Title:	Registry to evaluate the safety, tolerability and efficacy of Torisel® (temsirolimus), Sutent® (sunitinib) and Inlyta® (axitinib) during the treatment of patients with advanced renal cell carcinoma (mRCC), mantle cell lymphoma (MCL), and gastrointestinal stromal tumor (GIST). Amendment VII
Study Number:	B1771009
Version:	1.0
Date:	September 28, 2020
Name of active ingredient:	Temsirolimus, sunitinib, axitinib
Scientific question and objective	**Objective:** The aim of this registry is to gain an overall picture regarding the efficacy, tolerability, and safety of temsirolimus, sunitinib, or axitinib therapy in patients with advanced renal cell carcinoma, relapsed/refractory mantle cell lymphoma (MCL), and gastrointestinal stromal tumors (GIST) under the conditions of routine use. In a highly evolving therapeutic setting for advanced RCC, there is a lack of data e.g. from routine use of sunitinib, followed by novel therapy options, followed by axitinib, to assess the efficacy and tolerability of axitinib in the third or later line in a differentiated manner.
Author	**Dr. rer. nat.** PPD Pfizer PPD Berlin

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AMG	Arzneimittelgesetz [German Medicinal Products Act]
mRCC	Metastatic Renal Cell Carcinoma
GIST	Gastrointestinal stromal tumors
mTOR	Mammalian Target of Rapamycin
VEGF	vascular endothelial growth factor
c-KIT	Stem Cell Factor Receptor
MCL	Mantle cell lyphoma
FTL-3	FMS-like tyrosine kinase 3
RET	Rearranged During Transfection Receptor
CYP	Cytochrome P450
FKSI-15	FACT-Kidney Cancer Symptom Index-15
EQ-5D	EuroQoL-5D
RCC	Renal cell carcinoma
IRB/IEC	Institutional Review Board (IRB)/Independent Ethics Committee (IEC)
ISPE	International Society for Pharmacoepidemiology
ICI	Immune Checkpoint Inhibitor
TKI	Tyrosine Kinase Inhibitor

2. RESPONSIBILITIES

Scientific Director

Name	Title	Office	Address
Dr. rer. nat. PPD	CCI	Pfizer PPD	PPD Berlin
Dr. CCI	CCI	Pfizer PPD	PPD Berlin

3. AMENDMENTS AND UPDATES

Amendment Number	Date of Amendment	Substantial Amendment	Reason
I	09/16/2009	Registry to evaluate the safety, tolerability and efficacy of temsirolimus in the evaluation of patients with advanced renal cell carcinoma and mantle cell lymphoma	Approval extension in August 2009 for the treatment of relapsed/refractory mantle cell lymphoma (MCL)
II	10/28/2010	Registry to evaluate the safety, tolerability and efficacy of temsirolimus and sunitinib during the treatment of patients with advanced renal cell carcinoma, mantle cell lymphoma and gastrointestinal stromal tumor (GIST)	Extension to sunitinib
III	10/20/2012	Registry to evaluate the safety, tolerability and efficacy of temsirolimus, sunitinib and axitinib during the treatment of patients with advanced renal cell carcinoma, mantle cell lymphoma and gastrointestinal stromal tumor (GIST)	Extension to axitinib
IV	11/26/2015	Registry to evaluate the safety, tolerability and efficacy of temsirolimus, sunitinib and axitinib during the treatment of patients with advanced renal cell carcinoma, mantle cell lymphoma and gastrointestinal stromal tumor (GIST)	12-month recruitment extension
V	09/12/2016	Registry to evaluate the safety, tolerability and efficacy of temsirolimus, sunitinib and axitinib during the treatment of patients with advanced renal cell carcinoma, mantle cell lymphoma and gastrointestinal stromal tumor (GIST)	24-month recruitment extension

Amendment Number	Date of Amendment	Substantial Amendment	Reason
VI	10/30/2017	Interim documentation of non-Pfizer substances such as nivolumab or cabozantinib so that e.g. the therapy sequence of sunitinib followed by nivolumab followed by axitinib can be documented. Extension of recruitment phase by 3 years.	Data from routine use of sunitinib followed by novel therapy options, followed by axitinib, to assess the efficacy and tolerability of axitinib in the third or later line in a differentiated manner.
VII	09/28/2020	Discontinuation of question from Amendment VI due to insufficient inclusion of evaluable patients. Reduction of the recruitment period by 12 months	Based on the new approval of ICI in combinations with other ICI or TKI in the first line, the primary use of sunitinib in the therapy sequence shifts to later lines of therapy and as a result, this also applies to the interim documentation and the documentation of axitinib. After evaluation of patient recruitment and inclusion into the various documentation stages, the number of patients calculated to answer the question (Amendment VI) was not reached within the extension period, and the question cannot be answered.

4. MILESTONES

Milestone	Planned date
Start of data collection	January 2008
End of data collection	12/31/2021
Final Study Report	11/30/2022

5. RATIONALE AND BACKGROUND INFORMATION

5.1. Background information

The present registry is a multi-center, prospective, non-interventional investigation according to § 4, Number (23), Clause 3 AMG, which is being conducted according to the joint recommendations of the Federal Institute for Drugs and Medical Devices and the Paul Ehrlich Institute for planning, conducting and analyzing observational research.

Participation in this registry is not meant to lead to a change in routine therapy, i.e. diagnostic and therapeutic practices of the physicians involved will not be affected. Temsirolimus, sunitinib and axitinib are subject to prescription requirements, and are physician prescribed. Study medication will not be provided within the scope of the registry.

The registry will be reported to the German Association of Statutory Health Insurance, the umbrella association of health insurance funds, private health insurance funds, and to the Federal Institute for Drugs and Medical Devices, according to § 67 Paragraph 6 AMG.

This registry was registered based on the VFA recommendations for improving quality and transparency of non-interventional studies (May 2012). (http://www.clinicaltrials.gov).

The initial observational plan and the patient information sheet and informed consent form were submitted to the Ethics Committee in Münster for review and received a positive opinion on 11/21/2007. The positive vote for Amendment I took place on 09/16/2009. The positive vote for Amendment II was on 06/17/2010, for Amendment III on 10/08/2012, for Amendment IV on 01/11/2016 and for Amendment V on 09/30/2016. With Amendment VI, an updated version of the patient information sheet and Informed Consent Form for advanced RCC comes into effect. Amendment VII specifies that the recruitment period is to be shortened by 12 months since, due to the new approval of ICI in combinations with other ICI or TKIs in the first line, the primary use of sunitinib in the therapy sequence shifts to subsequent lines of therapy and as a result, this also applies to the interim documentation and the documentation of axitinib. After evaluation of patient recruitment and inclusion into the various documentation stages, the number of patients calculated to answer the question (Amendment VI) was not reached within the extension period, and the question cannot be answered.

Physicians participating in this registry agree to inform patients about the registry and obtain advance written informed consent from the patient. This includes the inclusion of pseudonymized patient data, the use of the data collected, and access to the medical records for review of the data by third parties.

5.2. Study Rationale

Renal cell carcinoma (RCC) accounts for two percent of all malignant tumors with an age peak between 50 and 70 years of age; men are affected two times more often than women. Due to a lack of effective therapy, locally advanced RCC is the sixth most common cause of cancer-related deaths.

