Study information

Title	A Retrospective Registry Based Study for Evaluating Treatment Response in Patients Targeted Treated with Metastatic Renal Cell Carcinoma (mRCC) with Sunitinib in First-line Therapy
Protocol number	A6181235
Protocol version identifier	3.0
Date	18 November 2022
Active substance	Sunitinib
Research question and objectives	Primary Objective: • Evaluation of Sunitinib treatment responses/objective response rate according to disease risk group in patients with mRCC targeted treated with Sunitinib in first-line therapy in Turkey Secondary Objectives: • Evaluation of survival and treatment response to Sunitinib treatment regimen, • Determination of factors affecting the treatment regimen change and the frequency of these factors in patients with mRCC • Determination of demographic, clinical and pathological characteristics of patients with mRCC • Determination of median duration use of patients using interferon (IFN)

Author	Assoc. Prof. PPD
Co-author	PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE-I	Angiotensin Converting Enzyme Inhibitor
AE	adverse event
AEM	Adverse Event Monitoring
ARB	Angiotensin Receptor Blockers
ARDS	acute respiratory distress syndrom
CRF	Case Report Form
CRO	Contracted Research Organization
DCT	Data Collection Tool
ECOG	Eastern Cooperative Oncology Group
FDA	food and drug administration
GPP	good pharmacoepidemiology practices
HD IL-2	high-dose interleukin 2
IEC	Independent Ethics Committee
IFN	interferon
IMDC	International Metastatic RCC Database Consortium
IQR	interquartile range
IRB	Institutional review board
LN	Lymph node
mRCC	Metastatic Renal Cell Carcinoma
MSKCC	Memorial Sloan Kettering Cancer Center
NIS	non-interventional study

RCC	Renal Cell Carcinoma
PFS	progression-free survival
SPSS	Statistical Package for Social Sciences
TKI	tyrosine kinase inhibitor
VEGF	vascular endothelial growth factor

3. RESPONSIBLE PARTIES

This study is being sponsored by Pfizer PFE İlaçları A.Ş.

Contracted research organization (CRO) of this study is Omega Araştırma Organizasyon Eğitim Danışmanlık Ltd. Şti.

This study is based on data extracted from "RCC Registry" database, which is managed by Principle Investigator PPD and owned by PPD

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD	Assoc. Prof.	PPD	PPD
PPD	PPD NIS Lead	PPD	PPD

4. ABSTRACT

A Retrospective Registry Based Study for Evaluating Treatment Response in Patients Targeted Treated with Metastatic Renal Cell Carcinoma (mRCC) with Sunitinib in First-line Therapy, dated 18 November 2022 and with version number of 3.0.

Objectives:
The aim of this study is to observe the treatment response in patients with mRCC targeted treated with Sunitinib in first-line therapy.

Primary Objective:

- Evaluation of Sunitinib treatment responses/objective response rate according to disease risk group in patients with mRCC targeted treated with Sunitinib in first-line therapy in Turkey

Secondary Objectives:

- Evaluation of survival and treatment response to Sunitinib treatment regimen
- Determination of factors affecting the treatment regimen change and the frequency of these factors in patients with mRCC
- Determination of demographic, clinical and pathological characteristics of patients with mRCC
- Determination of median duration use of patients using IFN.

This is a non-interventional, retrospective, evaluational study, based on data extracted and analyzed from the RCC Registry.

This study was designed to answer the Sunitinib treatment responses/objective response rate according to disease risk group in patients with mRCC.

All patient data in the RCC Registry, meeting all of the inclusion criteria will be included in the study.

The variables to be obtained from this study:

- Demographic information (age, sex)
- Physical measurements (height and weight measurements)
- Disease and concomitant disease history (Hypertension, Diabetes mellitus)
- Previous treatments (Angiotensin Converting Enzyme Inhibitor (ACE-I) / Angiotensin Receptor Blockers (ARB), statin)
- Age of start of Sunitinib,
- Smoking history,
- Date of diagnosis
- Surgery type (Radical nephrectomy, partial nephrectomy)

- Histopathological information
  - Pathological type,
  - Pathological stage and location,
  - T size and location
  - Fuhrman Grade,
  - Adrenal involvement,
  - Lymph node (LN) involvement,
  - Number of LNs removed,
  - Sarcomatoid feature,
- Other involvement information
- Treatment given (order of treatment given, starting date, dose, dose changes, if available)
- Discontinuation of treatment information and the reason
- Previous IFN use
- Toxicities leading dose reduction and treatment discontinuation
- Information of risk (International Metastatic RCC Database Consortium (IMDC), Memorial Sloan Kettering Cancer Center (MSKCC) subgroups)
- Performance scores (Eastern Cooperative Oncology Group (ECOG))
- Metastasis site information
- Laboratory values, if available
- Survival status

RCC Registry will be used as data source for this study and the patient data will be retrospectively recorded in the study database.

The annual disease burden in contributing centers to RCC Registry is approximately 100 patient/center, the treatment of an average of 250 patients per year is continued in the centers. Therefore, it is estimated that information of 400 eligible patients that were registered in RCC Registry from 2019 to 2022 will be included in the analysis.

The Statistical Package for Social Sciences (SPSS) 19.0 for Windows will be used for the analysis. A type-I error of less than 5% will be interpreted as statistically significant. Normality of data will be tested using the visual (histogram and probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Descriptive statistics will be expressed as numbers and percentages for categorical variables and as mean and standard deviation for normally distributed numerical variables, median and interquartile range (IQR) for non-normally distributed numerical variables. For Survival Analyses, Kaplan-Meier estimates will be calculated and for survival rate comparison of Kaplan-Meier estimates within selected categorical groups will be investigated using log rank test.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	01 September 2021	3	- Responsible parties of protocol revised.	- Principal investigators of the protocol added.
		8	- Research question and objectives revised.	- Objective of "Determination % of patients with PD-L1 positivity of 1% or more in mRCC patients." added.
		6, 9.2	- Editing data collection and milestone dates	- Changing the study starts, data collection and final study dates
2	18 November 2022	Study information, 2, 3, 4, 5, 6, 8, 9, 10, 11,	- Study information revised.	- Study title edited. - Research question and objectives revised. - Author section revised and co-author information added.
			- List of abbreviations revised.	- Abbreviations edited.
			- Responsible parties revised.	- Registry database information added.
			- Editing abstract.	- Study objectives, variables, sample size revised.

			- Editing data collection and milestone dates. - Research question and objectives revised. - Research methods revised. - Quality control revised. - Protection of human subjects information revised.	- Study timeline revised. - Objectives revised - Editing study design and study setting details as a secondary data collection. Study re-designed as a registry based study instead of collecting data by archive screening in different centers, data sources revised. - Study schedule revised according to revised milestones. - Inclusion criteria section revised for the revised study design. - Variables that will be extracted from RCC Registry revised. - Study size, data management and quality control section revised - Editing patient information/consent, ethics subject. - Editing safety language of study due to revised study type .

			- Management and reporting of adverse events/adverse reactions revised. - Principal investigators of the protocol were revised.	-The collection of data in the study design based on a structured registry rather than patient records.

6. MILESTONES

Milestone	Planned date
Start of data collection	9 January 2023
End of data collection	13 February 2023
Final study report	01 April 2023

7. RATIONALE AND BACKGROUND

Due to the widespread use of cross-sectional radiology in recent years and the increase in the frequency of renal cell carcinoma (RCC) risk factors such as smoking and obesity, RCC is increasingly common. More than 200,000 people are diagnosed with RCC each year worldwide, and nearly half die because of this reason. RCC is the 7th most common cancer in men in Turkey (1).

RCC is one of the cancers in which classical cytotoxic chemotherapies are not effective. For this reason, it is among the tumors in which the treatments targeting the immune system are mostly studied together with melanoma. However, although it has been more viable in recent years, immunotherapy in RCC is not new. The first strong data that immunotherapy is effective in RCC is based on studies of high-dose interleukin 2 (HD IL-2) and interferon. In addition, rare cases of spontaneous regression suggest that immune targeted therapies can be an effective approach in RCC. Despite the low response rates, sustainability of long-term remission with HD IL-2 in 5-10% of patients, even after discontinuation of treatment, has led to the "first line" treatment in selected patients for many years, it became the first "class" approved for use in the treatment of metastatic RCC by the Food and Drug Administration (FDA) in 1992 (2). However, due to serious toxicities such as hypotension, renal dysfunction, respiratory distress like Acute respiratory distress syndrom (ARDS), HD IL-2 could only be used in "fit" patients and in certain centers and could not be widespread.

Motzer stated in his 1996 review that "immunomodulation" may have a role in the treatment of RCC (3). However, with the understanding of the role of vascular endothelial growth factor (VEGF) in the pathogenesis of the disease, following the "cytokine" based treatments in the nineties, the 2000s have been the years when treatments targeting the VEGF "class 2" and mTOR "class 3" pathways came to the fore. Thus, since 2005, 9 agents targeting these pathways have been approved by the FDA for the treatment of metastatic RCC.

Everolimus, the mTOR inhibitor, was the first agent approved for use in patients who progressed after tyrosine kinase inhibitors (TKIs) (4). Its use was approved by the FDA in 2009 with the advantage of a progression-free survival (PFS) of 4.9 months versus 1.9 months in the placebo controlled RECORD-1 study (5). Therefore, everolimus has become

the standard arm in many randomized studies conducted in the following years. Other VEGF-based agents with shown efficacy in the second step are, in the order of being approved by the FDA; axitinib, lenvatinib and cabozantinib (6). However, despite the high response rates achieved with targeted agents, the median PFS achieved with first-line VEGF-targeted therapies varies between 8-12 months and 5-7 months in the second-level, and progression is often inevitable (7). In recent years, it has been shown that the ability of cancer cells to escape from the immune system is one of the hallmarks of cancer, and studies showing that immune therapies are effective in many tumors have begun to come one after another. As we mentioned at the beginning, RCC is one of the first tumors in which immune therapies were used.

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to observe the treatment response in patients with mRCC treated with Sunitinib in first-line therapy.

Primary Objective:

- Evaluation of Sunitinib treatment responses/objective response rate according to disease risk group in patients with mRCC treated with Sunitinib in first-line therapy in Turkey

Secondary Objectives:

- Evaluation of survival and treatment response to Sunitinib treatment regimen
- Determination of factors affecting the treatment regimen change and the frequency of these factors in patients with mRCC
- Determination of demographic, clinical and pathological characteristics of patients with mRCC
- Determination of median duration use of patients using IFN.

9. RESEARCH METHODS

9.1. Study design

This study is a non-interventional, retrospective, evaluational study based on data extracted and analyzed from the RCC Registry.

This study was designed to answer the Sunitinib treatment responses/objective response rate according to disease risk group in patients with mRCC.

9.2. Setting

Analysis for this study will be conducted on data anonimyzed and extracted from RCC Registry; time frame for this study data set is information of eligible patients that were registered in RCC Registry between March 2019 and October 2022.

RCC Registry is a data log where clinical information is recorded by inviting patients who meet the patient selection criteria according to registry protocol from 6 different centers since March 2019. In this study, RCC Registry will be used as sole data source.

The annual disease burden in contributing centers to RCC Registry is approximately 100 patient/center, the treatment of an average of 250 patients per year is continued in the centers. Therefore, it is estimated that information of approximately 400 eligible patients who were registered in RCC Registry from 2019 to 2022 will be included in the analysis.

Study ScheduleSTAGES / Timeline	**November 2022**	**December 2022**	**January 2023**	**February 2023**	**March 2023**	**April 2023**
Preparation phase and obtaining necessary approvals	X	X				
Extracting data from RCC Registry			X	X		
Data management, statistical analysis and reporting				X	X	X

9.2.1. Inclusion criteria

Data record in registry must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Being a Turkish citizen

2. Being older than 18 years-old

3. Being clinically diagnosed and treated with mRCC

4. Being treated with Sunitinib in first line

9.2.2. Exclusion criteria

Data record in registry meeting any of the following criteria will not be included in the study:

1. Patients whose treatment was initiated but excluded from follow-up for any reason.

9.3. Variables

The following variables will be extracted from RCC Registry in the scope of this study:

- Demographic information (age, sex)
- Physical measurements (height and weight measurements)
- Disease and concomitant disease history (Hypertension, Diabetes mellitus)
- Previous treatments (ACE-I / ARB, statin)
- Age of start of Sunitinib,
- Smoking history,
- Date of diagnosis
- Surgery type (Radical nephrectomy, partial nephrectomy)
- Histopathological information
    - Pathological type,
    - Pathological stage and location,
    - T size and location
    - Fuhrman Grade,
    - Adrenal involvement,
    - Lymph node (LN) involvement,
    - Number of LNs removed,
    - Sarcomatoid feature,

- Other involvement information
- Treatment given (order of treatment given, starting date, dose, dose changes, if available)
- Discontinuation of treatment information and the reason
- Previous IFN use
- Toxicities leading dose reduction and treatment discontinuation
- Information of risk (International Metastatic RCC Database Consortium (IMDC), Memorial Sloan Kettering Cancer Center (MSKCC) subgroups)
- Performance scores (ECOG)
- Metastasis site information
- Laboratory values, if available
- Survival status

9.4. Data sources

RCC Registry will be used as the sole data source for this study.

For this purpose, no Case Report Forms (CRFs) or Data Collection Tools (DCTs) will be utilized, but the RCC Registry database will be used directly. Eligible patients' data will be anonymized and extracted for analysis by the registry owner, for this study.

The RCC Registry was approved by Ankara University Ethical Committee in October 2018 and by Ministry of Health in March 2019.

9.5. Study size

In the scope of the study, RCC Registry will be screened for all patients who meets all inclusion criteria and who doesn't meet the exclusion criterion defined in the study protocol and who were treated with Sunitinib in first-line therapy for mRCC and were registered to the database between 2019 and 2022.

The annual disease burden in contributing centers to RCC Registry is approximately 100 patient/center, the treatment of an average of 250 patients per year is continued in the centers.Therefore, it is planned to include the information of approximately 400 patients whom records were registered in between 2019 and 2022 and who meet the patient selection criteria.

9.6. Data management

The below data in Registry database will be anonymized by registry administrators.

- Variables to be obtained from the Registry : Demographic information (age, sex), physical measurements (height and weight measurements), disease and concomitant disease history (Hypertension, Diabetes mellitus), previous treatments (ACE-I / ARB, statin), age of start of Sunitinib, smoking history, date of diagnosis, surgery type (Radical nephrectomy, partial nephrectomy), histopathological information and other involvement information, treatment given (order of treatment given, starting date, dose, dose changes, if available), discontinuation of treatment information and the reason, previous IFN use, toxicities leading dose reduction and treatment discontinuation, information of risk (IMDC, MSKCC subgroups), performance scores, metastasis site information, laboratory values, if available, survival status .
- This anonymized data will be transferred to the clinical database of the study in Omega CRO.
- Omega CRO will analyze this anonymized data and provide the results to Pfizer.

No individual anonymized patient data will be provided to Pfizer.

9.7. Data analysis

The Statistical Package for Social Sciences (SPSS) 19.0 for Windows will be used for the analysis. A type-I error of less than 5% will be interpreted as statistically significant. Normality of data will be tested using the visual (histogram and probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Descriptive statistics will be expressed as numbers and percentages for categorical variables and as mean and standard deviation for normally distributed numerical variables, median and interquartile range (IQR) for non-normally distributed numerical variables. For Survival Analyses, Kaplan-Meier estimates will be calculated and for survival rate comparison of Kaplan-Meier estimates within selected categorical groups will be investigated using log rank test.

9.8. Quality control

Records that meet eligibility criteria for Sunitinib in first line will be extracted from RCC Registry and anonymized by registry administrators. Extracted and anonymized data will be sent to CROs data management center. Once the anonymized data is received by CRO, data checking plan will be executed. If a problem is encountered regarding compliance with protocol or adverse events, data management department of the CRO will inform the principle investigator of the registry, and reconciliation will take place.

9.9. Limitations of the research methods

Limitation in this study is defined as not to reach enough patients data for statistical analysis.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format from RCC Registry database and contain no patient personal information.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

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

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

As this study designed as national, non-interventional, retrospective, registry based study, Observational Drug Study Guideline does not cover this study. This study will be conducted as secondary data collection from RCC Registry that has been approved by IEC and Ministry of Health. Copies of relevant IEC and Ministry of Health approvals will be forwarded to Pfizer.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP) and Declaration of Helsinki.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In no case, study results can be presented or published by the investigator without prior written consent of the sponsor, nor can study results be published by the investigator prior to the conclusion of the study.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, would be published or passed on to any third party without the prior written consent of the study sponsor.

All information concerning and relating to the study that is provided by Pfizer is considered confidential information. This confidential information shall remain the sole property of Pfizer and shall not be used for publication without express written consent of Pfizer.

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 party responsible for collecting data 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.

13. REFERENCES

1. Zhang GW, Tian X, Li Y, Wang ZQ, Li XD, Zhu CY. Down-regulation of ETS2 inhibits the invasion and metastasis of renal cell carcinoma cells by inducing EMT via the PI3K/Akt signaling pathway. Biomed Pharmacother. 2018 Aug;104:119-126. doi: 10.1016/j.biopha.2018.05.029. Epub 2018 May 15. PMID: 29772431.

2. Buchbinder EI, Dutcher JP, Daniels GA, Curti BD, Patel SP, Holtan SG, Miletello GP, Fishman MN, Gonzalez R, Clark JI, Richart JM, Lao CD, Tykodi SS, Silk AW, McDermott DF. Therapy with high-dose Interleukin-2 (HD IL-2) in metastatic melanoma and renal cell carcinoma following PD1 or PDL1 inhibition. J Immunother Cancer. 2019 Feb 18;7(1):49. doi: 10.1186/s40425-019-0522-3. PMID: 30777131; PMCID: PMC6380045.

3. Motzer RJ. New perspectives on the treatment of metastatic renal cell carcinoma: an introduction and historical overview. Oncologist. 2011;16 Suppl 2(Suppl 2):1-3. doi: 10.1634/theoncologist.2011-S2-01. PMID: 21346034; PMCID: PMC3868198.

4. Pal SK, Figlin RA. Treatment Options in Metastatic Renal Cell Carcinoma: Focus on mTOR Inhibitors. Clin Med Insights Oncol. 2010 Jun 9;4:43-53. doi: 10.4137/cmo.s1590. PMID: 20711245; PMCID: PMC2902205.

5. Buti S, Leonetti A, Dallatomasina A, Bersanelli M. Everolimus in the management of metastatic renal cell carcinoma: an evidence-based review of its place in therapy. Core

Evid. 2016 Sep 1;11:23-36. doi: 10.2147/CE.S98687. PMID: 27621699; PMCID: PMC5012611.

6. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A; RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008 Aug 9;372(9637):449-56. doi: 10.1016/S0140-6736(08)61039-9. Epub 2008 Jul 22. PMID: 18653228.

7. Basappa NS. Treatment options in advanced renal cell carcinoma after first-line treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitors. Can Urol Assoc J. 2016 Nov-Dec;10(11-12Suppl7):S242-S244. doi: 10.5489/cuaj.4292. PMID: 28096936; PMCID: PMC5215301.

8.

14. LIST OF TABLES

Not applicable.

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.