NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Real-world clinical patterns of care and outcomes among patients in Africa Middle East (AfME) with metastatic renal cell carcinoma (mRCC) receiving Sunitinib as first line therapy (OPTIMISE)
Protocol number	A6181223
Protocol version identifier	Version 1.0
Date of last version of protocol	13 June 2016
Active substance	Sunitinib
Medicinal product	Sutent®
Author	PPD, MD, MBA PPD

Protocol Authorization

This observational study will be conducted in compliance with the protocol, and the applicable regulatory requirements

Sponsors' Approval

PPD . MD, MBA

PPD *Signature* *Date*

TABLE OF CONTENTS

LIST OF FIGURES 5
APPENDICES 5
1. LIST OF ABBREVIATIONS 6
2. RESPONSIBLE PARTIES PROTOCOL SIGNATURE PAGE 8
3. ABSTRACT 9
3.1. Title 9
3.2. Rationale and Background 9
3.3. Research Objective, Endpoints and Questions 9
3.3.1. Research Questions 9
3.3.2. Objectives 9
3.3.3. End-points 10
CCI
3.4. Study Design and Study Population 12
3.5. Setting 13
4. AMENDMENTS AND UPDATES 14
5. MILESTONES 15
6. RATIONALE AND BACKGROUND 15
6.1. Selection of First-Line Treatment 16
6.1.1. First-Line Treatment in Patients With Favorable- to Intermediate-Risk Clear Cell mRCC 16
6.2. Selection of Second-Line Treatment 17
7. RESEARCH QUESTION AND OBJECTIVES 17
7.1. Objective 17
CCI
8. RESEARCH METHODS 19
8.1. Study Design 19
8.2. Setting 20
8.2.1. Inclusion Criteria 21
8.2.2. Exclusion Criteria 21
8.3. Variables 21
8.4. Data Collection Intervals & Recommended Data Collection Schedule 22
8.4.1. Recommended Data Collection Schedule 22

8.5. Study Procedures 23
8.5.1. Screening/Baseline 23
8.5.2. Treatment Phase 24
8.5.3. Follow-up Phase 24
8.6. Data Sources 25
8.7. Sample Size 25
8.8. Data Management 25
8.9. Data Analysis 26
8.10. Quality Control 26
8.11. Limitations of the Research Methods 27
8.12. Other Aspects 27
9. PROTECTION OF HUMAN SUBJECTS 27
9.1. Patient Information and Consent 27
9.2. Patient Withdrawal 28
9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 28
9.4. Ethical Conduct of the Study 28
10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 29
10.1. ADVERSE EVENT REPORTING 29
10.1.1. Requirements 29
10.1.2. Reporting Period and Requirements 29
10.2. DEFINITIONS OF SAFETY EVENTS 30
10.2.1. Adverse Events 30
10.2.2. Serious Adverse Events 31
10.3. Causality Assessment 33
10.4. Exposure During Pregnancy 33
10.5. Medication Error 34
10.6. Single Reference Safety Document 34
11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 35
11.1. Communication of Results by Pfizer 35
11.2. Investigator's Ability to Publish 35
12. INVESTIGATOR'S FILE/ CONDITIONS FOR RETENTION OF DOCUMENTS: 35

12.1. Audits and Inspections 36
12.2. Monitoring the Study 36
13. REFERENCES 37

LIST OF FIGURES

Figure 1. Study Flow Chart 20

APPENDICES

Appendix 1. FKSI-19 Questionnaire 40
Appendix 2. *FKSI-19 (version 4) – Scoring guidelines* 41
Appendix 3. ECOG Performance Status 44

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEM	Adverse Event Monitoring
AfME	Africa Middle East
ALT	Alanine Aminotransferase
AST	Aspartate Aminotranferase
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
CR	Complete Response
CSR	Case Study Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDP	Exposure during pregnancy
EIU	Exposure In-Utero
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology & Pharmacovigilance
ESMO	European Society for Medical Oncology
FKSI-19	Functional assessment of cancer therapy Kidney Symptom Index
GEP	Good Epidemiological Practice
HRQOL	Health Related Quality Of Life
ICF	Informed Consent Form
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics & Outcomes Research
LDH	Lactic Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
mRCC	metastatic Renal Cell Cancer
NIS	Non-interventional Study
NCCN	National Comprehensive Cancer Network
ORR	Objective response Rate
OS	Overall Survival
PFS	Progression Free Survival
Plt	Platelet Count
PR	Partial Response
QoL	Quality of Life
RR	Relapse Rate
SAP	Statistical Analysis Plan
SAE	Serious Adverse Events
SU	Sunitinib

Abbreviation	Definition
TTF	Time to Treatment Failure
TTR	Time to Response
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Cells

2. RESPONSIBLE PARTIES PROTOCOL SIGNATURE PAGE

I have read the attached protocol entitled "*Real-world clinical patterns of care and outcomes among patients in Africa Middle East (AfME) with metastatic renal cell carcinoma (mRCC) receiving Sunitinib as first line therapy*" and I agree to conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, with Good Clinical Practice (GCP), Good Pharmacoepidemiological Practice (GPP), as well as all applicable regulatory requirements.

PI Name	*Signature*	*Date*

[Site name & full address]

3. ABSTRACT

3.1. Title

Real-world clinical patterns of care and outcomes among patients in Africa Middle East (AfME) with metastatic renal cell carcinoma (mRCC) receiving Sunitinib as first line therapy (OPTIMISE).

3.2. Rationale and Background

According to the available literature, there is a gap in regards to the real world setting of care and treatment outcome for mRCC, especially in the Middle East and Africa region.

SU has become the standard of care (used as first-line treatment) in many countries as it has the most robust data in the first-line treatment of mRCC. It is also recommended as first line treatment in the NCCN and ESMO guidelines.

In order to understand how care is translated into positive treatment outcomes in the broader mRCC patient population and whether there are differences in outcome associated with various treatment patterns, a prospective observational study is necessary. This study will elucidate for the first time the patterns of care and associated outcomes in Africa Middle East patients with mRCC.