Following the Robert Koch Institute and the Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Society of Epidemiologic Cancer Registries in Germany), approximately 15000 men and women newly developed renal cell carcinoma in Germany in 2012. In contrast to most cancer types, the prevalence rate of RCC worldwide is increasing, with an estimated annual rate of 1.5 – 5.9%.

Approximately 40 - 45% of patients with RCC have "localized" disease (stage I) at the time of diagnosis, 10 - 20% of patients have "localized" disease of stage II, 20% have "locally advanced" disease (stage III) and 20 -30% have "metastatic" disease (stage IV).

In addition, approximately 30% of patients who have "localized" or "locally advanced" disease at the time of diagnosis will develop metastases in the later course.

The lung is the most common metastatic site with 55%, followed by the lymph nodes (34%) and liver (33%) and the skeletal system (32%). Patients with stage II, III, and IV RCC have a 5-year survival rate of 80%, 50 – 60%, and 10%, respectively. 75 – 85% of RCC cases are highly vascularized tumors overexpressing a range of growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF).

Mantle cell lymphoma (MCL) accounts for about five to ten percent of all Non-Hodgkin's Lymphomas (NHL). Most new cases occur at an age of 60 - 65 years, with a majority of male patients (gender distribution about 3:1). Due to the frequently aggressive course and diagnosis often only in advanced stages, the prognosis is poor and a cure by standard chemotherapy is generally not possible.

The incidence rate of MCL is two to three new cases per 100,000 residents annually. Standard of care is immunochemotherapy in combination with rituximab as a first-line therapy. In addition, the importance of high-dose therapy appears to be confirmed for younger patients. Unlike established therapeutic recommendations for first-line therapy, there is no international consensus regarding a recommendation for therapy in a relapsed/refractory situation.

Prognosis of MCL is affected by the stage at first diagnosis (Ann Arbor classification). Only in highly localized stages (I/IE), long-lasting remission may be achieved by radiation therapy. In patients with stage II to IV, the median survival time is approximately three to five years, depending on feasibility of intensive therapy measures. Specifically in elderly patients or patients who cannot receive intensive therapy for other reasons, life expectancy is low: After 5 years, fewer than 15% of these patients survive.

Mantle cell lymphomas are characterized by chromosomal translocation t (11;14) (q13;q32) leading to overexpression of cyclin D1 mRNA. Translation of this mRNA is an mTOR-dependent process that is inhibited by the specific mTOR inhibitor temsirolimus.

Gastrointestinal stromal tumors (GIST) are sarcomas that originate in connective tissue of the gastrointestinal tract. They are characterized by the expression of the surface molecule CD117 (c-KIT) and were only identified as a separate tumor entity a few years ago.

GIST are a relatively rare disease in Germany with 1,500-2,000 new cases per year. If detected early, surgery can achieve a complete cure. If the tumor is inoperable or metastatic, it is usually not possible to cure it. In this situation, however, modern drugs such as sunitinib or imatinib mesylate can achieve significantly longer survival with a higher quality of life at the same time, compared to even a few years ago.

Information on Torisel® (temsirolimus)

The antineoplastic agent Torisel® contains temsirolimus (TEMS) as an active ingredient, a specific inhibitor of mammalian target of rapamycin (mTOR) kinase. Temsirolimus is the first mTOR kinase inhibitor approved for tumor therapy. The drug received its initial approval for intravenous treatment of advanced RCC in the first line

in adult patients who had at least 3 of 6 prognostic risk factors. In August 2009, the marketing authorization was also extended for the treatment of relapsed and/or refractory MCL.

Temsirolimus binds to the intracellular protein FKBP-12. The protein-temsirolimus complex binds to and inhibits the activity of mTOR kinase, which plays a key role in the initiation and promotion of cell division. In cancer cells, inhibition of mTOR kinase can block the transcription of genes regulating the cell cycle. This mechanism also appears to be of particular importance in mantle cell lymphoma therapy. In addition, inhibition of mTOR kinase can lead to inhibition of increased expression of vascular cell growth factor (VEGF), which plays a role in the formation of new blood vessels. This can suppress vascularization in the tumor tissue and thus limit blood supply, which does not allow the tumor tissue to receive sufficient blood flow, causing it to die. This mechanism appears to be of particular importance in renal cell carcinoma. Temsirolimus is used according to the Summary of Product Characteristics.

The named contraindications, warnings and precautions for use, side effects, interactions and instructions on the dosage, type and duration of the application should be observed. According to the Summary of Product Characteristics, pre-treatment with an antihistamine is advised. The Summary of Product Characteristics of temsirolimus is part of this observational plan.

Information on Sutent® (sunitinib)

The oral multi-kinase inhibitor Sutent® (active substance sunitinib) is a so-called "small molecule". Sunitinib binds intracellularly to the signal transduction pathways of the cell. This is accomplished by inhibiting multiple receptor tyrosine kinases that are involved in tumor growth, pathological angiogenesis, and formation of metastases.

Sunitinib has direct anti-proliferative effects by inhibiting VEGF and PDGF receptors on the tumor cell. Sunitinib has extensive antiangiogenic effects by inhibiting the PDGF receptors a and ß to pericytes and VEGF receptors 1-3 on endothelial cells.

In addition, sunitinib inhibits the receptor tyrosine kinases c-KIT (Stem Cell Factor Receptor), Flt3 (FMS-like tyrosine kinase 3) and RET (Rearranged During Transfection Receptor) and thereby inhibits tumor growth and formation of metastases.

Sunitinib is used according to the Summary of Product Characteristics. The named contraindications, warnings and precautions for use, side effects, interactions and instructions on the dosage, type and duration of the application should be observed.

The Summary of Product Characteristics of sunitinib is part of this observational plan.

Information on Inlyta® (axitinib)

The oral multikinase inhibitor Inlyta® (active substance axitinib) is a "small molecule". Axitinib is a potent and highly selective tyrosine kinase inhibitor of the vascular endothelial growth factor receptors VEGFR-1, VEGFR-2, and VEGFR-3, involved in pathological angiogenesis, tumor growth, and metastases. Axitinib has been shown to be a potent inhibitor of VEGF-mediated endothelial cell proliferation and cell survival. Inlyta® is used according to the Summary of Product Characteristics. The named contraindications, warnings and precautions for use, side effects, interactions and instructions on the dose, type and duration of the application should be observed.

The Summary of Product Characteristics of axitinib is part of this observational plan.

Patient Interview Advanced RCC

For the patient interview, the validated FKSI-15 questionnaire and the validated EQ-5D questionnaire/VAS will be used to document the effect of the substances temsirolimus and/or sunitinib and/or axitinib by the patient.

The Functional Assessment of Cancer Therapy-Kidney Symptom Index-15 (FKSI-15) includes 15 questions subdivided into 4 groups. Signs and symptoms, respiratory symptoms, quality of life, emotional symptoms. EuroQol-5D (EQ-5D) includes EQ-5D Index and EQ-Visual Analog Scale (VAS). The EQ-5D in turn is divided into 5 groups: Mobility, independence, usual activities, pain/discomfort, and anxiety/depression.

