Real-world treatment patterns among patients with metastatic renal cell carcinoma receiving first-line therapy in the United States veteran population

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BACKGROUND

- Approximately 2.2% (403,262) of all incident malignant tumors worldwide are caused by renal cancers.[1] In 2018, renal cancer was diagnosed in an estimated 65,340 Americans and resulted in 14,970 deaths[2]
- Although 5-year survival rates are 90.8% for local disease and 63.3% for regional disease, the prognosis is poor for metastatic disease, with a 5-year survival rate of only 11.1%[3]
- Until recently, tyrosine kinase inhibitors (TKIs), particularly sunitinib, have been the standard-of-care for patients with advanced renal cell carcinoma (RCC) in the first-line (1L) setting. However, their clinical efficacy is limited because in many patients their disease progresses or becomes resistant to the antiangiogenic drugs[4]
- Since 2018, the US Food and Drug Administration (FDA) has approved combination regimens that include immune checkpoint inhibitors (ICIs) for the treatment of metastatic RCC (mRCC) based on their biological and clinical activity demonstrated in clinical trials[5,6]
- Veterans are susceptible to a heightened risk of renal cancer due to the high prevalence of certain risk factors, such as advancing age, obesity, and tobacco smoking[7,8]
- Despite the increased options in therapeutic approaches, to date, there has been limited real-world evidence examining mRCC treatment patterns among veterans

OBJECTIVE

- To assess patient characteristics and treatment patterns in the 1L setting among US Veterans Health Administration (VHA) patients with mRCC receiving monotherapy with TKI, mechanistic target of rapamycin (mTOR), ICI, or other therapies (Others)

METHODS

Data Source

- This retrospective claims-based study was conducted using administrative data from the VHA database between April 1, 2013 and March 31, 2018
- The VHA database, the largest integrated healthcare system in the US, contains claims data for over 9 million veterans across the nation[9]

Study Design and Patient Selection

- This was a retrospective claims-based study of patients with mRCC receiving 1L treatment
- Eligible patients included adults with ≥1 mRCC diagnosis followed by ≥1 systemic therapy during the identification period (October 1, 2013-December 31, 2017). The first systemic therapy date was designated as the index date and was considered the start of the 1L
- Patients were required to have continuous enrollment from ≥6 months prior to the mRCC diagnosis until ≥3 months post-index date to ensure the availability of complete patient history
- Patients who had any mRCC systemic therapy during the 6 months pre-index date (baseline period) and who had evidence of diagnosis for other cancer (other than RCC) in the 6 months pre-mRCC diagnosis date were excluded
- Patient data were assessed from index date to the earliest of death, health plan disenrollment, or study end

Cohort Assignments

- Based on the 1L systemic therapy initiated, patients were stratified into the following cohorts: TKI, mTOR, ICI, or Others

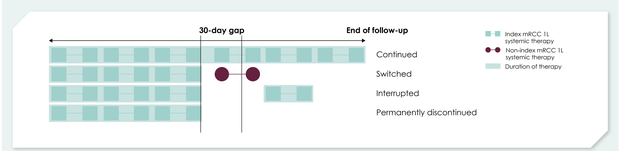
Baseline Characteristics

- The following study variables were assessed on the index date or during the baseline period:
  - Sociodemographic variables: age, sex, and race;
  - Clinical characteristics: Quan-Charlson Comorbidity Index (CCI) scores, National Cancer Institute (NCI) version of the CCI, and baseline comorbidities; and
  - Economic measures: all-cause healthcare resource utilization (HCRU) and healthcare costs per patient per month (PPPM)

