Real-World Treatment Patterns and Clinical Outcomes Among Patients With Advanced Renal Cell Carcinoma

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Abstract

This real-world study of patients with renal cell carcinoma (RCC) compared clinical outcomes for patients treated with tyrosine kinase inhibitors (TKI), or an immunotherapy combination (IO+TKI or IO+IO). Medical record data was collected retrospectively for 498 patients across North America, Europe, and the UK. Immunotherapy (IO) combination was associated with longer progression-free survival (PFS) and time to next treatment (TTNT) than tyrosine kinase inhibitor (TKI) monotherapy. Among IO combinations, IO+TKI was associated with significantly improved progression-free survival (PFS) and TTNT compared to IO+IO.

Background: Nearly 30% of new renal cell carcinoma (RCC) cases are diagnosed at an advanced or metastatic stage. Recent approvals of immunotherapies (IO) have significantly impacted patient care, but real-world outcomes of these treatments have not been widely evaluated. **Methods:** Eligible physicians abstracted demographic and clinical data from patient medical records for patients with advanced clear and non-clear cell RCC (aRCC) who initiated treatment between January 1, 2018, and December 31, 2020. Overall survival (OS) and progression-free survival (PFS) were estimated by the Kaplan-Meier method. A multivariate Cox regression model was developed to assess the impact of treatment category on clinical outcomes while controlling for International Metastatic RCC Database Consortium (IMDC) risk category, histology, and other patient characteristics. **Results:** A total of 498 patients were included (201 from US, 62 from Canada, 58 from UK, 59 from France, 58 from Germany, 60 from Spain). Of these, 250 received tyrosine kinase inhibitor (TKI) monotherapy, 197 received immunotherapy (IO) combination (119 IO+TKI, 78 IO+IO), and 32 received IO monotherapy as first-line treatment for aRCC; 19 patients received various other regimens. 16% of patients had a favorable IMDC risk score. Based on results of multivariable Cox regression, PFS (hazard ratio [HR] [95% confidence interval (CI)]: 0.50 [0.36-0.72]) ($P < .001$) and time to next treatment (TTNT) were significantly longer (HR [95% CI]: 0.54 [0.39-0.73]) ($P < .001$) for patients treated with IO combination versus TKI monotherapy. IO combination had a numerically reduced, but statistically insignificant, risk of death versus TKI monotherapy (HR: 0.66; $P = .114$). IO+TKI combination was associated with significantly longer PFS and reduced risk of progression (HR: 0.52; $P = .04$) versus IO+IO combination; similar results were observed for TTNT (HR: 0.57; $P = .03$). **Conclusion:** Our evaluation of real-world treatment outcomes in aRCC revealed that IO + TKI combination is associated with improved PFS and prolonged TTNT compared with TKI monotherapy and IO+IO combination.

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Introduction

Renal cell carcinoma (RCC) has been on the rise in Western countries for several decades,[1-3] with approximately 430,000 new cases diagnosed and over 179,000 new deaths in 2020 worldwide.[4] Renal cell carcinoma is twice as common in men as in women.[4,5] The most common subtype of RCC is clear-cell carcinoma, which accounts for nearly 3-quarters of cases; papillary and chromophobe subtypes make up an additional 15% of cases.[3]

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Nearly 30% of new RCC cases are diagnosed at the advanced or metastatic stage (aRCC).[6] Lungs, lymph nodes, and bones are the most common sites of metastasis in RCC, and survival rates drop from approximately 75% to approximately 15% once RCC metastasizes.[7-9] Selection of systemic therapies for aRCC is influenced by International Metastatic RCC Database Consortium (IMDC) risk scores; for patients with good-risk, tyrosine kinase inhibitors (TKIs), including sunitinib and pazopanib, were used extensively prior to approval of immunotherapy (IO) plus TKI combinations.[10,11] Sunitinib was approved by the United States (US) Food and Drug Administration in 2006 and has been highly studied in aRCC.[12-14] Guidelines for systemic aRCC therapy are rapidly evolving with recent approvals of IO + TKI combinations for aRCC (pembrolizumab + axitinib in 2019, nivolumab + cabozantinib and pembrolizumab + lenvatinib in 2021).[11,15] For patients with intermediate- and poor-risk scores, dual IO+IO combination such as nivolumab plus ipilimumab has become an important core of RCC care.[10,11,16] Current guidelines for aRCC recommend administering IO and TKI in combination in first-line (1L) settings.[11,17] Because of the evolving nature of the aRCC treatment landscape, there is a need to evaluate and understand real-world clinical outcomes of patients with aRCC treated in the first-line setting with the diverse treatment options available in North America and Europe.

Methods

Study Design and Patient Selection

We conducted a retrospective, non-interventional study in which data were abstracted from medical records for patients who received treatment for aRCC in a non–clinical trial setting in the US, Canada, France, Spain, Germany, and the United Kingdom (UK). Advanced RCC was defined as unresectable stage III (locally advanced) or IV (metastatic) RCC. Data were abstracted from the medical records of patients who initiated 1L therapy for aRCC between 1 January 2018 and 31 December 2020. Patients were eligible for inclusion in this study if they were aged at least 18 years at the time of their diagnosis of aRCC and had a known vital status at the last available medical record entry. Board-licensed oncologists performed data abstraction using an electronic data collection form. The participating oncologists were required to have at least 2 years of medical practice experience managing patients with aRCC, to have regularly treated or managed at least 1 patient with aRCC per year, and to practice within the specified country. Physicians were asked to select eligible patients randomly for data abstraction.

An electronic data collection form (eDCF) was used by clinical personnel participating in the study to screen patient records for study eligibility and to capture the required data elements from patients' medical records allowing for analyses and additional calculation of analytic variables to assess the primary objectives (ie, patient characteristics, disease characteristics, treatments, and health outcomes). The eDCF incorporated background linkages and logic checks between questions to facilitate real-time data cleaning and to increase the internal validity of the questionnaire. Prior to data collection, the eDCF was pilot tested with 2 participating oncologists to ensure its clinical relevance, completeness, and ease of use.

This study was subjected to applicable local, country-specific ethics reviews and approvals; information on the specific ethics review boards and procedures used for each country are available upon request. Due to the deidentified nature of patient data collected in this study and the noninterventional study design, the study was exempted by all ethics review committees and procedures from the collection of signed informed patient consent.

Study Measures

Baseline demographic information captured for each patient included age at aRCC diagnosis, gender, height, weight, geographic region of residence, histology, smoking history, and race/ethnicity. Baseline clinical characteristics that were collected included the patients' RCC tumor histology Memorial Sloan Kettering Cancer Center risk group, IMDC score, sites of metastasis at aRCC diagnosis, prior treatments, and their performance status as determined by the Eastern Cooperative Oncology Group guidelines or their Karnofsky score. Patients' comorbidity during the 12 months prior to aRCC was calculated using the Charlson Comorbidity Index based on documented history of CCI-specific comorbid conditions.[18]

The 1L systemic treatment received after patients' diagnosis with aRCC was categorized based on treatment class (TKI monotherapy, IO + TKI, or IO + IO) and the start and stop dates of each line of treatment, the reason for stopping treatment, and the reason(s) for not initiating a subsequent line of treatment, if applicable.