6. SCIENTIFIC QUESTION AND OBJECTIVE

The treatment of metastatic renal cell carcinoma has undergone substantial changes in a very short time. In recent years, the introduction of various new substances for the treatment of advanced RCC has led to new scientific questions. Temsirolimus and sunitinib are current standard therapies in the first-line therapy of advanced RCC. Temsirolimus is approved for first-line treatment of advanced RCC in adult patients who have at least 3 of 6 prognostic risk factors.

Sunitinib is approved for the treatment of advanced/metastatic RCC. Axitinib has been developed to treat advanced RCC in adult patients after failure of prior therapy with sunitinib or a cytokine.

As of August 2009, temsirolimus is also another therapy option for patients with relapsed and/or refractory mantle cell lymphoma (MCL). In addition, sunitinib is used in patients with unresectable and/or metastatic gastrointestinal stromal tumors (GIST) following imatinib failure or intolerance.

In April 2016, the active substance nivolumab was approved as the first immuno-oncology medicinal product for monotherapy of advanced renal cell carcinoma in adults after previous therapy. In addition, in August 2016, the combination of lenvatinib/everolimus was approved for the treatment of adult patients with advanced RCC after previous treatment with therapy targeted towards the vascular endothelial growth factor (VEGF) and in September 2016, the active substance cabozantinib was approved for therapy of advanced RCC in adults after previous therapy targeting VEGF.

Routine use of drugs in routine clinical practice is subject to additional challenges that are generally not fully covered by clinical trials. Therefore, the aim of this registry is to gain an overall picture regarding the efficacy, tolerability, and safety of temsirolimus, sunitinib, or axitinib therapy in patients with advanced renal cell carcinoma, relapsed/refractory mantle cell lymphoma (MCL), and gastrointestinal stromal tumors (GIST) under the conditions of routine use.

In a highly evolving therapeutic setting for advanced RCC, reflected in the current S3 guideline, there is a lack of data from routine use of sunitinib, followed by novel therapy options, followed by axitinib, to assess the efficacy and tolerability of axitinib in the third or later line in a differentiated manner.

Separate evaluations for third line use of axitinib following prior therapy with sunitinib in the first line followed by e.g. nivolumab, cabozantinib, or lenvatinib/everolimus in the second line are urgently needed. The efficacy of axitinib can continue to be documented after directly preceding therapy with sunitinib. These investigations allow a comparison of the efficacy and tolerability of axitinib in different lines.

Therefore, the following information is of particular interest during the course of the investigation:

- Efficacy (maximum response, survival time, progression-free time)
- Treatment tolerability (assessment by physician)
- Safety profile (overall incidence of adverse events and rate of side effects) of patients with advanced RCC, r/rMCL and GIST receiving treatment with temsirolimus, sunitinib, or axitinib
- Profile, comorbidities and characteristics of patients receiving treatment with temsirolimus, sunitinib, or axitinib
- The sequence of systemic therapies for advanced RCC, MCL, and GIST
- Patient interview on quality of life in advanced RCC patients

Temporal sequence

The following time points were defined as the minimum period for the implementation of the registry:

- Patient Recruitment Phase: January 2008 – December 2020
- Recruitment rate: 100 patients/year per product
- Average observation period per patient: 6 months for temsirolimus, 12 months for sunitinib, 6 months for axitinib
- Field Phase: December 2021
- Total duration: 14 years + 1 year evaluation and report (2022)

Since the goal is to keep patients in the registry for life, the registry can be continued indefinitely.

The end of data collection is scheduled for December 2021.

7. INVESTIGATION METHODS

7.1. Study design

This is a prospective, non-interventional, observational study. It is planned that a total of 1,600 patients is documented.

Patient Population

Additionally, the purpose of this registry is to document patients in accordance with Amendment III, for which the following criteria are applicable at enrollment:

7.2. Study Setting

Inclusion and exclusion criteria:

a) Patients with a histologically confirmed diagnosis of advanced renal cell carcinoma without prior therapy and at least 3 of 6 prognostic risk factors or relapsed/refractory mantle cell lymphoma for whom a decision was already made to treat with temsirolimus.

b) Patients with histologically confirmed diagnosis of advanced/metastatic renal cell carcinoma or unresectable and/or metastatic GIST, after imatinib failure, for whom a decision was already made to treat with sunitinib.

c) Patients with histologically confirmed diagnosis of advanced renal cell carcinoma after failure of prior therapy with sunitinib or a cytokine for whom a decision was already made to treat with axitinib.

d) Written informed consent form from the patient is obtained prior to enrollment into the registry.

Due to the non-interventional nature of the registry, no specific requirements apply regarding the management of treatment. Dosing and duration of treatment will be decided by the physician according to individual treatment requirements of the patient.

Extract from the Summary of Product Characteristics

During the treatment of patients with temsirolimus, sunitinib, and axitinib, among other things, the section "Contraindications" of the respective Summary of Product Characteristics must be taken into account. In case of hypersensitivity reactions, the advice in the relevant Summary of Product Characteristics must be observed.

a) In particular, the following excerpts are included under Section 4 "Clinical particulars" of the Summary of Product Characteristics of temsirolimus:

- Hypersensitivity to the active substance or to any of the excipients of temsirolimus
- It is recommended that patients be given an H1 antihistamine before an infusion of temsirolimus. In case of known hypersensitivity to antihistamines or in patients who cannot receive an antihistamine for another medical reason, temsirolimus should be used with caution.
- Concomitant use of substances that affect CYP3A metabolism: CYP3A4 inducers: e.g. dexamethasone, carbamazepine, phenytoin, phenobarbital, rifabutin, rifampicin, St John's wort
- CYP3A4 inhibitory agents: e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromyzine.
- Concomitant use of sunitinib
- Vaccinations
- Pregnancy.

b) In particular, the following excerpts are included under Section 4 "Clinical particulars" of the Summary of Product Characteristics of sunitinib:

Dose adjustment:

- Safety and Tolerability: Depending on individual safety and tolerability, the dose can be adjusted in 12.5 mg steps. The daily dose should not exceed 75 mg or drop below 25 mg.
- Dosing interruptions may be necessary depending on individual safety and tolerability.
- CYP3A4 inhibitors/ inducers: Concomitant administration with potent CYP3A4 inducers such as rifampicin must be avoided. If not possible, it may be necessary to increase the dose of sunitinib in 12.5 mg increments (up to 87.5 mg per day for advanced RCC and GIST) under careful monitoring of tolerability.
- Concomitant administration with potent CYP3A4 inhibitors such as ketoconazole must be avoided.
- If not possible, it may be necessary to reduce the dose of sunitinib down to a minimum of 37.5 mg per day for advanced RCC and GIST under careful monitoring of tolerability. The use of alternative concomitant medication with no or minimal CYP3A4 inducing or inhibitory effects should be considered.
- Co-administration of temsirolimus
- Pregnancy.

c) In particular, the following excerpts are included under Section 4 "Clinical particulars" of the Summary of Product Characteristics of axitinib:

- The recommended starting dose of axitinib is 5 mg twice daily.

