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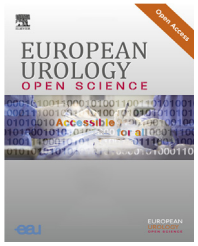

Trial Protocol

Design and Rationale of the Outcomes Database to Prospectively Assess the Changing Therapy Landscape in Renal Cell Carcinoma Registry: A Multi-institutional, Prospective Study of Patients with Metastatic Renal Cell Carcinoma

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Abstract

Introduction and hypotheses: The Outcomes Database to prospectivelY aSSEss the changing TherapY landscape in Renal Cell Carcinoma (ODYSSEY RCC) Registry is a large, nationally representative prospective registry of patients with metastatic renal cell carcinoma (mRCC) that aims to provide a real-world picture of longitudinal clinical management and patient experiences that impact clinical outcomes. The primary goal of this study is to understand the cancer management and health-related quality of life in patients with mRCC in routine real-world clinical practice in the USA.

Design: This is an observational, phase 4 study with planned enrollment of up to 800 patients aged ≥19 yr with mRCC in the USA. Patients will be identified through electronic health record (EHR) data from the PCORnet network of sites for care received at collaborating sites. A unique aspect of the study is the multiple data sources that will be linked to the EHR data. These include: (1) Medicare claims data, (2) laboratory results, (3) tissue specimens, (4) radiographic images, and (5) patient-reported outcomes, physicians' treatment selection, and discontinuation surveys.

Protocol overview: We created a novel data resource that can inform patient care. Investigators have the opportunity to use these to study novel research questions after submitting an ancillary proposal and upon approval of the executive committee. Limitations include the potential for selection bias, residual confounding, and missing information.

Summary: The ODYSSEY Registry will provide an advanced data resource that can examine numerous clinical questions related to patient and physician choice, and support methodological research related to omics and artificial intelligence.

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Patient summary: Cancer medications and treatments are changing rapidly. Collecting data on real-world clinical practice and patient-answered questionnaires will help us better understand cancer management and health-related quality of life while receiving metastatic renal cell carcinoma–specific treatment.

1. Introduction and hypotheses

Renal cell carcinoma (RCC) is among the ten most common cancers in the USA, with estimated annual cases of >82 000 and attributed to >14 000 deaths in 2023 [1]. Patients with metastatic renal cell carcinoma (mRCC) can vary widely in their tumor histology, age, and clinical presentations, with survival ranging from a few months to decades. Such range in outcomes is rarely represented in clinical trial populations. Multivariable prognostic models have been based on patients undergoing systemic treatment and have helped define patient populations into those with favorable-, intermediate-, and poor-risk disease with corresponding survival [2,3].

The clinical landscape of therapy for mRCC is evolving rapidly, with new approvals of tyrosine kinase inhibitors (TKIs) and immune-oncology (IO) agents alone or in combination for untreated patients with mRCC (Fig. 1) [4–9]. Recent data have already changed historical paradigms, with some treatment indications now based on risk stratification [10]. Furthermore, changing treatments in the first-line setting will undoubtedly affect the outcomes of patients treated with subsequent therapies in unknown ways, thereby creating new knowledge gaps. Despite this success, key knowledge gaps remain. Importantly, the longitudinal changes in health-related quality of life (QOL) and symptom burden of patients with mRCC initiated on these new IO-based regimens outside of an interventional clinical trial are poorly understood. Patient-reported outcomes (PROs) can measure the endpoints but are rarely captured in a systematic manner. In lieu of randomized controlled trials (RCTs), which can be impractical at times, a prospective multicenter observational cohort study can describe the association between different treatment patterns and outcomes in the real-world setting. These can also help better understand the biological mechanism that impact outcomes in patients. The clinical characterization of patients with mRCC has largely been defined by general prognostic factors such as performance status, hemoglobin level, neutrophil and platelet counts, and calcium level, which are not based on tumor pathogenesis or genetic/molecular profiles [2,3]. Addressing the evidence gap for how real-world patients change symptomatically with treatment combinations and sequences over time is a pressing unmet need. Head-to-head comparison studies of these various treatments are impractical and unlikely to clarify what first- and second-line approach will yield the best outcomes for patients. These analyses will advance hypotheses worthy of comparative effectiveness trials and add preliminary data to previously unstudied settings, thereby addressing another key evidence gap.