Best overall response to a specific therapy was collected as reported in the patient medical records by the treating physician. If utilized and reported in the medical record, the criteria used by the clinician to assess best response (eg, RECIST 1.1)[19] were collected. Other factors upon which clinicians' response assessments were made (eg, radiographic imaging, patient symptoms) were also collected. Independent assessment of clinical response using scans or images was not included in this study, as such personally identifiable data could not be collected based on the ethics review approvals received granting waiver of informed consent. Dates of each assessment for determining best response were also collected when available. For patients with a recorded date of best response, duration of best overall response was defined as the interval between the date of documented tumor response during each treatment line and the date of progression if the patient developed disease progression. Among patients who continued to have documented tumor response at the start of a subsequent treatment or at the time of data collection, the earliest of the following dates was used: start of next treatment, date of the latest available medical record entry, or date of death.

Time to progression (TTP) was defined as the time from initiation of 1L treatment to the first documented date of disease progression. Progression events include those occurring between start of 1L treatment and the earliest of discontinuation + 30 days (to allow for potential lag in data entry to the medical record), start of next treatment, or date of the latest available medical record entry. Patients without clinician-documented disease progression during the line of treatment were censored at the date of discontinuation of the treatment line + 30 days (patients for whom the line of treatment was ongoing at the time of data collection were censored on the

Table 1 Patient Characteristics

Total Patient Sample, N (%)[a]	Overall	IO Combination			TKI Monotherapy
		Total	IO + IO	IO + TKI	
	498	197	78	119	250
Median age (y)	62.7	62.5	63.8	62.0	62.9
Range	55.5,68.4	56.5, 68.3	57.1, 67.7	55.9, 68.6	56.1, 68.5
Gender, n (%)					
Male	342 (68.7)	134(68.0)	51 (65.4)	83 (69.8)	169 (67.6)
Female	156 (31.3)	63 (32.0)	27 (34.6)	36 (30.3)	81 (32.4)
Race, n (%)					
White/Caucasian	343 (68.9)	129 (65.5)	60 (76.9)	69 (58.0)	184 (73.6)
African/Black	59 (11.9)	28 (14.2)	6 (7.7)	22 (18.5)	20 (8.0)
Asian, Native Hawaiian, or other Pacific Islander	15 (3.0)	8 (4.1)	2 (2.6)	6 (5.0)	5 (2.0)
Other or not reported	81 (16.3)	40 (20.3)	12 (15.5)	28 (23.5)	46 (18.4)
Mean duration of follow-up (mo) (SD)	20.85 (10.7)	18.94 (9.7)	19.83 (9.6)	18.36 (9.8)	22.10 (11.1)
Geographic location, n (%)					
United States	201 (40.4)	90 (45.7)	22 (28.2)	68 (57.1)	83 (33.2)
Canada	62 (12.5)	21 (10.7)	15 (19.2)	6 (5.0)	32 (12.8)
United Kingdom	58 (11.7)	28 (14.2)	18 (23.1)	10 (8.4)	29 (11.6)
France	59 (11.9)	23 (11.7)	7 (9.0)	16 (13.5)	31 (12.4)
Germany	58 (11.7)	29 (14.7)	12 (15.4)	17 (14.3)	26 (10.4)
Spain	60 (12.1)	6 (3.1)	4 (5.1)	2 (1.7)	49 (19.6)

Abbreviations: IO = immunotherapy; SD = standard deviation; TKI = tyrosine kinase inhibitor.
[a] Certain subgroups, including IO monotherapy, were not included in the tables due to small n; therefore, totals may not sum to the overall population.

date of death or their last active medical record entry). Time to treatment discontinuation was calculated as the duration of time between treatment initiation and the end of that treatment. Patients continuing treatment until the end of follow-up were censored on the follow-up end date (last available medical record entry). Time to next treatment was calculated as the time from initiation of a respective line to initiation of the subsequent line of therapy or switch to best supportive care (BSC). For patients with no subsequent line of treatment or switch to BSC, the censoring date was the follow-up end date (last available medical record entry).

Progression-free survival (PFS) was defined as the time from initiation of 1L treatment to the date of progression or death (if reported while on 1L treatment). Patients without a clinician-documented progression event or death during the first line of treatment were censored at the earliest date of discontinuation of the treatment line + 30 days or the date of their last active medical record entry among patients with ongoing treatment.

Overall survival was calculated as the time from the start of 1L therapy for aRCC until the date of death from any cause; patients without a death event (ie, who were still presumed alive) were censored at the date of the latest available medical record entry.

Statistical Analyses

Descriptive statistics were reported for patient demographics and clinical characteristics. All analyses were conducted using SAS statistical software (Version 9.3; Cary, NC).

Time-to-event outcomes such as time to discontinuation (TTD), TTNT, PFS, and OS were estimated descriptively and using the Kaplan-Meier method. Time-dependent event probabilities (eg, the proportion of patients without an event at various landmark timepoints; ie, at 3, 6, 9, and 12 months) were reported by treatment category, in addition to median event times for these measures.

In addition, hazard ratios (HRs) were estimated for events of interest (ie, PFS, TTP, TTD, OS, TTNT) using Cox regression models. A stepwise selection method was used to identify baseline demographic and clinical characteristics as independent predictors with adjustment for relevant clinical covariates, including 1L systemic treatments received. The baseline demographic and clinical characteristics used for the Cox regression models after stepwise covariate selection included gender, IMDC risk score at 1L treatment initiation, clear-cell status, Charlson Comorbidity Index score, sites of metastasis, and year of 1L treatment initiation, as appropriate. Adjusted PFS, TTP, TTD, OS, and TTNT time-to-event estimates were reported, controlling for baseline covariates.

Results

Physician Characteristics

A total of 158 physicians (85 in North America and 73 in the UK/France/Germany/Spain) participated in data abstraction, most of whom were medical or clinical oncologists (n = 116; 73.4%) (Supplemental Table 1). On average, participating physicians had been in practice for 15.8 years (standard deviation [SD]: 6.24). The median number of patients with aRCC treated by the recruited physicians in the past year was 50 (range, 4-220 patients).

Patient Demographics and Clinical Characteristics

The final cohort comprised 498 patients: 201 (40.4%) from the US, 62 (12.5%) from Canada, 58 (11.7%) from the UK, 59 (11.9%) from France, 58 (11.7%) from Germany, and 60 (12.1%) from Spain (Table 1). Overall, 342 (68.7%) were male, 343 (78.1%; race collected for all countries except France) were White/Caucasian, 59 (11.9%) were Black, and 166 (82.6%; collected in the US only) were non-Hispanic. The median age at 1L treatment initiation for these patients was 62.7 years (range, 22.2-84.1 years), with more than half of all patients in the study receiving their diagnoses between the ages of 55 and 74 years (n = 346; 69.5%). The median follow-up duration from 1L treatment initiation to last available follow-up, which was defined as the earliest of death or last medical record entry date, was 18.7 months (range, 0.3-47.5 months). At last available follow-up, most of these patients were alive (n = 413; 82.9%).

