NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Treatment patterns with targeted therapies in metastatic renal cell carcinoma (mRCC) in Sweden – A retrospective analysis of data from national registries.
Protocol number	A6181234
Protocol version identifier	Version 2.0
Date	13 April 2021
Active substance	L01XE04 (sunitinib) L01XE17 (axitinib)
Medicinal product	Sutent, Inlyta
Research question and objectives	The objectives of this study are to investigate treatment patterns and outcomes for sunitinib and axitinib mRCC patients in a nationwide population-based setting in Sweden.
Author	PPD PhD PPD Sweden PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse event monitoring
ATC	Anatomical Therapeutic Chemical
CDR	Cause of Death Register
CI	Confincence interval
CRF	Case report forms
DCT	Data collection tool
GPP	Guidelines for Good Pharmacoepidemiology Practices
ICD	International Classification of Diseases
IEC	Independent ethics committee
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan Meier
mRCC	metastatic renal cell carcinoma
mTOR	mammalian target of rapamycin
NBHW	National Board of Health and Welfare
NI	Non interventional

NIS	Non interventional study
NPR	National Patient Register
OS	Overall Survival
PDR	Patient Drug Register
PIN	personal identification number
RCC	Renal cell carcinoma
SCR	Swedish Cancer Register
SPC	Summary of Product Characteristics
TKI	tyrasine kinase inhibitor
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor
YRR	your reporting responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	April 13, 2021	8.2	Change from 30 days grace period to 90 days in base case, when calculating treatment duration	Too many of the patients with a switch from 4:2 to 2:1 are lost with a 30 day grace period. The rational to move to 90 days is that the likelihood of having a longer gap is higher than that the patients get a treatment in the gap (it also has to be a treatment that we cannot see, we capture all oral treatments, which makes it even more unlikely)
2	April 13, 2021	8.1, 8.2	Time period for data collection modified; end date for data collection is changed to 31 December 2019	Access to data from SoS

5. MILESTONES

Milestone	Planned date
Milestone	**Planned date**
Start of data collection	15 December 2020
End of data collection	31 March 2021
Final study report	31 March 2021

6. RATIONALE AND BACKGROUND

Renal cell carcinoma (RCC) accounts for approximately 2% of all cancers worldwide, with the highest rates observed in North America, Australia and Europe [1]. In Western, Northern and Southern Europe, a total of over 87,000 patients are diagnosed with RCC each year, leading to an estimated 33,000 deaths [2]. RCC is often asymptomatic, or associated with non-specific symptoms such as fatigue, weight loss, fever and anemia [3]. Many patients present with advanced or unresectable disease, and around 30% of patients treated by nephrectomy for localized disease will relapse [4].

The worldwide and European annual increase in RCC incidence is approximately 2%, however in Denmark and Sweden, a continuing decrease has been observed during the last two decades [5]. In 2016, there were 1267 new cases of renal malignancy (excluding the renal pelvis) reported in Sweden, of which a majority was above 65 years of age [6]. The Swedish RCC death ratio reaches approximately 550 cases per year.

With the advent of modern targeted therapies, the prognosis of patients with metastatic RCC (mRCC) has improved. From a median survival of about a year, the new therapies reached a survival of over 2 years [7, 8]. These agents include the multitargeted receptor tyrosine kinase inhibitors (TKI) sunitinib (Sutent®, Pfizer Inc.), sorafenib (Nexavar®, Bayer HealthCare/Onyx Pharmaceuticals), pazopanib (Votrient®, GlaxoSmithKline Inc),

axitinib (Inlyta®, Pfizer Inc), cabozantinib (Cabometyx®, Ipsen), tivozanib (Fotivda®, EUSA Pharma), lenvatinib (Kisplyx®, EISAI), the vascular endothelial growth factor (VEGF) ligand-binding monoclonal antibody bevacizumab (Avastin®, Genentech, Inc.) and the mammalian target of rapamycin (mTOR) kinase inhibitors temsirolimus (Torisel®, Pfizer Inc) and everolimus (Afinitor®, Novartis).

Great progress in the area of immunotherapy with nivolumab (Opdivo®, BMS) and the combinations nivolumab/ipilimumab (Opdivo®/Yervoy®, both BMS), pembrolizumab/axitinib, (Ketruda®/Inlyta®, MSD and Pfizer) and avelumab/axitinib (Bavencio®/Inlyta®, Merck and Pfizer) has also been made in recent years that will benefit patients with metastatic RCC. In such revolutionized treatment landscape, where immunotherapy-based combinations are the new standard of care, TKI monotherapy maintains a role in the treatment of certain mRCC patients who are not suitable for immunotherapy [9]. Notably, TKI monotherapy is still today in Sweden the recommended treatment for the subgroup of patients with favourable prognosis [10].

To date, limited information on real-world treatment patterns such as dosing and time from initiation to discontinuation or drug survival exist in the mRCC setting. For other disease areas drug survival is commonly analyzed in Europe and in the United States, see Hetland et al (2010) for an analysis of tumor necrosis factor (TNF) inhibitors [11].

Wahlgren et al (2013) and Lindskog et al (2017), to some extent investigate mRCC treatment patterns in the Swedish setting but in a more general manner [12, 13]. Both these studies demonstrate a statistically significant improved survival for the Swedish mRCC patients treated with targeted therapies compared to no or a hormonal/chemotherapeutic intervention. In Redig et al (2019) the improved survival from modern targeted therapy is put in relation to the increased cost [14].

During the last years studies investigating effects on safety and outcomes from different dosing schedules have been published, focusing on sunitinib and mostly based on smaller

selected patient populations. Bracarda et al (2017) carried out a critical review of published studies until then and found that although the studies had a low level of evidence, the results indicated that the 2:1 schedule improved tolerability compared with the 4:2 schedule. Regarding efficacy no definitive conclusions could be drawn due to the methodologic limitations of the available studies [15].

Another example of study in this area is Bracarda et al (2015) where a retrospective sample of 249 mRCC patients is analysed. The authors found a longer drug survival for patients that moved to a modified 2:1 schedule, both compared to patients that started on a 2:1 schedule and patients that did not modify the dosing scheme. They also found that patients who moved to a 2:1 schedule experienced an improved safety profile compared to during the initial 4:2 schedule [16]. Crumbaker et al (2018) investigated 63 Australian mRCC patients and found that patients starting on a 2:1 dosing schedule had a drug survival that was longer than the overall survival (OS) times seen in the trials using the 4:2 schedule [17]. Boegemann et al (2018) evaluated efficacy and safety regarding sunitinib treatment modification in first line treatment of mRCC and found that in addition to mitigating adverse events (AEs), sunitinib treatment modification may help improve efficacy outcomes by prolonging treatment duration [18].

There is a need for additional research in this area and so far no studies based on Swedish data has been carried out. The current study aims at analyzing sunitinib drug survival and overall survival for Swedish mRCC patients treated in first line, and investigate how these outcomes are affected by different dosing schedules. The study will also investigate axitinib drug survival and overall survival in second line. Safety will not be analysed in this study due to the characteristics of the available data.

Sweden has a unique opportunity in its large number of health data registers run by the National board of Health and Welfare (NBHW). These long-history, high-quality, registers constitute the foundation of a very successful Swedish research tradition in the field of clinical epidemiology, and cover health data in the entire population that is easily

accessible by researchers. From July 2005, the Prescribed Drug Register (PDR), covers date and amount of medication prescribed and dispensed to the patient. It also stores personal identification number, which enables linkage to other registers. The National Patient Register (NPR) covers inpatient care episodes and outpatient visits, including information of procedures (i.e. surgery) and diagnosis codes. The Swedish Cancer Register (SCR) (since 1958) contains tumor and pathology data from all patients diagnosed with cancer in Sweden. The national Cause of Death Register (CDR) (1961) contain information on the cause of death.

Combining data from these four registers creates an opportunity to derive patterns of duration of treatment and overall survival for the full Swedish mRCC cohort.

7. RESEARCH QUESTION AND OBJECTIVES

The present study is an explorative retrospective study investigating treatment patterns and outcomes for sunitinib and axitinib mRCC patients in a nationwide population-based setting in sweden.

In more detail the primary objective is to:

- Investigate time to treatment discontinuation (treatment duration) for first line treatment with sunitinib for different treatment schedules: 4:2 (4 weeks on/2 weeks off) and 2:1 (2 weeks on/1 week off).

The secondary objectives are to:

- Investigate overall survival (OS) for first line treatment with sunitinib, for different treatment schedules, 4:2 (4 weeks on/2 weeks off) and 2:1 (2 weeks on/1 week off).
- For second line treatment with axitinib, investigate time to treatment discontinuation (treatment duration) and OS.

8. RESEARCH METHODS

8.1. Study design

To address the research objectives, the study will be carried out as a national retrospective population-based register study based on data from the NBHW.

Based on the study objectives, the primary endpoint in this study is:

- Time to treatment discontinuation in first line sunitinib patients. Time to event measure from index date to discontinuation of treatment, from 01 July 2005 to 31 December 2019 (assessed from index date up to 180 months). This will be investigated using Kaplan-Meier analysis.

8.2. Setting

The data used for the analyses includes all patients aged ≥ 18 years with at least one filled prescription of an oral targeted therapy relevant for treating mRCC registered in the Swedish Prescribed Drug Register between 01 July 2005 (there is no data available in the register before this date) and 31 December 2019. The Anatomical Therapeutic Chemical (ATC) codes for the oral drugs relevant for treating mRCC are the following: L01XE04 (sunitinib), L01XE05 (sorafenib), L01XE11 (pazopanib), L01XE17 (axitinib), L01XE10 (everolimus), L01XE26 (cabozantinib), L01XE34 (tivozantib), L01XE29 (lenvatinib). Selecting patients based on dispensed prescriptions ensure that all patients that have prescriptions on the relevant drugs are included in the analyses. The first identified prescription date will correspond to the patient's index date that is relevant for capturing the age.

The PDR does not provide any information on mRCC, which is the area of interest in this study. The analysis therefore combines the PDR, the SCR and the NPR with the aim to identify the mRCC cohort. The patients identified in the PDR that also are identified in the SCR with the International Classification of Diseases and Related Health Problems

(ICD)-7 diagnosis codes I800 or I809 and ICD-10 codes C64.0 and C64.9 from 01January 2000 until 31 December 2019;excluding ICD-7 code I801 (cancer of the renal pelvis) will be included in the analysis set.

The mRCC cohort derived above will then be further restricted into two different analysis sets that will be used to carry out the analyses.

- Analysis Set 1: patients treated with sunitinib in the first line mRCC setting
- Analysis Set 2: patients treated with axitinib in the second line mRCC setting

Analysis Set 1 will be derived in the following way, from the full mRCC cohort described above, individuals will be selected that have sunitinib as the first filled prescription (the earliest date) of the relevant drugs: (sunitinib), L01XE05 (sorafenib), L01XE11 (pazopanib), L01XE17 (axitinib), L01XE10 (everolimus), L01XE26 (cabozantinib), L01XE34 (tivozantib), L01XE29 (lenvatinib), and L03AB (cytokines medication). L03AB used to be a common treatment for this patient group in the beginning of the investigated period and is therefore needed to identify the correct treatment line.

Analysis Set 2 will be derived in the following way, from the full mRCC cohort described above, individuals will be selected that have axitinib as the second filled prescription (the earliest date) of the relevant drugs: (sunitinib), L01XE05 (sorafenib), L01XE11 (pazopanib), L01XE17 (axitinib), L01XE10 (everolimus), L01XE26 (cabozantinib), L01XE34 (tivozantib), L01XE29 (lenvatinib). In addition, to secure that axitinib is used as a second line treatment (i.e. not third line), L03AB (cytokines medication) is not allowed to have been dispensed before axitinib.

8.2.1. Study definitions

Time to treatment discontinuation

Time to treatment discontinuation, or persistence, is defined as the difference between the start and end-dates for a treatment episode (accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group) regardless of reason for discontinuation. The start date for a treatment episode is defined as the date of first dispensed package and the end date is defined as the date of the last dispensed package with the same ATC code, plus the number of days that package, as well as accumulated medicine (see more details below), is intended to cover. This end date is overruled if there is a new filled prescription of another relevant ATC code or death happens before this, then either of these dates represents the end date. If no end of prescribed supply is recorded, data is censored at latest available date in data.

Time to treatment discontinuation will be calculated while allowing for patient accumulation of medicine. The number of days covered by the dispensed volume will be determined based on information in the Summary of Product Characteristics (SPC), the volume of dispensed drug, and for sunitinib in first line also by using the prescriber's dosing instruction on the prescription available in the PDR.

For sunitinib, the treatment is provided in 4 + 2 (or 2 + 1) week cycles, where there is a two-week break in treatment after four weeks of continuous drug intake. Hence, the assumed number of days covered by each filled prescription will be adjusted accordingly (i.e. the 14 or 7 days corresponding to the cycle will be added).

When previously supplied dosing instructions cease to be specified, it is assumed that the daily dosage continues in accordance with the previous treatment pattern. Should there be a completeness issue with the variable containing dose information; the recommended average dose per day according to the SPC for each product will be used instead.

For axitinib, the treatment is provided in 4 week cycles, without breaks in between. The analysis relies on data on information relating to dispensed pack size and strength;

Axitinib is available in pack size of 56 tablets, and in strength 1, 3, 5 and 7 mg. Given the dosing recommendations in SPC, a dispensed pack with the strength 1 mg is assumed to last 14 days, whereas the other packs are assumed to last 28 days.

Patients will be allowed to have gaps between filled prescriptions, but once such a gap exceeds 90 days (the "grace period") they will be defined as non-persistent. As the Swedish pharmacy system allows patients to refill prescriptions when two-thirds of the previous refill has been consumed (e.g. after two months of a three-month prescription) patients may accumulate large amounts of medication. To account for that, patients will be permitted to accumulate medication from overlapping prescriptions and use it to cover future gaps between filled prescriptions. Figure 1 depicts the effect the grace period and accumulation of medication may have on persistence with the help of scenario 1 and 2.

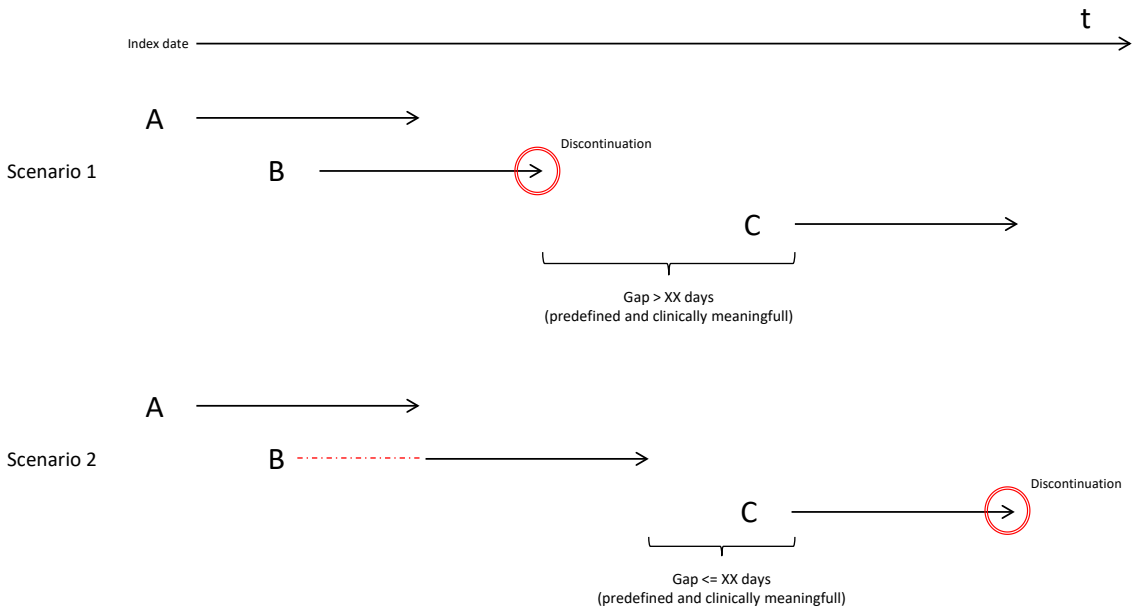

Figure 1. Grace period and accumulation of medication

Both scenarios in Figure 1 showcase the same subject having filled three prescriptions (A, B and C) of the index treatment. The "grace period" is set to 90 days. In scenario 1, the 2nd prescription (B) is filled before the initial prescription (A) has run out. In scenario 1, the subject is not allowed to accumulate medication and therefore the subject will discontinue and stop being persistent with medication when the supply from prescription B has run out. In scenario 2, accumulation is allowed enabling filled prescription B to close the gap between B and C so that it is equal to or less than 90 days. The subject is now persistent with medication until the supply from filled prescription C runs out. Hence, both the definition of grace period and allowing for accumulation of medication will affect persistence. To investigate the impact of the length of the grace period a sensitivity analysis with a grace period of 60 and 120 days will be carried out.

Dosing Schedule

The different treatment schedules for sunitinib that will be analysed (starting on 4:2, starting on 2:1 and starting on 4:2 and then switching to 2:1) will be defined based on the dosing instruction provided by the prescriber and will be reviewed manually (the variable DOSER in the Swedish Prescribed Drug Register). In the case no instruction is provided at the start of the treatment, a 4:2 dosing scheme (recommended dose in the SPC) will be assumed. When previously supplied dosing instructions cease to be specified, it is assumed that the daily dosage continues in accordance with the previous treatment pattern. A patient is defined as having swithed from a 4:2 to a 2:1 schedule if the dosing instruction clearly indicates this. Other sunitinib dosing schedules than the ones described above will not be included in the analysis but will be included in descriptive statistics.

Overall survival

Overall survival is defined as the time (number of days) from the start of the treatment (the date of the first dispensed package, of sunitinib or axitinib) until the date of death as documented in the Cause of Death Register. If no death is recorded, data is censored at latest available date in data.

8.3. Variables

Table 1 summarizes an overview of the variables needed for the outcomes and study variables of the proposed analyses.

Table 1. Overview of study variables

Variable	Role	Data source(s)	Operational definition
Total number of sunitinib 1L patients	Outcome	Prescription Register	Number of sunitinib users with at least one filled prescription (in total and per year over time)
Number of sunitinib 1L 4:2 schedule users	Outcome	Prescription Register	Number of sunitinib users that started on a 4:2 schedule and never had a modification in the schedule (total and per year over time)
Number of sunitinib 1L 2:1 schedule users	Outcome	Prescription Register	Number of sunitinib users that started on a 2:1 schedule and never had a modification in the schedule (total and per year over time)
Number of sunitinib 1L patients that was switched from a 4:2 schedule to a 2:1 schedule	Outcome	Prescription Register	Number of sunitinib users that started on a 4:2 shedule and later was swithed to a 2:1 schedule, in total and per year over time

Total number of axitinib second line patients	Outcome	Prescription Register	Number of axitinib 2L users with at least one filled prescription (in total and per year over time)
Gender	Baseline characteristics	Prescription Register	Male/Female (binary)
Age	Baseline characteristics	Prescription Register	Age will be defined as age at the date of first filled prescription of relevant mRCC medication (continuous; years).
Year of treatment initiation	Baseline characteristics	Prescription Register	Defines the year the treatment was initiated.
Region	Baseline characteristics	Prescription Register	County council of the prescribing physician at first prescription date (categorical), see Table 6 in Annex 3
Time to treatment discontinuation	Outcome	Prescription Register	Time from date of first filled prescription to the end of the prescribed supply, or prescription of other ATC code or death if either of these happen before (details in Section 8.2).
Overall survival	Outcome	Cause of Death Register, Prescription Register	Time from date of first filled prescription of the relevant drug to date of death (number of days) where death is defined as all-cause death; If no date of death is recorded, data is censored at latest available date in data.

8.4. Data sources

The Swedish administrative registries offer high quality data for research with nation-wide coverage and close to complete data for most available variables. Patient-level data from each register is available for research purposes and individual patients can be linked between all data sets via the personal identifier given to all citizens. The administrative registers to be used in this study are summarized in Table 2.

Table 2. Overview of data sources

Type of register	Name	Data holder	Start of data collection	Variables
Patient register	Swedish National Patient Register	NBHW	1987/2001	Diagnosis codes (ICD-9/10), dates, procedure codes and types of visit
Prescription register	Swedish Prescribed Drug Register	NBHW	2005	Dispatch dates, type of medication (ATC codes), strengths and dosages
Information on mortality	Swedish Causes of Death Register	NBHW	1961	Date and cause of death (ICD-10)
Cancer register	Swedish Cancer Register	NBHW	1958	Morphological diagnosis of the tumour (ICD-O/3)

The individual data will be extracted from the PDR and merged with the data from the SCR and the NPR using the personal identification numbers (PINs). The data extraction will cover all patients aged ≥ 18 years with at least one filled prescription of an oral targeted therapy relevant for treating mRCC registered in the Swedish Prescribed Drug Register between 01 July 2005 (there is no data available in the register before this date) and 31 December 2019. The Anatomical Therapeutic Chemical (ATC) codes for the oral drugs relevant for treating mRCC are the following: L01XE04 (sunitinib), L01XE05 (sorafenib), L01XE11 (pazopanib), L01XE17 (axitinib), L01XE10 (everolimus), L01XE26 (cabozantinib), L01XE34 (tivozantib), L01XE29 (lenvatinib).

The PDR does not provide any information on mRCC, which is the area of interest in this study. The analysis therefore combines the PDR, the SCR and the NPR with the aim to identify the mRCC cohort. The patients identified in the PDR that also are identified in the SCR with the International Classification of Diseases and Related Health Problems (ICD)-7 diagnosis codes I800 or I809 and ICD-10 codes C64.0 and C64.9 from 01 January 2000 until 31 December 2019; excluding ICD-7 code I801 (cancer of the renal pelvis) will be included in the analysis set.

The two analysis sets described in Section 8.2 will be derived and used in the analyses.

8.5. Study size

An estimated 17,000 to 18,000 patients are diagnosed with RCC between 01 January 2000 and 31 December 2019, approximately 1,000 patients per year. Of these patients, an estimated 4,000 to 5,000 are registered with at least one relevant dispensed prescription for mRCC. Approximately 1,000 of these patients are estimated to have received sunitinib as first line treatment during the investigated period. For axitinib, approximately 300 patients are estimated to have received it in second line during the investigated period.

8.6. Data management

In broad terms, the data management for this study will be initiated by the creation of a broad study population including patients with at least one filled prescription of (L01XE04 (sunitinib), L01XE05 (sorafenib), L01XE11 (pazopanib), L01XE17 (axitinib), L01XE10 (everolimus), L01XE26 (cabozantinib), L01XE34 (tivozantib), L01XE29 (lenvatinib)) identified in the PDR. A study key including the selected cases personal identifiable number (PIN) and a randomly created study identification number will be created by the NBHW. The data that is being extracted from the NBHW is described in Table 3 below.

Based on the data extracted from the NBHW two completely pseudonymized analytical dataset comprising all observations and variables required for the planned analyses will be compiled, see details in Section 8.2. The analytic datasets will be person-level.

All data management will be performed by ICON. A data validity quality check is always undertaken before data management is started to verify that all variables are complete and to create logs for corrupt or ambiguous data entries. Data will be analyzed using SAS version 9.2 or later.

One of the variables included in the material (DOSER) is in text format, requiring human review. The information in DOSER will be reviewed for Analysis Set 1 (patients indentified with sunitinib treatment in first line) and used to identify the initial dosing schedule and changes in the dosing schedule. The information in DOSER will be quantified in the following way. DOSER will be lifted out to an excel sheet together with study IDs and drug dispense dates. DOSER will be manually reviewed and dummy variables indicating the dosing schedule and dates for changes in the dosing schedule will be created. When the manual coding is done, the data will me merged with the original dataset based on the study IDs.

Table 3. Variables extracted from the NBHW

Variable	Explanation	Data source(s)
ICD7	ICD-7 code	Swedish Cancer Register
ICD9	ICD-9 code	Swedish Cancer Register
ICDO10	ICD-O/2-10	Swedish Cancer Register
ICDO3	ICD-O/3	Swedish Cancer Register
ALDER	Age at diagnosis	Swedish Cancer Register
M	Spread of tumor at diagnosis, distant metastases	Swedish Cancer Register
N	Spread of tumor at diagnosis, Lymph nodes	Swedish Cancer Register
DIADAT	Date of RCC diagnosis	Swedish Cancer Register
DODSDAT	Date of death	Swedish Cancer Register
DODSDATN	Date of death numeric	Swedish Cancer Register
KON	Gender	Swedish Cancer Register
SJUKHUS	Hospital where diagnosis was set	Swedish Cancer Register
DODSDAT	Date of death	Swedish Cause of Death Register
ALDER	Age at visit	National Patient Register
AR	Year of visit	National Patient Register
MVO	Medical focus area	National Patient Register
SJUKHUS	Hospital	National Patient Register
DIAGNOS	Diagnosis	National Patient Register
HDIA	Main diagnosis	National Patient Register
KON	Sex	National Patient Register

INDATUMA	Date for start of visit	National Patient Register
OP	Surgery	National Patient Register
UTDATUMA	Date for end of visit	National Patient Register
VTID	Duration of care	National Patient Register
ALDER	Age at the end of the year	Swedish Prescribed Drug Register
ARBLAN	The region of the prescribing clinic	Swedish Prescribed Drug Register
FDATE	Prescription date	Swedish Prescribed Drug Register
EDATE	Dispense date	Swedish Prescribed Drug Register
ANTAL	Number of packages	Swedish Prescribed Drug Register
DOSER	Dosing instructions	Swedish Prescribed Drug Register
EXPLAN	Region/County of dispensing pharmacy	Swedish Prescribed Drug Register
FVARUNR	Dispensed drug goods number	Swedish Prescribed Drug Register
ATC	ATC code	Swedish Prescribed Drug Register
PRODUKT	Name of product	Swedish Prescribed Drug Register
FORPS	Package size	Swedish Prescribed Drug Register
STYRKALF	Strength of the product	Swedish Prescribed Drug Register
STYRKAENHET	Unit of the strength	Swedish Prescribed Drug Register
KON	Gender	Swedish Prescribed Drug Register

8.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A DCT is required and should be completed for each included patient. The completed original DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. ICON shall ensure that the DCTs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

ICON has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCTs must be signed by ICON staff or by an authorized staff member to attest that the data contained on the DCTs are true. Any corrections to entries made in the DCTs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the DCTs must match those charts.

8.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, ICON agrees to keep all study-related records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), copies of all DCTs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by ICON according to local regulations or as specified in the vendor contract, whichever is longer. ICON must ensure that the records continue to be stored securely for so long as they are retained.

If ICON becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless ICON and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

ICON must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

8.7. Data analysis

An overview of the planned analyses are presented in this section. In general, the study is descriptive and does not involve hypothesis testing. Any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Time-to-event analyses will be carried out using standard Kaplan-Meier methods. Kaplan-Meier survival functions will be estimated with relevant events as failure. Time-to-event tables

and Kaplan-Meier curves will be presented. Log-Rank tests will be used to assess differences across cohorts. In addition, to explore potential determinants of persistence /drug survival and to adjust for differences across cohorts, semi-parametric cox-proportional hazard models will be deployed based on different covariates.

Relevant events for this study include:

- Time to treatment discontinuation
- Death

Time-to-event tables will present:

- Failed/Censored n (%).
- Median time to event.
- 95% confidence intervals of median.
- The 25th and 75th percentiles (q1 and q3).
- Min and max.
- n at risk by unit.
- Time point estimates and 95% Confidence Intervals (CI)by unit.

As described in Section 8.2 the analyses will be carried out based on two analysis sets. Analysis Set 1 consists of all patients indentified with sunitinib as the first line treatment. Analysis Set 2 consists of all patients indentified with axitinib as the second line treatment.

The Table 4 below displays the output from the time to treatment discontinuation and overall survival analyses that will be carried out based on Analysis Set 1. The output will be presented for three different dosing schemes of interest, patients that started on a 4:2 schedule and that did not switch, patients that started on a 4:2 schedule but later switched to a 2:1 schedule and patients that started on a 2:1 schedule and did not switch. Output will also be presented as Kaplan Meier (KM) curves.

To explore potential determinants drug survival and to adjust for differences across cohorts, semi-parametric cox-proportional hazard models will be deployed based on the following covariates: age, gender, year of treatment initiation, region.

Table 4. Time to treatment discontinuaton and OS, first line treatment with sunitinib

	L01XE04 Started on 4:2 schedule, no switch N=xxx	L01XE04 Started on 4:2 schedule, switch to 2:1 schedule N=xxx	L01XE04 Started on 2:1 schedule N=xxx
Censored n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Failed n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Survival time (Unit)			
Median (KM)	xx.x	xx.x	xx.x
95% CI of median (KM)	xxx.x , xxx.x	xxx.x , xxx.x	xxx.x , xxx.x
Q1, Q3 (KM)	xxx.x , xxx.x.	xxx.x , xxx.x.	xxx.x , xxx.x
Min , Max	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x
Kaplan-Meier survival point estimates – n at risk, % (95% CI)			
1 unit	x, x.xx (x.xx,x.xx)	x, x.xx (x.xx,x.xx)	x, x.xx (x.xx,x.xx)
2 unit	x, x.xx (x.xx,x.xx)	x, x.xx (x.xx,x.xx)	x, x.xx (x.xx,x.xx)
.	.	.	.
.	.	.	.
.	.	.	.
n units	x, x.xx (x.xx,x.xx)	x, x.xx (x.xx,x.xx)	x, x.xx (x.xx,x.xx)

The Table 5 below displays the output from the time to treatment discontinuation and overall survival analyses that will be carried out based on Analysis Set 2. Output will also be presented as KM curves.

To explore potential determinants drug survival and to adjust for differences across cohorts, semi-parametric cox-proportional hazard models will be deployed based on the following covariates: age, gender, year of treatment initiation, region.

Table 5. Time to treatment discontinuation and OS, second line treatment with axitinib

	L01XE All 2L patients N=xxx
Censored n (%)	xx (xx.x)
Failed n (%)	xx (xx.x)
Survival time (Unit)	
Median (KM)	xx.x
95% CI of median (KM)	xxx.x , xxx.x
Q1, Q3 (KM)	xxx.x , xxx.x
Min , Max	xx.x , xx.x
Kaplan-Meier survival point estimates – n at risk, % (95% CI)	
1 unit	x, x.xx (x.xx,x.xx)
2 unit	x, x.xx (x.xx,x.xx)
.	.
.	.
.	.
n units	x, x.xx (x.xx,x.xx)

8.8. Quality control

Data to be used in this study will be extracted from the registers managed by the NBHW and will be of the highest quality. The SCR has nearly 100% completeness and the coverage for inpatient data is almost 100% and nearly 80% for outpatient data.

Data will be ordered through a so-called research request, assessed by the NBHW after ethical approval of the study protocol. Data will be released on an individual basis but with a serial number instead of a social security number, thus preventing individual patients from being identified. Data will be treated with privacy and according to the Swedish Personal Data Act. It is the responsibility of the NBHW to ensure completion of, and to review and approve all the data, and to verify that data is verified to source data.

Quality control of data extraction will be done by reviewing of critical variables. Variables will be checked against the delivery specification from the NBHW. Errors will be listed, rectified, and sent to NBHW for correction. Further, the errors will be rectified in the analysis database. Pfizer will perform all programming of the final analysis data set, study database. Data management at Pfizer is tracked so that data editing, i.e. correction, and other data corrections in the preparation of the analysis data sets will be summarized.

The original data extraction from NBHW, or any copy, are the sole property of Pfizer and should not be made available, without written permission from Pfizer, in any form to third parties except for authorized representatives of Pfizer or appropriate authorities.

8.9. Limitations of the research methods

The retrospective design entails a risk of bias in the analyses, especially selection and misclassification bias. Furthermore, information on medication not dispensed on prescription (medication administered in a hospital) is not available at the NBHW. This will have as a consequence that potentially not all patients treated with oral targeted mRCC drugs are included in the analysis. Selecting patients based on dispensed prescriptions and a registered RCC diagnosis might have the consequence that some included patients also suffer from other malignancies for which they were treated with one of the specified drugs. However, we

believe that risk to be small. Insights from previous studies using this type of data (Wahlgren et al (2013) and Lindskog et al (2017)) will help us handle this in the best way possible. One additional limitation that concerns the definition of treatment line is that the data only allows us to evaluate the chronological order of received treatments, but no data on disease progression is available.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information

Data will be presented on an aggregate level and will not be possible to track individual patients.

The variable DOSER will go through manual review, data is unstructured data that require human review.

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.
To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the vendor contract and applicable privacy laws.

9.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

9.3. 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.

This study will be sent to the Swedish Ethical Review Authority for approval.

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) and Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Structured Data Analysis

This study involves structured data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.
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.

Human Review of Unstructured Data

In this study the analysis is based on one variable from the NBHW that is unstructured and that required human review. This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the DCT and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event

Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibility (YRR) Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results in this study is planned to be reported in an abstract, conference presentation and at least one manuscript that will be sent to a scientific journal for review and publication.

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 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.

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 3. ADDITIONAL INFORMATION

Table 6. Region codes

County name	County code
Region Stockholm	01
Region Uppsala	03
Region Sörmland	04
Region Östergötland	05
Region Jönköpings län	06
Region Kronoberg	07
Region Kalmar län	08
Region Gotland	09
Region Blekinge	10
Region Skåne	12
Region Halland	13
Region Västra Götaland	14
Region Värmland	17
Region Örebro	18
Region Västmanland	19
Region Dalarna	20

Region Gävleborg	21
Region Västernorrland	22
Region Jämtland Härjedalen	23
Region Västerbotten	24
Region Norrbotten	25