- Concomitant administration of axitinib with strong CYP3A4/5 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase plasma concentrations of axitinib.
- Likewise, grapefruit can increase the plasma concentrations of axitinib. It is recommended to select concomitant medication with no or only minimal CYP3A4/5 inhibitor potential. If a potent CYP3A4/5 inhibitor is to be administered concomitantly, an axitinib dose adjustment is recommended. CYP1A2 and CYP2C19 are subordinate pathways (<10%) of axitinib metabolism. The influence of strong inhibitors of these isoenzymes on the pharmacokinetics of axitinib was not investigated. Due to the increased risk of elevated axitinib plasma concentrations, caution should be exercised for patients taking potent inhibitors of these isoenzymes.
- The concomitant use of axitinib with strong CYP3A4/5 inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, and hypericum perforatum [St John's wort]) may decrease plasma concentrations of axitinib.
- It is recommended to select concomitant medication with no or only minimal CYP3A4/5 inducing potential. If a strong CYP3A4/5 inducer is required at the same time, an adjustment of the axitinib dose is recommended.
- Concomitant use of axitinib with CYP1A2 substrates may lead to increased plasma concentrations of CYP1A2 substrates (e.g. theophylline).
- Information on pregnancy, lactation, fertility and reproductive function.

8. DATA MANAGEMENT

Data collection and documentation forms

Data collection

The involvement of team members of the medical scientific field sales force (Manager Medical & Science Relations (MSR)) of Pfizer Pharma GmbH ensures that physicians and patients are included in all regions of Germany.

The MSR duties include handing out of the case report forms as well as investigator enrollment. Team members are not involved in the review of patient data to check for the presence of informed consent form or plausibility and completeness. At the end of the field phase, unreturned case report forms may be followed up with the support of MSR.

If a physician agrees to participate in the registry, a written agreement is made with them, specifying the amount of compensation for documentation of a patient. The collection of private addresses of participating physicians is done exclusively for tax reasons based on a landmark decision.

As no clinical and laboratory investigations are performed beyond the usual level, the reimbursement of medical services and medicinal products is paid by health insurance providers. The agreed fee refers to the workload for the provided documentation of treatment in the specified documentation sheet.

Documentation Sheets (CRF)

The report the findings, a special case report form will be provided, which will be completed by the participating physician in a timely manner at the time of enrollment, as well as at the regularly scheduled intervals, according to local guidelines (generally every 8-12 weeks), and at the end of treatment with temsirolimus, sunitinib, and axitinib.

There is an option to document two of the above Pfizer substances on the white or green documentation forms. A pink additional case report form is used to document new therapeutic options in the second line, for example nivolumab, following sunitinib and before axitinib; patient questionnaires are omitted here.

Since parts of the logistics (data collection and management, monitoring) are carried out by a contract research organization (Winicker Norimed GmbH, Nuremberg), the documentation should be sent back to the CRO.

Prepared shipment labels will be provided for this. Pfizer Pharma GmbH will pay the costs.

Documentation received by Winicker Norimed will be processed immediately and reviewed for completeness and plausibility of the documentation relating to pre-specified key fields.

If any queries arise, they will be made in writing and directly to the physician. In addition, to assure data quality and verification of documented patient data, it is also planned to conduct monitoring visits at random sites.

A reconciliation of the original patient data from the medical records with the available documentation will be performed. It is ensured that the transfer of all collected data to the Sponsor and to the contract research organization authorized to perform the evaluation will be performed in pseudonymized form in accordance with the federal data protection laws.

When signing the registration to participate, the physician declares their consent to the original data comparison. Since this work requires additional time from the monitoring physician, a separate lump sum per visit is scheduled for this.

Data storage

To enable inspections and/or audits by regulatory authorities or Pfizer, the study site agrees to keep all records: the identity of all participating patients (sufficient information for the unique attribution of the data, e.g. CRFs and patient files), all signed informed consent forms, copies of the CRFs, completed serious adverse event forms, source documents, all detailed treatment notes and study-related correspondence (e.g. letters, meeting/telephone call logs). All records will be kept by the study site in accordance with applicable regulations, however for at least 10 years.

If for any reason the study site becomes unable to retain the study records for the required period (e.g. retirement, relocation), Pfizer should be notified in advance. The study records must be transferred to another entity authorized by Pfizer, such as another site, another practice, or an independent third party appointed by Pfizer. Prior to disposing of the study documents, the study site shall notify Pfizer in writing, even after the retention period has elapsed.

Quality Control:

In a data validation plan (DVP), audits are defined for plausibility of the recorded data. As far as possible, these audits will be supported by programs, and queries will be submitted to sites by the CRO for deviations.

Outcome and query resolution will be tracked and data changes are performed in the database as applicable. All changes performed are logged in an Audit Trail File.

In addition, to assure data quality and verification of documented patient data, monitoring visits are planned at random selected sites.

Other aspects: Not applicable.

9. PROTECTION OF STUDY PARTICIPANTS

9.1. Patient information sheet and informed consent form

All parties guarantee the protection of the patient's personal data and will not include the name of the patient on any Pfizer forms, reports, publications or other disclosures unless required by law.

In case of data transfer, Pfizer maintains high standards of confidentiality and protection of patients' personal data.

Informed consent forms and any changes made during the course of the study must be approved prior to use by Pfizer and provided to the IRB/IEC for consultation.

The treating physician must ensure that each study patient or his/her legal representative is fully informed about the characteristics and aims of the study and the possible risks associated with participation. The treating physician or person mandated by him/her will obtain a written informed consent form from each patient or the patient's legal representative before any study specific activity is performed. The treating physician will retain the original of each patient signed informed consent form.

9.2. Termination of patient's participation:

The patient may withdraw consent to participation in the non-interventional study at any time or the treating physician may decide to discontinue the patient's participation for reasons of safety, due to compliance problems, or administrative reasons. In any case, the patient's clinical status should be documented as appropriate. The physician should ask the patient for the reasons for their decision and follow up with any unfinished adverse events. If the patient withdraws consent for further data collection, data will not be collected for them any longer from the non-interventional study.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The observational plan and the patient information leaflet and informed consent form will be provided to the competent Ethics Committee for consultation before any patients are enrolled.

9.4. Ethical conduct of the study

The present study is a multi-center, prospective, non-interventional study according to § 4, Number (23), Clause 3 AMG.

In addition, the vfa recommendations for improving quality and transparency of non-interventional studies apply as well as the guidelines provided by the "International Society for Pharmacoepidemiology" (ISPE) for the *"Good Pharmacoepidemiology Practices"* (GPP), the guidelines of the "International Society for Pharmacoeconomics and Outcomes Research" (ISPOR) and the guidelines of the "Pharmaceutical Research and Manufacturers of America" (PhRMA) will apply.

The patient provides the written informed consent form for the study, which was first submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for consultation.

Based on the vfa recommendations to improve quality and transparency of non-interventional studies, and to meet the specification to publish notifications of observational studies, this non-interventional study will be registered with a publicly accessible registry.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

10.1. Requirements

The table below lists the requirements for documentation of safety relevant events in the CRF and reporting of safety-relevant events on the Adverse Event Monitoring (AEM) form in non-interventional studies to the CRO Winicker Norimed GmbH.

These requirements are described for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs and (3) scenarios where drug exposure occurs, including exposure during pregnancy, exposure during breastfeeding, medication errors, overdosing, incorrect use, extravasation, lack of efficacy, and occupational exposure. These events are defined in further detail in the section "Definitions of safety-relevant results".

