



NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Observational Study Evaluating The Efficacy of Targeted Treatments Following Tyrosine Kinase Inhibitors in Metastatic Renal Cell Carcinoma Patients And Effects on Quality of Life: A National, Multicenter Study
Protocol number	A4061086
Protocol version identifier	2.1
Date of last version of protocol	09 March 2016
Active substance	Aksitinib, Everolimus, Sunitinib, Sorafenib, Pazopanib, Temsirolimus
Research question and objectives	<p>Primary objective of this study is; measurement of health-related quality of life and efficacy of targeted therapies used after second line Tyrosine Kinase Inhibitors (TKIs) in metastatic renal cell carcinoma patients.</p> <p>Due to the reimbursement rules for TKIs in Turkey, the use of cytokines (interferon alpha) is mandatory in the first-line treatment. The TKI therapy is applied after interferon alpha in Turkey as second line therapy. Therefore, in this study, the data will be collected to observe the quality of life and efficacy with targeted therapies used as third line treatment after first line interferon alpha and second line TKIs.</p>
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
mRCC	Metastatic Renal Cell Carcinoma
FSFV	First Subject First Visit
LSLV	Last Subject Last Visit
LSFV	Last Subject First Visit
SAE	Serious Adverse Event
NCI	National Cancer Institute
NIS	Non-Interventional Study
TKIs	Tyrosine Kinase Inhibitors
CTCAE	Common Terminology Criteria for Adverse Events
FKSI-15	The Functional Assessment of Cancer Therapy Kidney Symptom Index - 15
EQ5D-3L	EuroQoL-5 dimension – 3 level
FKSI-DRS	The Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-Related Symptoms
RECIST version 1.1	Response Evaluation Criteria in Solid Tumors
PFS	Progression-Free Survival
QoL	Quality of Life
ORR	Overall Response Rate
OS	Overall Survival
IFN	Interferon
KM	Kaplan Meier

SD	Standard Deviation
NUTS	Nomenclature D'unites Territoriales Statistiques
IRB	Institutional Review Board
WHO	World Health Organization
MedDRA	Medical Dictionary for Regulatory Activities
ADRs	Adverse Drug Reaction
e-CRF	Electronic Case Report Form

2. RESPONSIBLE PARTIES

Sponsor: Pfizer

Sponsor Affiliate: PPD, MD, PhD Medical Manager

Drug Safety: PPD, Pharm; Pharmacovigilance Country Lead

PPD

CRO: Trio Grup Clinical Research

CRO Affiliate: PPD, Bio

Participating Countries: Turkey

Coordinating Investigator: Prof. Dr PPD

Coordinator Investigator(s) of the Study

Name, degree(s)	Title	Affiliation	Address
PPD, Prof	MD	PPD	PPD

Country Coordinating Investigators

Not applicable

3. ABSTRACT

Observational Study Evaluating The Efficacy of Targeted Treatments Following Tyrosine Kinase Inhibitors in Metastatic Renal Cell Carcinoma Patients And Effects on Quality of Life: A National, Multicenter Study

Protocol Version: 2.1

Protocol Date: 09 March 2016

Main Author: PPD , Prof. at PPD
PPD , MD, PhD at Pfizer

Background

Metastatic renal cell carcinoma (mRCC) is the most common malignant tumour of the kidneys. Targeted therapies, which were recently introduced in the treatment of mRCC, have become the standard treatment in these patients [1]. With improved survival rate and a tolerable side effect profile, Tyrosine Kinase Inhibitors (TKIs) have largely replaced conventional immunotherapies worldwide. [2-3]

In Turkey, due to reimbursement conditions defined by the authority, cytokine (interferon alpha) treatment is the standard treatment as first-line therapy [4].

Rationale

TKI therapy is used after interferon alpha in Turkey due to current reimbursement status. Therefore, the data on quality of life (QoL) from the pivotal studies with standard TKI treatment does not reflect the QoL status of patients treated with TKIs as second or third line treatment in Turkey. In this study, the clinical outcomes and the impact on quality of life of targeted treatments following TKIs will be explored. To our knowledge, since there is no similar reimbursement condition in the world placing IFN as the first line standard treatment, this will be the first study evaluating the QoL status with targeted therapies used as 3rd line treatment in mRCC patients.

