Study information

Title	Clinical Outcome Of Advanced Renal Cell Carcinoma In Taiwan, A Retrospective NHIA Database Analysis
Protocol number	A6181222
Protocol version identifier	Ver. 1
Date of last version of protocol	31, August, 2016
Active substance	Sunitinib (ATC code: L01XE04) Pazopanib (ATC code: L01XE11)
Medicinal product	Sutent® capsules 12.5mg Votrient® tablets 200mg
Research question and objectives	1. Utilization of sunitinib and pazopanib in Taiwanese patients with advanced renal cell carcinoma 2. RCC related costs of sunitinib and pazopanib in Taiwanese patients with advanced renal cell carcinoma 3. Overall survival and occurrence of hypertension of Sunitinib and Pazopanib in Taiwanese RCC Patients
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
RCC	Renal cell carcinoma
ATC	Anatomical therapeutic chemical
CIPD	Catastrophic illness patient database
ED	Emergency Department
ICD9	Classifications of Diseases-9 codes
mRCC	Metastatic renal cell carcinoma
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI index	National Cancer Institute index
NHI	National health insurance
SEER	The Surveillance, Epidemiology, and End Results Program
TKI(s)	Tyrosine kinase inhibitor(s)

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
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3. ABSTRACT

- **Title:** Clinical Outcome Of Advanced Renal Cell Carcinoma In Taiwan, A Retrospective NHIA Database Analysis

  ■ **Main author:** PPD , Professor and PPD . School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences and Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan

- **Rational and Background:** Sunitinib and pazopanib have been used to treat Taiwanese patients with mRCC for more than 5 years while the prescribing patterns, RCC-related medical costs and their effectiveness and safety profiles were not yet explored.

- **Question and objectives:** The objectives are:
  1. To identify the incidence and the prevalence of mRCC in Taiwanese population
  2. To describe the prescribing pattern of sunitinib and pazopanib in Taiwanese mRCC patients
  3. To calculate RCC-related cost in sunitinib and pazopanib users
  4. To estimate the overall survival in sunitinib and pazopanib users
  5. To evaluate the incidence of sunitinib- and pazopanib-related hypertension

- **Study design:** retrospective cohort study

- **Population:** incident Taiwanese mRCC patients during 2010 to 2014

- **Data source:** Taiwan HNI datasets and CIPD

- **Data size:** Not applicable for this study

- **Data analysis:** descriptive statistics for prescribing patterns, medical costs, overall survival and time to hypertension.

- **Milestones:** Interim report (sunitinib data only) before 30, October, 2016 and Final study report before 30, September, 2017

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
NONE					

5. MILESTONES

Milestone	Planned date
Interim report (sunitinib data only)	30, October, 2016
Final study report	30, September, 2017

6. RATIONALE AND BACKGROUND

Renal cell carcinoma comprises approximately 3.8% of all new cancers, with a median age at diagnosis of 64 years. Approximately 90% of renal tumors are RCC, and approximately 80% of these are clear cell tumors[1,2]. Analysis of the SEER database indicates that the 5-year survival rate for kidney cancer has increased over time for localized disease (from 88.4% during 1992–1995 to 91.8% during 2004–2010) and for advanced disease (from 7.3% during 1992–1995 to 12.3% during 2004–2010)[3].

Cytoreductive nephrectomy before systemic therapy is generally recommended in patients with a potentially surgically resectable primary tumor mass. According to NCCN guideline, systemic treatment is suggested for patients with metastatic disease. Interferon-alpha, interleukin, TKIs (sunitinib and pazopanib) and mTOR inhibitors (everolimus and temsirolimus) are treatments that widely used in RCC patients with metastatic disease[4].

Sunitinib and pazopanib are 2 TKIs approved to treat patients with metastatic RCC in Taiwan currently. Sunitinib was reimbursed by NHI in January, 2010 and pazopanib was reimbursed by NHI in August, 2012. In a phase 3 trial, sunitinib demonstrates longer overall survival compared with interferon-alpha plus improvement in response and progression-free survival in the first-line treatment of patients with metastatic RCC[5]. Pazopanib is a newer generation of TKI to treat RCC. Compared with sunitinib, pazopanib showed similar efficacy, but favorable safety and quality-of-life profile[6].