3.3. Research Objective, Endpoints and Questions

3.3.1. Research Questions

OPTIMISE study objectives are dual and aim primarily to increase the knowledge regarding the outcomes from SU use on one hand; and outcomes from the combined SU- 2nd line sequence on the other hand in real life clinical practice. This will be addressed in many countries across AfME and in individual country cohorts to understand specificities and differences in use and outcomes.

3.3.2. Objectives

OPTIMISE is designed to provide knowledge regarding the use of the SU as 1st line treatment and 2nd line SU-different sequence with respect to efficacy outcomes, adverse events, and health related QoL in the real life setting.

Primary Objective:

- To assess the impact of SU as 1st line treatment on PFS and on TTF for patients with adv/mRCC.

Secondary Objective:

- To assess the ORR for adv/mRCC patients receiving SU as 1st line treatment.
- To describe the usage of different doses of SU in these patients in terms of: dosing change, dosing schedules and the average dose received during the SU period treatment.

- To assess the impact of the 2nd line sequence SU- different treatment on combined PFS and TTF for patients with adv/mRCC and according to the second line post SU treatment (TKI,mTOR).

- To describe the safety of 2nd line SU-different sequence treatment and the tolerability of patients receiving it.

- To measure Quality of Life (QoL).

3.3.3. End-points

Primary End-point:

1. Progression Free Survival (PFS) for patients with ad/mRCC receiving SU.

   PFS is defined as: the time from when the patient receives the first dose of SU to the time of progression or death due to any cause, which occurs first.

2. Time to Treatment Failure (TTF) for SU 1st line.

   TTF is defined as: from when the patient receives the first dose of SU to the time of SU discontinuation (date completed by the physician).

Secondary End-point:

1. Objective Response Rate (OOR) for adv/mRCC patients receiving SU as 1st line treatment.

   ORR is defined as the percentage of patients with confirmed CR or confirmed PR according to RECIST criteria v1.1.

2. Description of SU real life usage of doses across all centers, including description of treatment schedules (dose change, dose schedule, average dose received during the period treatment).

3. Combined PFS for patients with ad/mRCC receiving the 2nd line sequence SU-different treatment.

   Combined PFS is defined as: the time from when the patients receives the first dose of SU as first line, until progression or death due to any cause while on the 2nd line treatment, whichever occurs first during the 2nd line sequence treatment.

4. Combined TTF for the SU-2nd line sequence.

   Combined TTF is defined: as the time from when the patient receives the first dose with SU as first line, to the time of 2nd line sequence discontinuation (date completed by the physician).

5. OS for adv/mRCC patients receiving SU as first line followed by 2nd line as measured from date of first SU dose to the date of death of any cause. The OS median and the overall survival at month 24 (24 months OS) will be measured.

6. If possible, efficacy parameters (PFS, OS) for the combined 1st line SU- 2nd line sequences according to the second line post SU (other than SU-AXI):

   - SU in 1st line-Axitinib TKI in 2nd line.
   - SU in 1st line- other TKI in 2nd line (sorafenib, pazopanib).
   - SU in 1st line/mTOR in 2nd line (temsirolmus, everolimus).

7. Safety description with AE listing in patients receiving SU: frequencies of patients experiencing at least one AE will be displayed by body system.

8. QoL using the questionnaire Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (FKSI-19).

CCI [redacted]

3.4. Study Design and Study Population

OPTIMISE is an international (AfME), prospective, non-interventional, non-controlled, observational multicenter study.

Patients would be enrolled from several AfME countries including Algeria, Morocco, Tunisia, Egypt, UAE, Qatar & South Africa.

Investigators will be specialists in charge of adv/mRCC. These sites involved (at least when performing feasibility) will be representative of their respective countries in terms of practice. Participating physicians will not be influenced in their decision making and routine proceedings in any way.

Primary outcome measure will assess progression free survival (PFS) in patients receiving the SU and in patients receiving a second line treatment post SU; as well as TTF for patients with adv/mRCC.

Patients will be enrolled when they start a treatment with SU on 1st line. Patients enrolled at SU initiation, will be followed-up whatever the post 2nd line SU- different sequence treatment is (AXI, other drugs, no further active treatment, (supportive care)). The possible 1st and 2nd line sequences of treatment under investigation (ie, patient pools) will be (Figure 1):

- SU-AXI.
- SU- other second line treatment (sorafenib, pazopanib, everolimus, temsirolimus, other).
- SU- not further active treatment (supportive care).

The study will include a prospective data collection:

- Prospective data will be collected for all patients enrolled in the study at SU-1st line level, irrespective of 2nd line sequence treatment, or no further active treatment.
- Prospective data in terms of medical treatment records will be collected for all 2nd line patients.

The inclusion period of eligible patients is planned for 12 months, with minimum of 1 year follow-up period. Patients will be followed-up from their enrollment to the end of the study follow-up period.

3.5. Setting

The study will enroll patients according to the eligibility criteria in participating countries across Africa Middle East. The recruiting centers will be representative of each country involved in terms of care management systems, of size and of practices (at least when performing feasibility).

Any patient who meets the eligibility criteria will be invited to participate in the study with no selection by the investigators. The enrollment visit will be performed at the time of the patients' inclusion, after the patients' acceptation of enrollment in the study.

Data will come from medical records and will be collected in routine clinical practice. The enrollment visit will comprise a first section on patients' eligibility for every patient.

Follow-up will be ensured during visits in the context of usual patients' care management (non-interventional study). As long as the patients are treated with SU, AXI, other TKI (sorafenib, pazopanib everolimus, temsirolimus, other) or no further active treatment (supportive care), every visit to the center will be recorded. In accordance with ESMO guidelines and physicians clinical practice is real life, follow-up visits are approximately expected as below:

- During SU treatment: every 6 weeks (every cycle) with tumor assessment approximately every 3 months with respect to the clinical practice.
- When patients come off SU treatment: they will be followed-up every 6 months for survival until the end of the study.
- A deviation of +/- 6 weeks (1.5 months) is acceptable window for the follow-up visits.