Of the 498 patients, 250 received TKI monotherapy, 197 received IO combinations (119 received IO + TKI, 78 received IO+IO), and 32 received IO monotherapy as 1L treatment for aRCC; 19 patients received other regimens as 1L treatment. The majority of patients (88.8%) had clear-cell carcinoma; of the 11.2% with non-clear cell carcinoma, 6.6% had papillary RCC and 2.2% had chromophobe RCC. Over 3-quarters of patients (77.9%) were stage IV at initial RCC diagnosis (Table 2). More than 40% of patients had a nephrectomy prior to their RCC progressing to the advanced stage. Most of the patients (85.3%) had an Eastern Cooperative Oncology Group performance status of 0 (n = 116) or 1 (n = 302) at aRCC diagnosis. Nearly 60% of patients had intermediate-risk disease, and only 13% and 16% had favorable-risk disease for metastatic RCC according to IMDC risk category and Memorial Sloan Kettering Cancer Center risk category, respectively. The most common sites of distant metastases for these patients were lymph nodes (n = 293; 58.8%) and lungs (n = 290; 58.2%). Additional clinical characteristics can be found in Supplemental Table 2.

Treatment Characteristics

In the overall study population, 47 (9.4%) received treatment for RCC prior to being diagnosed with advanced or metastatic disease; the majority of those patients underwent radical nephrectomy (59.6%) or partial nephrectomy (25.5%) (Table 3). These trends were consistent across the North American and European subgroups. The Kaplan-Meier estimate of median 1L treatment duration (ie, TTD) for advanced disease was 13.0 months (95% CI, 12.3-13.8). The most common 1L treatments (Table 3; Supplementary Table 3) were sunitinib (26.1%; TKI monotherapy), axitinib plus pembrolizumab combination (18.9%; TKI + IO), and nivolumab plus ipilimumab combination (15.7%; IO + IO).

Nearly 40% of patients received a second-line (2L) treatment for aRCC, and only 29 patients (5.8%) received a third-line treatment. Of the 190 (38.2%) who received a 2L treatment, nivolumab (34.7%) and cabozantinib (24.7%) were the most common (Supplementary Table 4). Median time from advanced diagnosis to initiation of 1L treatment was 0.5 months. The Kaplan-Meier estimate of median duration of 2L treatments (TTD) was 12.0 months (95% CI, 10.8-14.5).

Clinical Outcomes

Landmark PFS probability estimates were 94.3% at 6 months after 1L treatment initiation and 72.4% at 12 months overall. The PFS probability at 12 months was 68.2% for patients treated with TKI monotherapy and 78.8% for patients treated with IO combination therapy (Table 4, Figure 1A). Among the IO combination subgroups, the 12-month PFS probability was 70.4% for IO+IO and 84.0% for IO+TKI (Table 4, Figure 1B). When survival outcomes were examined by IMDC risk categories, PFS probability at 12 months was 65.0% for patients in the poor-risk category, 71.6% for the intermediate-risk category, and 84.6% for the favorable-risk category (Figure 2A). Criteria used to assess response and additional clinical outcomes are given in Supplemental Table 5.

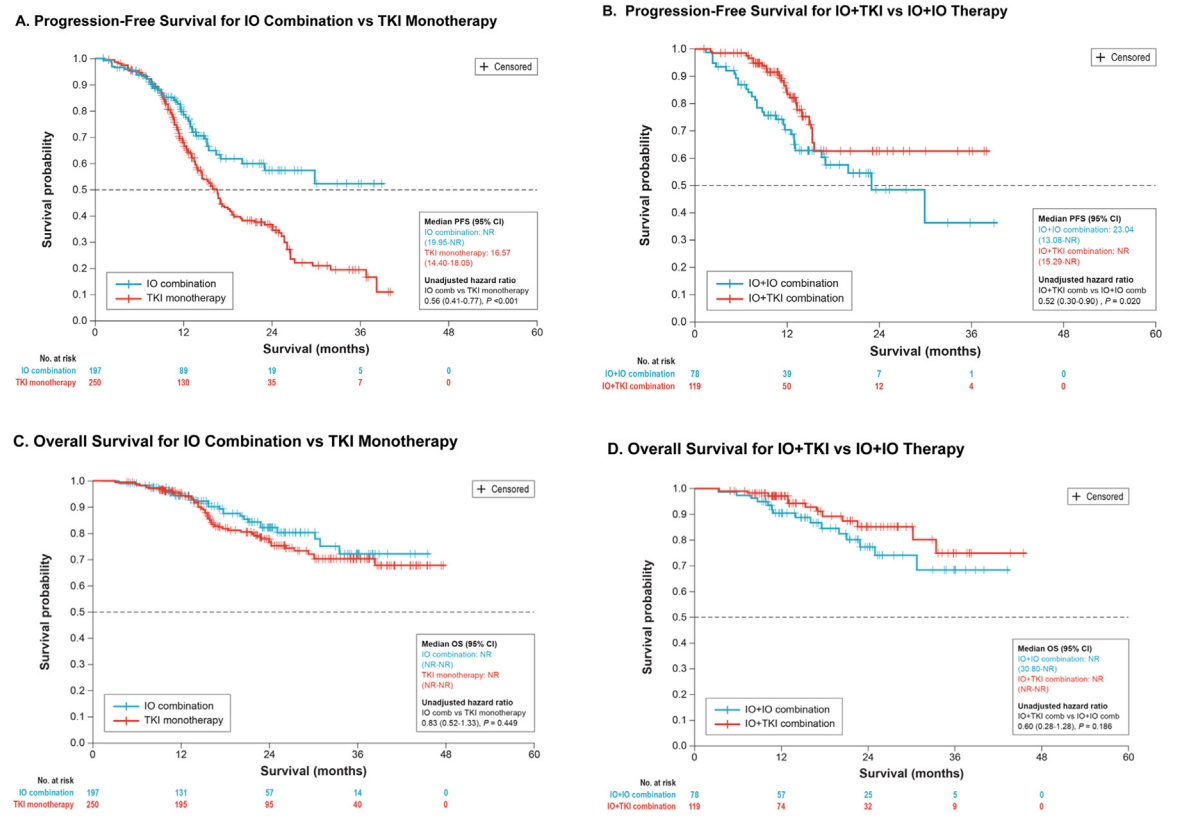
In the overall study cohort, 85 (17.1%) patients had died after initiation of 1L treatment; 71.8% of deaths were RCC related. The Kaplan-Meier–estimated median survival was not reached. Landmark OS probability estimates were observed to be 98.8% at 6 months after 1L treatment initiation and 94.8% at 12 months (Table 4). Overall survival probabilities at 12 months were 94.5% for patients treated with TKI monotherapy and 94.4% for patients on IO combination therapy (Figure 1C). Among the IO combination subgroups, the 12-month OS probability was 90.5% for IO+IO and 97.3% for IO+TKI therapy (Table 4, Figure 1D). The OS probability at 12 months was 88.4% for patients in the IMDC poor-risk category, 95.1% in the intermediate-risk category, and 100.0% in the favorable-risk category (Figure 2B).