Table 1: Requirements for documentation of safety-relevant events

Safety-relevant event	**Note on the documentation sheet**	**Report to Winicker Norimed within 24 hours of awareness, using the NIS AE Reporting Form**
Serious AE	All	All
Non-serious AE	All	Not applicable.
Scenarios involving drug exposure, including exposure during pregnancy, exposure during breastfeeding, medication errors, overdose, incorrect use, extravasation, lack of efficacy, and occupational exposure	**All** (regardless of whether they are related to an AE), **excluding occupational exposure**	**All** (regardless of whether they are related to an AE)

The physician must follow up each AE and obtain appropriate information to determine the outcome of the AE and assess whether it meets the classification criteria for an SAE (see the section "Serious Adverse Events" below).

The safety events listed in the right column of the above table must be reported to the CRO Winicker Norimed GmbH within 24 hours of the physician gaining knowledge, **regardless of whether the physician sees an association between the event and the investigational medicinal product.** In particular, in case of fatal or life-threatening SAEs, the CRO Winicker Norimed GmbH must be notified immediately, regardless of the extent of the information available about the event. This timeframe also applies to additional new information (follow-up) of safety-relevant events already reported. In the rare instances where the physician is not immediately aware of the occurrence of a safety-relevant event, the physician must report the event within 24 hours of gaining knowledge of it, and document the time at which he first gained knowledge of the event.

In case of safety-relevant events that are considered serious or which must be reported to the CRO Winicker Norimed GmbH in accordance with the right column of the above table after gaining knowledge thereof, the physician is obliged to follow up the event and submit all additional information to the CRO Winicker Norimed GmbH within 24 hours. In addition, a physician may be asked by CRO Winicker Norimed GmbH to obtain certain additional information more quickly.

Such information may exceed the scope and detail of the information collected in the CRF about adverse events. Typically, this is a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. All other relevant information on the event such as concomitant medication and conditions must also be provided. If a patient dies, a summary of any available autopsy findings must be provided to the CRO Winicker Norimed GmbH as soon as possible.

10.2. Reporting Period

For each patient, the reporting period for safety-relevant events will begin with the first dose of temsirolimus, sunitinib, and axitinib or at the time the informed consent form is provided if the patient is already receiving temsirolimus, sunitinib, and axitinib, and lasts until the end of the observation period, and up to 28 calendar days after the last dose of an investigational medicinal product given during the study period. All safety-relevant events from the above table that occur during this period must be reported to the CRO Winicker Norimed GmbH. If a patient is given the medicinal product on the last day of the observation period, the reporting period should be extended to 28 calendar days after the end of the observation. In most cases, the date on the informed consent form is the date of the patient's inclusion in the study.

In some situations, a time interval may lie between the date the informed consent form is provided and the inclusion into the study. In this case: If a patient provides the informed consent form but is never enrolled in the study (e.g. the patient changes his/her mind about participation or does not meet eligibility criteria), the reporting period will end on the day of the decision not to enroll the patient.

Serious adverse events that occur after the completion of the non-interventional study (NIS) and the observation period must also be reported to the CRO

Winicker Norimed GmbH if the physician sees a causal relationship with temsirolimus, sunitinib and axitinib.

Causality assessment

The physician must assess and document the causal relationship. For all AEs, the physician must obtain sufficient information to assess the causality of the AE.

For AEs with a causal relationship to temsirolimus, sunitinib, and axitinib, the physician must follow these up until the event and/or its consequences have resolved or stabilized at a level acceptable to the physician and Pfizer agrees with this assessment.

The physician's causality assessment of temsirolimus, sunitinib and axitinib verifies whether there is a potential that temsirolimus, sunitinib and axitinib caused or contributed to an AE. Even if causality is ultimately assessed as "unknown" and the physician cannot determine whether the event was caused by temsirolimus, sunitinib and axitinib, the safety-relevant event must be reported within 24 hours.

If the physician cannot determine the cause of the event but is convinced that the event was not caused by temsirolimus, sunitinib, and axitinib, it must be clearly documented on the CRF and the NIS AEM report form.

Definitions of safety-relevant events

Adverse events (AEs)

An AE is any undesirable medical event in a patient taking a medicinal product. It is not necessarily required that the event is causally related to the treatment or use of the medicinal product. Examples of AEs include, among others:

- Abnormal findings (circumstances where an abnormal finding is considered an adverse event are listed below);
- clinically important symptoms and signs;
- changes in physical examination findings;
- hypersensitivity;
- progression/worsening of underlying disease;
- lack of efficacy;
- abuse of the medicinal product;
- dependence on the medicinal product.

In medicinal products, this may also include signs or symptoms that have the following causes:

- overdose of the medicinal product;
- discontinuation of the medicinal product;
- incorrect use of medicinal product;
- off-label use;
- drug interactions;
- extravasation;
- exposure during pregnancy;
- exposure during breastfeeding;
- medication errors;
- occupational exposure.

Abnormal findings

The following criteria will determine whether an abnormal objective finding is reported as an AE:

- The findings are accompanied by symptoms and/or
- the finding requires further diagnostic or medical/surgical intervention and/or
- within the study, the findings lead to a dose modification of the observed medicinal product or study termination for the respective subject resulting in a significant additional concomitant treatment with a medicinal product or another treatment, and/or
- the physician or sponsor classifies the findings as an AE.

Recurring abnormal findings without the above conditions do not constitute an AE. An abnormal finding that turns out to be an error does not need to be reported as an AE.

Serious Adverse Events (SAEs)

An SAE is any undesirable medical event that occurs in a patient receiving a medicinal product or dietary supplement (including infant formula) at any dose, and that

- results in death;
- is life-threatening;
- requires an unforeseen hospitalization or prolongation of hospitalization (circumstances that do not constitute AEs are listed below);
- results in persistent or significant disability/incapacity (substantial impairment of the ability to perform daily activities);
- results in a congenital malformation/birth defect

Progression (including symptoms of progression) of the malignant disease assessed in the study **must only be reported as a serious adverse event if** it causes **death** during the study or within the observation periods specified for reporting adverse events. **Hospital treatment due to symptoms of progression** of the malignant disease is not reported as a serious adverse event.

If the malignant disease is fatal during the study or within the reporting periods specified for reporting adverse events, the event that resulted in death must be documented as an Adverse Event and reported as a serious adverse event of grade 5 CTC (Common Toxicity Criteria).

In addition, medically significant adverse events must be classified as "serious". The determination of whether an event is medically significant is performed according to medical and scientific judgment. Medically significant events are those that are not directly fatal or life threatening or lead to hospitalization. However, if the event presents a risk for the patient or requires medical action to prevent one of the other outcomes listed in the above definition, the medically significant event must be reported as serious.

Examples of such events include intensive medical treatment for an allergic bronchospasm in the emergency room or at home; changes in blood counts or seizures that do not result in hospitalization; or development of a dependency on the medicinal product or abuse of the medicinal product.