Research Question and Objectives

Research Question:

There is no data available in the literature explaining the effect of targeted therapies used as 3rd line treatment following IFN and TKIs in metastatic renal cell carcinoma patients. Therefore, it is essential to understand health-related quality of life and efficacy of targeted therapies used as 3rd line treatment due to current reimbursement conditions in Turkey.

Primary Objective:

- Measurement of health-related quality of life with targeted therapy used as 3rd line treatment
- Overall response rate at the end of follow up
- Median progression free survival according to RECIST version 1.1

Secondary Objectives:

- Overall survival rate
- Effect of quality of life on prognosis.
- Adverse events during 3rd line targeted treatment according to CTCAE.4.03
- Dose modifications due to adverse events
- Correlation between efficacy (overall response rate at month 12 and median PFS) and dose modifications due to adverse events
- Correlation between efficacy (overall response rate at month 12 and median PFS) and blood pressure

Study Design

This is a multi-center, national, non-interventional/observational study. It has been defined according to the NUTS (Nomenclature of Territorial Units for Statistics: Nomenclature d'unités Territoriales Statistiques, French) criteria, which is a regional classification, created in order to reduce interregional disparities in socio-economic analysis of the regions, and to produce data comparable to that of the European Union (EU). Turkey has been divided into 12 NUTS regions depending on the economic, social, cultural, and geographical aspects, and the population size. In this study, patients with metastatic renal cell carcinoma from centers in 12 NUTS regions of Turkey will be included, who meet the inclusion criteria. In this study, approximately 152 patients planned to be recruited in 12 months and followed-up for 12 months. Additionally, every patient will be followed-up once for survival follow-up in order to assess the overall survival before the site close out visit. Survival follow-up will be performed via telephone visit or site visit if exist.

Study Population

Metastatic renal cell carcinoma patients under 3rd line targeted therapy following 1st line interferon alpha and 2nd line TKI. All patients will be ≥ 18 years old and have signed the informed consent document.

Variables

Age, gender, height, weight, and vital signs such as blood pressure

Socio-demographic characteristics

ECOG performance status

Concomitant diseases and medication

Medical history

Histopathological findings

Type of the surgical procedure

Treatment history and current treatment information

Metastatic features

MSKCC risk factors

Laboratory findings

The quality of life questionnaire (FKSI-15, EQ5D-3L, FKSI-DRS) on each visit.

Blood pressure diary

Other treatment during follow-up, if any, the dose and the duration

Side effects (treatment of the side effects, interruption of the treatment, dose reduction, dose-elevation)

PFS, OS and ORR evaluation during 3rd, 6th, 9th and 12th months performed according to RECIST version 1.1, additionally, every patient will be followed-up once for survival follow-up in order to assess the overall survival before the site close out visit. Survival follow-up will be performed via telephone visit or site visit if exist.

ORR: The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

PFS: The length of time during and after the treatment of a disease, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works.

OS: 1 year Overall Survival (OS), defined as the time from the start of 3rd line treatment until death or 1 year due to any cause (measured at the end of follow-up).

Data Sources

The source of the data will be the electronic or the written patient records of the participating centers. The patient's data can be accessed through a patient file. In the centers, both systems can be used in conjunction. The data can be accessed using both systems.

Sample Size

This is a multi-center, national, non-interventional/observational study. In this study, patients with metastatic renal cell carcinoma who meet the inclusion criteria will be included from centers in 12 NUTS regions of Turkey. Since this is a non-interventional observational study, there is no specific follow-up protocol. In this study, approximately 152 patients will be evaluated.

According to Turkish Statistical Institute data at the end of 2013 population of Turkey is approximately 80 million [5]. In the project of Turkey Association of Cancer Research Control which was named Cancer Record and Incidence shows that cancer incidence is 100-150 in 100.000 [6] and 2% of all new cancers are renal cell carcinoma [7]. There would be 1800 new RCC patients in 1 year, and according to the OS of the disease, there would be 4000 RCC patients in Turkey. 15% of these are metastatic at the time of diagnosis and 30-40% of these are metastatic after a period of a time [8]. Presuming that there are 1800 patients with metastatic renal carcinoma in Turkey, the minimum sample size with 7,6 confidence interval, 95% confidence level and 80% power was calculated as 152.

Data Analysis

Data Analysis:

Statistical analyses will be primarily of explorative and descriptive nature. Patients who received at least one dose of 3rd line therapy and have sufficient information whether they had an adverse event or not will be valid for safety analysis. Patients who received at least one dose of 3rd line therapy and have any information regarding efficacy of therapy will be valid for intent-to-treat efficacy analysis.