Because of the inclusion criteria (patients being treated with SU in 1st line according to the approved therapeutic indication), the medication prescribed within the regular practice of the physician. Because of the non-interventional nature of the study, there will be no specific requirements in regards to the treatment process. The physician will determine dosage and duration of the treatment as guided by the local approved country. Prescribing information will be according to his assessment of the individual therapeutic needs of the patient.

4. AMENDMENTS AND UPDATES

Any change in the study plan requires a protocol amendment. An investigator must not make any changes to the study without IRB/IEC and sponsor approval except when necessary to eliminate apparent immediate hazards to the subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC within 5 working days, and submitted to the appropriate regulatory agency in the required time frame. All protocol amendments must be reviewed and approved following the same process as the original protocol.

5. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	Aug-2016
Start of data collection FSFV	Sep-2016
End of data collection, last subject last visit (LSLV)	Sep-2019
Final study report	Jan-2020

6. RATIONALE AND BACKGROUND

According to the WHO GLOBOCAN program, the annual incidence of RCC (renal cell carcinoma) is 213,924 people, with 90,802 deaths per year leaving a 5-year prevalence of 580,700 people. RCC is age-related (ie, more common in older patients) and is most common in the more developed countries of the world like the United States and countries of Europe. In the United States, the ASR (age-specific rate) of RCC is 12.0 per 100,000 people. Most Arab countries of the Middle East have rates between 2.0 and 3.0. Turkey has the highest ASR of 5.6 for RCC.[1]

Most of the figures are likely inaccurate and underestimate the true incidence of RCC as data in not consistently shared among countries and institutions within countries. Recently Ghosn et al, reported results from The Africa–Middle East Genitourinary Tumor Working Group questionnaire distributed between 2011 and 2012 to a network of reference oncologists across North Africa and the Middle East, identified through institutions, professional organizations, and personal contacts. Similar to other countries around the world, most RCC are low-grade, early stage tumors, however the significant proportion of patients that present with high-stage or metastatic disease mirrors the 20-30% seen globally.[2]

In the 1990's, the mainstays of mRCC treatment consisted of systemic cytokine therapies such as high-dose systemic interleukin-2 (IL-2) or interferon-alpha (IFN- α). Molecular research into the pathogenesis of RCC has provided valuable information on the signaling pathways known to be altered in RCC, including vascular endothelial growth factor (VEGF), its receptor (VEGFR) and the mammalian target of rapamycin (mTOR), a key kinase regulating cell growth and proliferation, cellular metabolism, and angiogenesis.

Molecularly targeted therapies were developed specifically to target the signal transduction pathways. Recently, several targeted therapies have become available for first- and second-line treatment of mRCC.[3]

New treatment options include the multitargeted receptor tyrosine kinase inhibitors (TKIs) Sunitinib (Sutent ®, Pfizer Inc.), sorafenib (Nexavar ®, Bayer HealthCare/Onyx pharmaceuticals), pazopanib (Votrient ®, GlaxoSmithKline Inc), Cabozantinib (Cometriq®, Exelixis) and axitinib (Inlyta ®, Pfizer Inc); the VEGF ligand binding monoclonal antibody bevacizumab (Avastin ®, Genentech, Inc.), usually given in combination with IFN-α; and the mTOR kinase inhibitors temsirolimus (Torisel ®, Pfizer Inc) and everolimus (Afinitor ®, Novartis), in addition to Nivolumab (Opdivo ®, Bristol-Myers Squibb). These new agents have dramatically changed the management of mRCC in the last 5 years and the current international guidelines recommend a number of these new treatment options for first- and second-line treatment based on category 1 to 3 evidence.[4]

6.1. Selection of First-Line Treatment

6.1.1. First-Line Treatment in Patients With Favorable- to Intermediate-Risk Clear Cell mRCC

Currently, Phase III data originating from four randomized trials support the use of three molecules in the first-line setting, ie, Sunitinib,[5,6] pazopanib,[7] and bevacizumab, in combination with interferon-α.[8,9] The criteria for choosing between Sunitinib and pazopanib currently represent the hottest topic of debate. Its importance prompted the design and conduct of the first head-to-head Phase III trial comparing two first-line treatment alternatives for mRCC patients.[10]

A head-to-head prospective Phase III trial of Sunitinib and pazopanib [COMPARZ], ClinicalTrials.gov identifier NCT00720941)[10] the randomized design rested on the non-inferiority comparative effectiveness of 800 mg once daily continuous dosing of pazopanib relative to 50 mg once daily 4/2 weeks dosing of sunitinib. Although there is no doubt that direct comparison of Sunitinib versus pazopanib represents an effort aimed at providing evidence data in regards to two management alternatives for clear cell mRCC patients, many questions pertaining to study results and their interpretation remain unanswered.

The observation of differences in patterns of care between community and academic practice dovetails with other retrospective reports. Choueiri et al. published a series of 144 RCC patients from two tertiary oncology centers in the US. Patients were treated with Sunitinib, sorafenib, or bevacizumab from 2003 to 2008. Treatment patterns, response rates, and adverse events were described.[12] Similar data were obtained from a retrospective review of 250 patients with mRCC treated at 18 community oncology clinics. Differences in outcomes between these two studies included median duration of first line therapy for both Sunitinib (5.9 months in the community vs. 10.5 months in the academic centers) and sorafenib (5.5 vs. 8.1 months). In addition, patients in the community were more likely to receive lower doses of Sunitinib and sorafenib and were more likely to have dose reductions and interruptions than patient in the academic centers. These differences in practice patterns are an important area of further research and may lead to the understanding of more optimal treatment regimens for patients.[13]

A study was conducted based on medical records of 291 patients in 5 countries showed that using first line Sunitinib on naïve treatment patients exposed those patients to adverse events. Those adverse events consequently affected the alteration of treatment in the first months. Thus, outcome was not optimal. On the other hand, using Sunitinib as first line showed longer time to progression, more tumor size decrease, longer OS, higher response probability.[14] Although first line Sunitinib was associated with adverse events, they were mild to moderate.[15]