Line of Treatment Algorithm

- 1L regimen was defined based on all systemic therapies prescribed within 14 days of the index date
- Patients were categorized as having switched to non-index therapy, interrupted, permanently discontinued, or continued index systemic therapy as defined in **Figure 1**
- The start of second-line (2L) systemic therapy was defined based on the earliest evidence of switching to any non-index systemic therapy from 1L
- Duration of 1L therapy was measured from index date to the earliest of last index prescription's end date, a day before the start of 2L therapy start date, or follow-up end (**Figure 1**):
  - For patients with interrupted 1L systemic therapy, the treatment holiday period was not included in the calculation of duration of therapy and only the days with index therapy exposure before and after the treatment holiday period were added
  - The recommended dosing schedule for sunitinib is 4 weeks of drug administration followed by 2 weeks off therapy. However, the majority of the sunitinib claims had 28 or 30 days of supply, which does not account for the 2-week off period. Therefore, a 42-day supply was applied for all claims of sunitinib with 28 or 30 days of supply to better reflect the 4-week on, 2-week off dosing schedule[10,11]

Figure 1. Treatment Line Algorithm



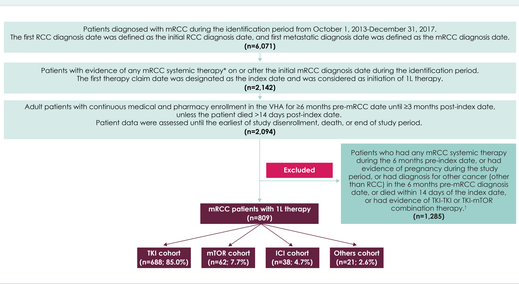
Treatment line algorithm figure adapted from MacLean et al. (2016) with modifications[10]

Statistical Analysis

- Analyzing differences in patient characteristics and treatment patterns:
  - Descriptive statistics were presented for all variables
  - Bivariate analysis was conducted using $\chi 2$ tests and student t-tests to assess the differences for categorical and continuous variables, respectively
  - Event rate was calculated by dividing the number of patients who had the event by the person-years at risk for developing the event. Univariate Poisson regression was used to compare patients treated with TKI vs mTOR, ICI, or other therapy, separately, based on rates (in 100-person years [100-PYs])
  - Kaplan-Meier analysis was used to examine median duration (in days) of 1L therapies
- Sensitivity analysis:
  - *Days of supply for nivolumab:*
    - Based on the recommended treatment regimen of using nivolumab + ipilimumab on an administration schedule of every 3 weeks, a 21-day supply was used to calculate the treatment pattern for nivolumab for the main analysis
    - However, real-world application using nivolumab as monotherapy in the 1L for mRCC treatment was observed. To strengthen the validity of the main analysis, we conducted a sensitivity analysis using a 14-day supply for nivolumab monotherapy as the regimen schedule is indicated to be every 2 weeks
  - *Channeling bias:* Given the approval of ICI therapies in late 2015 by the US FDA, channeling bias may have affected the results. Hence, we conducted a sensitivity analysis using an identification period from 2016-2017 to account for the bias

RESULTS

Figure 2. Patient Selection and Attrition



* mRCC systemic therapies include TKIs (pazopanib, sunitinib, axitinib, cabozantinib, sorafenib, lenvatinib, erlotinib), mTOR (temsirolimus, everolimus), ICIs (ipilimumab, nivolumab, atezolizumab, pembrolizumab), and Others (high dose interleukin-2, bevacizumab, interferon alfa-2b, interferon alfa-2a)
† Patients on combined treatments were excluded from the study for simplified interpretation of the results
RCC diagnosis was identified based on ICD-9-CM diagnosis codes 189.0 and 189.1 and ICD-10-CM diagnosis codes C64 and C65. Metastasis diagnosis on or after initial RCC diagnosis date was identified based on ICD-9-CM diagnosis codes 196, 197, 198, and 199 and ICD-10-CM diagnosis codes C77, C78, C79, and C45.9

Baseline Characteristics

- Across all treatment cohorts, mean age ranged from 65-69 years and the majority of the patients were white men with high mean Quan-CCI scores (**Table 1**)
- Compared with the TKI cohort (**Table 1**):
  - Patients in the Others cohort were significantly younger;
  - The ICI cohort was significantly more likely to have comorbid chronic pulmonary disease but significantly less likely to have metastatic solid tumors;
  - The mTOR cohort had significantly higher baseline all-cause pharmacy visits PPPM;
  - The ICI cohort encountered significantly higher baseline all-cause total costs PPPM; and
  - Patients in the Others cohort incurred significantly higher baseline all-cause outpatient stay costs PPPM and pharmacy costs PPPM

Table 1. Baseline characteristics of mRCC patients receiving various 1L therapies

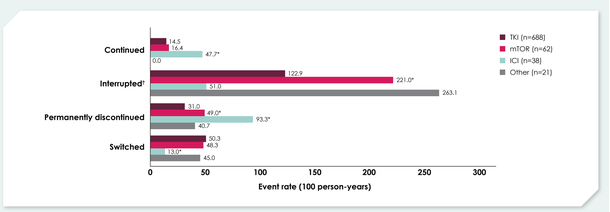
Demographic and Clinical Characteristics	TKI cohort (N=688)	mTOR cohort (N=62)	p-value*	STD	ICI cohort (N=38)	p-value*	STD	Others cohort (N=21)	p-value*	STD
Age (years), mean ± SD	68.7 ± 9.7	67.1 ± 11.6	0.3099	14.5	67.0 ± 7.9	0.5671	18.5	65.1 ± 13.4	0.0127	30.5
Age Category, n (%)										
<65 years	188 (27.3)	19 (30.6)	0.5755	7.3	12 (31.6)	0.5684	9.3	12 (57.1)	0.0048	62.4
≥65 years	500 (72.7)	43 (69.4)	0.5755	7.3	26 (68.4)	0.5684	9.3	≤11†	N/A	
Sex, n (%)										
Male	677 (98.4)	61 (98.4)	0.9933	0.1	37 (97.4)	0.6306	7.1	21 (100.0)	N/A	
Race, n (%)										
White	562 (81.7)	45 (72.6)	0.0805	21.7	23 (60.5)	0.002	47.6	16 (76.2)	0.5245	13.3
Baseline Clinical Characteristics, mean ± SD										
Quan-CCI score	9.1 ± 2.7	9.6 ± 2.1	0.0717	21.8	8.4 ± 3.5	0.3218	20.9	8.8 ± 2.3	0.9262	11.7
NCI comorbidity index	1.9 ± 1.9	2.2 ± 2.1	0.1871	16.8	2.1 ± 1.8	0.4442	8.5	1.9 ± 1.6	0.6399	0.6
Baseline Comorbidities, n (%)										
Any malignancy	662 (96.2)	61 (98.4)	0.3805	13.4	37 (97.4)	0.7175	6.5	21 (100.0)	N/A	
Chronic pulmonary disease	115 (16.7)	14 (22.6)	0.2411	14.7	12 (31.6)	0.022	35.0	≤11†		
Diabetes w/o chronic complications	251 (36.5)	23 (37.1)	0.9234	1.3	13 (34.2)	0.7769	4.7			
Metastatic solid tumor	624 (90.7)	60 (96.8)	0.1057	25.2	29 (76.3)	0.0061	39.1	18 (85.7)	0.4462	15.3
Other	349 (50.7)	32 (51.6)	0.8937	1.8	17 (44.7)	0.4731	11.9	13 (61.9)	0.3166	22.4
Mean Baseline Economic Measures										
Baseline All-Cause HCRU (days PPPM), mean ± SD										
Inpatient LOS	1.9 ± 4.8	3.8 ± 12.2	0.2233	20.7	2.5 ± 4.6	0.4777	12.3	1.7 ± 3.4	0.8252	4.8
Inpatient visit	0.2 ± 0.4	0.3 ± 0.4	0.2997	13.6	0.3 ± 0.4	0.5152	12.8	0.2 ± 0.2	0.6769	14.1
Outpatient visit	2.9 ± 1.9	3.2 ± 1.9	0.1625	18.3	3.9 ± 2.1	0.0007	54.3	3.5 ± 2.1	0.1243	31.6
Pharmacy visit	2.7 ± 2.1	3.3 ± 2.3	0.0253	28.3	4.0 ± 2.7	0.0003	55.8	2.6 ± 2.1	0.9161	2.3
Baseline All-Cause Healthcare Costs ($ PPPM), mean ± SD										
Inpatient stay costs	2,352 ± 4,625	3,185 ± 5,429	0.1817	16.5	3,249 ± 6,000	0.0525	16.8	2,878 ± 4,880	0.3629	11.0
Outpatient stay costs	1,936 ± 1,798	1,990 ± 1,864	0.8215	2.9	5,062 ± 5,845	<.0001	72.3	3,164 ± 2,602	0.0266	54.9
Pharmacy costs	239 ± 720	573 ± 1,380	0.0641	30.4	3,504 ± 7,829	<.0001	58.7	404 ± 849	0.0177	21.0
Total costs	4,527 ± 5,665	5,748 ± 6,724	0.1104	19.6	11,816 ± 14,255	<.0001	67.2	6,446 ± 5,276	0.1107	35.1

LOS: length of study; **SD**: standard deviation; **STD**: standardized differences
* Pair-wise comparison between each cohort vs TKI cohort
† Results with sample sizes ≤11 could not be reported pursuant the VHA data user agreement

Treatment Pattern

- Compared with the TKI cohort (**Figure 3**):
  - The ICI cohort had a significantly lower switching rate and a significantly higher continuation rate and permanent discontinuation rate
  - The mTOR cohort had a significantly higher permanent discontinuation rate and interruption rate

Figure 3. Treatment Patterns in Patients with mRCC Receiving Various 1L Therapies

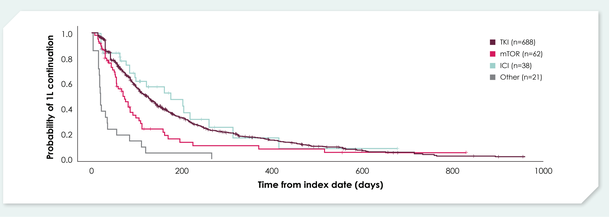


* Drug vs TKI: significant at p<0.05
† Patients with interrupted 1L therapy were considered as a part of 1L until a subsequent event of continuation, switch or permanent discontinuation was observed

Duration of 1L Therapy

- The median duration of 1L therapy in patients treated with TKI, mTOR, ICI, and other therapy was 121, 69, 175, and 20 days, respectively (Log-rank p<0.0001, **Figure 4**)

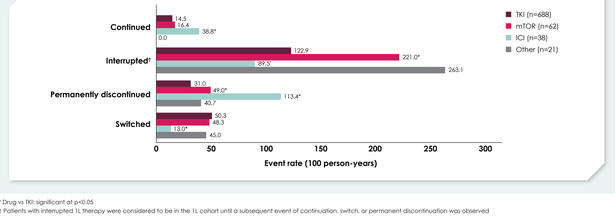
Figure 4. Kaplan-Meier Curve for Duration of 1L Therapy by Treatment Cohort



Sensitivity Analysis

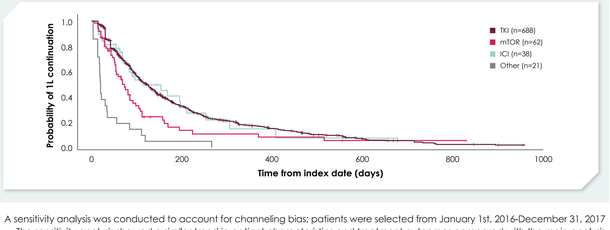
- A sensitivity analysis for treatment pattern using 14 days of supply for nivolumab was conducted to account for administration schedule of once every 2 weeks for nivolumab monotherapy:
  - The trend for the treatment pattern using 14 days of supply for nivolumab remained consistent with the main analysis (**Figure 5**)
  - The duration of 1L therapy from KM curve remained significantly differently among treatment cohorts (Log-rank p<0.0001, **Figure 6**). However, the median duration of 1L therapy in patients treated with ICI was numerically lower using a 14-day vs 21-day supply (114 days vs 175 days)

Figure 5. Sensitivity Analysis: Treatment Patterns in Patients with mRCC Receiving Various 1L Therapies



* Drug vs TKI: significant at p<0.05
† Patients with interrupted 1L therapy were considered to be in the 1L cohort until a subsequent event of continuation, switch, or permanent discontinuation was observed

Figure 6. Sensitivity Analysis: Kaplan-Meier Curve for Duration of 1L Therapy by Treatment Cohort



- A sensitivity analysis was conducted to account for channeling bias; patients were selected from January 1st, 2016-December 31, 2017
  - The sensitivity analysis showed a similar trend in patient characteristics and treatment outcomes compared with the main analysis (data not shown)

DISCUSSION

- This is the first retrospective real-world study examining patterns of 1L treatment patterns in elderly male veterans with mRCC
- The median duration of therapy among patients with mRCC receiving monotherapy with TKI, mTOR, and ICI was short in our study (ranged from 0.7 to 5.8 months). As observed in recent clinical trials, the ICI+TKI combination therapies have demonstrated notably longer duration of therapy (avelumab + axitinib: median of 8.6 months[12]; pembrolizumab + axitinib: median of 8.3 months[13]) relative to the monotherapies used in a real-world setting, as seen in our study
- Future real-world studies should evaluate the clinical outcomes, tolerability, and side effects profile of various 1L treatment regimens among patients with mRCC
- While evaluating the actual dose of nivolumab in the ICI monotherapy cohort, we observed that the administration schedule of once every 2 weeks was more accurate. Thus, future analyses will be pursued using a 14-day supply of nivolumab

LIMITATIONS

- These findings are subject to administrative claims data limitations, eg, coding errors or lack of certain clinical and disease-specific information that could influence study outcomes. Also, diagnostic codes on health claims do not indicate disease presence
- Patients were placed into 4 cohorts by systemic therapy initiation, but misclassification is possible, as patients may be in different disease stages or have differing health status
- Pursuant to the VHA data user agreement, results with sample sizes ≤11 could not be reported
- The results from this study may not be generalizable to female, younger, or uninsured patients. However, findings from VHA studies are largely consistent with those from previous retrospective studies in patients with other cancer types having commercial health plan coverage[14]

CONCLUSIONS

- **These descriptive findings provide important insights into the real-world treatment patterns in patients with newly-diagnosed mRCC in the VHA population**
- **Despite all treatment cohorts having received a limited duration of therapy, patients with mRCC who were treated with a 1L TKI showed similar duration vs those who were treated with a 1L ICI. However, ICI therapy demonstrated higher continuation rates compared with TKI therapy**
- **Based on existing real-world literature, current monotherapy treatment approaches in the 1L setting among patients with mRCC indicate the presence of unmet needs, and consequently the need for leveraging ICI combination regimens with different mechanisms of action, such as ICIs + TKIs, for improved clinical outcomes in patients with mRCC**

DISCLOSURES

AB, GP, and HP are employees of EMD Serono Inc., Rockland, Massachusetts, USA. RK is an employee of Pfizer Inc., New York, NY. SK is an employee of Pfizer Inc., Collegeville, PA. SP and LW are employees of STATinMED Research, Plano, TX, USA. Funding for this research was provided to STATinMED by EMD Serono Inc., a business of Merck Healthcare KGaA, as part of an alliance between Merck Healthcare KGaA and Pfizer Inc.

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