Demographic data, baseline characteristics, diagnosis and prior treatment of RCC, concomitant diseases, and concomitant medication will be described with summary statistics such as mean, SD, minimum, 1, 5, 25, 75, 95, 99 percent quartiles, median, maximum for continuous variables, and category counts and frequencies (percentages) for categorical variables. Concomitant diseases on the case report form correspond to MedDRA terms. Concomitant medication will be coded using WHO's drug dictionary.

Descriptive summaries of Kaplan-Meier (KM) estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% confidence level and median with 95% Confidence level) and KM curves will be presented for time-to-event efficacy variables (PFS, TTP, time to treatment failure). Mean, SD, minimum, 1, 5, 25, 75, 95, 99 percent quartiles, median, maximum will be produced for duration of treatment. Category counts and frequencies (percentages) will be calculated for tumor status at different visits and general subjective rating of efficacy of 3rd line therapy from the treating physician.

Adverse events will be summarized using the CTCAE.4.03 coding system. Event rates for single adverse events will be calculated based on the total number of patients valid for safety. Adverse events will be categorized according to relation, seriousness, CTCAE grade (version 4.03), and discontinuation of therapy, action taken and outcome. Special attention will be paid to serious adverse events and unexpected or unlisted ADRs.

Category counts and frequencies (percentages) will be calculated for overall tolerability.

Since the enrollment is after the initiation of the treatment, some information will be collected and analyzed retrospectively.

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation.

4. AMENDMENTS AND UPDATES

None

5. MILESTONES

Project Task or Milestone	Planned Timeframe for Completion
FSFV	May 2015
LSFV	December 2016
LSLV	December 2017
Database lock for interim analysis	March 2017
Final database lock	April 2018
Final results available	October 2018

6. RATIONALE AND BACKGROUND

Background

Metastatic renal cell carcinoma (mRCC) is the most common malignant tumour of the kidneys. Targeted therapies, which were recently introduced in the treatment of mRCC, have become the standard treatment in these patients [1]. With improved survival rate and a tolerable side effect profile, Tyrosine Kinase Inhibitors (TKIs) have largely replaced conventional immunotherapies worldwide. [2,3]

These developments have led to new research to identify the effects of these therapies on the quality of life and the treatment-related side effects.

In Turkey, due to reimbursement conditions defined by authority, cytokine (interferon alpha) treatment is the standard treatment in the first-line therapy [4]. Therefore, the data on quality of life from the pivotal studies with standard TKI treatment doesn't reflect QoL of the patients treated with TKIs as second or third line treatment in Turkey.

Rationale

TKI therapy is used after interferon alpha in Turkey due to current reimbursement status.

Therefore, the data on quality of life from the pivotal studies with standard TKI treatment doesn't reflect the QoL status of the patients treated with TKIs as second or third line treatment in Turkey. In this study, the clinical outcomes and the impact on quality of life of targeted treatments following TKIs will be explored. To our knowledge, since there is no similar reimbursement condition in the world placing IFN as the first line standard treatment, this will be the first study evaluating the QoL status with targeted therapies used as 3rd line treatment in this setting.

7. RESEARCH QUESTION AND OBJECTIVES

Research Question:

In this study, different from other studies in the literature, the data will be collected to observe the quality of life and efficacy after first line interferon alpha and second line TKI treatments.

Primary Objective:

- Measurement of health-related quality of life with targeted therapy used as 3rd line.
- Overall response rate at the end of follow up
- Median progression free survival according to RECIST version 1.1

Secondary Objectives:

- Overall survival rate
- Effect of quality of life on prognosis.
- Adverse events during 3rd line targeted treatment according to CTCAE.4.03
- Dose modifications due to adverse events
- Correlation between efficacy (overall response rate at month 12 and median PFS) and dose modifications due to adverse events
- Correlation between efficacy (overall response rate at month 12 and median PFS) and blood pressure

8. RESEARCH METHODS

8.1. Study design

This is a multi-center post-marketing observational study. It has been defined according to the NUTS (Nomenclature of Territorial Units for Statistics: Nomenclature d'unités Territoriales Statistiques, French) criteria, which is a regional classification, created in order to reduce interregional disparities in socio-economic analysis of the regions, and to produce data comparable to that of the European Union (EU). Turkey has been divided into 12 NUTS regions depending on the economic, social, cultural, and geographical aspects, and the population size. In this study, patients with metastatic renal cell carcinoma from centers in 12 NUTS regions of Turkey will be included, who meet the inclusion criteria. Since this is a non-interventional observational study, there is no specific follow-up protocol. In this study, approximately 152 patients planned to be recruited in a year and followed-up 12 months.