It has been shown that dose reduction or interruption is required for 50% of the patients in order to control the adverse events.[16] Toxicity management through using dynamic approaches such as alternative schedules positively impact the treatment outcome.[17]

The Rainbow study proved that provision of alternative schedule 2/1 in selected patients enhances the safety profile and reduces toxicities such as hypertension and fatigue.[18]

Other troublesome toxicities such as hand-foot syndrome, mucositis and thrombocytopenia were significantly decreased for mRCC patients who switched from 4/2 to 2/1 schedule.[19]

Consequently, the alleviation of Sunitinib toxicities exposed mRCC patients to significant improvement of the HRQOL.[20]

6.2. Selection of Second-Line Treatment

Treatment sequencing in second-line after first-line TKI failure may consist of either a second-line TKI or a second-line mammalian target of rapamycin (mTOR) inhibitor or recently immunotherapy integration.[21-24]

Given the availability of multiple new mRCC targeted agents that have been approved within the last 7 years and new agents expected to launch in the next several years, it is important to understand real world mRCC practice patterns in the Middle East & Africa. Clinical trial populations will not suffice as they are not representative of real-life populations of patients given the selection criteria and specific focus on a single drug or line of therapy. As of January 2016, there are no prospective longitudinal mRCC registries in that region that could be identified in www.clinicaltrials.gov website or in the published literature/abstracts other than the studies described above. Clearly, a prospective study reflecting longitudinal treatment patterns and outcomes in academic and community practice is needed.

The overall aim of the study is to describe patterns of treatment and outcomes across multiple lines of treatment in the mRCC setting, among newly diagnosed patients treated in Middle East & North Africa.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Objective

The primary goal of this prospective, observational Phase IV study is to provide knowledge regarding the use of SU as first line treatment as well as 2nd line SU- different sequence with respect to efficacy outcomes, adverse events and health related quality of life (QoL) in the real life setting.

Primary Objective:

To assess the impact of SU as 1st line treatment on Progression Free Survival (PFS) and on Time to Treatment Failure (TTF) for patients with adv/ mRCC.

Secondary Objective:

- To assess the Objective Response Rate (ORR) for adv/ mRCC patients receiving SU as 1st line treatment.
- To describe the usage of different doses of SU in these patients in terms of: dosing change, dosing schedules and the average dose received during the SU period treatment.

- To assess the impact of the 2nd line sequence SU- different treatment on combined PFS and TTF for patients with adv/mRCC and according to the second line post SU treatment (TK1,mTOR).

- To describe the safety of 2nd line SU-different sequence treatment and the tolerability of patients receiving it.

- To measure Quality of Life (QoL).

The study will collect data based on selection criteria for SU, including therapy management, treatment tolerance and safety among others.

Moreover, this study will collect and assess information on the sequence therapies (SU- different) used such as duration, the drivers of physician selection of particular agents as first & second lines, changes in therapy over time, dose modifications, discontinuation/interruptions of therapies, disease staging, toxicity from treatment and survival post stopping therapy.

Subsequent therapy post SU will also be documented. The following treatment outcomes will also be assessed:

- Treatment patterns (dose/duration) for SU.

- Patterns of toxicity exhibited by patients.

CCI

[redacted]

8. RESEARCH METHODS

8.1. Study Design

OPTIMISE is an international (AfME), prospective, non-interventional, non-controlled, observational multicenter study.

Patients will be enrolled from several AfME countries including Algeria, Morocco, Tunisia, Egypt, UAE, Qatar & South Africa. Investigators will be specialists, in charge of adv/mRCC. These sites involved (at least when performing feasibility) will be representative of their respective country in terms of practice. Participating physicians will not be influenced in their decision making and routine proceedings in any way.

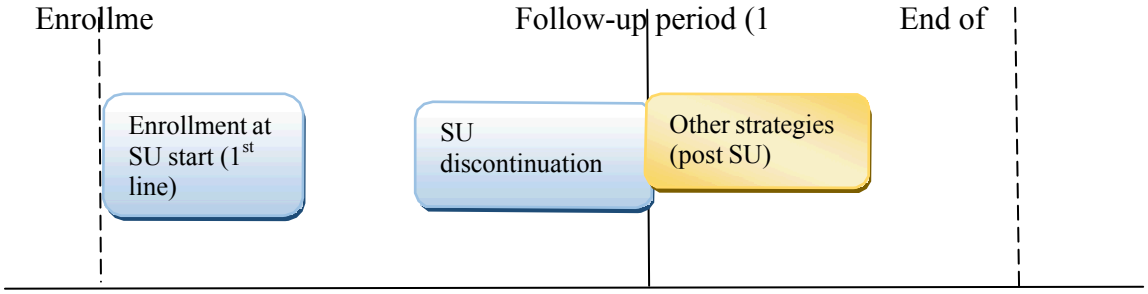
Primary outcome measure will assess PFS in patients receiving the SU and in patients receiving a second line treatment post SU; as well as TTF for patients with adv /mRCC.

Patients will be enrolled when they start a treatment with SU on 1st line. Patients enrolled at SU initiation, will be followed-up whatever the post SU-2nd line treatment is (AXI, other drugs, no further active treatment, (supportive care)). The possible 1st and 2nd line sequences of treatment under investigation (ie, patient pools) will be (Figure 1):

- SU-AXI.
- SU- other second line treatment (sorafenib, pazopanib, everolimus, temsirolimus, other).
- SU- not further active treatment (supportive care). The study will include a prospective data collection:
    - Prospective data will also be collected for all patients enrolled in the study at SU- 1st line level, irrespective of 2nd line treatment, or no further active treatment;
    - Prospective data in terms of medical treatment records, will be collected for all 2nd line patients.

The inclusion period of eligible patients is planned for 12 months, with minimum of 1 year follow-up period. Patients will be followed-up from their enrollment to the end of the study follow-up period.

Figure 1. Study Flow Chart



8.2. Setting

The study will enroll patients according to the eligibility criteria in participating countries across Africa Middle East. The recruiting centers will be representative of each country involved in terms of care management systems, of size and of practices (at least when performing feasibility).

Any patient who meets the eligibility criteria will be invited to participate in the study with no biased selection by the investigators. The enrollment visit will be performed at the time of the patients' inclusion, after the patients' acceptation of enrollment in the study.

Data will come from medical records and will be collected in routine clinical practice. The enrollment visit will comprise a first section on patients' eligibility for every patient whatever pool they belong to and a second section on SU treatment started at the inclusion.

Follow-up will be ensured during visits in the context of usual patients' care management (non-interventional study). No extra visits will be required by the protocol of the study.

As long as the patients are treated with SU as first line, every visit to the center will be recorded. In accordance with ESMO guidelines and physicians clinical practice is real life, follow-up visits are approximately expected:

- During SU treatment: every 6 weeks (every cycle) with tumor assessment approximately every 3 months with respect to the clinical practice.
- When patients come off SU treatment (and after receiving the SU-2nd line sequence) they will be followed-up every 6 months (separate form) for survival until the end of the study.
- A deviation of +/- 6 weeks (1.5 months) is acceptable window for the follow-up visits.

As the inclusion criteria (patients being treated with SU in 1st line according to the approved therapeutic indication), the medication prescribed within the regular practice of the physician. In addition, as of the non-interventional nature of the study, there will be no specific requirements with regards to the treatment process. The physician will determine dosage and duration of the treatment, guided by the local country approved Prescribing Information and according to his assessment of the individual therapeutic needs of the patient.

8.2.1. Inclusion Criteria

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

- Adult patients (males and females) 18 years of age and over.
- Patients being treated with SU as 1st line treatment according to the approved therapeutic indication.
- Histologically confirmed diagnosis of adv/mRCC (clear cell RCC as well as non-clear cell RCC) with measurable disease according to RECIST 1.1.
- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

8.2.2. Exclusion Criteria

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

- Patients being treated with cytokines or any other treatment other than SU in 1st line setting.
- Patients presenting with a known hypersensitivity to SU or its metabolites will not be included in the study per the label.

8.3. Variables

Detailed definitions of variables that will be collected or derived for statistical analyses and summaries will be included in the Statistical Analysis Plan (SAP).

8.4. Data Collection Intervals & Recommended Data Collection Schedule

8.4.1. Recommended Data Collection Schedule

Variables	Screening/Baseline Visit 1 (Day0)	Treatment phase Visit 2-5 (3, 6, 9, 12 month)	Follow-up phase Visit 6-7 (18, 24 month)	EOS
Inclusion/ Exclusion Criteria Check	X			
Informed Consent	X			
Patient Demographics	X			
Medical History & Physical examination	X			
Tumor, Site of Metastasis & Prior treatment history	X			
Baseline Lab Tests	X			
Concomitant medications	X	X	X	X
Adverse Event assessment	X	X	X	X
Update in Disease Status	X	X	X	X
Update in Treatment Status/ Change in therapy		X	X	X
Reporting of routine labs collected	X	X	X	X
Performance Status, weight (BMI) & blood pressure	X	X	X	X
QOL Questionnaire (FKSI 19 only)	X	X	X	X

8.5. Study Procedures

Since this is primarily an observational study, there are no patient visits specified by virtue of this protocol. Data to be collected on the electronic case report forms (eCRF) is normally available in patient records.

All data would be collected per the investigator's practice. At any visit, if any of the parameters are not collected, the relevant section in the eCRF will be left blank.

8.5.1. Screening/Baseline

The following observational parameters are recommended to be collected at the screening/baseline Visit (Visit 1: Day 0):

- Informed Consent.
- Inclusion and exclusion criteria check.
- Patient Demography (date of birth, gender, race, country/nationality).
- Sites of Metastasis.
- Medical History (including previous history of myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, pulmonary embolism, hypothyroidism, hypertension and diabetes mellitus).
- Physical examination (General, Lungs, Heart, Musculoskeletal, Genitourinary, Neurological, Lymph nodes, Skin, Abdomen and Other).
- Tumor stage and prior treatment history (including the dose and schedule of SU being 1st line, duration of various therapies).
- Baseline Lab Tests (as per institutional routine practice):
    - Hematology: hemoglobin (Hgb), platelet count (Plt), white blood count, WBC White blood cell differentials (%) -Neutrophils, Lymphocytes, monocytes, basophils and eosinophils;
    - Chemistry: total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactic dehydrogenase (LDH), albumin, sodium, potassium, Magnesium, chloride, calcium, blood urea nitrogen (BUN), phosphorus, creatinine and uric acid;
    - Thyroid function tests (serum): T3, T4, and TSH;
    - Urinalysis: Urine Protein.

- Concomitant medications (a window period of 28 days prior to the start of the study treatment, during the study and up to 28 days post the last dose of treatment applies.
- Adverse Events Assessment.
- Performance Status (ECOG).
- Vital Signs; including body weight (BMI) and blood pressure.
- QOL questionnaire (FKSI 19) (Appendix 1).

N.B. please refer to Section 8.4.1 for the recommended schedule interval (a deviation of +/- 6 weeks (1.5 months) is acceptable window for the visits.

8.5.2. Treatment Phase

The following observational parameters are recommended be collected at the Treatment phase, which is visit 2-5 at month 3, 6, 9 and 12.

- Concomitant medications (a window period of 28 days prior to the start of the study treatment, during the study and up to 28 days post the last dose of treatment applies.
- Adverse Events Assessment.
- Update in Disease Status (including PFS, RR, TTR, TTF, OS).
- Update in Treatment Status/ Change in therapy.
- Reporting of routine labs collected.
- Performance Status (ECOG), weight (BMI) and blood pressure.
- QOL questionnaire (FKSI 19) (Appendix 1).