In addition, any suspected transmission of an infectious agent (pathogenic or non-pathogenic) by a Pfizer medicinal product is considered to be serious. Suspicion of such an event occurs when clinical symptoms or laboratory findings suggestive of infection occur in a patient following

use of a Pfizer medicinal product. The terms "suspected transmission" and "transmission" are used synonymously. These cases are considered unexpected and are expedited by team members of the pharmacovigilance department as serious cases. In such cases, an event may also be reported as a product deficiency.

Hospital stay

A hospital stay is defined as any initial admission (even shorter than 24 hours) to a hospital or appropriate healthcare facility or prolongation of hospitalization.

The admission also includes a transfer within the hospital to an acute intensive care unit (e.g. from psychiatry to a general unit, from a general unit to a coronary unit, from neurology to a tuberculosis unit). An emergency room visit is not necessarily a hospital stay; however the event that causes an emergency room visit will need to be assessed with regard to medical significance.

A hospital stay without any medical AE is not considered an AE and is not reportable. For example, the following hospitalizations do not need to be reported without a medical AE:

- Admission for social reasons (e.g. patient has no place to sleep)
- Admission for formal reasons (e.g. for an annual examination)
- Optional admission not triggered by a medical event (e.g. elective cosmetic surgery)
- Hospitalization for observation without the presence of a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or worsening of this illness (e.g. to clarify a persistent laboratory abnormality that has already occurred prior to treatment)
- Protocol-specific admission during the clinical trial (e.g. for a procedure required by the protocol)

Scenarios to be reported to CRO Winicker Norimed GmbH within 24 hours

The following scenarios are described below: Exposure during pregnancy, exposure during breastfeeding, medication errors, overdose, misuse, paravasation, lack of efficacy and occupational exposure.

Exposure during pregnancy

Exposure During Pregnancy (EDP) applies if:

1. a woman who is receiving or has been exposed to temsirolimus, sunitinib, and axitinib (e.g. environmental exposure) becomes pregnant or a pregnancy is determined, or the woman has become pregnant after stopping or after being exposed to temsirolimus, sunitinib, and axitinib, or a pregnancy is determined under these conditions (maternal exposure.

As an example of environmental exposure, a case of a pregnant woman in direct contact with a Pfizer product is:

- A nurse reported her pregnancy and was exposed to a chemotherapeutic agent).
- a man was treated before or around the time of conception with temsirolimus, sunitinib, and axitinib or had contact with temsirolimus, sunitinib and axitinib and/or had contact with the medicinal product during the pregnancy of his partner (paternal exposure).

Generally, all prospectively and retrospectively reported exposures during pregnancy must be reported, regardless of whether or not an adverse event has occurred. Such exposures should be reported as serious adverse events.

If a subject or partner of a subject becomes pregnant during the course of the study treatment with temsirolimus, sunitinib and axitinib, or if pregnancy is determined, this information must be reported to the CRO Winicker Norimed GmbH immediately with the NIS-AEM report form, regardless of the occurrence of an AE.

In addition, information regarding environmental exposure to temsirolimus, sunitinib, and axitinib in a pregnant woman (e.g. if a subject reports that she is pregnant and has been exposed to a cytostatic agent by inhalation or spills) must be reported using the NIS-AEM report form. This should be done independently of the occurrence of an AE.

The information submitted must include the estimated delivery date (see below for information regarding termination of the pregnancy).

Follow-up takes place to obtain general information about the pregnancy. In addition, follow-up will be performed to collect information on the outcome of exposure during pregnancy (EDP) for all EDP reports where the outcome of the pregnancy was unknown. Any pregnancy will be followed up until conclusion or termination (e.g. termination of pregnancy), and CRO Winicker Norimed GmbH will be notified of the outcome. This information will be provided as follow-up to the original EDP report. In case of a live birth, the newborn's external integrity may be assessed at the time of birth.

In the event of termination of the pregnancy, the respective reasons should be specified and, if clinically possible, the external integrity of the aborted fetus should be assessed by visual examination (unless the test results obtained prior to the procedure show congenital malformation and the results are reported).

If the pregnancy outcome meets criteria for an SAE (e.g. extrauterine pregnancy, spontaneous abortion, stillbirth, neonatal death, or congenital malformation [in a live birth, an aborted fetus, stillbirth, or neonatal death]), the SAE reporting procedures are to be followed. Additional information about pregnancy outcomes reported as SAEs will be collected for the following events:

- Spontaneous abortion (including miscarriage and retained abortion);
- Neonatal death occurring within 1 month of birth; these are reported as SAEs regardless of causality. Also, any infant deaths occurring after the first month of life must be reported as SAEs if the physician sees a connection or suspected connection with exposure to the study medication and the infant's death.

Additional information may be requested regarding exposure during pregnancy. Further follow-up of post-delivery is handled individually (e.g. follow-up of premature infants to identify developmental delays).

In the event of paternal exposure, the subject receives a form for the release of information for the pregnant partner, which he should give to his female partner. It must be documented that this letter was given to the subject to give to his partner.

Exposure during breastfeeding

Exposure during breastfeeding scenarios must be reported regardless of whether there is an AE related to exposure. If a Pfizer product (e.g. vitamins) approved specifically for use in nursing mothers is used as specified, a report of exposure during breastfeeding is not required. However, if an AE occurs in the infant in relation to the use of such a medicinal product, the AE should be reported together with exposure during breastfeeding.

Medication Errors

A medication error is any inadvertent error in prescribing, dispensing or administering a medicinal product by a healthcare professional, patient or user that can result in improper use of the medicinal product or injury to the patient. Such events may be related to medical practice, healthcare products, procedures, or systems including prescription, communication of instructions, labeling, packaging and nomenclature of the medicinal product; self-preparation; dispensing; distribution; management; training; monitoring; and application.

Medication errors include, among others:

- Near accidents, regardless of a patient's direct involvement (e.g. accidental/erroneous administration, which is the inadvertent use of any medicinal product in deviation from the product information or prescription by the physician or the patient/user);
- Confusion regarding a trade name (e.g. trade name, brand name).

The physician must report the following medication errors to the CRO Winicker Norimed GmbH regardless of whether an AE/SAE related to it is present:

- Medication errors that include the patient's exposure to the medicinal product, regardless of whether the medication error is associated with an AE.
- Medication errors that do not directly affect a patient (e.g. potential medication errors or near accidents). If a medication error does not include patient exposure to the medicinal product, the medication error report must contain the following minimum information:
- an identifiable reporter;
- a suspected medicinal product;
- a medication error.
- Overdose, misuse,
- extravasation;

Reports of misuse, overdose and extravasation related to the use of a Pfizer medicinal product are to be reported by the physician to the CRO Winicker Norimed GmbH, regardless of the presence of an associated AE/SAE.

Lack of efficacy

Reports of lack of efficacy for a Pfizer medicinal product are to be reported by the physician to the CRO Winicker Norimed GmbH, regardless of the presence of an associated AE/SAE or the area of application of the medicinal product.

Occupational exposure

Reports of occupational exposure related to the use of a Pfizer medicinal product are to be reported by the physician to the CRO Winicker Norimed GmbH, regardless of the presence of an associated AE/SAE.

Reference Document for Safety Information

The temsirolimus, sunitinib and axitinib Summary of Product Characteristics (SPC) will serve as a reference during the study which the Pfizer safety department will use to assess all safety events reported by physicians to the CRO Winicker Norimed GmbH. The prescribing information should also be provided to the physician for prescription and as guidance.