This is a multi-center post-marketing observational study. In this study, patients with metastatic renal cell carcinoma from centers in 12 NUTS regions of Turkey will be included,

who meet the inclusion criteria. Since this is a non-interventional observational study, there is no specific follow-up protocol.

Presuming that there are 1800 patients with metastatic renal carcinoma in Turkey, the minimum sample size was calculated as 152.

There will be a total of 25 centers in various cities of Turkey.

The centers will consist of medical oncology clinics.

In this study, the patient follow-up period is 12 months. Each patient will be followed up to 5 times; the data will be collected at baseline, the 3rd, 6th, 9th and 12th months according to the routine practice. Additionally, every patient will be followed-up once for survival follow-up in order to assess the overall survival before the site close out visit. Survival follow-up will be performed via telephone visit or site visit if exist.

Because of the observational nature of the study, there is no predefined treatment protocol. The participating physician will continue to treat the patients at his/her own discretion. Frequency of visits will be continued per physician's preference.

The patients will be asked to fill in the quality of life questionnaire (FKSI-15, EQ5D-3L, FKSI-DRS) on each visit.

The assessment of the side effects will be based on the "Common Terminology Criteria for Adverse Events". The CTCAE V.4.03 will be used.

Outcome Measures are overall objective response rate (ORR) [Time frame: from enrollment to objective response], progression-free survival (PFS) [Time frame: from enrollment to disease progression or death, whichever occurs first], overall survival (OS) [Time frame: from enrollment to death or the end of the study duration] and probability of patient survival at 1 year [Time frame: from enrollment to 1 year]

8.2. Setting

Metastatic renal cell carcinoma patients who progressed after a TKI therapy following a cytokine (interferon alpha) treatment will be enrolled to the study. The study enrollment period is 12 months And the follow-up period of a patient is 12 months. The study period is 36 months.

8.2.1. Inclusion criteria

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

- Histologically confirmed metastatic renal cell cancer patients who have already been using targeted therapies for up to 1 months as 3rd line treatment
- Patients 18 years and older than 18 years
- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal 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 with contraindications for the use of the study medications
- Patients with (suspected) pregnancy or in lactation period
- Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees directly involved in the conduct of the trial.
- Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks before included in the current study.

8.3. Variables

The outcome variables for the objective(s) are time to treatment failure (from start of treatment to progression or permanent discontinuation), overall survival (from start of treatment to the date of last follow up or death), therapeutic response to therapy based on response evaluation criteria in solid tumors (RECIST version 1.1), and safety (type, incidence, severity of adverse events graded by the National Cancer Institute [NCI] CTCAE V.4.03)

Variable	Role	Data source(s)	Operational definition
Age, gender, height, weight, blood pressure, socio-demographic characteristics	Baseline characteristic	Medical Records	
Concomitant diseases	Baseline Characteristic	Medical Records	
Medication	Baseline Characteristic	Medical Records	
Histopathological findings	Baseline Characteristic	Medical Records / Pathology Reports	
Surgical Operations	Baseline Characteristic	Medical Records	
The cytokine (interferon alpha) usage in the first-line treatment, TKI usage in the 2 nd line treatment and the dosage and the duration of the treatment	Baseline Characteristic	Medical Records	
Metastatic features	Baseline Characteristic	Medical Records	
MSKCC risk factors	Baseline Characteristic Follow-up Characteristic	Medical Records	
3 rd line treatment	Baseline Characteristic Follow-up Characteristic	Medical Records	

	Close-out Characteristic		
The performance score before the second and third-line treatment		Medical Records	
The quality of life questionnaire (FKSI-15, EQ5D-3L, FKSI-DRS) on each visit	Baseline Characteristic Follow-up Characteristic Close –out Characteristic	Patient interview	
Blood pressure		Patient diary	
Other treatment during follow-up, if any, the dose and the duration	Follow-up Characteristic	Medical Records	
Treatment of the side effects, interruption of the treatment, dose reduction, dose-elevation	Baseline Characteristic Follow-up Characteristic	Medical Records	
Duration of PFS, OS and ORR	Follow-up Characteristic Close-out Characteristic	Medical Records	