8.5.3. Follow-up Phase

For each subject, after treatment, there would be two follow-up visits (Visit 6-7) in one year, one visit every 6 months (month 18 and 24).

- Concomitant medications (a window period of 28 days prior to the start of the study treatment, during the study and up to 28 days post the last dose of treatment applies.
- Adverse Events Assessment.
- Update in Disease Status (including PFS, RR, TTR, TTF, OS).
- Update in Treatment Status/ Change in therapy.
- Reporting of routine labs collected.

- Performance Status (ECOG), weight (BMI) and blood pressure.
- QOL questionnaire (FKSI 19) (Appendix 1).

In case of no treatment failure till month 12, more treatment visits will be scheduled until SU discontinuation.

8.6. Data Sources

Data will be collected in routine clinical practice and from medical records as the inclusion criteria (Patients being treated with SU in 1st line according to the approved therapeutic indication) and the medication are prescribed within the regular practice of the physician. As a non-interventional study, there are no specific requirements in regards to the treatment process.

A case report form (eCRF) will be used for data collection. The eCRF must be signed by the investigator. The signatures serve to attest that the information contained on the eCRFs is true. At all times the investigator has the final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered into the eCRFs.

An investigator performs an assessment of new or ongoing adverse events, relative to a patient's baseline history, at each study visit. Generally, the identification of new or ongoing adverse events is determined till the last scheduled visit.

8.7. Sample Size

Due to the non-existences of a sample size calculation/justification for estimating the median progression free survival in phase IV trials and the exploratory/observatory nature of this study, we opt not to base the sample size on the main objective. However, we will use the secondary objective of estimation of the ORR for adv/mRCC patients receiving SU in the 1st line as the basis of the sample size. With 140 patients we will be able to assess the ORR to within a margin of error of at most ±8% using 95% confidence intervals. This is based on the assumption that the ORR will be less than 37% as per the literature.[12,25] This sample size is also within the range of samples sizes of other studies investigating SU for first line and where PFS and TTF were estimated.[25]

The 140 patients will be enrolled at 14 sites in the Middle Eastern & African countries; namely UAE, Qatar, RSA, Egypt, Algeria, Tunisia and Morocco. Each site is expected to enroll an average of 10 patients. This will ensure diverse and possibly representative sample of the Middle East and North Africa region.

8.8. Data Management

The electronic data capture (EDC) system for this study is Viedoc, a web-based EDC system. It will be used to collect, monitor, and report clinical data as specified in the protocol.

Clinical staff will enter the data via a web-portal. All data collected via the eCRF will be reviewed by remote data monitors for clarity and completeness. Instances of missing or unclear data will be communicated back to the investigator for resolution. The database and data management plan will be generated according to approved specifications.

8.9. Data Analysis

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.

Demographic and other clinical characteristics of the patients will be summarized using the mean, standard deviation, median, minimum, and maximum values, for numeric variables such as age and duration of follow up and frequency distributions for categorical data such as gender. The median and 95% confidence intervals for the main outcomes PFS and TTF will be estimated using the method of Kaplan-Meier. The ORR for adv/mRCC patients receiving SU in the 1st line will be computed along with its 95% confidence interval using the Clopper-Pearson formula. Cox proportional hazard models may be used to explore the potential influences of baseline characteristics on PFS or TTF. A multiple logistic regression model can be used to assess the effect of prognostic variable on ORR.

Change in other variables such as Quality of life and weight at last visit as compared to the baseline will be assessed using the paired t-test at each visit in addition to computing mean differences along with 95% confidence intervals. Moreover, repeated methods can be used to look for trends over time and adjust for possible confounders.

All AEs occurring during the study will be considered as treatment-emergent, and the frequency of AEs will be summarized. Sub-group analyses of association between efficacy outcomes, safety measurements, and baseline factors will be performed for exploratory reasons as needed.

8.10. Quality Control

Investigators will be trained with an initial on-site visit to the clinic on the protocol, EDC system, site master file, documentation, and any applicable study processes. Any new information relevant to the performance of this NIS will be forwarded to the staff during the study. Remote data monitoring will be conducted during the life of the study to ensure timely reporting of safety data, data integrity, and consistency. eCRFs for all included patients will be made available to the remote data monitor for review. A list of critical variables will be created as required elements for review during the remote data monitoring process. The study sites will be contacted to request resolution to any issues that may arise during the course of the study.

Monitoring visits may be made, if necessary, to monitor study process by Pfizer, Inc. or its delegate. In the event of a visit, direct access to original source data will be required for monitoring visits and/or inspections/audits, which will be carried out with due consideration for data protection and patient confidentiality.

Items routinely checked during on-site visits include:

- Documentation of the informed consent process.
- Compliance with patient eligibility criteria.
- Proper maintenance of records, such as study protocol.
- Completed eCRFs.
- Documentation of adverse events, and transmission of serious adverse events.
- Identification of patients lost to follow up.
- Study correspondence.
- Compliance with IRB approval requirements.

8.11. Limitations of the Research Methods

The source data described in this protocol contain the inherent limitation of any current non-interventional, real world study. These studies have the potential for missing, inaccurate, or incomplete data. The limitations of the observational nature can result in methodological challenges in attributing causality to outcomes. The patient selection and the diagnostic or monitoring procedures are those applied per the usual treatment paradigm of the treating physician and not dictated by the protocol. Heterogeneous patient populations could make the interpretation of the outcomes difficult. Hence, this study is intended for hypothesis generation, as opposed to hypothesis confirmation.

8.12. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

9.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

9.4. 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 Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry:

Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. ADVERSE EVENT REPORTING

10.1.1. Requirements

All observed or volunteered adverse events for which the investigator has determined that the adverse event is related to SU will be recorded as described on the adverse event page(s) of the electronic case report form (eCRF).

For all adverse events, sufficient information should be obtained by the investigator is to determine the causality of the adverse event. The investigator is required to assess causality.

For adverse events with a causal relationship to SU, follow-up is required until the event resolve; and Pfizer concurs with that assessment.

If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

10.1.2. Reporting Period and Requirements

All adverse drug reactions and other safety information as mentioned below should be documented and reported to Pfizer; for the sake of continuous monitoring of product safety.

Non-AEs and other safety information should be reported to Pfizer, if possible, upon recognition but no later than 10 days.

Patients should be asked to inform the treating physician of any AE or other relevant safety information, immediately. The treating physician has to assess the causal relationship for AEs and report AEs and other relevant drug safety information.

If a SAE occurs that in in the opinion of the investigator is related to *Sutent*®, Pfizer is to be notified within 24 hours of awareness of the event and a non-Interventional Study Adverse Event Report Form must be completed and submitted to Pfizer Safety.

In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure during breast feeding and medication error cases.

Suspected adverse reactions that are both serious and unexpected are subject to expedited reporting in accordance with all applicable laws and regulations.

For each patient, the safety event reporting period begins at the time of the patient's informed consent, which is obtained prior to the patient's enrollment in the study, and lasts through the end of the observation period of the study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period.

If a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation or if patients are screened for eligibility following informed consent, and fail screening criteria), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the serious AE to be related to Sutent® (Sunitinib), the SAE also must be reported to Pfizer Safety.

10.2. DEFINITIONS OF SAFETY EVENTS

10.2.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage.

Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;

- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

10.2.2. Serious Adverse Events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a serious adverse event. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life- threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non- pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep).
- Administrative admission (eg, for yearly exam).
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery).

- Hospitalization for observation without a medical AE.

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality).

- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

10.3. Causality Assessment

The reviewer of the medical chart will identify all adverse events where an investigator‟s assessment of causality relative to the use of *Sutent*® (serious and non-serious) is provided in the medical chart. The reviewer of the medical chart must record those adverse events with a causal relationship to *Sutent*® in the eCRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements if applicable.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that *Sutent*® caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether *Sutent*® caused the event, then the event will be handled as related to *Sutent*® for reporting purposes. If the investigator's causality assessment is unknown but not related to *Sutent*® this should be clearly documented in the eCRF.

10.4. Exposure During Pregnancy

An exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) Sutent® or the female becomes, or is found to be, pregnant after discontinuing and/or having been being directly exposed to Sutent® (maternal exposure).

2. A male has been exposed, either due to treatment or environmental, to Sutent® prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE/SAE.

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

If a study patient or study patient's partner becomes, or is found to be, pregnant during the study patient's treatment with *Sutent*®, the investigator must submit this information to Pfizer within 24 hours of awareness of the pregnancy, irrespective of whether an adverse event has occurred. Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the

pregnancy until completion or until pregnancy termination (eg, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero report.

For clinical studies conducted in pregnant women, data on the pregnancy outcome and non-serious AEs are expected to be collected and analyzed in the clinical database. In such instances only EIUs associated with a SAE are to be reported.

10.5. Medication Error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE/SAE:

Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

- An identifiable reporter;
- A suspect product;
- The event medication error.

10.6. Single Reference Safety Document

For this NI Study we will use the current package inserts for Sutent® (Sunitinib) as the single reference safety document.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Communication of Results by Pfizer

Pfizer fulfils its commitment to publicly disclose the results of studies through posting the results of this study on ClinicalStudyResults.org. Pfizer posts the results of studies that fall into either of the following categories:

- Studies that Pfizer registered on www.clincaltrials.gov regardless of the reason for registration; OR
- All other studies for which the results have scientific or medical importance as determined by Pfizer.

The sponsor's policy is to publish or otherwise communicate the results of its hypothesis-testing clinical studies, regardless of outcome, for marketed products, compound(s) or product(s) being investigated that are later approved for marketing.

The sponsor's decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and sponsor policies regarding publication and communication of clinical study results.

11.2. Investigator's Ability to Publish

The institution and investigator shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the investigator expects to participate in the publication of data generated from this site, the institution and investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 calendar days to respond with any requested revisions, including, without limitation, the deletion of confidential information. The investigator shall act in good faith upon requested revisions, except that the investigator shall delete any confidential information from such proposed publication. The investigator shall delay submission of such publication or presentation materials for up to an additional 90 calendar days in order to have a patent application(s) filed.

12. INVESTIGATOR'S FILE/ CONDITIONS FOR RETENTION OF DOCUMENTS:

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc. In addition at the end of the study the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, which also has to be kept with the Investigator's Study File.

Subject clinical source documents would include patient hospital/clinic records, physicians' and nurses' notes, appointment book, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrolment logs. The Investigator must keep these two categories of documents file available for inspection until further notification by the sponsors.

Pfizer will collect copies of signed protocol/amendments, Independent Ethics Committee/Institutional Review Board and governmental approval, sample copies of informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. Subject confidentiality will be strictly followed.

12.1. Audits and Inspections

The Investigator should understand that source documents for this trial should be made available to the health authority inspectors. The verification of the electronic Case Report Form data must be by direct inspection of source documents.

12.2. Monitoring the Study

It is understood that the responsible monitor (or designee) will contact and visit the Investigator and will be allowed, on request, to inspect the various records of the trial (Case Report Forms and other pertinent data) provided that patient confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the Case Report Forms at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the Case Report Form. The Investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13. REFERENCES

1. GLOBACAN 2012.

2. Ghosn et al. Pan Arab Journal of Oncology/Vol. 8/No. 2/ June 2015.

3. Motzer RJ. New Perspectives on the Treatment of Metastatic Renal Cell Carcinoma: An Introduction and Historical Overview, The Oncologist 2011; 16 (suppl 2):1–3.

4. National Comprehensive Cancer Network, Kidney Cancer www.nccn.org.

5. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009; 27(22):3584–3590.

6. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007; 356(2):115–124.

7. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized Phase III trial. J Clin Oncol. 2010;28(6):1061–1068.

8. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol. 2010; 28(13):2144–2150.

9. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010; 28(13):2137–2143.