However, the burden on individual sites to prospectively transcribe these longitudinal data into an electronic database has become increasingly difficult to prioritize with staffing constraints. Therefore, we designed this registry to minimize the longitudinal burden of data collection on sites in order to maximize accrual and control costs. In this manu-

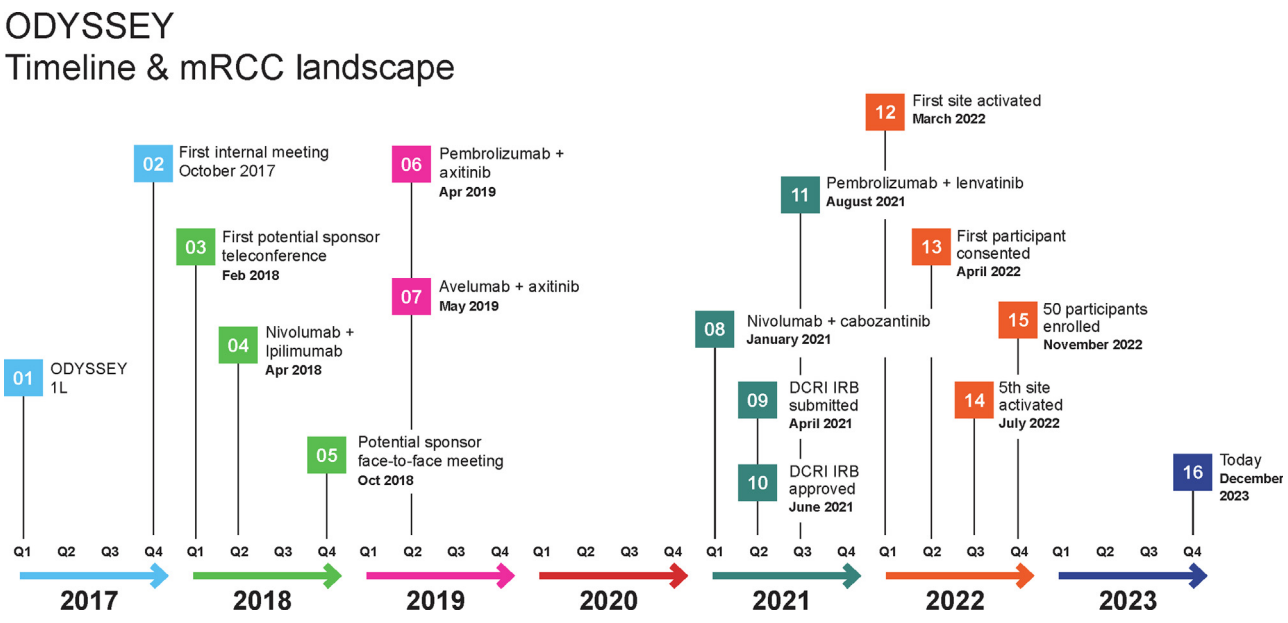

Fig. 1 – Timeline of mRCC landscape and ODYSSEY development. 1L = first line; mRCC = metastatic renal cell carcinoma; ODYSSEY = Outcomes Database to prospectivelY aSSEss the changing TherapY landscape.

script, we describe the design and rationale for a multi-institution, observational registry of patients with mRCC that includes both passive (ie, secondary collection of treatment outcomes and survival) and active (ie, blood draws, surveys, and PROs) data collection. This registry, called the Outcomes Database to prospectivelY aSSEss the changing TherapY (ODYSSEY) Registry, will provide a real-world picture of longitudinal clinical management and patient experiences associated with clinical outcomes in mRCC.

The primary goal of this study is to understand cancer management and health-related QOL in patients with mRCC in routine real-world clinical practice in the USA, including both community and academic treatment settings. Primarily, the study will evaluate patient experience through collection of PROs through the NCCN-FACT Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19) and Functional Assessment of Cancer Therapy—General (FACT-G). The study will also collect and assess information on the therapies used such as first-line treatment selection, treatment sequence and duration, drivers of physician selection, and discontinuation of therapies. Secondary goals of this study include quantifying endpoints such as the time to discontinuation of mRCC treatment, identifying patterns of clinical management in the real-world setting of patients with mRCC on various treatment regimens, and evaluating overall survival of patients with mRCC. The secondary outcomes of interest include first- and subsequent-line management choices, dosing, dose holds, time to next treatment, early discontinuation, reason for physician treatment selection and discontinuation, and healthcare utilization.

2. Design

2.1. Governance and working groups

ODYSSEY has a governance structure to guide study operations and use of data. ODYSSEY has working groups that work synergistically with the Executive Committee, the Clinical and Data Coordinating Center (Duke Clinical Research Institute [DCRI]), and the Scientific Oversight Committee (study team, clinical and PCORnet investigators, patient and advocates, and nonvoting industry funders). The Executive Committee oversees all aspects of ODYSSEY and is composed of the principal investigators and key senior staff of DCRI. Working groups are composed of investigators, study staff, and other scientists and clinicians within the ODYSSEY community. The study was approved by the Duke University Health System Institutional Review Board. The study was registered on clinicaltrials.gov (https://clinicaltrials.gov/study/NCT04919122).

ODYSSEY investigators, collaborators, and industry funders may propose ideas for independent or collaborative ancillary studies that leverage data from ODYSSEY. The proposed project will be reviewed by the executive committee of ODYSSEY, potential investigators, and applicable working groups for review and comments. If the ancillary study is considered feasible and in accordance with the overall goal and objectives of ODYSSEY, the executive committee will approve the ancillary study proposal.

2.2. Study design

This is an observational, phase 4 study with planned enrollment of up to 800 patients with mRCC in the USA. Patients will be identified through care received at collaborating sites using electronic health record (EHR) data through the PCORnet network of sites (details below). The ODYSSEY Registry received institutional review board approval in June 2021. The first site was activated in March 2022 and the first participant was consented in April 2022 (Fig. 1).

2.3. Study participants

Eligible participants include individuals aged 19 yr or older at the time of informed consent with a diagnosis of mRCC with <6 wk of first-line systemic therapy for mRCC. Surgery and radiation therapy are permitted. Prior neoadjuvant and adjuvant therapy for non-mRCC is also permitted. Patients currently not on systemic therapy and being observed (eg, active surveillance) are permitted. Participants are ineligible if they are being treated for metastatic solid tumors other than mRCC. Noncytotoxic oral agents for adjuvant or maintenance therapy of other cancers are permitted. Patients will also be excluded if they do not intend to undergo follow-up care at a study site within PCORnet.

Participants will undergo consent and baseline assessments, including optional research blood collection and processing, by the study site team. Subsequent follow-up with be coordinated centrally by the coordinating center for outcomes (see Table 1). Every 3 mo, a retrospective complication sweep of all linked databases will be done. The intent of this sweep is to capture all clinically important events such as hospitalizations (eg, grade 3–5 cardiac and infectious adverse events for which a patient is hospitalized [not exhaustive]). We will also capture surgical interventions and radiation therapy in the linked databases (Fig. 2). As these events will be collected retrospectively and in the absence of the treating physician's input as well as other pertinent information, we will not be able to assess the causation of adverse events. However, in compliance with the Food and Drug Administration guidelines, study site investigators will be responsible for reporting serious and unanticipated adverse events. Patients may be on active surveillance or a formal treatment regimen. Participation in this study is not intended to change the routine management that patients receive, as determined by their treating clinicians; all management decisions such as the type and timing of disease monitoring are at the discretion of the treating physician and patient. This approach will introduce heterogeneity of treatments within the cohort, thereby permitting exploration of outcomes associated with different treatment patterns and sequences.

2.4. Site selection

Sites were selected by identifying medical centers with medical oncologists treating patients with kidney cancer and participating in PCORnet. The goal was to allow for a diverse source population for the study including diversity in age, race/ethnicity, urban and rural population, socioeconomic status, and geographic regions.

Table 1 – Schedule of data collection

Event	Screen/initial visit 1	Every 3 mo in years 1–2	Every 6 mo until progression on first-line therapy	Every 6 mo after year 2 (until year 3)	At least annually	End of follow-up
Informed consent	×					
Review inclusion/exclusion criteria	×					
Baseline history/PE	×					
Tumor/prior treatment history	×					
Baseline laboratory tests	×					
Enquiry on availability of archival tissue or fresh biopsy [a]	×					
Blood biomarkers [b]	×					
Enquiry on availability of existing imaging biomarkers [c]	×					
Concomitant medications	×	×		×		×
Update of RCC treatment		×		×		×
Routinely collected lab values	×	×		×		×
Physician treatment questionnaires	×		×			
Patient-reported Outcomes: FACT-G, FKSI-19	×	×		×		×
Health resource utilization, pain scale	×	×		×		×
Voils medication adherence tool		×		×	×	
Complication sweep [d]					×	×

ctDNA = circulating tumor DNA; FACT-G = Functional Assessment of Cancer Therapy—General; FKSI-19 = Functional Assessment of Cancer Therapy Kidney Symptom Index-19; mRCC = metastatic RCC; PBMC = peripheral blood mononuclear cell; PE = physical examination; RCC = renal cell carcinoma.

[a] Archival tissue specimen or optional biopsy if archival tissue is not available—assess for availability at screening only; tissue will not be collected until a later time point in the study due to epitope degradation on stored slides.

[b] Plasma for ctDNA and cytokines, PBMCs, and serum for metabolites. Blood can be drawn up to 6 wk after enrollment or until first-line therapy begins, whichever occurs first.

[c] Patient will be consented for collection and these will be collected retroactively, as budget permits.

[d] Includes hospitalizations, as well as surgeries, procedures (eg, ablation), or radiation therapy for mRCC management.

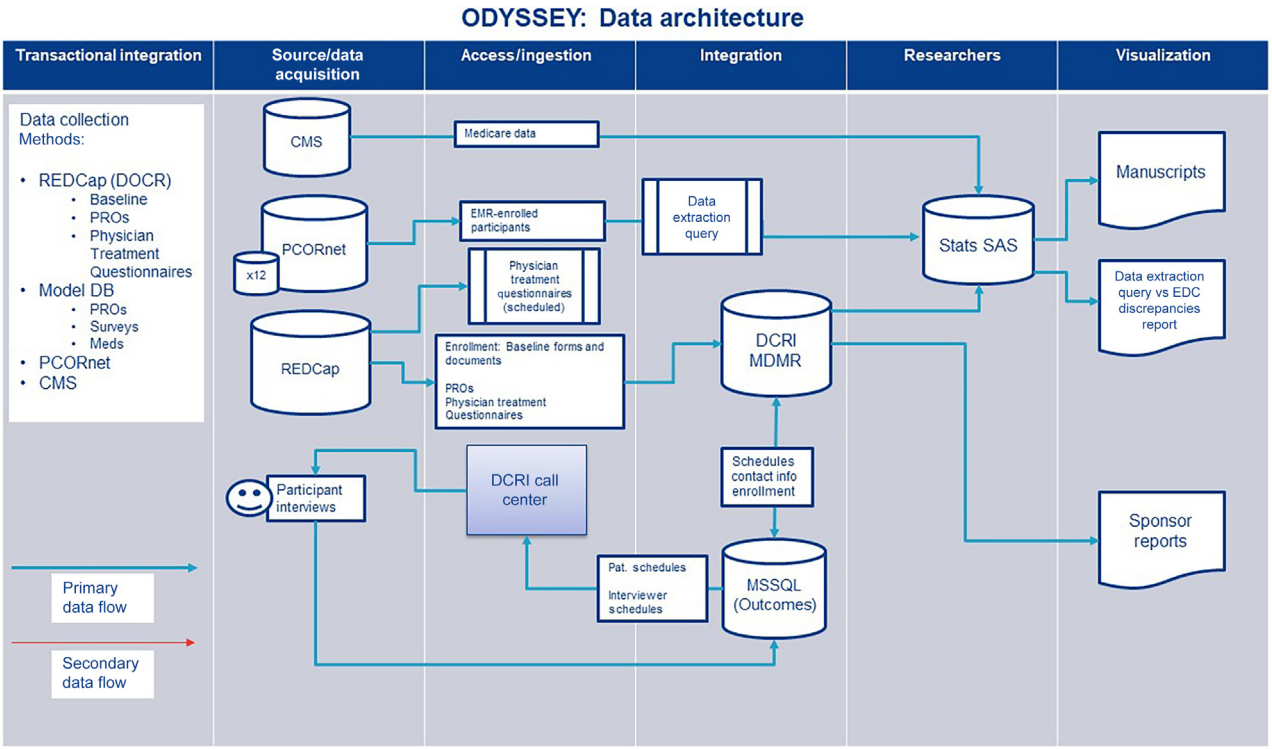

Fig. 2 – Data linkage and flow. DB = database; DCRI = Duke Clinical Research Institute; EMR = electronic medical record; ODYSSEY = Outcomes Database to prospectivelY aSSEss the changing TherapY landscape; Pat. = patient; PRO = patient-reported outcome.

3. Protocol overview

3.1. Data sources

We will use multiple data sources (Fig. 3). We will leverage PCORnet to prospectively identify patients and collect data from across the country from a network of health systems to evaluate management practices for mRCC. With web-enabled data collection, information on new interventions will be captured seamlessly, allowing for examination of early adoption patterns. In addition to PCORnet, for Medicare eligible patients, we will leverage Medicare claims data to identify therapies, diagnoses, and outcomes that occur outside of the PCORnet network.

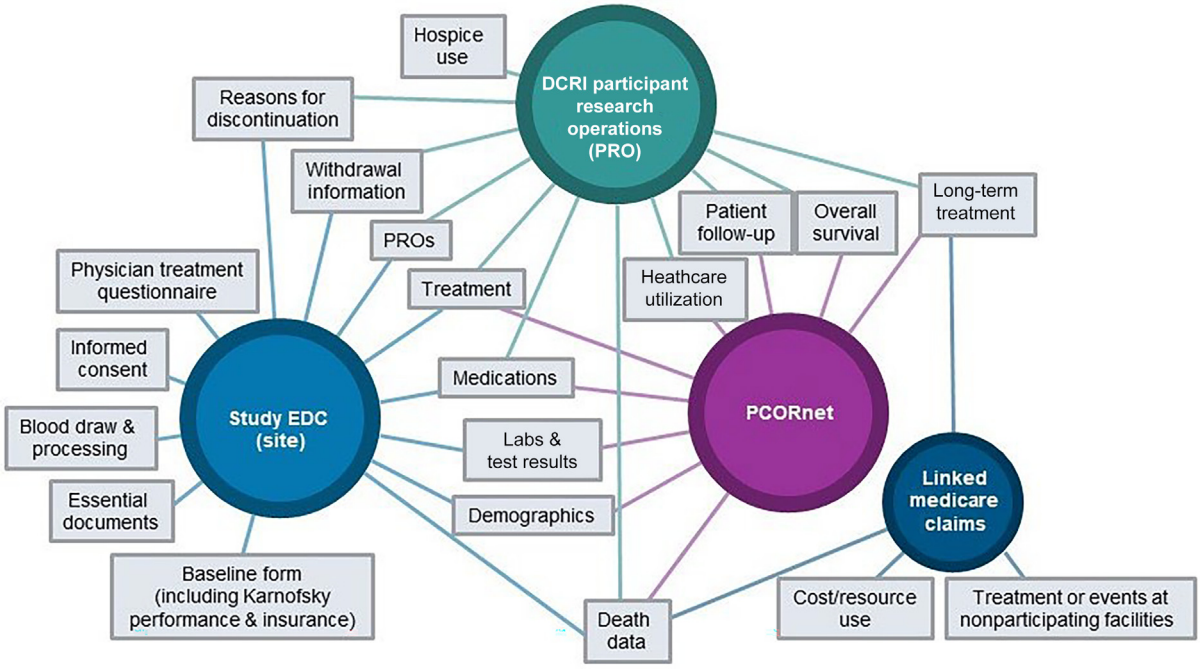

Fig. 3 – Data sources. DCRI = Duke Clinical Research Institute; PRO = patient-reported outcome.

3.2. *PCORnet*

PCORnet is a distributed research network of >60 health systems that facilitates multisite research while allowing each participating organization to maintain physical and operational control over their data. Each of PCORnet's partners securely collects and stores their data in data centers within their own institutions. As information is often recorded in different ways across institutions within the network, PCORnet's common data model provides an opportunity to organize their clinical data in the same format.

3.3. *Medicare claims*

Medicare provides health insurance for 97% of Americans aged 65 yr and older, and provides detailed claims data, including health care utilization and costs. In the ODYSSEY study, patients with fee-for-service Medicare insurance will have their Medicare claims data linked to the EHR data from PCORnet sites. Of note, our analysis will also include Medicare part D data (oral prescription drugs). The median age of patients at diagnosis of RCC is 64 yr; therefore, it can be anticipated that over half of our study population will be Medicare eligible and that roughly one-third of the total study population will be able to have Medicare claims data analyzed.

3.4. *Data elements*

Information collected at study visits include informed consent, demographics, baseline medical history, tumor characteristics, medication orders, dispensing, and administration, laboratory results, procedures, and PROs (Table 2).

3.5. *Biospecimens*

Metastatic RCC is a heterogeneous disease with wide variation in genetic, genomic, and molecular profiles. Understanding intersections between germline and somatic variations within each of these clinical subtypes of disease is critical to enrichment strategies for future targeted therapy development. The ODYSSEY study will prospectively collect serum, plasma, germline DNA, circulating tumor DNA, and peripheral blood mononuclear cells (PBMCs) from patients at baseline and at the time of disease progression on their therapies, in order to characterize the disease heterogeneity in the various clinical phenotypes of disease. Plasma will be collected for circulating free DNA analysis. Plasma will be analyzed for, but not limited to, exosomes, microRNAs, and cytokines and angiokines that correlate with treatment response or clinical outcomes that may have clinical utility. PBMCs will be collected for RNA and germline DNA analyses. Serum will be collected and analyzed for metabolites.

Table 2 – Data sources and linkages across different datasets

Domain	CDM (s)	CMS	Patient	Physician	EDC
Demographics	×	×			×
Diagnoses	×	×			×
Procedures	×	×			×
Patient-reported outcomes			×		×
Medication orders	×				×
Medication dispensing	×	×			×
Medication administration	×	×	×		×
Laboratory results	×				×
Tumor characteristics [a]					×
Specific details related to treatment protocols					×
Biospecimen information					×
Radiographic assessments [a]					×
Physician treatment questionnaires				×	×

CDM = common data model; EDC = electronic data capture.
[a] Retrospective and captured only if additional funding is obtained.

3.6. Patient-reported information (references for PRO instruments)

PROs collected include the FKSI-19, Pain Numeric Rating Scale, and FACT-G [11–13]. The FKSI-19 is a continuous measure of participant QOL and will be assessed on each participant before treatment, every 3 mo for 2 yr, and then every 6 mo for up to 36 mo after study entry. The FACT-G is a 27-item questionnaire designed to measure four domains of health-related QOL (ie, physical, social, emotional, and functional well-being) in cancer patients. The FACT-G and Pain Numeric Rating Scale will be measured at the same frequency as the FKSI-19 (Table 1).

3.7. Physician treatment questionnaire

There are little empirical data enumerating the reasons for treatment selection and discontinuation in mRCC. In our previous prospective observational Metastatic Renal Cell Carcinoma (MaRCC) registry, we developed a physician treatment questionnaire to record the reasons for treatment initiation and reason for treatment discontinuation [14]. The questionnaire was modified, based on our experience in MaRCC Registry, for use in ODYSSEY.

4. Statistical analysis

This is a prospective observational study with a total of up to 800 patients to be recruited from approximately 17 ODYSSEY RCC sites within a 21-m period. The study sample size was determined to support an analysis of the primary endpoint—FKSI-19—and the key secondary endpoint of the time to treatment discontinuation. As described in detail in the study protocol, we determined that a sample of 800 participants would provide 80% power to detect clinically meaningful differences in the mean FKSI-19 score (3–3.75 points) comparing patient subgroups (eg, IO/IO vs IO/TKI), with sample allocation ratios varying from 1:1 (equal group sizes) to 1:4 (20% of the sample in one group and 80% in the other) at the conventional two-sided alpha of 5% [15,16]. Our estimates for the key secondary treatment discontinuation outcome assumed that 800 participants would be accrued over 1.75 yr, with 1 yr of follow-up per patient. Based on these assumptions and a 10% censoring probability, 800 patients provide $\geq$80% power to detect at least a 35% increase in the risk of treatment discontinuation (hazard ratio = 1.35) over an expected 50% at 1 yr assuming sample allocation ratios ranging from 1:1 to 1:4 and two-sided alpha of 5%, under usual assumptions regarding exponential event times. To be sure, we will follow participants beyond 1 yr through passive data collection from PCORnet and Medicare claims.

5. Summary

The rapidly changing landscape for mRCC therapy, including five new front-line combinations in the past 5 yr, necessitates flexible and adaptable systems of collecting data on cancer management and health-related QOL in patients with mRCC in real-world clinical practice. Addressing the evidence gap for how real-world patients with mRCC symptomatically change with treatment combinations and sequences over time is a pressing unmet need.

While the traditional "gold standard" approach to understanding novel therapies has been an RCT, the RCTs that led to the approval of these five regimens are limited. These all had a common comparator arm, sunitinib, which is no longer the standard of care, and followed patients across one line of therapy only. Furthermore, all these trials were conducted in slightly different time frames and geographic distributions. By definition, patients not on therapy were excluded. In contrast, the ODYSSEY study will capture treatments across multiple lines of therapy, even those that have not been approved at the time of study design, as well as patients not receiving systemic therapy (ie, active surveillance). For example, data from our prior prospective observational study (MaRCC Registry) demonstrated that active surveillance occurs frequently in real-world clinical practice, and appears to be a safe and appropriate alternative to immediate systemic therapy in select patients; our data are now referenced in the National Comprehensive Cancer Network guidelines for kidney cancer [17].

Prospective observational studies have the potential to address many of the known limitations of RCTs. A novel aspect of the ODYSSEY study is the use of PCORnet and Medicare data to minimize data collection burden on sites. This allows subsequent follow-up to be centrally coordinated by the coordinating center; thus, it is less resource intensive than an RCT.

Limitations to prospective observational studies, such as ODYSSEY, include the potential for a selection bias if ODYSSEY participants are different from the broader mRCC population. To address this, we have capped the proportion of patients in active surveillance and treated in the first line with any one regimen. Other potential limitations include incomplete adjustment for confounders and the potential for missing information. However, notwithstanding these potential limitations, we believe that ODYSSEY will be a unique, rich, and valuable resource for patients, health care providers, researchers, industry sponsors, regulatory bodies, and payers. The ODYSSEY study is well positioned to examine the evolving landscape of mRCC management from a patient-centric point of view, which also captures elements not studied in clinical trials, such as reasons for physician management decisions.

Author contributions: Nrupen A. Bhavsar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bhavsar, George, Harrison, Scales, Zhang.
Acquisition of data: Ward, Jabusch, Lampron.
Analysis and interpretation of data: Troy, Bhavsar, Harrison, George.
Drafting of the manuscript: Bhavsar, George, Harrison.
Critical revision of the manuscript for important intellectual content: Bhavsar, George, Harrison, Scales, Zhang.
Statistical analysis: Troy.
Obtaining funding: None.
Administrative, technical, or material support: Ward, Jabusch.
Supervision: None.
Other: None.

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