Schedule Procedure	Initial visit	Follow-up 3.month	Follow-up 6.month	Follow-up 9.month	Follow-up 12.month	Survival Follow-up
Demographic data	X					
Histopathological Findings	X					
Medical history	X					
Previous therapy of mRCC	X					
MSKCC Risk Factors	X	X	X	X	X	
Surgical Operations	X					
Metastases Information	X					
FKSI-15, EQ5D-3L, FKSI-DRS Questionnaire	X	X	X	X	X	
Evaluation of PFS, OS and ORR		X	X	X	X	
Concomitant medication	X	X	X	X	X	
Visit date	X	X	X	X	X	
ECOG and Karnofsky Performance Status	X	X	X	X	X	
Prescribed TKI and dose	X					
3 rd line treatment	X	X	X	X	X	
Assessment of Response		X	X	X	X	
Adverse Events (Serious Adverse Events must be reported to the sponsor within 24 hours)		X	X	X	X	
Survival status						X

8.4. Data sources

The source of the data will be the electronic or the written patient records of the participating centers. The patient records form the basic source for the information about the state of a patient's health. For this reason, all the data of the patient are archived in various ways in the center. One of the most commonly used data source is the computer-based patient record system. The patient data can be accessed using these systems generated with various computer programs.

Another common use in the hospital is the hard-copy filing system in the form of log file. The patient's data can be accessed through a patient file with a specific code number. In the centers, both systems can be used in conjunction.

The data can be accessed using both systems.

8.5. Study size

Since this is a multi-center post-marketing observational study, there is no hypothesis to be tested. In this study, patients with metastatic renal cell carcinoma from centers in 12 NUTS regions of Turkey will be included, who meet the inclusion criteria. Since this is a non-interventional observational study, there is no specific follow-up protocol. In this study, approximately 152 patients will be evaluated.

According to Turkish Statistical Institute data at the end of 2013, Turkey population is approximately 80 million [5]. In the project of Turkey Association of Cancer Research Control which was named Cancer Record and Incidence shows that cancer incidence is 100-150 in 100.000 [6] and 2% of all new cancers are renal cell carcinoma [7]. There would be 1800 new RCC patients in 1 year, and according to the OS of the disease, there would be 4000 RCC patients in Turkey. 15% of these are metastatic at the time of diagnosis and 30-40% [8] of these are metastatic after a period of a time. Presuming that there are 1800 patients with metastatic renal carcinoma in Turkey, the minimum sample size with 7,6 confidence interval, 95% confidence level and 80% power was calculated as 152.

8.6. Data management

The data will be analyzed using the statistical package program. The categorical variables will be given as number and percentages, and the continuous variables will be presented as averages and standard deviations. For between-group comparisons of categorical variables, the chi-square test will be used. The continuous variables will be tested for normal distribution using the Kolmogorov-Smirnov test and the Shapiro Wilks test. For the normally distributed continuous variables, the parametric tests (the t-test, the ANOVA, the repeated measures analysis of variance, etc.), and for the continuous variables without a normal distribution, the non-parametric tests (the Mann-Whitney U test, the Kruskal Wallis analysis of variance, the Friedman Analysis of Variance, etc.) will be used. The level of significance will be taken as $p = 0.05$.

8.7. Data analysis

Statistical analyses will be primarily of explorative and descriptive nature. All issues concerning patient validity, data consistency checks, permissible data modifications will be described in detail in the Data Management Plan.

Patients who took at least one dose of 3rd line treatment and have sufficient information whether they had an adverse event or not will be valid for safety analysis. Patients who took at least one dose of 3rd line treatment and have any information regarding efficacy of 3rd line treatment will be valid for intent-to-treat efficacy analysis.

Demographic data, baseline characteristics, diagnosis and prior treatment of RCC, concomitant diseases, and concomitant medication will be described with summary statistics such as mean, SD, minimum, 1, 5, 25, 75, 95, 99 percent quartiles, median, maximum for continuous variables, and category counts and frequencies (percentages) for

categorical variables. Concomitant diseases on the case report form correspond to MedDRA terms. Concomitant medication will be coded using WHO's drug dictionary.

Descriptive summaries of Kaplan-Meier (KM) estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% confidence level and median with 95% confidence level) and KM curves will be presented for time-to-event efficacy variables (PFS, TTP, time to treatment failure). Mean, SD, minimum, 1, 5, 25, 75, 95, 99 percent quartiles, median, maximum will be produced for duration of TKI treatment. Category counts and frequencies (percentages) will be calculated for tumor status at different visits and general subjective rating of efficacy of TKI from the treating physician.

Adverse events will be summarized using the MedDRA and the CTCAE coding system. Event rates for single adverse events will be calculated based on the total number of patients valid for safety. Adverse events will be categorized according to relation, seriousness, CTCAE grade (version 4.03), and discontinuation of therapy, action taken and outcome. Serious adverse events and unexpected or unlisted ADRs will be evaluated separately.

Category counts and frequencies (percentages) will be calculated for overall tolerability.

The factors, which might have impacted the duration of treatment, will be studied by retrospectively.

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

8.8. Quality control

Data will be captured with e-CRF. Missing data should be completed or commented upon by the physician. After data checked, missing or implausible data will be queried. A check for multiple documented patients will be done. The data will be verified by an error analysis. Finally source data verification will be conducted in all of patients, 100% SDV will be performed. All investigators will be sufficiently trained for participation in the study.

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified.

The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

8.9. 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, (e.g., 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 Pharmacoeconomics Practices (GPP) issued by the International Society for Pharmacoeconomics (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA).

This is a non-interventional study where the 3rd line targeted treatment are prescribed in the usual manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a particular therapeutic strategy, the treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods shall be used for the analysis of the collected data.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Safety event	Recorded on the case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent

of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For those safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of *3rd line treatment* or the time of the patient's informed consent if s/he is already exposed to *3rd line treatment*, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under 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 the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to *3rd line treatment*, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to *3rd line treatment*, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that *3rd line treatment* caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether *3rd line treatment* caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that *3rd line treatment* did not cause the event, this should be clearly documented on the case report form and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

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 (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- 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.

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 (e.g., 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 (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., 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 (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) 3rd line treatment, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to 3rd line treatment (maternal exposure).

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

2. A male has been exposed, either due to treatment or environmental exposure to 3rd line treatment prior to or around the time of conception and/or is exposed during the partner 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 and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with 3rd line treatment, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to 3rd line treatment in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report

Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy, in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such

a drug's administration, the AE is reported together with the exposure during breastfeeding.

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 (e.g., 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 (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, 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 (e.g., 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.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.1. Single reference safety document

The local product label information highlighted in the appendix 3 will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The SRSD should be used by the investigator for prescribing purposes and guidance.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Not applicable

COMMUNICATION OF ISSUES

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

12. REFERENCES

- [1] Hutson TE. Targeted therapies for the treatment of metastatic renal cell carcinoma: clinical evidence. *Oncologist* 2011; 16 Suppl 2:14-22.
- [2] Motzer RJ, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584-90.
- [3] Escudier B, et al. Sorafenib in advanced clear-cell renal cell carcinoma. *New Engl J Med* 2007 Jan 11;356(2):125-34.
- [4] (Sağlık Uygulama Tebliği, 25.07.2014 tarihli değişiklik işlenmiş güncel SUT 2013)
- [5] (TUIK, Haber Bülteni, Sayı:13425, tarih:31.12.2012)
- [6] Türk Kanseri Araştırma ve Savaş Derneğinin Kanser Kayıt ve İnsidansı Çalışması.
- [7] (McLaughlin JK, et al. Epidemiologic aspects of renal cell carcinoma. *Semin Oncol.* 2006;33(5):527-533.)
- [8] <http://kanser.gov.tr/daire-faaliyetleri/kanser-istatistikleri.html>

13. LIST OF TABLES

Not applicable

14. LIST OF FIGURES

Not applicable

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

FKSI-15

EQ5D-3L

FKSI-DRS

Blood Pressure Diary

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Inlyta 1 mg product label for Turkey

Inlyta 5 mg product label for Turkey

Afinitor 5 mg product label for Turkey

Afinitor 10 mg product label for Turkey

Nexavar 200 mg product label for Turkey

Sutent 12,5 mg product label for Turkey

Sutent 25 mg product label for Turkey

Sutent 37,5 mg product label for Turkey

Sutent 50 mg product label for Turkey

Votrient 200 mg product label for Turkey

Votrient 400 mg product label for Turkey

Votrient 800 mg product label for Turkey

Torisel 25 mg/ml i.v. product label for Turkey