10. Motzer RJ, McCann L, Deen K. Pazopanib versus sunitinib in renal cancer. N Engl J Med. 2013; 369(20):1970.

11. Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES study. J Clin Oncol. 2014 Apr 31.

12. Choueiri TK, Duh MS, Clement J, Brick AJ, et al. Angiogenesis inhibitor therapies for metastatic renal cell carcinoma: effectiveness, safety and treatment patterns in clinical practice based on medical chart review. BJU Int. 2010 May; 105(9):1247-54.

13. Feinberg BA, Jolly P, Wang ST, Fortner B, Scott J, Gilmore J, Neary MP, Duh MS. Safety and treatment patterns of angiogenesis inhibitors in patients with metastatic renal cell carcinoma: evidence from US community oncology clinics. Med Oncol.2012: 29(2):786-94.

14. Porta C, Levy A, Hawkins R, Castellano D, Bellmunt J, Nathan P, McDermott R, Wagstaff J, Vekeman F, Neary MP, Diaz J, Mehmud F, Duh MS. Impact of adverse events, treatment modifications and dose intensity on survival among patients with advanced renal cell carcinoma treated with first-line sunitinib: A medical chart review across ten centers in five European countries. Cancer medicine. 2014: 3(6):1517-1526.

15. Houk BE, Bello CL, Poland B, Rosen LS, Demetri GD, Motzer RJ. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis. Cancer Chemother. 2010:66:357–371.

16. Motzer RJ, Hutson TE, Tomczak P et al: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007; 356: 115.

17. Atkinson BJ, Kalra S, Wang X, Bathala T, Corn P, Tannirt N, Jonasch E. Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules. Journal of Urology. 2014: 191: 611-618.

18. Bracarda S, Iacovelli R, Rizzo M, Rossi M, Galli L, Procopio G, Longo F, Santoni M, Morelli F, Lorenzo G, Porta C, Camerini A, Bella S, Martignetti A, Gasparro D, Sabbatini R, Ceresoli G, Mosca A, Santini D, Boni L. Retrospective observational study of sunitinib administered on schedule 2/1 in patients with metastatic renal cell carcinoma (mRCC): the RAINBOW study. ASCO:2014.

19. Najjar YG, Mittal K, Elson P, Wood L, Garcia JA, Dreicer R, Rini BI. A 2 weeks on 1 week off schedule of sunitinib is associated with decreased toxicity in metastatic renal cell carcinoma. European journal of cancer. 2014:50: 1084-1089.

20. Miyake H, Harada K, Miyazaki A, Fujisawa M. Improved health related quality of lofe of patients with metastatic renal cell carcinoma treated with a 2 weeks on and 1 week off schedule of sunitinib. Med oncol. 2015: 32:78.

21. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised Phase 3 trial. Lancet. 2011; 378(9807):1931–1939.

22. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer. 2010; 116(18):4256–4265.

23. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5; 373(19):1814-23.

24. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5; 373(19):1803-13.

25. Bernard Escudier, Cezary Szczylik, Camillo Porta & Martin Gore " Treatment selection in metastatic renal cell carcinoma: expert consensus"*Nature Reviews Clinical Oncology* **9**, 327-337.

Appendix 1. FKSI-19 Questionnaire

NCCN-FACT FKSI-19

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	HI12	I feel weak all over	0	1	2	3	4
	RCC 2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

Appendix 2. *FKSI-19 (version 4) – Scoring guidelines*

Instructions:

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the symptom index score.
4. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

Note: If >50% of items were completed, the FKSI scores were calculated as the sum of the item responses divided by the number of items completed multiplied by the total number of items in the scale (eg, 19 in the case of the FKSI-19).

If fewer than 50% of the items were completed, the scores were considered missing.

Scale	Item Code	Reverse item		Item response	Item Score FKSI-19
Total	GP1	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-76	C2	4	-	_____	=_____
	HI7	4	-	_____	=_____
	B1	4	-	_____	=_____
	BRM3	4	-	_____	=_____
	BP1	4	-	_____	=_____
	L2	4	-	_____	=_____
	HI12	4	-	_____	=_____
	RCC2	4	-	_____	=_____
	C6	0	+	_____	=_____
	GF5	0	+	_____	=_____
	GE6	4	-	_____	=_____
	GP2	4	-	_____	=_____
	C5	4	-	_____	=_____
	GP5	4	-	_____	=_____
	GF1	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 19: _

_____

Divide by number of items answered:

_____ **= FKSI-19 score**

Subscale	Item Code	Reverse		Item response	Item Score
FKSI-DRS-P (Disease Related Symptoms-Physical)	GP1	4	-	_____	=_____
	GP4	4	-	_____	=_____
	C2	4	-	_____	=_____
	HI7	4	-	_____	=_____
	B1	4	-	_____	=_____
	BRM	4	-	_____	=_____
	3	4	-	_____	=_____
	BP1	4	-	_____	=_____
	L2	4	-	_____	=_____
	HI12	0	+	_____	=_____
	RCC	0	+	_____	=_____

Sum individual item scores: _____

Multiply by12: _____

Divide by number of items answered: _____ **=FKSI-DRS-P**

DRS-P score

Subscale	Item Code	Reverse item		Item response	Item Score
FKSI-DRS-E (Disease Related Symptoms-Emotional)	GE6	4	-	_____	=____= **FKSI-DRS-E score**

Score range: 0-4

Subscale	Item Code	Reverse		Item response	Item Score
FKSI-TSE (Treatment Side	GP	4	-	_____	=_____
	2	4	-	_____	=_____
		4	-		

Score range: 0-12

Sum individual item scores: _____

Multiply by 3: _____

Divide by number of items answered: _____ **=FKSI-TSE Score**

Subscale	Item Code	Reverse item		Item response	Item Score
FKSI-F/WB (Function/ Well-Being)	GF1	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF7	0	+	_____	=_____

Score range: 0-12

Sum individual item scores: _____

Multiply by 3: _____

Divide by number of items answered: **=FKSI-F/WB score**

Appendix 3. ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead