for 1L = 10.000 patients in 24 months
Π = 0,5 (consensus, if attribute is unknown before study)
E = margin of error = 5% = 0,05
Z = 1,96 (for confidence interval of 95%)

Based on these assumptions (PFS of 1L therapies included in guidelines was 8.4 – 151 months in clinical studies) the number of patients needed for representative statement regarding the primary objective (= PFS rates at defined time points under real world conditions) is at least n = 370. With a buffer of around 10% the sample size in the study should be n = 400 patients with aRCC and 1L therapies in the period from 01 January 2020 – 31 December 2021. Based on published data for PFS it could be assumed for part 2, that also the number of patients with combination therapies in part 2 (n = 300) will grant a representative statement to all research questions. Based on information of urological and oncological experts as well as own data of the GermanOncology *[1] network (see below), the following assumptions could be set:

- Number of patients with new 1L in urological practices (per practice 1- 3 urologists) = 4 - 6 per year
    - Number of patients with new 1L in period of 24 months = 8 - 12
- Number of patients with new 1L in oncological practices (per practice 2- 4 oncologists) = 4 - 6 per year
    - Number of patients with new 1L in period of 24 months = 8 – 12
- Number of patients with new 1L in hospitals with urological focus = 8 - 12 per year
    - Number of patients with new 1L in period of 24 months = 16 – 24
- Proportion of 1L therapies in urological and oncological practices: 50% : 50%
- Proportion of patients treated with 1L in practices and hospitals (as most of therapies are oral therapies): 65% : 35%

Based on the assumptions the needed number of sites are at least:

- Number of urological practices: 15
- Number of oncological practices: 15
- Number of hospitals with urological focus: 10
- Total number of sites across Germany: 40

9.5. Data management

The main purpose of the specific eCRF is to obtain data required by the study protocol in a complete, accurate, legible and timely manner. The data in the eCRF should be consistent with the relevant source documents in the practices and hospitals. The investigator or his/her designee is responsible for ensuring that the data collected in the course of this study are accurate and documented appropriately and completely in all applicable forms. Data will be documented, processed, evaluated, and stored in fully anonymous form in accordance with applicable data protection regulations. The investigator must ensure that the eCRFs and any other associated documents forwarded to the project management contain no mention of any subject names or other personalized information. The data will be entered by the eCRF into a validated database. The project management will be responsible for data processing, in accordance with the Sponsor's data management procedures. The sponsor will receive only full anonymized data or aggregated reports, without any options for re-identification of patients and/or sites. Database lock will occur once quality control and quality assurance procedures and second, that activities of documentation and coding have been completed. The eCRF has a modular structure with separation of contents to build up all sequences and information of treatments from date of first diagnosis up to the present date or death or lost-of-follow-up. Data must be filled in completely and legibly by choosing parameters out of a pre-defined drop-down-list, or in a few cases by writing free text. All corrections will be listed in a history trail with name of corrector and date of correction. Relevant fields are declared as mandatory und must be fulfilled definitively before triggering any payment. As part of the data quality process, all entries in the eCRF will be checked by data manager. In cases of implausibility or incorrectness or inaccuracy or relevant missing data, the data manager together with the medical lead of GermanOncology are allowed to reject patients with a statement of an appropriate reason. Every patient´s documentation file is given a randomized code of numbers and letters, automatically generated by an encryption algorithm. As only anonymized data will be sampled, this data handling and storage can be described as "full anonymized" in accordance to the recital 25 of the German and EU General data protection regulation.

9.5.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to electronic data record.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFsare true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.5.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, copies of all CRFs, safety reporting forms, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless *GermanOncology* or as required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.6. Data analysis

The data analysis are carried out for all evaluable patients for whom the inclusion criteria are met, first-line therapy with at least 1 application has been documented and no exclusion criteria exist.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7. Quality control

The most relevant step in quality control and quality assurance will be an avoidance of inaccuracies or mismatches in terminology by data entries in data fields over a selection of parameters or descriptions out of pre-defined drop-down-lists. Free text is only intended for descriptions after selection of “other”, which will be possible in some data fields, where a pre-definition cannot be

implemented for 100%. For all dates regarding parameters like first diagnosis, pre-treatments, therapy administrations automatic checks are implemented for data entries, so that the course of treatment will be shown correctly (e.g. adjuvant therapy after OP and before palliative therapy, end of 1L before start of 2L, end of therapy after last administration). In defined data fields new explanation fields will open up after selection of specific documentations (e.g. after selection of dose modification query for modified dose, after selection of end of therapy query for reason). In data fields with information like weight, height or age, automatic standard range checks, are implemented to avoid input errors. In addition to these automatic checks every data entry will also be checked by an experienced data manager and, if needed, by the medical lead.

In case of relevant inaccuracy or implausibility, patient´s data files will be rejected before further analytical processes will start. After the decision for rejection of patients the investigator will be informed about the reason for rejection and all data will be deleted immediately.

9.8. Limitations of the research methods

For this data project only data out of the medical records of patients, who are treated under daily routine in oncological institutions like practices or hospitals will be used and these data of investigations or visits have to be generated under standard conditions. The documentation in the eCRF and so also the analyses are dependent on the availability of the data in the medical records. Such availability should be given for most of the mandatory data fields, as these will be standard facts during oncological treatments. If data are not available, this has to be documented explicitly. In case of a high amount of missing data, a patient can be rejected by the data manager or medical lead, as otherwise no representative analyses can be performed.

9.9. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

As only fully anonymized data of patients will be used in the project, all requirements for data protection in accordance to the national and EU General Data Protection Regulations are fully preserved. The data will be captured retrospectively, so that all patients were already treated under standard daily conditions without any kind of additional investigations or other interventions.

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of documeted patient data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The documented patient data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the documented patient

data can be recovered in the event of disaster. In the event of a potential documented patient data breach, the study site shall be responsible for determining whether a documented patient data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of documented patient data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' documented data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer should not be required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective official statement or approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in policies for Good Clinical Practice (GCP), Good Epidemiological Practice (GEP), Good Pharmacovigilance Practice (GVP) and the Declaration of Helsinki by the World Medical Association.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- For exposure during pregnancy in studies of pregnant women, data on the exposure to avelumab, axitinib, or sunitinib, during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness," "Study Drug," and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.">

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) Training for Vendors."*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

\Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.