Cox Regression Models for Clinical Outcomes

Multivariate Cox regression models were developed to adjust for confounding variables and estimate adjusted median time to clinical events (progression, next treatment, and death) by 1L treatment category (Figure 3). After adjustment for confounding via Cox regression, PFS was significantly longer with lower risk of progression for patients treated with IO combination (HR [95% CI], 0.50 [0.36-0.72]) compared with TKI monotherapy ($P < .001$) (Figure 1A). Adjusted median PFS from 1L treatment was 27.1 months among those receiving IO combination and 15.5 months among those receiving TKI monotherapy. The adjusted median PFS was not reached for IO + TKI combination therapy and was estimated to be 23 months for IO + IO (Figure 1B). The adjusted median PFS in patients with clear-cell RCC was 14.8 months for patients treated with TKI monotherapy and 26.5 months for patients treated with IO combination therapy (HR [95% CI], 0.46 [0.32-0.66]) ($P < .001$).

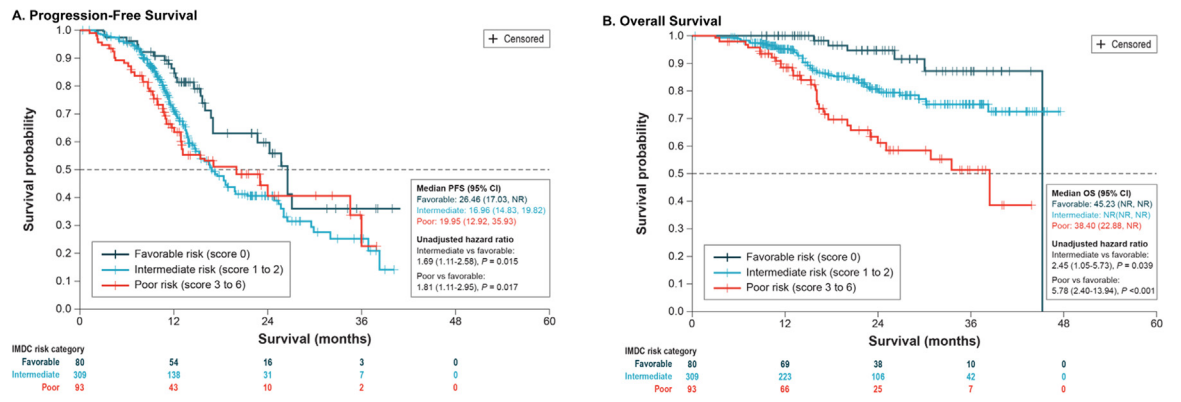
Based on the results of multivariate Cox regression analysis, time to next treatment (TTNT) was significantly longer with reduced risk of starting a subsequent treatment for patients treated with IO combination (HR [95% CI], 0.54 [0.39-0.73]) ($P < .001$) compared with TKI monotherapy (Figure 3). Adjusted median TTNT from 1L treatment was 16.7 months among those receiving TKI monotherapy and 30.1 months among those receiving IO combination. For patients receiving IO + TKI, the median TTNT

Figure 1 Kaplan-Meier estimates of progression-free and overall survival by treatment category.
CI = confidence interval; IO = immunotherapy; NR = not reached; TKI = tyrosine kinase inhibitor.



CI = confidence interval; IO = immunotherapy; NR = not reached; TKI = tyrosine kinase inhibitor.

Figure 2 Kaplan-Meier estimates of progression-free and overall survival by IMDC risk and treatment categories.
CI = confidence interval; IMDC = International Metastatic RCC Database Consortium; NR = not reached.



CI = confidence interval; IMDC = International Metastatic RCC Database Consortium; NE = not reached.

Table 2 Clinical Characteristics

Total Patient Sample, N (%)[a]	Overall	IO Combination			TKI Monotherapy
		Total	IO + IO	IO + TKI	
	498	197	78	119	250
Clinical stage at initial diagnosis (n, %)					
Stage I	10 (2.0)	2 (1.0)	1 (1.3)	1 (0.8)	6 (2.4)
Stage II	36 (7.2)	16 (8.1)	7 (9.0)	9 (7.6)	17 (6.8)
Stage III	63 (12.7)	19 (9.6)	5 (6.4)	14 (11.8)	33 (13.2)
Stage IV	388 (77.9)	160 (81.2)	65 (83.3)	95 (79.8)	193 (77.2)
IMDC risk category (n, %)					
Favorable risk (score 0)	80 (16.1)	22 (11.2)	2 (2.6)	20 (16.8)	51 (20.4)
Intermediate risk (score 1-)	309 (62.1)	109 (55.3)	38 (48.7)	71 (59.7)	163 (65.2)
Poor risk (score 3-6)	93 (18.7)	62 (31.5)	38 (48.7)	24 (20.2)	26 (10.4)
Not assessed	16 (3.2)	4 (2.0)	0 (0.0)	4 (3.4)	10 (4.0)
MSKCC risk category (n, %)					
Favorable risk (score 0)	66 (13.3)	15 (7.6)	0 (0.0)	15 (12.6)	44 (17.6)
Intermediate risk (score 1-2)	295 (59.2)	107 (54.3)	37 (47.4)	70 (58.8)	153 (61.2)
High risk (score 3-5)	90 (18.1)	52 (26.4)	33 (42.3)	19 (16.0)	31 (12.4)
Not assessed	47 (9.4)	23 (11.7)	8 (10.3)	15 (12.6)	22 (8.8)
Receipt of radical nephrectomy (n, %)					
Yes	202 (40.6)	76 (38.6)	32 (41.0)	44 (37.0)	99 (39.6)
No	286 (57.4)	115 (58.4)	46 (59.0)	69 (58.0)	147 (58.8)
Not reported	10 (2.0)	6 (3.1)	0 (0.0)	6 (5.0)	4 (1.6)
Histology of RCC at advanced diagnosis (n, %)					
Clear cell	442 (88.8)	175 (88.8)	66 (84.6)	109 (91.6)	229 (91.6)
Non-clear cell (papillary)	33 (6.6)	11 (5.60)	6 (7.7)	5 (4.2)	12 (4.8)
Non-clear cell (chromophobe)	11 (2.2)	6 (3.1)	3 (3.9)	3 (2.5)	2 (0.8)
Non-clear cell (Other)	3 (0.6)	2 (1.0)	1 (1.3)	1 (0.8)	1 (0.4)
Not reported	9 (1.8)	3 (1.5)	2 (2.6)	1 (0.8)	6 (2.4)
PD-L1 status (n, %)		**N = 86**	**N = 23**	**N = 63**	**N = 73**
Positive	157 (80.5)	79 (91.9)	21 (91.3)	58 (92.1)	52 (71.2)
Negative	37 (19.0)	7 (8.1)	2 (8.7)	5 (7.9)	20 (27.4)
Result inconclusive	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
ECOG performance status at or before index (n, %)	**N = 490**	**N = 195**	**N = 77**	**N = 118**	**N = 244**
0	116 (23.7)	55 (28.2)	25 (32.5)	30 (25.4)	56 (23.0)
1	302 (61.6)	124 (63.6)	48 (62.3)	76 (64.4)	153 (62.7)
2	58 (11.8)	13 (6.7)	3 (3.9)	10 (8.5)	28 (11.5)
3	14 (2.9)	3 (1.5)	1 (1.3)	2 (1.7)	7 (2.9)
Site(s) of distant metastases at advanced diagnosis (n, %)					
Lymph nodes	299 (60.0)	119 (60.4)	44 (56.4)	75 (63.0)	141 (56.4)
Lung	293 (58.8)	132 (67.0)	59 (75.6)	73 (61.3)	142 (56.8)
Liver	122 (24.5)	53 (26.9)	20 (25.6)	33 (27.7)	55 (22.0)
Bone	155 (31.1)	78 (39.6)	41 (52.6)	37 (31.1)	71 (28.4)
Brain	10 (2.0)	4 (2.0)	1 (1.3)	3 (2.5)	4 (1.6)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IO = immunotherapy; MSKCC = Memorial Sloan Kettering Cancer Center; PD-L1 = programmed death-ligand 1; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor.
Bolded values indicate sample sizes for the corresponding analyses.
[a] Certain subgroups, including IO monotherapy, were not included in the tables due to small n; therefore, totals may not sum to the overall population.