11. METHODOLOGY

The registry is designed to document the disease progression in patients with advanced renal cell carcinoma, relapsed/refractory mantle cell lymphoma, and gastrointestinal stromal tumor intended by the treating physician for systemic therapy.

During the course of the registry, the following (minimum) number of survey times and endpoints are planned:

At observation start:	Enrollment Visit
During the course of the observation:	Follow-up documentation (as per local guidelines, generally every 8 - 12 weeks)
End of observation:	Completion/Discontinuation Form
1-year follow-up for subjects who discontinue therapy:	Survival form (every 6 months thereafter)

The temporal sequence and number of follow-up documentation items depends on medical practice to perform confirmatory imaging procedures and patient survival.

The completion of the continuous observation documentation (follow-up visits) takes place with the completion or discontinuation of the case report form below:

- Patient death,
- Patient lost to follow up due to patient request/withdrawal of patient informed consent,
- Change in therapy or discontinuation due to intolerance to temsirolimus, sunitinib, and axitinib or progression.

For the indication **metastatic renal cell carcinoma,** prospective documentation of sequential therapy is an option. According to the approvals of temsirolimus, sunitinib and axitinib, e.g. the following therapy sequences are possible:

- Sunitinib (as first-line therapy) followed by axitinib

- Temsirolimus (as first-line therapy) followed by sunitinib
- Axitinib (as second-line therapy, 1st Pfizer therapy sequence) followed by sunitinib
- Sunitinib (as first-line therapy) followed by a second-line approved active substance (interim documentation) followed by axitinib (in the third line or a later line)

Herein two consecutive Pfizer lines of therapy or two Pfizer lines of therapy with one or more intermediate therapies can be documented. The following documentation sheets are available for this purpose:

White documentation section: 1. Pfizer Therapy sequenze, e.g. Sunitinib

- Enrollment Visit
- Follow-up documentation every 8-12 weeks
- Final Assessment/Discontinuation of documentation

Pink Documentation section. Interim documentation for non-Pfizer products, e.g. nivolumab

- Every 8-12 weeks

Green documentation section. 1. Pfizer Therapy Sequence

- Initial visit to change treatment
- Follow-up documentation every 8-12 weeks
- Final Assessment/Discontinuation of documentation

Survival Sheets

After two documented Pfizer therapy sequences for advanced RCC, or if the treatment of advanced RCC, mantle cell lymphoma or gastrointestinal stromal tumor is terminated, the documentation changes to the "survival sheets".

The query will be initiated for the first time 12 months after the final visit, then every 6 months thereafter. For this purpose, a separate case report form will be provided to you by Winicker Norimed.

The patient interview in the indication area will be conducted during therapy with temsirolimus, sunitinib and axitinib at each visit.

For the indications **mantle cell lymphoma and gastrointestinal stromal tumors,** only

the documentation for temsirolimus and sunitinib should be used:

- Enrollment Visit
- Follow-up documentation (as per local guidelines, generally every 8-12 weeks)
- Final Assessment/Discontinuation of documentation
- 1-year follow-up for patients who discontinue therapy: Survival form (every 6 months thereafter)

Safety Criteria

In contrast to the usual procedure in clinical trials, patients will not be selected at the start of treatment (baseline) for this register. According to Amendment VI, this investigation may provide new information on the safety of sunitinib, temsirolimus, and axitinib following sunitinib and other therapeutic options.

It is intended to document any intolerances that the physician observes during the observation period related to the documented medicinal products. Additionally, adverse events (AEs) and serious adverse events (SAEs) will be collected, as defined below.

In addition, the physician's subjective assessment of tolerability of the therapy will be obtained at each visit.

Efficacy Criteria

The efficacy of treatment with temsirolimus, sunitinib and axitinib will be assessed during routine treatment evaluation and documented at each visit based on the following tools (examinations):

- Computed tomography (if available) and/or
- Magnetic resonance imaging (MRI) (if available)
- Ultrasound examination (if available)
- Chest X-ray (if available)

The following criteria will be used to assess efficacy:

- Survival time (OS)
- Progression-free time (PFS)
- Physician's assessment of therapy response (CR, PR, SD, PD)
- Physician's assessment of efficacy and tolerability of the therapy

The evaluation of therapy response is to be performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) as follows whilst following the below-mentioned measurement conditions:

- Use of consistent metric information (here: height in mm)
- Use of consistent imaging procedures (method and technique, e.g. CT)
- Measuring in a uniform manner. The following procedure should be followed:
- It is intended to select the 5 largest indicator lesions that can be measured well; the greatest longitudinal diameter is measured in each case
- Lesions that have a size of at least ≥20 mm in at least one direction are deemed measurable
- Exception: Magnetic resonance imaging; minimum size ≥10 mm required
- All other lesions will be documented without measurement of size.

For the overall tumor assessment, definitions will be applied according to RECIST:

		Target lesions	**Non-target lesions**
Complete remission	CR	Complete disappearance of all lesions	Complete disappearance of all lesions
Partial remission	PR	Reduction of the measured total by at least 30%	-
Stable disease	SD	Neither PR nor CR or PD	-
Progression	PD	Enlargement of the measured sum by 20% or one or more new lesions	One or more new lesions. Definite enlargement of existing lesions

Verification by imaging procedures after at least four weeks is required to assess a "confirmed" CR and PR.

For the assessment of a "confirmed" SD, the assessment must meet the established criteria at least once over the course of ≥6-8 weeks.

Documentation during the treatment course

The physician will be provided with an indication-specific documentation sheet for each patient to document the findings for the duration of the observation. Data are collected entirely prospectively; i.e. documentation of previous treatment courses is not allowed.

The dose and duration of treatment with the documented medicinal products will be specified by the treating physician according to clinical and individual requirements.

To provide accurate information on the treatment mode of temsirolimus, sunitinib and axitinib, the loading dose at the start of the observation and any changes during the observation period are documented, indicating the time points, current dose and reasons for change.

Each concomitant medication will be used at the discretion of the treating physician and will be recorded in the case report form upon enrollment.

The following is a schematic of all parameters to be recorded as part of this registry (imaging examination results if available).

Flow chart for the registry course for GIST and MCL

	Enrollment visit	Follow-up visit (every 8-12 weeks)	Completion Exam/ Discontinuation	Survival sheet (12 months after completion/ discontinuation)
Demographic data	x	x	x	x
Inclusion/exclusion criteria	x			
Patient Informed Consent	x			
Tumor history	x			
Karnofsky Performance	x	x		
Treatment/Medication				
Pretreatment	x			
Concomitant medication	x			
Tumor therapy	x	x		x
Safety				
Concomitant diseases/ physical	x			
Lab values	x	x		
Electrocardiogram	x	x		
Documentation of adverse events		x	x	
Efficacy				
Subjective prognostic assessment by	x			
CT/ MRI scan	x	x		
Ultrasound	x	x		
Chest X-ray	x	x		
Assessment of response to therapy by		x		
Therapy assessment of efficacy and tolerability		x		
Physician's overall assessment of therapy response			x	

Flow chart of mRCC sequence documentation:

	1. Pfizer Therapy Sequence			Interim documentation for non-Pfizer products	2. Pfizer Therapy Sequence			Survival Sheets
	Enrollment Visit	Follow-up visit every 8-12 weeks	Completion/ Discontinuation of Documentation	Interim documentation every 8-12 weeks	Initial visit to change treatment	Follow-up visit every 8-12 weeks	Completion/ Discontinuation of Documentation	Survival Sheet 12 months after discontinuation, then every 6 months
Demographic data	X	X	X		X	X	X	X
Inclusion/exclusion criteria	X							
Patient Informed Consent	X			(x)				
Tumor history	X				X			
Karnofsky Performance Status/Height/Weight	X	X			X	X		
Treatment/ Medication								
Pretreatment	X							
Concomitant medication	X				X			
Tumor therapy	X	X		X	X	X		X
Safety								
Concomitant disease(s)/physical exam	X				X			

Lab values	X	X			X	X		
Blood pressure	X	X			X	X		
Electrocardiogram	X	X			X	X		
Echocardiogram	X	X			X	X		
Pain assessment	X	X			X	X		
Documentation of adverse events		X	X	X	X	X	X	
Efficacy								
Subjective prognosis assessment by the physician	X				X			
CT/MRI scan	X	X				X		
Ultrasound	X	X				X		
Chest X-ray	X	X				X		
Tumor Assessment		X		x		X		
Physician's assessment of efficacy and tolerability of the therapy		X				X		
Global assessment of therapy response by the physician			X	x			X	

Patient Quality of Life Survey	X	X			X	X		

Biometric evaluation

The biometric evaluation of the patient data (including statistical analysis plan) takes place, appropriate to the design of a registry, in a purely descriptive manner, and will be performed by a Contract Research Organization (Winicker Norimed GmbH, Nuremberg). An annual interim analysis will be performed.

Definition of analysis set

All prospectively documented patients with a histologically confirmed diagnosis of renal cell carcinoma, MCL, and GIST will be included in the "safety population".

All patients to whom at least one of the following criteria apply will be included in the "efficacy population": Date of death, time of progression, physician's assessment of therapy response, or therapy assessment of efficacy and tolerability by the physician are available.

Retrospectively documented information will not be included in the analysis.

Analysis of Safety Criteria

The absolute and relative frequency of patients with adverse events will be shown in a tabular form, both globally and according to the system organ classes and the MedDRA "preferred terms". In addition, the absolute and relative frequency of therapy dropouts will be presented both overall and according to discontinuation reasons. Serious adverse events will be evaluated separately. Previous and concomitant therapies will also be tabulated.

Laboratory analysis and electrocardiogram results will be analyzed per visit. In addition, the physician will assess information on tolerability during therapy.

Analysis of Efficacy Criteria

The change in disease activity will be described using the following parameters:

- Assessment of response to therapy by the physician
- Physician's assessment of efficacy
- Overall survival (OS)
- Progression-free survival (PFS)
- Maximum Response

For the analysis in STAR-TOR, the duration of treatment is defined as the period between inclusion in the registry and occurrence of any of the events of either death or discontinuation of the documentation or termination of therapy.

The duration of treatment will be evaluated using methods from the field of "survival time analysis".

Other analysis parameters

Comorbidities will be coded in accordance with MedDRA and concomitant medications according to WHO-DD. Frequencies for appropriate coding levels will be presented. Evaluation of sequence and therapy regimens and quality of life (advanced RCC) will be performed.

Case number estimate

In total, the treatment of approximately 100 patients per year and product should be documented. This number of patients was chosen to capture a broad range of medical prescription habits and assess the target criteria as significantly as possible. The probability of occurrence of at least one "uncommon" (>1/1000, <1/100) AE is between 0.33 and 0.98 and for a "rare" AE (>1/10,000, <1/1000), between 0.04 and 0.33.

The planned number of 200 sites to be included according to Amendment III allows a representative cross-section across German oncology practices or clinics.

With Amendment VI, the efficacy of axitinib regarding the progression-free survival and overall survival is to be evaluated in the 3rd (and 4th) line of therapy and a correlation with patients on axitinib in the 2nd line of therapy is to be performed.

Patients already documented in STAR-TOR (n = 92; status of 06/30/2017) who received axitinib in the 2nd line of therapy, i.e. with a treatment course of sunitinib-axitinib, will be used as a (historical) comparison group for the comparison with the 3rd and 4th line of therapy, particularly because patients with axitinib in the 2nd therapy line are only rarely expected after the guideline amendments and therefore cannot be newly enrolled.

Patients already documented in STAR-TOR with axitinib in the 3rd line of therapy or 4th line of therapy should not be used to answer the expanded question (see above) as none of these patients received nivolumab or another active substance newly approved in 2016 in the 2nd line of therapy, but received other therapeutic options. It cannot be excluded that the deviating pretreatment/treatment course will impact the efficacy of axitinib in the subsequent lines of therapy as compared with current therapy guidelines.

Approximately 45 patients with a PFS event should be documented in the 3rd line with axitinib after the previous therapy sequence, e.g. sunitinib - nivolumab. Therefore, mPFS and mOS can be estimated with sufficient precision (see Statistical Analysis Plan). In order to recruit 45 new third-line axitinib patients after e.g. sunitinib-nivolumab pretreatment in STAR-TOR, approximately 45 months will be required (assuming the usual therapy periods).

Assuming that the last patient is enrolled after 45 months and a progression event (or death) occurs after approximately 6 months, a runtime of approximately 4 years should be assumed after implementation of Amendment VI.

With Amendment VII, the additional documentation period defined in Amendment VI is reduced by one year. As of September 15, 2020, 17 patients were registered in an interim documentation. Of these, 2 patients received follow-up therapy with axitinib. It is shown that the approval of three new ICI combinations which are all prominently represented in guidelines has reduced recruitment for sunitinib patients in first-line therapy (prerequisites for later use of axitinib) and/or has been moved to later lines of therapy. Documentation of 45 patients in the stated time does not seem possible at this recruitment rate to answer the question of Amendment VI. Therefore, the further recruitment phase is reduced by one year (to the end of December 2020).

Discussion of potential bias sources

In this non-interventional registry, the selection of documented patients is not subject to a randomization mechanism, so that a selection bias cannot be excluded.

A comparison of the safety and efficacy of temsirolimus, sunitinib, and axitinib is planned. Potential confounders will be considered and will be included in the statistical analysis plan accordingly. Subgroup analyses, e.g. patients stratified by concomitant diseases, age, and gender, may be performed in addition, if appropriate.

12. COMMUNICATION AND PUBLICATION OF RESULTS

12.1. Publication Plan

It is planned to perform annual interim analyses and present their results as an abstract at the appropriate national and international specialist conferences. Formal interim reports are not planned. It is planned to publish the final study results in a peer-reviewed journal.

The final CSR is planned for 2022.

12.2. Communication of safety problems

In case of any enacted prohibition or restriction (e.g. suspension of the study) by a competent authority, or if the treating physician becomes aware of any new information that might affect the benefit/risk assessment of a Pfizer product, Pfizer should be informed immediately.

In addition, the treating physician will notify Pfizer immediately of any actions he has taken to protect the study patients from immediate harm to health. He also will inform Pfizer of any serious violations of the observational plan of this non-interventional study of which he is aware.