IMPACT RCC real-world study: economic impact of early progression among patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors in the first-line setting

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BACKGROUND

- In 2020, the estimated number of new cases of renal cell carcinoma (RCC) in the United States is 73,750 with an estimated 14,830 deaths[1]
- An estimated 25% to 30% of cases are diagnosed as advanced or metastatic RCC (mRCC),[2] and another 20% to 40% of cases are diagnosed as localized disease that will progress to mRCC,[3] which is associated with a poor 5-year relative survival rate of 8% to 12%[1]
- Since progression-free survival (PFS) directly predicts overall survival, use of optimal first-line (1L) treatment options is critical to prolonging survival in these patients with mRCC[4]
- Until early 2018, tyrosine kinase inhibitors (TKIs), such as sunitinib and pazopanib, were the standard of care for 1L treatment of mRCC[5]; however, these drugs are associated with drug resistance and rapid progressive disease, as demonstrated by a median PFS of ≈8 months[6]
- At present, there is a dearth of available medical literature that could assist in quantifying the potential financial impact of early progression in mRCC on the healthcare system

OBJECTIVE

- To assess the economic impact of early disease progression in patients with mRCC treated with 1L TKIs followed by second-line (2L) therapy in the US Veterans Health Administration (VHA) database

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 United States, contains claims data for over 9 million veterans[7]

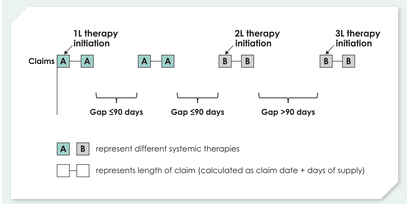
Study design and patient selection

- This was a retrospective claims-based study of patients with mRCC who received 1L therapy with TKI agents and advanced to 2L therapy
- Eligible patients included adults with ≥1 mRCC diagnosis followed by ≥1 systemic therapy during the identification period (October 1, 2013, to March 31, 2018); the first systemic therapy date was designated as the index date and was considered the start of 1L therapy
- Patients were required to have continuous enrollment from ≥6 months prior to the mRCC diagnosis (baseline period) until ≥6 months after the index date to ensure the availability of complete patient histories
- Patients who had any mRCC systemic therapy during the 6 months prior to the index date, had evidence of diagnosis of another cancer (other than RCC) in the 6 months prior to the mRCC diagnosis date, had received TKI-TKI and TKI-mechanistic target of rapamycin kinase (mTOR) combinations, or were pregnant during the study period were excluded
- Among patients who received 1L TKI therapy, patients who had received a 2L therapy, defined as the earliest of a switch to a non-index systemic therapy (ie, different TKI therapy from 1L or an ICI or mTOR therapy) or reinitiation of 1L therapy after a >90 day gap, were identified; selected patients were required to have continuous enrollment for ≥6 months after the 2L initiation date, unless the patient died >14 days after the 2L initiation date
- Patient data were assessed from the index date until death or study end, whichever was earlier

Line of treatment algorithm

- The 1L regimens were defined based on all systemic therapies administered within 14 days of the index date (**Figure 1**)

Figure 1. Treatment line algorithm



3L, third-line

Cohort assignments

- Based on the Kaplan-Meier–derived median time from the index date to 2L initiation, patients were stratified into 2 progression groups: early progression (≤ median) and delayed progression (> median) cohorts

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, time from mRCC diagnosis to index date, and baseline comorbidities
  - *Economic measures*: all-cause per-patient-per-month (PPPM) healthcare resource utilization (HCRU) and healthcare costs

Economic outcomes

- All-cause and mRCC-related PPPM HCRU and healthcare costs were examined from the index date until the end of follow-up (ie, death or end of study period [March 31, 2018], whichever was earlier)
- Medical claims with a diagnosis code for mRCC and pharmacy claims for mRCC systemic therapies were considered for calculation of mRCC-related PPPM HCRU and healthcare costs until the end of follow-up
- HCRU and healthcare costs were reported according to site of care: inpatient, outpatient, and pharmacy. In addition, medical (inpatient + outpatient) and total (medical + pharmacy) costs were reported

Statistical analysis

Descriptive analysis

- Analyzing differences in patient characteristics between the cohorts:
  - Descriptive statistics were presented for all variables
  - Bivariate analyses were conducted using χ^2 tests and Student *t* tests to assess differences in categorical and continuous variables, respectively; p<0.05 was considered statistically significant
  - Standardized differences (STDs), defined as the absolute difference in sample means divided by an estimate of the pooled standard deviation and multiplied by 100, were calculated for each variable

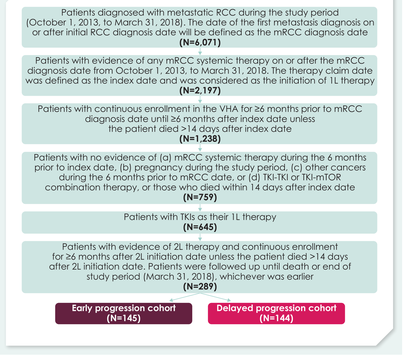
Multivariable analysis

- Generalized linear models (GLMs) with negative binomial and gamma distributions were used to estimate the mean all-cause and mRCC-related HCRU and healthcare costs, respectively
- Covariates included in the GLMs were age, sex, and race, Quan-CCI score, time from mRCC diagnosis to the index date (≤1 year, >1 year), and number of inpatient, outpatient, and pharmacy visits during the baseline period

RESULTS

- Among a total of 289 eligible patients with mRCC, the median time from 1L to 2L therapy initiation was 6 months
- Based on this median, 50.2% (n=145) and 49.8% (n=144) were included in the early and delayed progression cohorts, respectively (**Figure 2**)

Figure 2. Patient selection



Baseline characteristics

- The average age of the total population was 67.5 years, and most patients were white men (n=231 [80%]), with a high average Quan-CCI score of 9.0
- All-cause baseline HCRU and healthcare costs were generally higher for the early vs delayed progression cohort; however, these differences were not statistically significant (**Table 1**)
- No significant differences were observed in other demographic and clinical characteristics between patients in the early and delayed progression cohorts (**Table 1**)

Table 1. Demographic and baseline clinical characteristics, by progression status

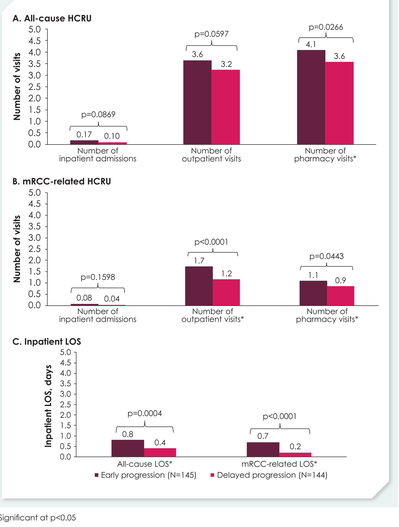
Demographic and baseline (6 months pre-index) clinical characteristics	Patients with mRCC receiving 2L therapy			
	Early progression cohort (N=145)	Delayed progression cohort (N=144)	p value	STD
Age, mean ± SD, (median), years	68.0 ± 7.9 (68)	66.7 ± 8.2 (67)	0.1676	16.3
Age group, n (%)				
<65 years	39 (26.9)	46 (31.9)	0.3464	11.1
≥65 years	106 (73.1)	98 (68.1)	0.3464	11.1
Sex, n (%)				
Male	143 (98.6)	140 (97.2)	0.4045	9.8
Race, n (%)				
White	119 (82.1)	112 (77.8)	0.3625	10.7
Comorbid condition, mean ± SD (median)				
Quan-CCI score	8.9 ± 2.8 (9.0)	9.2 ± 2.8 (9.0)	0.3868	10.2
NCI-CCI	1.9 ± 1.9 (1.6)	1.9 ± 1.8 (1.6)	0.9819	0.3
CCI conditions, n (%)				
Any malignancy	140 (96.6)	140 (97.2)	0.7428	3.8
Chronic pulmonary disease	24 (16.6)	27 (18.8)	0.6240	5.7
Diabetes without chronic complications	54 (37.2)	53 (36.8)	0.9388	0.9
Metastatic solid tumor	126 (86.9)	130 (90.3)	0.3662	10.6
Renal disease	40 (27.6)	47 (32.6)	0.3491	11.0
Time from mRCC diagnosis date to index date, mean ± SD (median), days	100.1 ± 173.0 (33)	103.2 ± 163.4 (46)	0.8738	1.9
Time to index date ≤1 year, n (%)	135 (93.1)	132 (91.7)	0.6452	5.4
Baseline all-cause PPPM HCRU, mean ± SD (median)				
Inpatient visits, n	0.2 ± 0.4 (0.0)	0.2 ± 0.3 (0.0)	0.2524	13.5
Inpatient LOS, days	0.6 ± 1.2 (0.0)	0.4 ± 0.9 (0.0)	0.1046	19.1
Outpatient visits, n	3.1 ± 2.2 (2.7)	2.7 ± 1.9 (2.3)	0.1039	19.2
Pharmacy visits, n	2.6 ± 2.1(2.0)	2.6 ± 1.9 (2.3)	0.9357	0.9
Baseline all-cause PPPM healthcare costs, mean ± SD (median), $				
Inpatient stay costs	2,677 ± 5,191 (0)	1,925 ± 4,196 (0)	0.1762	15.9
Outpatient stay costs	2,196 ± 2,127 (1,682)	1,866 ± 1,745 (1,453)	0.1496	17.0
Pharmacy costs	338 ± 1,276 (85)	210 ± 425 (72)	0.2511	13.5
Medical costs	4,874 ± 5,858 (2,677)	3,791 ± 4,948 (1,945)	0.0905	20.0
Total costs	5,212 ± 6,371 (2,755)	4,000 ± 5,197 (2,013)	0.0774	20.8

LOS, length of stay

GLM-adjusted follow-up economic outcomes

- The early progression cohort had a significantly shorter mean length of follow-up than the delayed progression cohort (18.1 vs 28.9 months; p<0.0001), with respective medians of 15.1 and 27.9 months
- Compared with patients with delayed progression, those with early progression had significantly more all-cause PPPM pharmacy visits, longer all-cause PPPM length of inpatient stay, and similar all-cause PPPM inpatient admissions and outpatient visits. In addition, patients with early progression had significantly longer mRCC-related PPPM length of inpatient stay and more mRCC-related outpatient visits than those with delayed progression (**Figure 3**)

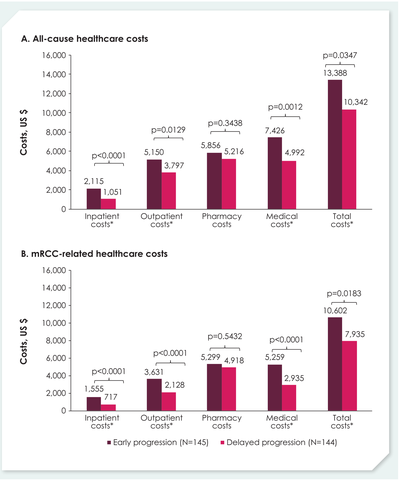
Figure 3. GLM-adjusted PPPM all-cause and mRCC-related HCRU during the follow-up period, by progression status



*Significant at p<0.05

- Similarly, patients with early progression incurred significantly higher all-cause and mRCC-related PPPM inpatient, outpatient, total medical, and total costs than those with delayed progression (**Figure 4**)
  - All-cause and mRCC-related PPPM pharmacy costs were similar among patients with early vs delayed progression

Figure 4. GLM-adjusted follow-up PPPM all-cause and mRCC-related healthcare costs during the follow-up period, by progression status



*Significant at p<0.05

DISCUSSION

- To our knowledge, this is the first retrospective real-world study examining the economic burden associated with early progression among patients with mRCC in the United States and among the VHA community
- Our results demonstrate higher HCRU and associated costs among early vs delayed progressors. The most plausible reasons for increased utilization of healthcare services and costs, especially in the outpatient setting, among patients who experienced early progression may be increased monitoring, more frequent requirement of care for RCC-related deterioration, and need for medication intensification
- Future research should explore possible reasons for the higher burden due to early progression as well as prognostic factors that inform patients who will likely progress early in order to allow for optimal choice of 1L therapy

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
- The results from this study may not be generalizable to a broader population, such as women, people without insurance, those covered by commercial health plan companies, or those covered by Medicare or Medicaid
- Progression was defined using 2L initiation as a proxy; however, a switch in regimen may have occurred for reasons other than disease progression, and the information to delineate the cause for 2L initiation was not available in the data

CONCLUSIONS

- **These findings provide important insights into the economic burden due to disease progression among patients with mRCC**
- **Patients who advanced early to 2L from 1L TKIs incurred higher PPPM HCRU and associated health care costs than patients who advanced later**
- **This underscores one of the limitations of current 2L treatment strategies for mRCC and demonstrates the need for more efficacious treatment options, such as immuno-oncology–based combination therapies, that can delay disease progression and potentially reduce the economic burden among patients with mRCC**

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DISCLOSURES

AB, YZ, and FXL are employees of EMD Serono, Inc, Rockland, MA, USA; a business of Merck KGaA, Darmstadt, Germany. VK was an employee of EMD Serono, Inc, at the time the study was conducted. RK is an employee of Pfizer Inc, New York, NY. SK is an employee of Pfizer Inc, Collegeville, PA. TEH is an employee of Texas Oncology Sammons Cancer Center, Dallas, TX, USA. SP and CD are employees of STATinMED Research, Plano, TX, USA, which received funding for this research from EMD Serono, Inc, a business of Merck KGaA, Darmstadt, Germany, as part of an 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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