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A prospective multicenter evaluation of initial treatment choice in metastatic renal cell carcinoma prior to the immunotherapy era: The MaRCC Registry experience

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A Prospective Multicenter Evaluation of Initial Treatment Choice in Metastatic Renal Cell Carcinoma Prior to the Immunotherapy Era: The MaRCC Registry Experience

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Abstract

The Metastatic Renal Cell Carcinoma Registry provides prospective data on real-world treatment patterns and outcomes in patients with metastatic renal cell carcinoma (mRCC). A total of 376 patients with mRCC and no prior systemic therapy were included in this study. This report describes initial real-world treatment patterns. Physician emphasis on efficacy over quality of life and toxicity suggests more data and education are needed.

Introduction: The Metastatic Renal Cell Carcinoma (MaRCC) Registry provides prospective data on real-world treatment patterns and outcomes in patients with metastatic renal cell carcinoma (mRCC). **Methods and Materials:** Patients with mRCC and no prior systemic therapy were enrolled at academic and community sites. End of study data collection was in March 2019. Outcomes included overall survival (OS). A survey of treating physicians assessed reasons for treatment initiations and discontinuations. **Results:** Overall, 376 patients with mRCC initiated first-line therapy; 171 (45.5%) received pazopanib, 75 (19.9%) sunitinib, and 74 (19.7%) participated in a clinical trial. Median (95% confidence interval) OS was longest in the clinical trial group (50.3 [35.8-not reached] months) versus pazopanib (39.0 [29.7-50.9] months) and sunitinib 26.2 [19.9-61.5] months). Non-clear cell RCC (21.5% of patients) was associated with worse median OS than clear cell RCC (18.0 vs. 47.3 months). Differences in baseline characteristics, treatment starting dose, and relative

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dose exposure among treatment groups suggest selection bias. Survey results revealed a de-emphasis on quality of life, toxicity, and patient preference compared with efficacy in treatment selection. **Conclusion:** The MaRCC Registry gives insights into real-world first-line treatment selection, outcomes, and physician rationale regarding initial treatment selection prior to the immunotherapy era. Differences in outcomes between clinical trial and off-study patients reflect the difficulty in translating trial results to real-world patients, and emphasize the need to broaden clinical trial eligibility. Physician emphasis on efficacy over quality of life and toxicity suggests more data and education are needed regarding these endpoints.

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Introduction

Beyond a desire for delayed time to disease progression and survival, little is known about initial treatment selection and factors that influence the choice of treatment by oncologists for patients with advanced cancer.[1] Treatment selection is especially important in circumstances where multiple treatment options exist and individual comorbidities and treatment goals vary, as is the case for patients with metastatic renal cell carcinoma (mRCC). Prospective randomized controlled studies, as well as US Food and Drug Administration (FDA) drug approvals, have formed the basis for many clinical guidelines and treatment pathways, which are presumably followed by physicians. However, even within guidelines, such as those of the National Cancer Center Network (NCCN), there may be multiple treatment options and, further, little guidance about exactly when to start or stop treatment. To what extent physicians follow guidelines, and to what extent adherence to guidelines matters in terms of outcomes, remains unknown. These factors will become even more relevant to understand with the availability of newer treatment options in the first-line setting and beyond.

For mRCC, there have been a significant number of new FDA-approved treatments since December 2005, involving targeted agents against vascular endothelial growth factor (VEGF) including tyrosine kinase inhibitors (TKIs), the VEGF receptor, mammalian target of rapamycin, and monoclonal antibodies that target programmed cell death protein 1 and its ligand 1 or cytotoxic T-lymphocyte-associated protein 4, as well as more recently, some combinations of these drugs.[2] The increasing number of therapeutic options may result in greater practice variability and further reliance on clinical judgment in choosing initial treatment. Which factors influence physician selection of one treatment approach over another in clinical practice is unknown.

Characteristics of patients with mRCC enrolled in clinical trials can often differ from those in the real-world setting, resulting in potential challenges in generalizing to a broader population.[3,4] In fact, many real-world patients would have been ineligible for clinical trials of systemic therapies, for reasons that include presence of non-clear cell histology, functional impairment, and brain metastases.[3,5] Current knowledge of real-world treatment patterns and clinical outcomes in patients with mRCC is based on data from retrospective studies. These are typically based on medical, pharmacy, or billing records as well as registries, that are usually not designed for research purposes, although the International Metastatic RCC Database Consortium is a notable exception. This type of retrospective data may miss important information about the factors influencing physician treatment selection and other factors that might have influenced disease outcomes.

The Metastatic Renal Cell Carcinoma (MaRCC) Registry is a US-based, nationally representative, prospective observational study of patients with mRCC.[6] The goals of the current analysis are to describe initial real-world treatment patterns for patients included in the MaRCC study, the primary reasons for physicians' management decisions, and dosing patterns in patients initiating therapy, as well as treatment outcomes.

Materials and Methods

Study Population

The MaRCC study is a prospective observational cohort study that enrolled 505 patients with mRCC across academic and community sites in the US. The study design and methodology have been previously described.[6] Briefly, patients were eligible if they were 18 years of age or older with treatment-naïve mRCC. Patients who had surgery, radiation therapy, or prior neoadjuvant or adjuvant therapy for non-mRCC disease and those not receiving systemic therapy but currently under observation were eligible. Patients were excluded if they were treated for active malignancies other than mRCC unless all systemic therapy was completed at least 3 months prior to enrollment. All study participants provided written informed consent. The study was approved by the Duke University School of Medicine Institutional Review Board (IRB) and central or local IRBs for each participating academic or community site.

Selection of Cohorts and Data Elements

This analysis includes all patients in the MaRCC Registry who initiated first-line therapy for mRCC between March 24, 2014 and July 11, 2018, either at the time of enrollment or after an initial period of surveillance. The treatments used were those that were appropriate and available at the time of enrollment. Patients for whom active surveillance was selected as the initial management strategy have been described separately.[7] Some of the patients included in this analysis were started on first-line treatment after a period of initial surveillance. Information collected at baseline included demographic characteristics, tumor and prior

treatment history, laboratory tests, Eastern Cooperative Oncology Group performance status (ECOG PS), physician treatment selection survey (reasons for starting and stopping therapy, or not initiating first-line therapy), and patient-reported outcomes (Functional Assessment of Cancer Therapy, Kidney Symptom Index 19, and Functional Assessment of Cancer Therapy – General). Information collected at subsequent visits included laboratory tests, performance status, physician treatment discontinuation survey, and patient reported outcomes. Patients were followed for overall survival (OS) until death and censored at the earliest date of either death, study discontinuation, or end of study data collection on March 13, 2019.

Statistical Analysis

Descriptive statistics were used to summarize demographic and baseline characteristics. Wilcoxon two-sample rank-sum and chi-square tests were used to assess differences between first-line therapy and no-therapy groups in continuous and categorical variables, respectively. Kaplan-Meier curves and estimates were used to summarize time-to-event outcomes, which included treatment failure and death; the curves were stratified by first-line treatment group. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 505 patients were enrolled in the MaRCC Registry from both academic and community sites between March 24, 2014, and December 22, 2016. This paper considers all 376 patients in the MaRCC Registry who initiated first-line therapy for mRCC and met inclusion criteria. The study disposition is shown in Supplementary Figure 1. Among these, 287 (76.3%) patients started first-line therapy as the initial treatment strategy and 89 (23.7%) started first-line therapy after a period of deferred systemic therapy, defined as patients who the treating physician deemed as being under active surveillance initially but who started systemic therapy >90 days after the start of active surveillance.

Table 1 describes the baseline demographics for this analysis. The first-line therapy cohort was 71.0% men with a median age of 62.0 years. The age distribution was similar in men and women. Of the 376 patients receiving first-line therapy, 320 (85.1%) received initial treatment with standard of care pazopanib or sunitinib, or participated in a clinical trial (Table 1). Pazopanib was the most commonly used first-line treatment (n = 171, 45.5%), followed by sunitinib (n = 75, 19.9%). Among the 295 (78.5%) patients with clear cell histology, 142 (48.1%) received pazopanib, 66 (22.4%) participated in a clinical trial, and 49 (16.6%) received sunitinib. Among the 81 (21.5%) patients with non-clear cell histology, pazopanib and sunitinib were the most commonly prescribed treatments (29 [35.8%] and 26 [32.1%] patients, respectively), and 10.8% participated in a clinical trial. Dosing patterns of first-line pazopanib and sunitinib demonstrated that a smaller proportion of patients started at the recommended full-dose treatment in the pazopanib group (67.8%) compared with the sunitinib group (90.7%). Furthermore, dose reductions were observed in both groups. In the pazopanib group, 33.9% required dose reduction and 28.0% in the sunitinib group. Some patients may have also had changes in dosing schedule, though this data was not collected.

Overall, 74 (19.7%) patients participated in a clinical trial of first-line therapy. Patients in the clinical trial group were younger (median age, 60.0 years), while patients in the pazopanib group were older (median age, 65.0 years), as compared with the overall cohort. Notably, a greater proportion of clinical trial patients had an ECOG PS of 0 (60.8%) than those treated with off-study therapy (34.1%), and the majority of the clinical trial patients had clear cell histology (89.2%). There was a broad range of first-line systemic therapies in the 'Other' category, with the most common being high-dose interleukin-2 (5.3%) and temsirolimus (3.2%). Figure 1A compares the four major first-line treatment groups in terms of time to treatment failure (TTF), which is defined as time from initiation of first-line treatment to discontinuation of that therapy. The clinical trial group had the longest median (95% confidence intervals [CI]) TTF at 8.0 (5.2-12.0) months. Median TTF was similar in the remaining groups; in the 'Other' category median TTF was 5.0 (3.2-7.6) months, while in the pazopanib and sunitinib groups it was 4.6 (3.4-6.7) and 5.6 (2.9-7.7) months, respectively.

All treating physicians completed a survey to understand the reasons for specific treatment selections in the first-line setting (Table 2). The most common primary reason cited for each of the 376 patients for first-line treatment selection was likelihood of clinical benefit, specifically benefit in terms of OS and/or progression-free survival (PFS) (n = 135, 35.9%), followed by likelihood of tumor regression (n = 87, 23.1%). Overall, patient characteristics accounted for only 25.8% (n = 97) of the primary reasons for treatment selection. Within this category, prognostic factors were listed as the most common primary reason for treatment selection (12.8%), followed by performance status/frailty, age, and comorbidities. Patient-centered reasons such as quality of life (QoL), side effect profile, and cost or patient preference were least likely to be listed as the primary reason for choosing a particular treatment, accounting for 7.4% (n = 28) of patients (Table 2).

Additionally, a survey of treating physicians was performed to understand the reasons for treatment discontinuation (Table 2). Among all patients who received first-line treatment, 71.5% discontinued therapy during the study period with the highest percentage in the sunitinib group (78.7%), closely followed by the clinical trial group (78.4%). At the time of data cut-off after a median duration of 20.9 months of follow-up, 28.5% of patients remained on first-line therapy. Progressive disease was the most common reason for discontinuation (59.9%) followed by drug toxicity (25.7%). Patients treated with sunitinib were more likely to go off treatment due to progression (74.6%) compared with those in the clinical trial group (62.1%) or the pazopanib group (57.6%). However, more patients treated with pazopanib came off treatment for toxicity (35.6%) compared with the clinical trial group (19.0%) or the sunitinib treatment group (15.3%). Drug cost, transition to hospice, and patient refusal of treatment were uncommon reasons for discontinuation.

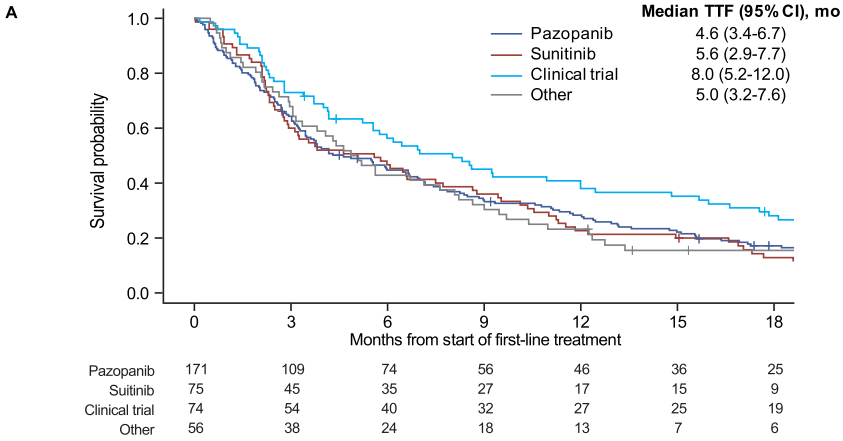
Considering histologic subtypes, patients with clear cell RCC receiving pazopanib or sunitinib had longer durations of initial therapy than those with non-clear cell RCC (Figure 1B). Median (95% CI) TTF in the pazopanib group with clear cell histology was 5.6 (3.6-7.2) months versus 3.4 (2.0-5.5) months in those with non-clear cell histology. The difference in median TTF for the sunitinib

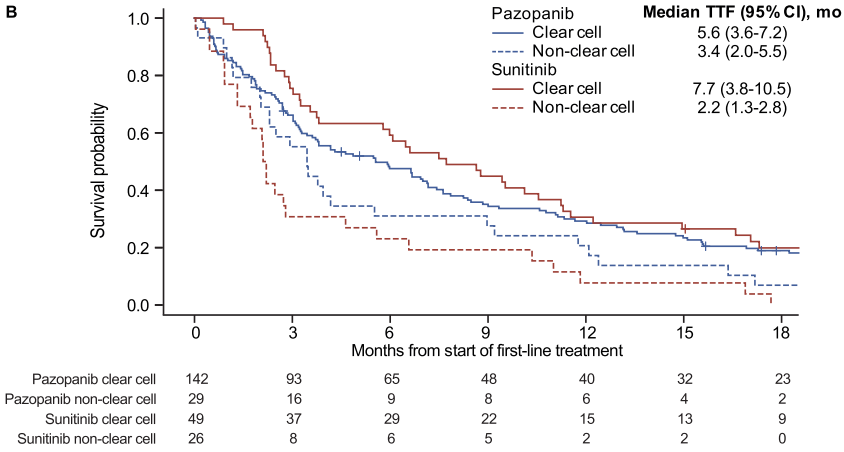
Table 1 Baseline Demographic and Clinical Characteristics for Patients Who Started First-Line Therapy by Treatment Selection, And Pazopanib and Sunitinib Dosing Patterns

	Pazopanib	Sunitinib	Clinical Trial	Other[a]	Total	*P* value
Demographic and clinical characteristics						
n (%)	171 (45.5)	75 (19.9)	74 (19.7)	56 (14.9)	376 (100)	
Site type, n (%)						.2020
Academic	116 (67.8)	55 (73.3)	60 (81.1)	41 (73.2)	272 (72.3)	
Community	55 (32.2)	20 (26.7)	14 (18.9)	15 (26.8)	104 (27.7)	
Age, median (25%, 75%), y	65.0 (56.0, 73.0)	62.0 (57.0, 68.0)	60.0 (54.0, 68.0)	61.0 (51.5, 68.0)	62.0 (55.0, 70.0)	.0122
Sex, n (%)						.1031
Men	115 (67.3)	51 (68.0)	54 (73.0)	47 (83.9)	267 (71.0)	
Women	56 (32.7)	24 (32.0)	20 (27.0)	9 (16.1)	109 (29.0)	
Ethnicity, n (%)						.9507
White	140 (81.9)	63 (84.0)	65 (87.8)	45 (80.4)	313 (83.2)	
Black	13 (7.6)	5 (6.7)	3 (4.1)	3 (5.4)	24 (6.4)	
Hispanic	11 (6.4)	5 (6.7)	2 (2.7)	6 (10.7)	24 (6.4)	
Asian	1 (0.6)	0	1 (1.4)	0	2 (0.5)	
Other	4 (2.3)	2 (2.7)	2 (2.7)	2 (3.6)	10 (2.7)	
Unknown	2 (1.2)	0	1 (1.4)	0	3 (0.8)	
ECOG PS, n (%)						.0004
0	54 (31.6)	28 (37.3)	45 (60.8)	21 (37.5)	148 (39.4)	
1	62 (36.3)	34 (45.3)	23 (31.1)	24 (42.9)	143 (38.0)	
2	25 (14.6)	7 (9.3)	5 (6.8)	3 (5.4)	40 (10.6)	
3	8 (4.7)	2 (2.7)	0	0	10 (2.7)	
Missing	22 (12.9)	4 (5.3)	1 (1.4)	8 (14.3)	35 (9.3)	
Histology type, n (%)						.0003
Clear cell	142 (83.0)	49 (65.3)	66 (89.2)	38 (67.9)	295 (78.5)	
Non-clear cell	29 (17.0)	26 (34.7)	8 (10.8)	18 (32.1)	81 (21.5)	
Time from metastatic diagnosis to systemic treatment, median (25%, 75%), months	1.6 (0.8, 5.7)	1.9 (0.9, 3.8)	3.0 (1.6, 8.8)	3.0 (1.4, 9.4)	2.1 (1.0, 6.5)	.0046
Prior nephrectomy, n (%)						.0272
Yes	94 (55.0)	32 (42.7)	53 (71.6)	30 (53.6)	209 (55.6)	
Missing	4 (2.3)	3 (4.0)	0	2 (3.6)	9 (2.4)	
Heng risk level[b], n (%)						.5346
Favorable	38 (22.2)	11 (14.7)	19 (25.7)	10 (17.9)	78 (20.7)	
Intermediate	99 (57.9)	49 (65.3)	46 (62.2)	35 (62.5)	229 (60.9)	
Poor	34 (19.9)	15 (20.0)	9 (12.2)	11 (19.6)	69 (18.4)	
Dosing patterns						
Starting dose, mg/d						
Mean (SD)	681.3 (194.6)	48.7 (4.4)	–	–	–	–
Median (25%, 75%)	800.0 (600.0, 800.0)	50.0 (50.0, 50.0)	–	–	–	–
End dose, mg/d						
Mean (SD)	602.9 (218.7)	43.9 (9.2)	–	–	–	–
Median (25%, 75%)	600.0 (400.0, 800.0)	50.0 (37.5, 50.0)	–	–	–	–
Patients starting at full dose, n (%)	116 (67.8)	68 (90.7)	–	–	–	–
Patients with dose reduction, n (%)	58 (33.9)	21 (28.0)	–	–	–	–
Follow-up period, median (25%, 75%), mo	20.0 (7.1, 28.6)	17.7 (3.8, 26.7)	–	–	–	–

Abbreviations: ECOG PS = eastern cooperative oncology group performance status; SD = standard deviation.
[a] Other medications were interleukin-2, temsirolimus, nivolumab, cabozantanib, sorafenib, bevacizumab, axitinib, gemcitabine, bevacizumab plus erlotinib, carboplatin plus paclitaxel, gemcitabine plus doxorubicin, and gemcitabine plus carboplatin.
[b] Patients in the no-treatment group were assigned a Heng score of 0 for answer in agreement to "<1 y from time of diagnosis to systemic therapy."

Figure 1 Time to treatment failure by (A) treatment group and (B) tumor histology in pazopanib or sunitinib treated patients, and (C) overall survival by treatment group. For C, one of the patients in the pazopanib group did not have a subject summary CRF page, and another patient in this group who died had a missing date of death. Neither patient was included in the analysis of overall survival. CI, confidence interval; NR, not reached; OS, overall survival; TTF, time to failure.





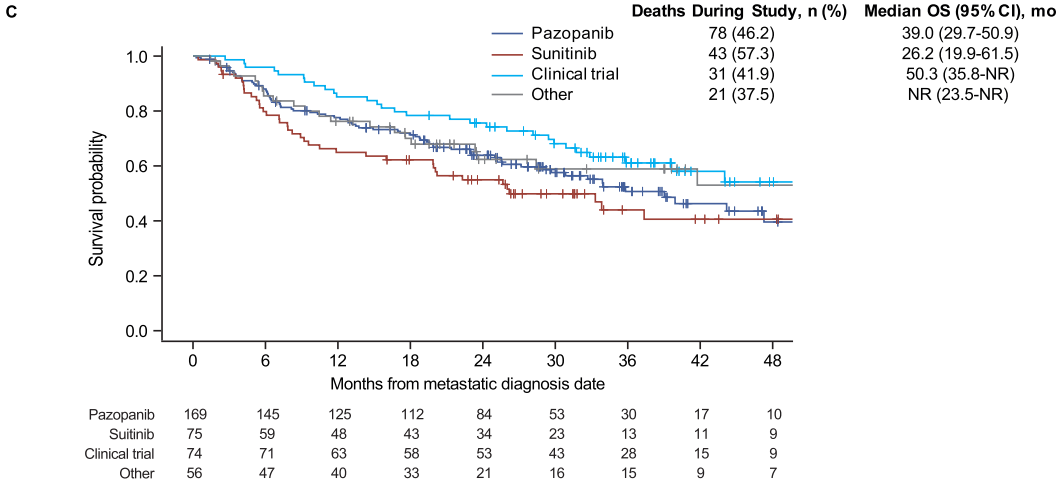


Table 2 Physician Treatment Survey: Primary Reasons for Selection of First-Line Treatment and Reasons for Discontinuation of First-Line Treatment

	Pazopanib n = 171	Sunitinib n = 75	Clinical trial n = 74	Other n = 56	Total n = 376
Treatment selection, n (%)					
Likelihood of treatment benefit					
OS/PFS	69 (40.4)	25 (33.3)	31 (41.9)	10 (17.9)	135 (35.9)
Tumor regression	38 (22.2)	19 (25.3)	15 (20.3)	15 (26.8)	87 (23.1)
Patient characteristics					
Prognostic factors	16 (9.4)	12 (16.0)	9 (12.2)	11 (19.6)	48 (12.8)
Performance status/frailty	17 (9.9)	6 (8.0)	2 (2.7)	3 (5.4)	28 (7.5)
Age	4 (2.3)	0	3 (4.1)	7 (12.5)	14 (3.7)
Comorbidities	3 (1.8)	2 (2.7)	0	2 (3.6)	7 (1.9)
Patient-centered reasons					
Quality of life	6 (3.5)	3 (4.0)	1 (1.4)	0	10 (2.7)
Side effect profile	8 (4.7)	1 (1.3)	0	0	9 (2.4)
Cost, patient preference	0	3 (4.0)	3 (4.1)	3 (5.4)	9 (2.4)
Other	10 (5.9)	4 (5.3)	10 (13.5)	5 (8.9)	29 (7.7)
Treatment discontinuation, n (%)					
Did not discontinue first-line treatment	53 (31.0)	16 (21.3)	16 (21.6)	22 (39.3)	107 (28.5)
Discontinued first-line treatment	118 (69.0)	59 (78.7)	58 (78.4)	34 (60.7)	269 (71.5)
Primary reason for discontinuation					
Progression	68 (57.6)	44 (74.6)	36 (62.1)	13 (38.2)	161 (59.9)
Toxicity	42 (35.6)	9 (15.3)	11 (19.0)	7 (20.6)	69 (25.7)
Cost/unable to afford treatment	1 (0.8)	1 (1.7)	0	0	2 (0.7)
Referred/transferred hospice	1 (0.8)	0	0	0	1 (0.4)
Patient declined	4 (3.4)	2 (3.4)	2 (3.4)	2 (5.9)	10 (3.7)
Other	2 (1.7)	3 (5.1)	9 (15.5)	12 (35.3)	26 (9.7)

Abbreviations: OS = overall survival; PFS = progression-free survival.

group was much wider, with those in the clear cell group having a median TTF of 7.7 (3.8-10.5) months versus 2.2 (1.3-2.8) months in the non-clear cell group.

In Figure 1C, median OS is depicted for each group and was defined as time from date of metastatic diagnosis to death. The clinical trial group demonstrated a median (95% CI) OS of 50.3 (35.8-not reached) months, pazopanib 39.0 (29.7-50.9) months, and sunitinib 26.2 (19.9-61.5) months, whereas for the 'Other' treatment group median OS could not be estimated because fewer than half of the patients died in this group during the follow-up period. Additionally, non-clear cell RCC was associated with worse median OS compared with clear cell RCC (18.0 [8.2-27.2] vs. 47.3 [39.0-62.7] months, respectively).

Discussion

The prospective MaRCC Registry allows us to assess real-world practice patterns during the VEGF TKI era, prior to the current setting of immunotherapy-based regimens. However, the results from this study highlight findings and common themes that are also of potential relevance to the treatment of patients with mRCC even as the treatment landscape has continued to evolve rapidly because the time of this study. Reviewing first-line therapy for patients in the current analysis, the vast majority (85.1%) received therapy supported by the NCCN guidelines for RCC prevailing at the time the MaRCC registry was conducted, such as clinical trial participation or treatment with pazopanib or sunitinib, indicating general adherence to the guidelines in day-to-day practice.[8] In all, 19.7% of patients were treated with first-line treatment in a clinical trial, much higher than the estimated <5% of adult cancer patients who enroll in clinical trials.[9,10] It is noteworthy to recognize that NCCN guideline recommendations have significantly evolved over the course of this study period (NCCN Kidney 3.2014, 1.2015, 1.2017, 1.2018, 4.2018, 2.2020, 3.2021), for instance the recent inclusion of combined TKI and immunotherapy and immunotherapy combinations (eg nivolumab and ipilimumab) as first-line treatments.[11]

In reviewing the registry data by histologic subtype, 78.5% of patients initiating first-line therapy had clear cell carcinoma, consistent with population trends.[12] Pazopanib was the most commonly prescribed treatment in this subgroup but was also associated with more dose reductions at baseline compared with sunitinib, which was less commonly used but also less likely to be started with a dose reduction. One interpretation of these results is that physicians were aware of favorable QoL data and felt more comfortable using pazopanib in frail patients who might not tolerate full-dose treatment.[2,13] When they felt comfortable with full-dose treatment, perhaps based on patient fitness, they were more likely to enroll patients in a clinical trial (where sunitinib was the standard of care arm) or on sunitinib off-study. The higher percentage of patients with ECOG PS 0 in clinical trials (60.8%) supports this hypothesis.

Further, this finding of initial dose reductions in our study has implications for combined immuno-oncology-tyrosine kinase inhibitor (IO-TKI) treatment. In combined therapy, IO treatment is a set dose, whereas the dose of the TKI can be reduced. One might expect some clinicians to adopt a similar approach to TKI dose reduction with combined therapy as they do for monotherapy. In terms of clinical outcomes, unsurprisingly off-study treatment outcomes were generally worse than those reported in the clinical trial group.[14] Patient frailty, co-morbidities, dosing, and compliance are just some of the issues that may affect these results. Disease assessment with centralized review may also be a factor.

Overall 21.5% of those on first-line treatment were classified as having non-clear cell histology, which is consistent with prior reports.[12] Not surprisingly, only 10.8% of the clinical trial patients in the Registry had non-clear cell RCC, considering that trials usually focus on patients with clear cell RCC. A similar percentage of the 81 patients with non-clear cell carcinoma initiating first-line therapy were treated with pazopanib or sunitinib. Importantly, patients with non-clear cell histology were associated with a shorter TTF and OS. In a retrospective review of clinical trials from 2003-2013, de Velasco et al. corroborated these results and found that median OS for those with non-clear cell RCC (n = 337; 15.7 months) was shorter than for those with clear cell RCC (n = 4235; 20.2 months).[15] Furthermore, when only VEGF-targeted therapy was considered, patients with non-clear cell RCC also showed shorter median OS than those with clear cell histology (19.8 versus 23.9 months, respectively). Importantly, no patients in the non-clear cell group received pazopanib and only 21.8% received sunitinib. These poor outcomes for patients with non-clear cell histology identified in the MaRCC registry and in the retrospective review by de Velsaco et al are a concern and represent an unmet need in the field, even in the current age of immunotherapy. Robust, prospective data is needed in patients with non-clear cell RCC treated with first-line immunotherapy.

Patients treated in a clinical trial had a remarkable median OS of 50.3 months, probably reflecting a component of selection bias as well as advances in treatment. We postulate that several factors may have contributed to this, most notably a higher percentage of patients with an ECOG PS of 0, a high rate of prior nephrectomy, younger median age, and more effective treatment options. Of particular note, there were a higher proportion of favorable-risk patients in the clinical trial group, particularly compared with the sunitinib, but not the pazopanib, group. Perhaps more importantly there were fewer poor-risk patients in the clinical trial group compared with both the sunitinib and pazopanib groups, although the risk groups were not statistically significantly from each other ($P = .5346$). Furthermore, there was a substantially higher percentage of patients with clear cell histology in the clinical trial group (89.2%), particularly when compared with the sunitinib group (65.3%), and to a lesser extent the pazopanib group (83.0%). These factors all portend a better prognosis for mRCC and therefore may have contributed to the longer median OS observed in the clinical trial group. Further, the proportion of individuals receiving treatment on a clinical trial in the MaRCC Registry is high (19.7%) and exceeds what we would typically expect under these circumstances. The relatively high clinical trial participation may, in part, reflect potential access to a number of promising immunotherapy-based combination studies. Although we do not have access to the specific treatment regimens used in these trials, our analysis occurred while several pivotal phase III immunotherapy trials were being conducted and pre-dated the FDA approval of immunotherapy in the first-line setting. These clinical trials incorporating immunotherapy and using a sunitinib-treated control population have been conducted in the recent past, and it is likely that a proportion of patients in the MaRCC registry had access to such trials. The median OS results for the overall clinical trial population suggest that even the sunitinib-treated patients in this group achieved a positive effect on survival. These findings, along with the observed difference in starting dose between sunitinib- and pazopanib-treated patients, suggest that in off-study populations, patient characteristics may be a more influential driver of dosing and outcomes than any differences among the drugs themselves. The observation of initial TKI dose reductions has implications for combined IO-TKI therapy as well. For instance, TKI dose reductions in combination-treated patients due to patient characteristics may affect efficacy in day-to-day clinical practice compared with clinical trials.

Utilizing prospectively collected physician questionnaires, we reported physician-selected reasons for choosing a specific first-line therapy. Likelihood of clinical benefit (OS/PFS, likelihood of tumor regression) was highest at 59.0%, followed by patient characteristics (prognostic factors, performance status/frailty, age, co-morbidities) at 25.8%, as the top reasons for treatment choice. In a different study of physician treatment preferences, efficacy was also the main reason for choosing a first-line therapy for mRCC, but other often-stated reasons included treatment guidelines and the physician's personal experience, which were not reported in our study.[16] Our findings also highlight that other factors, such as QoL, side effect profile, cost, and patient preference, were infrequently cited as the primary reason for drug selection. The focus on clinical benefit may be reflective of oncologists' orientation to clinical trial data in general and evidence-based medicine being the "science" in determining drug selection. It may also reflect the relatively low emphasis of QoL endpoints in RCC trials. Patient preference studies are also underreported in this population. These results give insight into the thought processes of treating physicians regarding factors they believe are important when selecting a specific therapy for their patient. We postulate that the reasons behind the selection of a specific therapy are universal considerations and apply not only to the TKI era but will also apply to the immunotherapy era. Understanding these reasons is especially important now that there are an increasing number of immunotherapy-based first-line treatments to choose from, including ipilimumab plus nivolumab,[17] pembrolizumab plus axitinib,[18] avelumab plus axitinib,[19] nivolumab plus cabozantanib,[20] and pembrolizumab plus lenvantinib.[21] A move toward routine assessment and wider availability of patient-reported outcomes (PROs) with these combinations will help physicians in their decision making. For instance, PRO data from the phase III, CheckMate 214 trial of ipilimumab plus nivolumab showed that patients who received this combination had fewer symptoms and better health related QoL than those treated with single-agent sunitinib.[22] Thus, as more PRO and QoL data become available from these trials, it may help physicians decipher how to best choose a regimen

for each patient in the setting of multiple first-line options, and we could see a shift of primary reasons for choosing a given treatment to include factors such as QoL and patient preference.

The limitations of the MaRCC Registry include a relatively short follow-up of patients and a relatively high percentage of patient accrual at academic medical centers. Further, we acknowledge that registry data are less likely to capture low-grade toxicities compared with prospective clinical trials. The bulk of the data in the MaRCC Registry for upfront RCC therapy was primarily with the two TKIs pazopanib and sunitinib, which reflected the treatment paradigm during the study period. In the interim, the treatment landscape of RCC has continued to evolve rapidly, with immunotherapy just coming into the mainstream during the period that this analysis was conducted. In addition, since then, other TKIs such as cabozantinib have been approved in the first-line setting.

Conclusion

The MaRCC Registry data gives unique insights into first-line treatment selection, outcomes, and physician reasons for drug choice in a real-world setting. It thus provides a benchmark for future studies into understanding such aspects of RCC management as newer treatments have become available, including TKIs either in combination with or following immunotherapy. These data and this approach to studying real-world patients with advanced RCC are therefore relevant in the immunotherapy era. As such, next steps in our Registry will be to look prospectively at evolving and prevailing practice patterns using immunotherapy-based first-line treatments as the current standard of care.

Clinical Practice Points

Little is known about initial treatment selection and what factors influence the choice of treatment by oncologists for patients with metastatic kidney cancer. Prospective randomized controlled studies and FDA drug approvals have formed the basis for many clinical guidelines and treatment pathways. However, drug selection varies and treatment outcomes differ in the real-world setting compared to clinical trials. This study highlights practice patterns for the initial treatment of patients with mRCC and physician rationale for treatment selection. The prospective MaRCC Registry allows assessment of real-world practice patterns during the VEGF TKI era, prior to the current setting of immunotherapy-based regimens. Reviewing first-line therapy for patients on the MaRCC study, the vast majority (85.1%) were put on therapy supported by the prevailing guidelines of the TKI era. The most common primary reason cited for first-line treatment selection was likelihood of clinical benefit, specifically overall survival and/or progression-free survival (35.9%), followed by likelihood of tumor regression (23.1%). The MaRCC Registry data gives unique insights into first-line treatment selection, outcomes, and physician reasons for treatment selection, and provides real-world outcomes data that can be used to counsel patients. It provides a benchmark for future studies into understanding such aspects of mRCC management as newer treatments come on line, including TKIs either in combination with, or following, immunotherapy. As such, next steps in our registry are to look prospectively at evolving and prevailing practice patterns as immunotherapy becomes a dominant primary treatment used in metastatic kidney cancer.

Disclosure

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Supplementary materials

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