Table 3 Treatment Characteristics

Total Patient Sample, N (%)[a]	Overall	IO Combination			TKI Monotherapy
		Total	IO+IO	IO+TKI	
	498	197	78	119	250
Treatments received prior to aRCC (n, %)	**N = 47**	**N = 18**	**N = 8**	**N = 10**	**N = 24**
Surgery (partial nephrectomy)	12 (25.5)	4 (22.2)	1 (12.5)	3 (30.0)	7 (29.2)
Surgery (simple nephrectomy)	4 (8.5)	2 (11.1)	0 (0.0)	2 (20.0)	2 (8.3)
Surgery (radical nephrectomy)	28 (59.6)	11 (61.1)	6 (75.0)	5 (50.0)	14 (58.3)
Radiation therapy	5 (10.6)	3 (16.7)	1 (12.5)	2 (20.0)	1 (4.2)
Adjuvant systemic treatment	2 (4.6)	1 (5.9)	0 (0.0)	1 (10.0)	1 (4.4)
Number of patients initiating treatment line (n, %)					
First-line	498 (100.0)	197 (100.0)	78 (100.0)	119 (100.0)	250 (100.0)
Second-line	190 (38.2)	49 (24.9)	25 (32.1)	24 (20.2)	128 (51.2)
Third-line	29 (5.8)	4(2.0)	3 (3.9)	1 (0.8)	23 (9.2)
Treatment received after advanced diagnosis (n, %)					
Chemotherapy	8 (1.6)	3(1.5)	1 (1.3)	2(1.7)	2 (0.8)
Targeted therapy	416 (83.5)	143(72.6)	24 (30.8)	119 (100.0)	250 (100.0)
Immunotherapy	299 (60.0)	195 (99.0)	77 (98.7)	118 (99.2)	68 (27.2)
Other	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
3 most frequently received first-line regimens (n, %)					
Sunitinib	130 (26.1)	0 (0.0)	0 (0.0)	0 (0.0)	130 (52.0)
Axitinib/pembrolizumab	94 (18.9)	94 (47.7)	0 (0.0)	94 (79.0)	0 (0.0)
Nivolumab/ipilimumab	78 (15.7)	78 (39.6)	78 (100.0)	0 (0.0)	0 (0.0)
Discontinuation of first treatment line (n, %)	311 (62.5)	94 (47.7)	42 (53.9)	52 (43.7)	178 (71.2)
Duration of first-line treatment (TTD; KM estimate)					
Median (95% CI)	13.0 (12.4-13.8)	14.8 (12.8-19.6)	16.8 (12.4-23.9)	13.5 (12.2-15.8)	13.1 (12.4-14.5)
Duration of second-line treatment (TTD; KM estimate)	**N = 190**	**N = 49**	**N = 25**	**N = 24**	**N = 128**
Median (95% CI)	12.0 (10.8-14.5)	13.1 (8.7-27.6)	15.2 (5.8-NE)	12.0 (7.2-15.3)	12.0 (10.4-15.0)

Abbreviations: aRCC = advanced or metastatic renal cell carcinoma; CI = confidence interval; IO = immunotherapy; KM = Kaplan-Meier; TKI = tyrosine kinase inhibitor; TTD = time to deterioration. Bolded values indicate sample sizes for the corresponding analyses.
[a] Certain subgroups, including IO monotherapy, were not included in the tables due to small n; therefore, totals may not sum to the overall population.

was significantly longer with reduced risk of starting a subsequent treatment versus patients who received IO + IO combinations (HR [95% CI], 0.57 [0.34-0.96]) (P = .035); median 42.1 months compared with 23.9 months.

After adjustment for confounding via Cox regression, time to progression was longer in patients treated with IO combination therapy than in patients treated with TKI monotherapy (HR [95% CI], 0.50 [0.3-0.72]) (P < .001). Among patients treated with IO combination therapy, patients treated with IO + TKI had longer TTP than patients treated with IO + IO (HR [95% CI], 0.52 [0.28-0.97]) (P = .040). Median TTP for patients with clear cell RCC was 15.5 months for patients receiving TKI monotherapy and 26.5 months for patients who received IO combination therapy (HR [95% CI], 0.48 [0.34-0.69]) (P < .001).

The adjusted median TTD of therapy was not statistically significantly different for TKI monotherapy (12.9 months) and IO combination therapy (14.5 months) (HR [95% CI], 0.82 [0.62-1.08]) (P = .166). Among IO combination therapies, the adjusted median TTD was 15.2 months for IO + IO combination and 16.5 for IO + TKI (HR [95% CI], 0.99 [0.6-1.56]) (P = .980). In patients with clear-cell advanced RCC, median TTD was 13.1 months for patients treated with TKI monotherapy and 14.5 months for patients treated with IO combination therapy (HR [95% CI], 0.84 [0.62-1.13]) (P = .241).

The adjusted median OS was not reached for any treatment group; therefore, no statistically significant differences were found in OS between patients treated with IO combination compared with TKI monotherapy (adjusted HR [95% CI], 0.66 [0.39-1.11]), (P = .114) (Figure 3), nor between patients treated with IO + IO and IO + TKI (HR [95% CI], 1.69 [0.70-4.11]) (P = .247) (Figure 3). Similarly, no statistically significant difference in OS was observed between TKI monotherapy and IO combination therapy (HR [95% CI], 0.72 [0.42-1.23]) (P = .226) in patients with clear-cell RCC.

Table 4 Clinical Outcomes

Total Patient Sample, N (%)[a]	Overall	IO Combination			TKI Monotherapy
		Total	IO + IO	IO + TKI	
	(N=498)	(N=197)	(N=78)	(N=119)	(N=250)
Progressed between start of first-line treatment and end of first-line treatment + 30 d or end of follow-up (n, %)					
Yes	195 (39.2)	52 (26.4)	30 (38.5)	22 (18.5)	128 (51.2)
No	284 (57.0)	140 (71.1)	47 (60.3)	93 (78.2)	108 (43.2)
Not reported	19 (3.8)	5 (2.5)	1 (1.3)	4 (3.4)	14 (5.6)
Time to progression[b]	**N = 195**	**N = 52**	**N = 30**	**N = 22**	**N = 128**
Mean (SD)	12.41 (7.1)	10.06 (5.6)	9.72 (6.6)	10.52 (3.9)	13.34 (7.0)
Median	11.1	9.3	8.1	11.3	11.4
Progression-free survival rate at 12 mo (%, SE)	72.4 (2.2)	78.8 (3.3)	70.4 (5.5)	84.0 (4.1)	68.2 (3.1)
Overall survival rate at 12 mo (%, SE)	94.8 (1.0)	94.4 (1.7)	90.5 (3.4)	97.3 (1.6)	94.5 (1.5)

Abbreviations: IO = immunotherapy; SD = standard deviation; SE = standard error; TKI = tyrosine kinase inhibitor.
Bolded values indicate sample sizes for the corresponding analyses.
[a] Certain subgroups, including IO monotherapy, were not included in the tables due to small n; therefore, totals may not sum to the overall population.
[b] Calculated among patients with a progression event.

Discussion

This multinational, real-world study evaluated treatment patterns and estimated treatment effectiveness in patients with aRCC in routine practice settings across North America and Europe. As more treatments enter the clinical practice, we need to understand how their availability impacts treatment patterns and patient outcomes with real-world use, not just within clinical trials. Patients treated with IO combination in this study had a significantly longer TTNT and PFS than patients treated with TKI monotherapy, and patients treated with IO + TKI had the longest estimated TTNT of all subgroups, indicating that while TKI monotherapy is not the most effective treatment course for most patients, TKIs remain an important piece of aRCC care. Multivariate Cox regression analyses indicated that patients with IO combination therapy had better outcomes compared with TKI monotherapy.

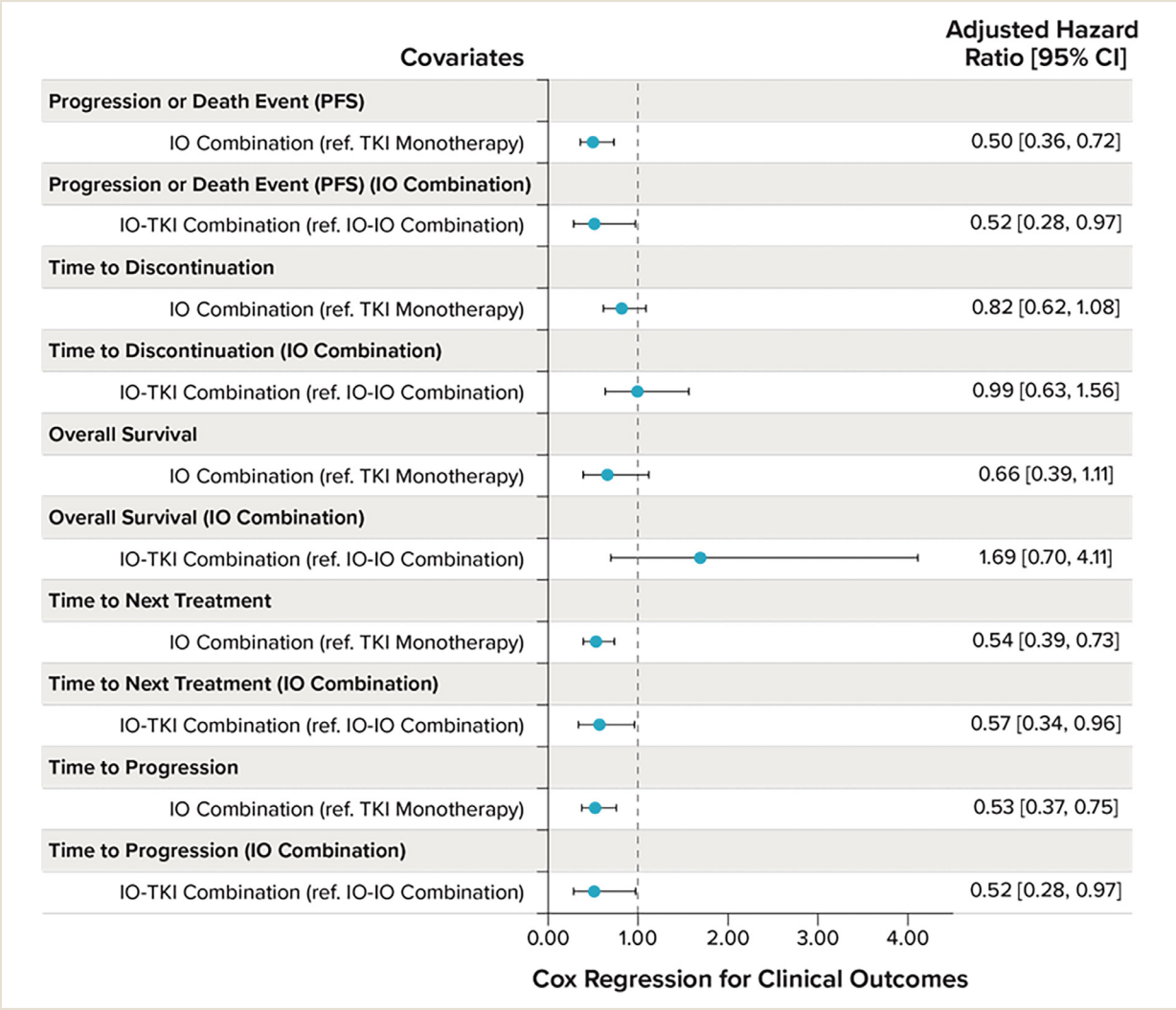
In recent years, 4 randomized controlled trials (CheckMate 214, KEYNOTE-426, CheckMate 9ER, and CLEAR study) evaluated IO + IO or IO + TKI combinations compared with TKI monotherapy (sunitinib) and have reported improved survival for the IO combinations and led to IO approvals that have become part of the standard of care.[20-26] However, there are often significant differences between outcomes in clinical trials and those in real-world studies, due to the nature of these studies. Clinical trials are conducted under strict eligibility criteria and standardized definitions (ie, RECIST) for response and progression. This real-world chart review, however, did not require progression or response to be determined using a specific set of guidelines, nor did it require patients to have received scans at set intervals. In this respect, only trends should be compared between real-world studies and clinical trials. In our study, the adjusted PFS was shortest for 1L TKI monotherapy, with better outcomes seen with IO combination therapy. This is in line with findings in clinical trials that show a greater overall survival benefit with the use of IO than with TKI monotherapy in patients with intermediate- and poor-risk disease, as well as with recent real-world studies that have found that patients treated with IO combination therapy had higher rates of complete response than those treated with TKI alone.[27,28]

A recently conducted network meta-analysis of clinical trials reported all IO combinations exhibiting better OS and PFS benefits compared with sunitinib. In particular, lenvatinib + pembrolizumab and nivolumab + cabozantinib combinations (IO + TKI combinations) exhibited maximum survival/PFS benefit among all the IO combinations.[29] Our study also reported better PFS and longer TTNT among patients receiving IO + TKI compared with IO + IO (hazard ratio [95% CI], 0.52 [0.28-0.97]).

Our study supports recent trends in studies comparing IO combination and TKI in RCC but with some significant strengths. Clinical trial data were collected under strict conditions that are often not reflective of real-world use. The real-world data collected comparing IO combination and TKI were primarily performed in single countries. This study gathered patient data from 6 countries across Europe and North America. Treating physicians specialized in medical oncology or hematology/oncology, with decades of experience treating patients with RCC and consenting to participate in the research study, submitted de-identified data from patient medical records. In addition to assessing clinical outcomes at a descriptive level, we constructed a Cox regression model to adjust for baseline risk, clinical, and demographic factors and compare survival outcomes and TTNT among treatment groups. These multivariate analyses provided adjusted clinical outcomes along with identifying associated factors.

During the timeframe in which treatments were initiated in this study (ie, between 2018 and 2020), the treatment landscape for RCC was rapidly evolving. In 2018, the results of the CARMENA study, a noninferiority study of cytoreductive nephrectomy (CN), were made public. The CARMENA study indicated that TKI monotherapy is not inferior to CN and encouraged the standard of care for RCC patients be updated to remove CN as upfront strategy in the management of patients with metastatic RCC.[30,31]

Figure 3 Forest plot of cox regression results for clinical outcomes. CI = confidence interval; IO = immunotherapy; PFS = progression-free survival; TKI = tyrosine kinase inhibitor. Other treatments include IO monotherapy, TKI + antineoplastic agent, bevacizumab, antineoplastic agent, other bevacizumab combination, or interferon. Model selection was performed for each outcome to control for potential confounders; covariates in the final models included gender, IMDC score at index, stage at diagnosis, clear cell, CCI score, year of index, and sites of metastasis (ie, lymph node, liver, or lung), as appropriate.



This finding sparked debate among oncologists, particularly around its generalizability.[32-35] In our study, more than half of the patients initiated 1L treatment for aRCC in 2018, and roughly 40% of all patients had CN prior to their diagnosis with advanced RCC. This proportion is likely higher than would be found among patients being treated several years after the CARMENA study. However, it is also lower than observed in many of the clinical trials that TKI and IO approvals were based upon.[20,21,24,36] This shift in CN may play an important role in treatment outcomes, which may account for some of the data in this study.

There are several limitations to our study. Due to the low prevalence of non-clear cell RCC, the sample size of non-clear cell RCC in our study was too small for separate analysis. Additionally, the field of immuno-oncology is growing rapidly, with new approvals of immunotherapies occurring frequently. Given these rapid advancements, the IO-based regimens observed in this study may not reflect the evolving contemporary guidelines for aRCC treatment in the near future. The latest a patient in this study could initiate treatment was December 2020; since that time, several IO combinations have been approved, but their use was not captured in this study. Our study depended on physicians who were willing to participate and directly enter clinical data into the eDCF. Only data available in the medical records at the time of abstraction were included in this study. Therefore, data could be subject to inadvertent entry or keying errors. Clinical best response was reported by physicians as recorded in patient medical charts. No independent assessment by

blinded radiologists using RECIST was conducted, and the physicians were not required to retrospectively apply a specific set of response criteria to the patient records. The best overall response reported here is the best response reported on 1L treatment with no stringent time limits. Stable disease could have been reported as a partial response, which may have inflated best overall response. Safety data were not collected in our study, which could have impacted TTD and overall survival analysis. The adjusted median OS was not reached for any of the subgroups in this study, so we were not able to determine if there is a greater benefit to OS associated with one treatment group over another. This may have been due to the median follow-up of the study (18 months). Future studies with longer follow-up would be beneficial to our understanding of the impact of IO combination therapy on long-term benefits like overall survival.

Conclusion

After controlling baseline demographic and clinical characteristics, we found that treatment with IO combination in the real world was associated with longer TTNT, TTP, and PFS than TKI monotherapy. When compared with IO + IO, IO + TKI resulted in the longest TTNT, TTP, and PFS among IO combinations. Cox regression analysis indicated that clinical outcomes (TTP, TTNT, PFS) were prolonged for patients treated with IO combinations.

Clinical Practice Points

- Large retrospective, cross-regional (North America, Europe), real-world study evaluating treatment patterns and clinical outcomes in patients with advanced renal cell carcinoma (aRCC) initiating first treatment after 2017 amidst recent approvals of immunotherapies for aRCC.
- After controlling for baseline demographic and clinical characteristics, we found that first-line treatment with immunotherapy (IO) combinations was associated with progression-free survival (PFS) and longer time to next treatment (TTNT) than tyrosine kinase inhibitor (TKI) monotherapy.
- Among IO combinations, IO+TKI was associated with significantly improved PFS and longer TTNT than IO+IO.
- A favorable trend was observed in overall survival for patients treated with IO combination compared to those treated with TKI monotherapy but was not found to be statistically significant.

Disclosure

SPN, KLD, and EE are full-time employees of RTI Health Solutions, an independent nonprofit research organization, that was retained by Eisai, Inc. to conduct the research that is the subject of this manuscript. Their compensation is unconnected to the studies on which they work. SI is an employee of Eisai, Inc. NMT has received honoraria from Eisai Medical Research, Bristol-Myers-Squibb, Intellisphere, Oncorena, Merck Sharp & Dohme, Neoleukin, Exelixis, and AstraZeneca. He serves as a consultant and/or on a scientific advisory committee for Bristol-Myers-Squibb, Eli Lilly, Eisai Medical Research, Oncorena, Merck, Sharp & Dohme, and Nektar Therapeutics. He has received research funding from Bristol-Myers-Squibb, Nektar Therapeutics, Arrowhead Pharmaceuticals, Novartis, Calithera Biosciences, and Exelixis.

Author Contributions

EE: Methodology, formal analysis, investigation, data curation, visualization, writing-review and editing. *SI:* Conceptualization, methodology investigation, supervision, writing-review and editing. *SN:* Methodology, investigation, project administration, writing-review and editing. *KLD:* Conceptualization, supervision, writing-review and editing. *NMT:* Supervision, writing, review and editing.

Data Availability

Data from this study will not be made available.

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Supplementary materials

Supplemental Table 1 Physician Characteristics

	All Physicians (N, %)	North America (US/CA)	Europe (UK, FR, GE, SP)
	158 (100%)	**85**	**73**
Specialty (n, %)			
Medical/clinical oncology	116 (73.4)	53 (62.4)	63 (86.3)
Hematology-oncology	41 (26.0)	32 (37.7)	9 (12.3)
NIO	1 (0.6)	0 (0.0)	1 (1.4)
Years in practice (n, %)			
Mean (SD)	15.8 (6.2)	16.2 (6.8)	15.3 (5.5)
Median	16.0	16.0	16.0
Range (min, max)	11.0-20.0	10.0-21.0	11.0-19.0
Past-year advanced RCC caseload (no. of patients)			
Mean (SD)	63 (48.7)	62 (47.0)	65 (50.86)
Median	50	50	60
Range (min, max)	25-80	27-90	25-80

SD = standard deviation.

Supplemental Table 2 Additional Clinical Characteristics

	IO Combination	IO Combination, IO + IO	IO Combination, IO + TKI	TKI Monotherapy
Total patient sample (N, %)	N = 197	N = 78	N = 119	N = 250
Common conditions (> 10%) (n, %)	**N = 129**	**N = 48**	**N = 81**	**N = 180**
Hypertension	80 (40.6)	33 (42.3)	47 (39.5)	109 (43.6)
Depression	21 (10.7)	3 (3.9)	18 (15.1)	35 (14.0)
Diabetes without chronic complications	24 (12.2)	10 (12.8)	14 (11.8)	32 (12.8)
Multiple sclerosis	4 (2.0)	2 (2.6)	2 (1.7)	4 (1.6)
FGFR signaling pathway status (n, %)	**N = 40**	**N = 12**	**N = 28**	**N = 18**
Altered FGFR	7 (17.5)	2 (16.7)	5 (17.9)	7 (38.9)
Unaltered FGFR	33 (82.5)	10 (83.3)	23 (82.1)	11 (61.1)
Charleston Comorbidity Index score				
Mean (SD)	1.0 (1.1)	0.9 (1.1)	1.0 (1.1)	1.1 (1.0)
Median	1.0	1.0	1.0	1.0
Range	0.0-6.0	0.0-6.0	0.0-5.0	0.0-6.0

FGFR = fibroblast growth factor receptor; IO = immunotherapy; SD = standard deviation; TKI = tyrosine kinase inhibitor.

Supplemental Table 3 First-Line Treatment Regimens

Treatment	N	%
Sunitinib	130	26.1
Axitinib+Pembrolizumab	94	18.9
Nivolumab+Ipilimumab	78	15.7
Pazopanib	72	14.5
Sorafenib	23	4.6
Pembrolizumab	21	4.2
Cabozantinib	20	4.0
Axitinib+Avelumab	13	2.6
Nivolumab+Cabozantinib	11	2.2
Nivolumab	10	2.0
Axitinib	5	1.0
Bevacizumab	5	1.0
Other	16	3.2

Supplemental Table 4 Additional Treatment Outcomes

	Overall	IO Combination	IO Combination, IO + IO	IO Combination, IO + TKI	TKI Monotherapy
Total patient sample (N, %)	N = 498	N = 197	N = 78	N = 119	N = 250
3 most frequently received second-line regimens (n, %)					
Nivolumab	66 (34.7)	2 (4.1)	0 (0.0)	2 (8.3)	64 (50.0)
Cabozantinib	47 (24.7)	20 (40.8)	12 (48.0)	8 (33.3)	24 (18.8)
Nivolumab/ipilimumab	11 (5.8)	1 (2.0)	0 (0.0)	1 (4.2)	7 (5.5)
Reason for discontinuation (n, %)					
Adverse event/treatment intolerance related to an adverse event	12 (3.9)	3 (3.2)	–	–	8 (4.5)
Patient decision	37 (11.9)	11 (11.7)	–	–	18 (10.1)
Progressive disease	176 (56.6)	45 (47.9)	–	–	120 (67.4)
Completion of planned course of treatment	53 (17.0)	17 (18.1)	–	–	17 (9.6)
No clinical benefit with this treatment	19 (6.1)	6 (6.4)	–	–	9 (5.1)
Planned switch to another treatment regimen	5 (1.6)	2 (2.1)	–	–	2 (1.1)
Physician decision	24 (7.7)	8 (8.5)	–	–	7 (3.9)
Treatment holiday	16 (5.1)	8 (8.5)	–	–	6 (3.4)
Decision to switch to best supportive care	8 (2.6)	2 (2.1)	–	–	5 (2.8)
Lost to follow-up	4 (1.3)	1 (1.1)	–	–	3 (1.7)
Death	6 (1.9)	3 (3.2)	–	–	3 (1.7)
Other	1 (0.3)	0 (0.0)	–	–	0 (0.0)
Don't know	9 (2.9)	2 (2.1)	–	–	7 (3.9)

IO = immunotherapy; TKI = tyrosine kinase inhibitor.

Supplemental Table 5 Additional Clinical Outcomes

	IO Combination	IO Combination, IO + IO	IO Combination, IO + TKI	TKI Monotherapy
Total patient sample (N, %)	(N = 197)	(N = 78)	(N = 119)	(N = 250)
Criteria used to assess best response (n, %)	**N = 197**	**N = 78**	**N = 119**	**N = 250**
CT scan	155(79.1)	69(89.6)	86(72.3)	186(77.2)
PET-CT	44(22.5)	9(11.7)	35(29.4)	45(18.7)
Ultrasound	16(8.2)	6(7.8)	10(8.4)	20(8.3)
MRI	29(14.8)	9(11.7)	20(16.8)	21(8.7)
X-ray	4(2.0)	3(3.9)	1(0.8)	8(3.3)
Biopsy	7(3.6)	1(1.3)	6(5.0)	3(1.2)
Clinical assessment	11(5.6)	3(3.9)	8(6.7)	10(4.2)
Other: bone scan	4(2.0)	2(2.6)	2(1.7)	2(0.8)
Unknown	7(3.6)	1(1.3)	6(5.0)	12(5.0)
Number of patients who died during follow-up (n, %)	27(13.7%)	15(19.2%)	12(10.1%)	52(20.8%)
Reason for death (n, %)				
RCC related	22(81.5)	12(80.0)	10(83.3)	34(65.4)
Not RCC related	3(11.1)	1(6.7)	2(16.7)	17(32.7)
Don't know	2(7.4)	2(13.3)	0(0.0)	1(1.9)

CT = computerized tomography; IO = immunotherapy; PET-CT = positron emission tomography–computerized tomography; MRI = magnetic resonance imaging; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor.