Real-world treatment patterns and healthcare resource utilization in patients with metastatic renal cell carcinoma

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BACKGROUND

- Renal cell carcinoma (RCC) is one of the most common tumor types in the United States, with an estimated 73,820 new cases and 14,770 deaths in 2019[1]
- The prognosis of patients with RCC is relatively good when the disease is detected early, with a 5-year survival rate as high as 92.5%[2]
- However, as most RCCs are asymptomatic, as many as 1 in 3 cases are at an advanced stage at diagnosis.[3] The 5-year survival rate drops to 69.6% in patients with regional metastases and 12.0% in those with distant metastases[2]
- Until recently, a number of agents targeting the vascular endothelial growth factor pathway, tyrosine kinases (TKIs), or the mechanistic target of rapamycin kinase (mTOR) pathway were at the core of first-line (1L) and second-line treatments for metastatic RCC (mRCC)[4]
- The recent approval of both immuno-oncology (IO) regimens and IO-based combinations has drastically changed the treatment landscape in mRCC[5-7]
- Evidence about contemporary treatment patterns and outcomes in patients with mRCC who are treated in a real-world setting is limited

OBJECTIVE

- To describe real-world treatment patterns and healthcare resource utilization (HRU) in patients with mRCC

METHODS

Data source

- This retrospective claims-based analysis was conducted using medical and pharmacy claims from the HealthCore Integrated Research Database (HIRD) from June 30, 2014, to June 30, 2019
- The HIRD contains longitudinal medical and pharmacy claims on >47 million patients in the United States covered by Blue Cross and/or Blue Shield licensed plans

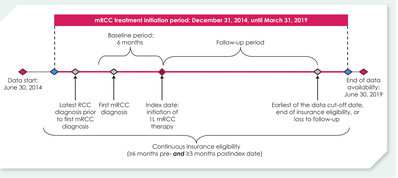
Patient selection and study design

- The study used an intent-to-treat design (**Figure 1**)
- Adult patients with a diagnosis of mRCC (**Figure 2**) followed by ≥1 systemic therapy between December 31, 2014, and March 31, 2019, were selected
  - The date of the first dispensing for a systemic therapy was defined as the index date and considered as the date of initiation of 1L therapy for mRCC
- Patients were required to have continuous health plan eligibility for ≥6 months prior to and ≥3 months after the index date
- Patient observation period started on the index date and continued until the earliest of the data cut-off date, end of insurance eligibility, or loss to follow-up

Study cohorts

- Patients who met the selection criteria were stratified into mutually exclusive cohorts based on the treatment regimen initiated in 1L: (1) IO, (2) TKI, (3) mTOR, and (4) other therapies (patients initiating interleukin-2 or bevacizumab)
- Patients initiating a combination therapy including treatments from >1 class (eg, IO + TKI) were classified based on the order of priority listed above; this represented <1% of patients

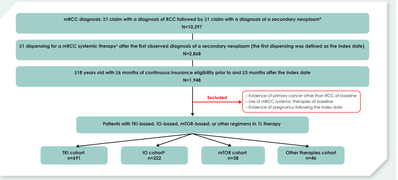
Figure 1. Study design



Identification of lines of therapy

- A line of therapy was defined as the time between the initiation of the treatment regimen to the earlier of either (1) the discontinuation of the regimen, defined as a treatment gap ≥90 consecutive days, or (2) a switch to any other systemic therapy
  - For oral treatments, treatment gaps were measured between the end of the days of supply of a filled prescription and the subsequent filled prescription
- For injections/infusions, the planned date of the next injection/infusion was used as the starting point to measure treatment gaps

Figure 2. Patient selection flow chart



* Diagnosis codes for RCC included ICD-9-CM codes: 189.0x, 189.1x and ICD-10-CM codes: C64.x, C65.x. Diagnosis codes for secondary neoplasm included ICD-9-CM codes: 196.x, 197.x, 198.x, 199.x and ICD-10-CM codes: C45.9, C77.x, C78.x, C79.x, C80.x
† Systemic therapies included: axitinib, cabozantinib, erlotinib, lenvatinib, pazopanib, sorafenib, sunitinib, everolimus, temsirolimus, avelumab, ipilimumab, nivolumab, pembrolizumab, interleukin-2, and bevacizumab
‡ One patient was on a combination of IO and TKI, and 1 patient was on a combination of IO and bevacizumab

Outcomes

Baseline characteristics

- The following variables were assessed on the index date or during the baseline period:
  - Demographic characteristics: age and sex as of the index date
  - Clinical characteristics: metastatic sites prior to/on the index date, Charlson Comorbidity Index (CCI), and presence of selected comorbidities at baseline
  - HRU at baseline

Treatment patterns

- The following metrics were assessed:
  - The most common treatment regimens received in 1L therapy
  - Median duration of the 1L therapy (in months), assessed using Kaplan-Meier analyses
  - Sequences of therapy received following initiation of 1L therapy up to the end of third-line (3L) therapy, at the class level and the treatment regimen level

HRU

- All-cause HRU during 1L therapy and during the follow-up period were assessed and compared between cohorts for the following categories:
  - Inpatient (IP) stays
  - Emergency department (ED) visits
  - Outpatient (OP) visits associated with mRCC treatment administration (ie, visits associated with Healthcare Common Procedure Coding System codes for mRCC treatments)
  - Other OP visits
  - Hospice/long-term care stays
  - Other ambulatory encounters

Statistical analyses

Baseline characteristics

- Patient characteristics were compared between cohorts using Wilcoxon rank-sum tests for continuous variables and Fisher exact tests for categorical variables

HRU

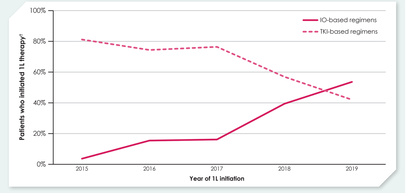
- HRUs were reported as incidence rates (IRs) per-patient-per month (PPPM) to account for the varying length of observation across patients
- Comparisons between cohorts were conducted using negative binomial regression models adjusting for age, sex, CCI, presence of lymph node metastases, number of metastatic sites, OP visits, and IP stays at baseline
- Results were reported as incidence rate ratios (IRRs) with their associated 95% CIs

RESULTS

Therapy trends

- A total of 997 patients were identified, 691 (69.3%) received TKI-based regimens, 222 (22.3%) IO-based regimens, 38 (3.8%) mTOR-based regimens, and 46 (4.6%) other therapies in 1L (**Figure 2**)
- Stratification by year of 1L initiation showed a sharp increase in 1L use of IO-based regimens from 2017 (16.2%) to 2018 (39.4%) and 2019 (53.6%) (**Figure 3**)

Figure 3. Trends over time in 1L treatment for mRCC by drug class (2015-2019)*



* Trend lines for the mTOR and other therapies cohorts were not included because counts/percentages computed based on <11 patients were masked for privacy reasons
† Percentages are calculated out of the total population, including the mTOR and other therapies cohorts

- Because only a few patients were treated with mTOR-based regimens and other therapies, outcomes assessment and comparisons focus on the TKI and IO cohorts

Patient baseline characteristics

Table 1. Baseline characteristics

	All patients (IO, TKI, mTOR, and other therapies cohorts) N=997	TKI cohort N= 691	IO cohort N=222	p value (TKI vs IO)
Demographics				
Age, mean ± SD (median)	60.99 ± 10.56 (61)	61.04 ± 10.41 (61)	61.70 ± 10.34 (61)	0.5000
Male, n (%)	725 (72.72)	495 (71.64)	166 (74.77)	0.3888
Clinical characteristics				
Metastatic sites recorded prior to or on the index date, n (%)				
Bone	364 (36.51)	244 (35.31)	88 (39.64)	0.2618
Brain	117 (11.74)	73 (10.56)	33 (14.86)	0.0917
Liver	164 (16.45)	109 (15.77)	39 (17.57)	0.5310
Lung	572 (57.37)	382 (55.28)	133 (59.91)	0.2436
Lymph nodes	319 (32.00)	203 (29.38)	87 (39.19)	0.0079*
No. of metastatic sites, mean ± SD (median)	1.54 ± 0.92 (1.00)	1.46 ± 0.88 (1.00)	1.71 ± 0.99 (2.00)	0.0003*
CCI, mean	7.46	7.43	7.64	0.1114
Presence of selected comorbid conditions, n (%)				
Chronic kidney disease	252 (25.28)	176 (25.47)	52 (23.42)	0.5931
Chronic obstructive pulmonary disease	108 (10.83)	79 (11.43)	22 (9.91)	0.6229
Diabetes	278 (27.88)	205 (29.67)	58 (26.13)	0.3489
Hyperlipidemia	460 (46.14)	325 (47.03)	99 (44.59)	0.5370
Hypertension	667 (66.90)	462 (66.86)	148 (66.67)	1.0000
Ischemic heart disease	201 (20.16)	140 (20.26)	48 (21.62)	0.7028
Liver disease	226 (22.67)	155 (22.43)	55 (24.77)	0.4649
Other cardiovascular disease	312 (31.29)	227 (32.85)	63 (28.38)	0.2460
No. of selected comorbid conditions, mean ± SD (median)	2.51 ± 1.78 (2.00)	2.56 ± 1.80 (2.00)	2.45 ± 1.81 (2.00)	0.3416
Economic measures				
All-cause HRU PPPM, mean ± SD (median)				
IP stays	0.15 ± 0.21 (0.00)	0.15 ± 0.22 (0.17)	0.12 ± 0.18 (0.00)	0.0494*
OP visits	2.77 ± 2.00 (2.37)	2.68 ± 1.91 (2.37)	2.85 ± 1.58 (2.54)	0.0351*
ED visits	0.07 ± 0.14 (0.00)	0.08 ± 0.15 (0.00)	0.07 ± 0.12 (0.00)	0.7361
Hospice/long-term care stays	0.00 ± 0.00 (0.00)	0.00 ± 0.00 (0.00)	0.00 ± 0.00 (0.00)	–
Other ambulatory encounters	0.50 ± 1.29 (0.00)	0.50 ± 1.30 (0.00)	0.44 ± 1.10 (0.00)	0.4217

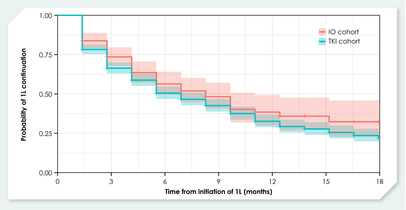
* Statistically significant at the 5% level

- Of the 997 patients identified, mean age was 61 years, and most patients were male (72.7%)
- No statistically significant differences were observed between cohorts with regard to CCI and selected comorbid conditions (**Table 1**)
- Patients in the IO cohort had a statistically significantly greater number of metastatic sites (1.71 vs 1.46; p=0.0003) and lymph node involvement (39.2% vs 29.4%; p=0.0079) compared with TKI patients
- When compared with the TKI cohort, the mean number of OP visits PPPM at baseline was statistically significantly higher in the IO cohort (2.85 vs 2.68, p=0.0351). In contrast, the mean number of IP stays PPPM at baseline was statistically significantly lower in the IO cohort (0.12 vs 0.15, p=0.0494)

Treatment patterns

- Most common 1L treatment regimens in the TKI cohort were pazopanib (54.1%) and sunitinib (29.7%). In the IO cohort, treatment regimens received were split almost equally between ipilimumab + nivolumab combination (48.2%) and nivolumab monotherapy (45.5%)
- Median duration of 1L therapy was 6.9 and 8.3 months for the TKI and IO cohorts, respectively (p=0.1033) (**Figure 4**)

Figure 4. Duration of 1L therapy by treatment cohort



- Over the follow-up period (median: TKI=13.7 months; IO=7.7 months), 54.4% of patients in the TKI cohort and 29.3% of patients in the IO cohort received ≥2 lines of therapy
  - Most patients who received only 1 line of therapy were still treated with their 1L therapy as of the end of the follow-up period (TKI=72.7%; IO=75.2%)
- Sequences of treatments received at the class level are presented in **Tables 2a** and **2b**
- **Figure 5** presents the most common treatment sequences observed at the regimen level (sequences with ≥11 patients)

Table 2a. Treatment sequences in the TKI cohort

Sequence of treatment*	No. of patients (%) N=691
TKI	315 (45.6)
TKI → IO	142 (20.6)
TKI → TKI	67 (9.7)
TKI → IO → TKI	58 (8.4)
TKI → TKI → IO	36 (5.2)
TKI → IO → IO	21 (3.0)
TKI → TKI → TKI	12 (1.7)
TKI → mTOR	11 (1.6)

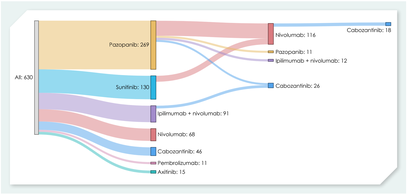
* Treatment sequences were not reported for 29 patients because counts/results computed based on <11 patients were masked for privacy reasons

Table 2b. Treatment sequences in the IO cohort

Sequence of treatment*	No. of patients (%) N=222
IO	157 (70.7)
IO → TKI	30 (13.5)
IO → IO	15 (6.8)

* Treatment sequences were not reported for 20 patients because counts/results computed based on <11 patients were masked for privacy reasons

Figure 5. Treatment sequences (with ≥11 patients) from 1L to 3L therapy following mRCC diagnosis - at the regimen level



HRU during 1L therapy

- When compared with the IO cohort, the IRs of OP visits not related to treatment administration (IRs PPPM: 2.99 vs 2.57; p<0.05) and other ambulatory encounters (IRs PPPM: 0.78 vs 0.60; p<0.05) were statistically significantly higher for the TKI cohort (**Table 3**)
- The IRs of OP visits for mRCC treatment administrations were statistically significantly higher for the IO cohort compared with the TKI cohort (IRs PPPM: 1.56 vs 0.02; p<0.05)
  - However, this difference is explained by the treatments' respective route of administration (ie, infusion for IO and oral for TKI)
- Frequency of other 1L HRU was similar between the IO and TKI cohorts

HRU during the follow-up period

- Findings remained consistent when assessing HRU during the entire follow-up period, except for OP visits not related to treatment administration, for which the difference was no longer statistically significant

Table 3. HRU PPPM

HRU component	IRs PPPM		IRR (95% CI) TKI cohort/IO cohort	
	TKI cohort (N=691)	IO cohort (N=222)	Unadjusted	Adjusted*
1L therapy				
IP stays	0.08	0.10	1.01 (0.73-1.40)	0.98 (0.71-1.34)
Length of stay in days, mean ± SD (median)	5.09 ± 4.12 (4.00)	4.92 ± 4.04 (4.00)	–	–
ED visits	0.06	0.08	0.87 (0.64-1.18)	0.88 (0.65-1.21)
OP visits for mRCC treatment administration	0.02	1.56	0.01 (0.01-0.02)†	0.01 (0.01-0.02)†
Other OP visits	2.99	2.57	1.26 (1.14-1.39)†	1.26 (1.15-1.38)†
Hospice/long-term care stays	0.00	0.00	–	–
Other ambulatory encounter‡	0.78	0.60	1.61 (1.12-2.27)†	1.53 (1.07-2.14)†
Entire follow-up period				
IP stays	0.11	0.12	1.01 (0.81-1.26)	1.05 (0.84-1.31)
Length of stay in days, mean ± SD (median)	5.49 ± 4.15 (4.67)	5.61 ± 5.18 (4.33)	–	–
ED visits	0.07	0.09	0.92 (0.74-1.16)	0.96 (0.77-1.20)
OP visits for mRCC treatment administration	0.34	0.92	0.28 (0.22-0.35)†	0.27 (0.21-0.33)†
Other OP visits	2.86	2.83	1.07 (0.99-1.17)	1.08 (0.99-1.17)
Hospice/long-term care stays	0.01	0.01	1.13 (0.50-2.60)	1.14 (0.51-2.66)
Other ambulatory encounter‡	0.86	0.82	1.35 (1.01-1.78)†	1.41 (1.06-1.85)†

* Adjusted for age and sex on the index date, the presence of lymph node metastases and the number of metastatic sites prior to or on the index date, as well as the CCI, OP visits, and IP stays at baseline
† Statistically significant at the 5% level
‡ Other ambulatory encounter includes patient home, skilled nurse facilities, and other unlisted facilities

LIMITATIONS

- This study was subject to inherent limitations of administrative claims data, such as coding errors and data omissions
- Moreover, lack of clinical information (eg, disease staging, risk classification, biopsy, and laboratory results) as well as physician and patient preferences are not recorded in the database and can influence the choice of therapy
- The lines of therapy were identified based on the information available over the period covered by the data. Accordingly, it is possible that we did not observe the full treatment history for some patients, including prior therapy for mRCC
- The limited sample size of patients initiating mTOR-based regimens and other therapies did not allow for comparative analyses as initially planned
- Treatment patterns of dispensed medications were assessed based on claims for filled prescriptions and may not reflect actual utilization by patients
- For privacy reasons, all counts/results computed based on <11 patients were masked
- The HIRD database consists of patients covered by Blue Cross and/or Blue Shield licensed plans. The results may not be representative of the overall mRCC patient population in the United States or of patients covered by other types of commercial/public healthcare plans

CONCLUSIONS

- **Results from this real-world study provide a contemporary portrait of treatment patterns and HRU in the rapidly evolving treatment landscape for mRCC in the United States**
- **Novel combinations with an IO backbone are being increasingly incorporated into routine clinical practice; a sharp increase in 1L use of IO-based regimens was observed starting in 2018, with TKI and IO representing an even split in the first quarter of 2019**
- **Although duration of 1L therapy was similar in the IO and TKI cohorts, patients in the IO cohort had lower utilization of selected healthcare services**
- **Considering the array of newly approved agents and therapy combinations with complementary antitumor activity, further research is needed to inform on optimal treatment sequencing and outcomes in patients with mRCC**

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DISCLOSURES

AB and FL are employees of EMD Serono, Inc, Rockland, MA, USA; a business of Merck KGaA, Darmstadt, Germany. KR is an employee of Pfizer Inc. GG, FV, KD, MR, and EM are employees of StatLog Inc. Consultancy fees for this research were provided to StatLog Inc by EMD Serono, Inc, a business of Merck KGaA Darmstadt, Germany, and are part of the alliance between Merck KGaA and Pfizer. This research was financially supported by EMD Serono, Inc, Rockland, MA, USA; a business of Merck KGaA, Darmstadt, Germany, and is part of an alliance between Merck KGaA and Pfizer.

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