Although being used to treat RCC patients with metastatic disease for more than 5 years, the prescribing pattern, the RCC-related medical cost, as well as effectiveness and the safety of sunitinib and pazopanib utilization among Taiwanese population is not yet well understood. In this study, we will describe the prescribing pattern of sunitinib and pazopanib

and estimate the medical costs among users. We also aim to evaluate the survival benefits and safety of sunitinib and pazopanib in Taiwanese population.

7. RESEARCH QUESTION AND OBJECTIVES

The objectives are:

1. To identify the incidence and the prevalence of mRCC in Taiwanese population
2. To describe the prescribing pattern of sunitinib and pazopanib in Taiwanese mRCC patients
3. To calculate RCC-related cost in sunitinib and pazopanib users
4. To estimate the overall survival in sunitinib and pazopanib users
5. To evaluate the incidence of sunitinib- and pazopanib-related hypertension

8. RESEARCH METHODS

8.1. Study design

This is a retrospective cohort study using NHI datasets from January, 2004 to December, 2014. We define patients that were diagnosed with RCC with both records in CIPD and NHI. We will then identify RCC patients that were treated with TKIs (sunitinib and pazopanib) and describe the prescribing pattern, including time from the initial diagnosis to first TKI prescription, systemic treatment prior and after TKI(s), treatment duration and cumulative doses per every 3 months during treatment.

We will estimate RCC-related medical cost between sunitinib and pazopanib users based on the expenditure of claims. We will also evaluate the overall survival and the occurrence of hypertension among sunitinib and pazopanib users.

8.2. Setting

Objective 1: mRCC incidence and prevalence

We will identify patients who were newly diagnosed as RCC with NHI claims and records in CIPD. Patients who had at least one outpatient visit or admission and ED records with a primary and/or secondary diagnosis of RCC (ICD9 codes: 189, 1890 and 1899) will be

included. The RCC diagnosis will be reconfirmed by records in CIPD. The RCC diagnosis date is defined as the first RCC diagnosis record identified in the database.

We will report RCC incidence and prevalence based on the year of the diagnosis date.

Objective 2: prescribing pattern of sunitinib and pazopanib

We will describe how sunitinib and pazopanib were prescribed in Taiwanese mRCC patients with claims in NHI datasets since January 2010 to December 2014.

TKI users would be followed since the first TKI prescription to the end of the study period. We estimate the time from diagnosis date to first TKI prescription, RCC treatment prior and after TKI(s), treatment duration of TKI, average daily doses and cumulative doses per every 3 months during treatment.

Objective 3: RCC-related medical costs of sunitinib and pazopanib

We estimate direct costs that related to RCC treatments in sunitinib users and pazopanib users respectively. We will calculate RCC-related medical costs from the diagnosis date to the first dose of TKI and the cost from the first dose of TKI to the end of observation periods. All TKI users will be grouped by the initial TKI that they were prescribed.

Objective 4: the overall survival in sunitinib and pazopanib users

We will estimate the overall survival in sunitinib users and pazopanib users. The survival benefits will be described descriptively. Patients will receive follow-up from the date of the first TKI prescription to the end of study period or death. Death is defined by the record on CIPD.

Objective 5: the incidence of sunitinib- and pazopanib-related hypertension

For the risk assessment of TKI-related hypertension, we will include hypertension-free incident mRCC patients that received sunitinib or pazopanib. TKI users will receive follow-up from the date of the first prescription to the end of study period, occurrence of hypertension or death.

We will also report the changes in prescribing patterns of antihypertensive agents before and after TKI initiation among TKI users with hypertension. As blood pressure increment has been reported after 4 weeks and 10 weeks of treatments[7], we will compare the changes in prescribing pattern at 1 month, 3 months, 6 months and 1 year after TKI initiation.

8.3. Variables

Objective 1 & 2: mRCC incidence and prescribing pattern of sunitinib and pazopanib

The variables include patient baseline characteristics (age, sex, income levels, co-morbid conditions and co-medications), health resource utilization (hospital level and geography location), sunitinib and pazopanib exposures, treatment duration, persistence and cumulative doses.

Co-morbid conditions include hypertension (ICD-9 codes: 401-409, excluded 402.11, 402.91), coronary arterial diseases (ICD-9 codes: 410-414, excluded 414.1, 36.0, 36.1), diabetes mellitus (ICD-9 code: 250), dyslipidemia (ICD-9: 272) and chronic kidney disease (ICD-9: 585, 586).

We also define information about medication to treat these comorbidities. Patients will be considered as taking these medications if there were at least 2 prescriptions a year prior sunitinib/ pazopanib initiation. The medications included: beta blockers (ATC: C07), dihydropyridine calcium channel blockers (ATC: C08C, C08E, C08G, C09BB, C09Db, C09XA53 and C09XA54), non-dihydropyridine calcium channel blockers (ATC: C08D), diuretics (in all kinds of administration routes; ATC: C02L, C03, C07B, C07C, C07D, C08G, C09BA, C09DA, C09XA52 and C09XA54), angiotension converting enzyme inhibitors (ATC: C09A, C09B), angiotension receptor blockers (ATC: C09C, C09D), insulins (ATC: A10A), biguanides (ATC: A10BA, A10BD01, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15), alpha-glucosidase inhibitors (ATC: A10BF), sulfonylureas (ATC: A10BB, A10BC, A10BD01, A10BD02, A10BD04, A10BD06, A10BD14), dipeptidyl peptidase 4 inhibitors (ATC: A10BH, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13, A10BD18), thiazolidinediones (ATC: A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09,

A10BD12), antiplatelets (ATC: B01AC, C10BX01, C10BX02, C10BX04, C10BX05, C10BX06, C10BX08), anticoagulants (ATC: B01AA), statins (ATC: C10AA, C10BA, C10BX), fibrates (ATC: C10AB, C10BA03, C10BA04), bile acid sequestrants (ATC: C10AC), nicotinic acids (C10AD, C10BA01) and ezetimibe (C10AX09, C10BA02, C10BA05, C10BA06).

We will also record RCC treatments other than TKIs. These treatments/procedures are surgery (partial nephrectomy and radical nephrectomy, defined by procedure codes in NHI datasets) and systemic treatment, including interferon-α 2a (ATC code: L03AB04), interleukin-2 (ATC code: L03AC) and mTOR inhibitors (everolimus and temsirolimus, ATC code: L01XE10/L04AA18 and L01XE09, respectively).

Treatment durations of TKIs will be calculated from the date of the first TKI prescription to the last dose of the last prescription. We will compute the cumulative doses per every 3 months during the first year after TKI initiation.

All information was retrieved from the inpatient and outpatient claims from the NHI datasets.

Objective 3: RCC-related medical costs of sunitinib and pazopanib

We will calculate the direct medical costs that relate to RCC with NHI datasets. Outpatient visits and admission of the following settings will be considered to be RCC-related:

1. Claims with a diagnosis code (either primary or secondary) that indicated RCC (cost 1)
2. Urologist or oncologist outpatient visits and admissions to urology or oncology wards, regardless of the diagnosis of the claims (cost 2)

We assess the overall RCC-related medical costs by summing up cost 1 and cost 2.

Objective 4: the overall survival in sunitinib and pazopanib users

[redacted]

The variables include patient baseline characteristics (age, sex, income levels, co-morbid conditions and co-medications) and health resource utilization (hospital level and geography location).

The definitions of comorbidities and co-medications have been described previously of this section (in the statements of the objective 1 & 2).

We will define the date of death using records from CIPD.

Objective 5: the incidence of sunitinib- and pazopanib-related hypertension

Patients are considered to be newly diagnosed as hypertension after TKI(s) if there are at least 2 claims or prescriptions of antihypertensive agents that are at least 30 days apart during the follow-up period.

For hypertensive patients, we will report the antihypertensive agents that had been applied before and 1, 3, 6 months and 1 year after TKI initiation. We will also compare antihypertensive prescriptions at the different time points (before and after TKIs) for each TKI users and classify the patterns of changes into unchanged, switched, increased and decreased. Shifting to other class(es) of antihypertensive agents without changes in counts of antihypertensive medication is defined as being switched. Dosage titration and/or addition in types of antihypertensive agents received are defined as increment. Dosage tapering and/or reductions in types of antihypertensive agents received are defined as decrement.

8.4. Data sources

We will apply information from NHI datasets and CIPD to determine exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables.

8.5. Study size

This is a descriptive study and we do not know the expected number of patients eligible for the study.

8.6. Data management

We will analyze and report the results based on data availability. The results in Study Progress Report 1 and Interim Report are based on the datasets from 2004 to 2013. Because pazopanib is available since August, 2012, we acknowledge that the prescriptions of pazopanib might be limited. When NHI datasets of 2014 becomes available, supposedly at the end of 2016, we will have more information about pazopanib prescribing and a longer the follow-up period for overall survival and hypertension after TKI(s).

We will present Final Report base on the NHI datasets from 2004 to 2014.

8.7. Data analysis

Objective 1: mRCC incidence and prevalence

We will estimate the annual crude rate of mRCC incidence and prevalence from 2010 to 2014. The crude mRCC incidence/prevalence is calculated by dividing the incident/prevalence mRCC case numbers during a particular year (for example, year 2010) with the total population number at the end of that year.

We will report sex-specific and overall mRCC crude incidence/prevalence and age-adjusted mRCC incidence/prevalence.

Objective 2: prescribing pattern of sunitinib and pazopanib

We will present patient characteristics and prescribing patterns with descriptive statistics. For continuous variable, mean (SD) and median (min-max) will be both present. Proportion (%) will be present for all categorical variables.

We will also apply the Cochran-Armitage trend test to estimate the trends of sunitinib and pazopanib prescribing pattern over the observation periods.

Objective 3: RCC-related medical costs of sunitinib and pazopanib

We will assess the overall RCC-related medical cost (from the RCC diagnosis date to the first TKI prescription and TKI initiation to the end of follow-up period) and the cost during TKI treatment (from the initial TKI dose to the day that the last dose of TKI was given). We will also report the RCC-related medical cost of sunitinib users and pazopanib users during the first year of treatment separately.

We will present the mean (SD) and the median (min-max) of the medical cost.

Objective 4: the overall survival in sunitinib and pazopanib users

We will calculate the survival time from the date of the first TKI prescription to the date of death. Survival time will be presented with descriptive statistics (mean, median, minimum and maximum of survival time). We will plot the survival curves for sunitinib users and pazopanib users using Kaplan-Meier method. We will report the 1-, 2-, 3- and 4-year overall survival among sunitinib users. 1- and 2-year overall survival of pazopanib users will be reported.

Objective 5: the incidence of sunitinib- and pazopanib-related hypertension

A sub-cohort of incident mRCC cohort that included TKI users without a previous history of hypertension will be used to estimate the risk of hypertension. Time to hypertension will be presented with descriptive statistics. We will plot the cumulative incidence curves for sunitinib users and pazopanib users. We will report the 1-, 3-, 6-months and 1-year cumulative incidence for hypertension among sunitinib and pazopanib users.

For hypertensive patients, we will report changes in the antihypertensive agent prescribing patterns before and 1, 3, 6 months and 1 year after TKI initiation.

[redacted]

8.8. Quality control

Annual incident RCC patient counts in Taiwan Cancer Registry will be the external referent for the estimates with our protocol.

8.9. Limitations of the research methods

We believe that the records regarding RCC diagnosis in CIPD to be valid because a diagnosis of RCC in NHI datasets needs a histologic or image confirmation to be reported in the Registry for Catastrophic Illness Patient Database. However, we cannot exclude the possible misclassification for non RCC patients as RCC patients, as vice versa, because the information regarding the validity of the diagnosis codes that will be used to identify patients with RCC is not available.

Under the infrastructure of NHI criteria, sunitinib and pazopanib are indicated for mRCC patients and patients could only using reimbursed-sunitinib or pazopanib after approvals. Sunitinib and pazopanib users are mRCC patients for sure but for patients without any systemic treatment, we cannot identify the metastatic disease status. We thus cannot have an estimation on percentage of TKI users among mRCC population.

It is unknown whether non-users had chosen to pay out of pocket for sunitinib and/or pazopanib in NHI datasets. The percentage of TKI users will thus be underestimated. For a patient who received 50mg sunitinib once daily for on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2), the cost per every 3 months would be more than 290,000 NTD. For a pazopanib user who received an 800 mg daily dosage, the cost would be more that 220,000 NTD per every 3 months. Since sunitinib and pazopanib are very expensive, the number of patients who would have been able to afford sunitinib and pazopanib are deemed very limited.

8.10. 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.

Informed consent is not required for this study as it is a secondary data collection study without identified subjects data.

9.2. Patient withdrawal

Not applicable

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 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) 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.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes unstructured data (e.g., narrative fields in the database) that will be converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, 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 (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available* and adverse events are not reportable as individual AE reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Final study report and/or manuscript will be developed for this study.

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

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6. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *The New England journal of medicine.* 2013;369(8):722-731.
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13. LIST OF TABLES

None

14. LIST OF FIGURES

None

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable