Patterns of first-line targeted therapy utilization and adherence among older adults diagnosed with metastatic renal cell carcinoma

Hicks B. M*,[1] Chun D.S*,[2] Peacock Hinton S, [3] Hsu C,[2] Tan HJ,[4,5] Lund J.L[2,5]

1. Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland.
2. Department of Epidemiology, University of North Carolina, Chapel Hill, NC USA
3. Division of Pharmaceutical Outcomes and Policy, University of North Carolina, Chapel Hill, North Carolina.
4. Department of Urology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
5. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA

***** Authors made equal contribution to the manuscript

Correspondence:

Dr Blánaid Hicks
Centre for Public Health, ICSB,
Royal Victoria Hospital
Belfast, N. Ireland,
BT12 6BA
E-mail: B.Hicks@qub.ac.uk
Phone: +44 (0)28 9063 5009

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ABSTRACT

Background

Despite the rapid approval of targeted therapies for metastatic renal cell carcinoma (mRCC) evidence on real world treatment patterns remains limited. This study evaluated patterns of first-line targeted therapy utilization and adherence in older adults, a population with a high burden of RCC.

Methods

2,093 patients aged ≥66 years with a primary diagnosis of mRCC were identified from United States (US)-based cancer registry and administrative claims data (2007-2015). We included only patients with de novo disease. We assessed the initiation of first-line targeted therapy within four months of diagnosis and persistence and adherence to targeted therapy, using the proportion of days covered (PDC). Multivariable logistic regression yielded adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to describe characteristics associated with targeted therapy versus no targeted therapy initiation and for high (≥80% PDC) versus low adherence.

Results

28.8% of patients received first-line targeted therapy within four months of diagnosis, with the proportion of patients receiving targeted therapy increasing over time. Older age (one-year increment OR:0.95 95%CI 0.93, 0.97), high comorbidity burden (OR:0.65 95%CI0.46, 0.93) and clear cell histology (OR:1.54 95%CI 1.19, 2.00) were associated with targeted therapy initiation. 48.2% of patients exhibited a high PDC to oral targeted therapy at 120 days, which was attenuated with inclusion of patients who died during the time period (34.2% PDC ≥80%).

Conclusion

Increasing age, high comorbidity burden and non-clear cell histology were associated with decreased targeted therapy initiation among patients with de novo mRCC. Our findings suggest adherence to oral therapies was low; future research exploring the mechanisms and impact of low adherence in this older patient population is warranted.

Key Words: renal cell carcinoma; metastatic; targeted therapy; sunitinib; pazopanib; adherence

INTRODUCTION

Approximately half of all patients diagnosed with renal cell carcinoma (RCC) are over 65 years old and 30% are diagnosed with locally advanced or metastatic disease [1,2]. While previous treatment of metastatic RCC (mRCC) relied on the use of cytokine therapies (interleukin 2 and interferon alpha), these were less commonly used in older adults due to increased toxicity and reduced tolerability in those with multiple comorbidities.[3] However, the treatment landscape has shifted dramatically with the approval of new oral targeted therapies including those targeting the vascular endothelial growth factor pathway (tyrosine kinase inhibitors [TKIs]) and the mammalian target of rapamycin (mTOR) pathway. These agents have demonstrated extended survival and reduced toxicity [4–6]. Yet, as older patients are often underrepresented in trials, much remains unknown on the efficacy, toxicity and adherence to these medications and optimizing treatment selection remains a challenge in older patients [3,7,8].

As outlined in Figure 1, since 2005 the Food and Drug Administration (FDA) has approved fourteen targeted therapies for mRCC of which seven are administered orally [5,9]. Recent developments has also seen the approval of various monoclonal antibodies and checkpoint inhibitors, which may be used in combination with oral TKIs, including pembrolizumab or avelumab in combination with axitinib in the first line setting [10,11]. Unlike infusional therapies, oral targeted therapies are delivered at home, thus raising concerns about both utilization and adherence. Studies evaluating first-line treatment patterns are largely outdated [12–15], or focus on specific patient groups (i.e. limited to those only receiving targeted therapy, individual drugs or nephrectomy [12–19]) and few have assessed factors associated

with utilization. Even fewer studies have evaluated adherence patterns, [20–22] with no previous studies evaluating factors associated with adherence.

Even with the development of newer agents for mRCC, oral targeted therapies continue to be a key component of systemic therapy. The improved survival observed with these combination therapies relies on strong adherence to targeted therapies, yet patterns and determinants of adherence to these therapies remain unknown. Therefore, this study aimed to describe the patterns of targeted therapy utilization and adherence within four months of mRCC diagnosis in the first-line. This study evaluated all systemic therapies available between 2007 and 2015 among patients with metastatic disease at their first RCC diagnosis (i.e. did not include patients with a previous RCC that had subsequently metastasized).

METHODS

Data Sources

Renal cell carcinoma cases were identified from the National Cancer Institute's Surveillance, Epidemiology and End Results Program (SEER)-Medicare linked dataset. SEER registries contain tumor, demographic and mortality information for patients diagnosed with cancer within 21 regions, covering approximately 34% of the United States' population. Among those with an incident cancer diagnosis living within a SEER region, who are 65 years and older and insured by a fee-for-service Medicare coverage, around 96% have been successfully linked to Medicare enrollment and claims data, using an iterative, deterministic algorithm [23]. This linkage of patients in SEER with their Medicare enrollment and claims data allows for the identification of cancer treatments. Indeed, several studies have highlighted the utility and validity of Medicare claims data to capture comorbidity and frailty [24,25], surgery [26,27] and systemic cancer treatment [28–30].

Study Population

We identified 38,313 patients diagnosed with a first primary RCC between January 2007 and October 2015. RCC diagnoses were identified using the International Classification of Disease for Oncology, Third Edition site code: C64.9 and histology codes indicative of RCC (8260, 8310, 8316–20, 8510, and 8959). Patients diagnosed with urothelial, mesothelioma or lymphoma were excluded as were those patients with tumours classified as American Joint Commission on Cancer (AJCC) 6th Edition, summary stage or TNM Classification of Malignant Tumours (TNM) stage 0-III and those aged <66 years at diagnosis (**Figure 2**). To ensure complete claims were available, all patients were required to have continuous

enrollment in Medicare Parts A & B fee-for-service six-months prior to diagnosis and Medicare Parts A, B & D enrollment for four months post-diagnosis. Finally, patients with a history of nephrectomy six months prior to their primary mRCC diagnosis date were excluded to prevent the inclusion of patients with a previous RCC that had subsequently metastasized.

Ascertainment of first-line targeted and non-targeted therapy utilization

We identified all targeted (sunitinib, pazopanib, sorafenib, axitinib, temsirolimus, everolimus, and bevacizumab) and non-targeted therapies (interferon alpha and high-dose interleukin 2) that were available between 2007 and 2015. Healthcare Common Procedural Coding System codes were used to identify intravenous therapies including temsirolimmus, bevacizumab, interferon alpha and high-dose interleukin 2. National Drug Codes were used to identify oral therapies from Medicare Part D (sunitinib, pazopanib, sorafenib, axitinib, and everolimus). First-line therapy was considered as the first recorded claim for a targeted or non-targeted therapy within 120 days (four months) from mRCC diagnosis. The 120-day treatment window was determined by clinician input as a relevant time period for the initiation of first-line targeted therapies in this population. This definition is consistent with previous studies [31].

Adherence and persistence

As Medicare Part D only covers oral targeted therapies, adherence and persistence was evaluated only among those initiating an oral targeted therapy within four months of diagnosis (sunitinib, pazopanib, sorafenib, axitinib, and everolimus). Adherence was calculated using the proportion of days covered (PDC). PDC is

calculated as the ratio of the number of days covered by a prescription to the number of days in the measurement window. To account for cycling of sunitinib (four weeks on, two weeks off), the PDC for patients who had four-week days' supply was set to six weeks. Based on the Centers for Medicare and Medicaid Services (CMS) Star Ratings program guidance, the PDC was adjusted for inpatient stays at hospitals and skilled nursing facilities. This assumes that beneficiaries receive their medications from the facility during stays if continued. As such a hospitalization was considered as a prescription fill for any patient with a targeted therapy prescription when hospitalized [32]. The PDC measure was dichotomized as a value of ≥ 80% considered as high adherence and <80% as low [33]. Persistence to oral targeted therapy was considered as time to treatment discontinuation. A 30-day grace period between successive claims was included to allow for delays in regular refilling. Discontinuation was considered either a switch to a second-line therapy or no subsequent claim for a targeted therapy by the end of the days' supply plus the grace period, or death. The grace period was increased to 60-days in sensitivity analyses.

Patient Characteristics

A set of patient characteristics were selected a priori to describe in relation to targeted therapy utilization and adherence. From SEER we determined demographic information including age, sex, race/ethnicity, SEER region, and marital status. Census tract socioeconomics, low-income subsidy, urban or rural location, and tumour histology (clear cell or non-clear cell) were also determined. Comorbidity information was defined using the Gagne Combined Comorbidity Index. The Gagne comorbidity score combines several conditions from the Charlson Comorbidity Index and Elixhauser classification into a new score, which has been shown to outperform

each of the component parts in predicting short and long-term mortality [34]. A higher score reflects a greater the comorbidity burden. Based on findings from Gagne *et al* [34], we categorized the score as low intermediate and high (≤0, 1 and 2 or more, respectively). Frailty was categorized according to the Faurot frailty prediction score [35]. This is a Medicare claims-based algorithm that calculates the predicted probability of dependency in activities of daily living as a proxy for frailty. The score includes 20 claims-based indicators for conditions, symptoms, and medical equipment predictive of dependency, as well as age, sex, and race. The score has been externally validated reporting good discrimination (c-statistic=0.71) and high predictive validity compared to the Fried frailty phenotype as a reference standard. [25,35] The predicted probability of frailty was scaled to reflect a 0.1-unit change. Unfortunately information on prognostic risk scores, including the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score was unavailable [36]. Such risk stratification scores are factors in the decision to initiate treatment [11]. Receipt of nephrectomy within four months was also identified. All claims-based covariates were defined six months prior to diagnosis.

Statistical Analyses

To describe the utilization of first-line therapies within four months of diagnosis among all mRCC patients we assessed the proportion of patients receiving first-line therapies and the prevalence of specific agents, by year using descriptive statistics. To assess the impact of death, we evaluated the cumulative proportion of patients receiving first-line therapy within four months of diagnosis, among those surviving each month, from month one through to month four post-diagnosis. The

median and interquartile range (IQR) of time (in days) to first-line therapy initiation was also reported.

For patient characteristics categorical variables were reported as counts and percentages and continuous variables as medians with interquartile ranges. Multivariable logistic regression was used to describe patient characteristics associated with first-line targeted therapy initiation compared to no targeted therapy (non-targeted therapy or no systemic therapy) within four months of diagnosis, estimating adjusted ORs and 95% confidence intervals (CIs). Model discrimination was evaluated using the c-statistic. C-statistic values range from 0 to 1 with a value of 0.5 representing prediction no better than random chance. In general C-statistic values ranging from 0.5–0.6 are considered poor, 0.6–0.7 as moderate, 0.7–0.8 as good, 0.8–0.9 as very good, and over 0.9 as excellent [37].

The median and IQR (in days) of time to discontinuation was reported among those initiating an oral targeted therapy within four months of diagnosis. Adherence was calculated using the PDC, at 120 days and 365 days post-diagnosis, and was assessed both including and excluding those who died within the given time periods. To identify characteristics associated with high adherence (PDC ≥80%), compared to low at 120 days, logistic regression models were used to calculated ORs and 95% CIs, controlling for all other characteristics, as listed above. This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

RESULTS

In total 2,093 patients were included in our study cohort, of which 602 (28.8%) received a targeted therapy within four months of diagnosis, 83 (4.0%) received a non-targeted therapy and 1,408 (67.3%) received no systemic therapy within four months of diagnosis. Those in the no systemic therapy group may include those who received nephrectomy only or experienced treatment delays beyond four months. The median time to first-line therapy initiation (targeted and non-targeted therapy) was 73 days (IQR 46-122). In total 510 (24.4%) patients underwent nephrectomy within four months of diagnosis, of which 26.3% received targeted therapy and 13.7% non-targeted therapy, with 83.6% of patients receiving their first-line therapy within two months of nephrectomy (data not shown).

First-line therapy utilization

Analyses of temporal trends revealed that the proportion of patients receiving targeted therapy in the first-line setting increased with time, from 26.2% of patients in 2007 to 31.2% of patients in 2015, peaking in 2013 during which time 36.6% of patients received first-line targeted therapy (**Figure 3**), reflecting increases in targeted therapy approvals over the study time period. Among those patients receiving first-line targeted therapy within four months of diagnosis, overall the most common therapies included sunitinib (51.5%), pazopanib (19.7%) and temsirolimus (18.1%).Sunitinib was the most commonly used targeted therapy in 2007 (19.7%) followed by sorafenib (6.1%), which decreased from 2009. The use of temsirolimus increased from 2009 (approved in 2007) and pazopanib (approved in 2009) from 2011, with pazopanib being the most commonly used targeted therapy by 2015

(13.9%; **Figure 4**). The proportion of patients initiating sunitinib decreased over time with the simultaneous increase in first-line therapy treatment options (**Figure 4**).

The study population had a high mortality rate, with 857 (41.0%) of patients dying within four months of diagnosis. When evaluating the cumulative proportion of patients receiving first-line therapy within one to four months, among patients surviving one month after diagnosis, over 96% of patients did not receive any first-line therapy (**Figure S1**). When evaluating treatment initiation among patients surviving the four-month treatment window, the proportion of patients who did not receive any first-line therapy decreased to 54.1%, while 40.0% received first-line targeted therapy and 5.9% received non-targeted therapy.

When investigating characteristics associated with initiation of targeted therapy (compared to no targeted therapy), we found that initiation of first-line targeted therapy was less likely with increasing age (in one-year increments OR_{adj}: 0.95, 95% CI: 0.93, 0.97; **Table 1**). Those patients residing in a census tract with the highest percentage living under the poverty level were also less likely to initiate a targeted therapy within four months of diagnosis (4^{th} quartile OR_{adj}: 0.68, 95% CI 0.49, 0.95), as were those patients who were not married. Regional variation was observed with patients residing outside of the Northeast having higher odds of targeted therapy receipt. Patients with a higher Gagne comorbidity score (high vs low OR_{adj}: 0.65, 95% CI 0.46, 0.93) and increasing frailty (per 0.1-unit increase in predicted probability OR:0.78, 95% CI 0.68, 0.88) had lower odds of targeted therapy initiation within four months of diagnosis. Finally, those patients diagnosed with mRCC with clear cell histology were more likely to initiate first-line targeted therapies than those with non-clear cell histology (OR_{adj}:1.54, 95% CI 1.19, 2.00). The c-statistic for discrimination of targeted therapy utilization was 0.680.

Adherence to first-line targeted therapy

In total, 485 patients received oral targeted therapies within four months of their mRCC diagnosis, with an average time to initiation of 59 days (IQR 40-80). The median time to treatment discontinuation was 71 days (40-132 IQR). Similar results were observed when extending the grace period to 60 days (77 days, IQR 42-162). Overall, 155 patients (32%) died within 120 days of treatment initiation. Among those surviving 120 days, 159 (48.2%) had a PDC ≥80%. This is in contrast to 34.2% of patients with high adherence when not limiting to those who survive. The proportion of patients who were adherent to oral targeted therapy decreased at 365 days (17.9% among those surviving 365 days; 11.3% all patients). Among those surviving 120 days, older adults were less likely to have a PDC ≥80% at 120 days (one-year increment $OR_{adj:}$ 0.96 95% CI 0.92, 1.00; **Table 2**). Similarly females were less likely to be adherent to their therapy at 120 days than males (OR_{adj}: 0.49, 95% CI 0.28, 0.83), while those who were divorced/widowed/separated were more likely to have high adherence (OR_{adj}: 1.89, 95% CI 1.02, 3.49). The model had moderate discrimination of targeted therapy adherence (c-statistic=0.683).

DISCUSSION

We observed small increases in the utilization of first-line targeted therapies among older adults with mRCC at the time of diagnosis over time, corresponding with a decline in cytokine use. A number of factors were associated with first-line targeted therapy initiation including age, comorbidity, frailty and histology. The PDC by oral targeted therapies was generally low and decreased with increasing time from initiation. This was the first study to assess factors associated with adherence to targeted therapies in mRCC, with age, gender and marital status appearing to be correlated.

Our analyses of temporal trends of first-line therapy utilization are reflective of NCCN guidelines [11]. The use of sorafenib decreased substantially from 2008 (<11 receiving this treatment each year thereafter), coinciding with emerging alternative efficacious treatment options [38]. Similar to previous studies, we observed a rapid uptake of sunitinib and pazopanib upon FDA approval (2006 and 2009, respectively), with pazopanib overtaking sunitinib as the most commonly used targeted therapy by 2015 [15,18]. Although the COMPARZ trial found pazopanib to be non-inferior to sunitinib for survival outcomes [39], this shift in dominance likely reflects safety profiles and better quality of life outcomes for patients and cost-effectiveness [39,40]. Furthermore, consumption externalities may also emerge when the increasing use of a drug by physicians and patients influences perceptions about its efficacy, safety, and 'acceptability,' thus accelerating rates of adoption by others.

In this older mRCC population, 67.3% of patients did not receive any first-line systemic therapy within four months of diagnosis. While this may appear high, it is important to note some patients may have received nephrectomy only as initial treatment, systemic treatment may have been delayed beyond four months post-

diagnosis or some may have died prior to treatment receipt. Indeed, when we limited analysis to those surviving 120 days post-diagnosis the proportion of patients receiving first-line therapy increased from 28.8% to 40.0%. Similar to our findings, results from an older SEER Medicare analyses (2007-2011) found that 34% of patients received systemic therapy within six months of diagnosis [41]. Contrastingly, in studies of a younger population from the Veterans Health Administration (VHA; average age 66.3 years) and a Medicare population with a similar age distribution to our cohort (median age group 70-79 years) 23.1% and 32.9% of patients with metastatic kidney cancer did not receive anticancer therapy, respectively [42,43]. The reason for these discrepancies is unclear; however, it may be attributable to previous studies identifying therapy use any time after diagnosis, or the exclusion of patients that actively progress to metastatic disease in our study [42].

In this study 24% of patients received nephrectomy within four months of diagnosis of which 26.3% received a targeted therapy within four months of the date of surgery. This is in line with previous reports from the National Cancer Database, were 39% of mRCC patients treated with cytoreductive nephrectomy received systemic therapy, up to twelve months post-surgery [14]. There are a number of explanations for this finding such as patient preference, perioperative mortality or treatment delays due to post-operative complications. In addition, among patients with low metastatic burden, treatment may be delayed to avoid toxicity in the short-term; with clinicians opting for surveillance until disease progression is identified. In contrast, systemic therapy may also be avoided among those patients that show rapid progression of disease or poor performance status after nephrectomy, which has been reported in 30% of patients who did not receive therapy post-nephrectomy [44].

Previously poor performance and comorbidities were associated with receiving no therapy [41,42]. Similarly, we found evidence that increased comorbidity, frailty and age may be associated with decreased first-line therapy initiation. This is unsurprising as this likely reflects performance status, a component of prognostic risk scores such as the IMDC score [36], and an important driver in the decision to initiate treatment [11]. Unfortunately, our study lacked information on clinical risk scores as well as other factors, which may influence treatment initiation or delays, such as patient or physician preferences [36]. In addition, marital status and census tract poverty status may also influence utilization of targeted therapy among older Medicare beneficiaries. Low-income subsidy was not associated with initiation in our study, contrasting with a previous study, which found that high cost sharing was associated with reduced access under Medicare Part D, however this study did not include those with partial income subsidies and categorized treatment within six months [45].

We found patients with clear cell histology were significantly more likely to initiate a targeted therapy. Much of the data guiding treatment for non-clear cell mRCC has been inferred from trials of patients with clear cell histology, leading to a knowledge gap on optimal treatments for this group. In response, enrollment in clinical trials is the preferred strategy for first-line treatment in patients with non-clear cell mRCC [11]. Importantly, we were unable to determine if patients were enrolled in or to capture treatment information from clinical trials, which is a standard of care for patients with both non-clear cell and clear cell mRCC. We observed declines in targeted therapy use in 2014 and 2015, corresponding with increases in the proportion of patients receiving no systemic therapy. While the reason behind this phenomenon

is unclear, this may reflect an increase in patients enrolling in clinical trials during this time period, such as the CheckMate 214 trial [46,47].

The observed treatment duration of first-line oral targeted therapy was relatively short (median 71 days, IQR 40-132), and was in agreement with that observed from the VHA (86 days) [42]. While other studies have reported longer times to discontinuation, these often focused on individual drug types, or may reflect differing censoring criteria and younger study populations [16,18,20,21]. The PDC was generally low among the study population (at 120 days among those who survived 48.2 % PDC ≥80), and decreased with increasing time. This generally corresponds with previous studies reporting high adherence in 50-55% of patients,[20,48] yet evidence remains mixed [16,21]. Discrepancies may represent adjustment for hospitalizations, different time windows for assessment or inclusion of individual targeted therapies and younger populations.

Adherence to oral antineoplastic treatments has been reported to be correlated with factors such as age, race, comorbidities and cost [49]. This was the first study to describe factors associated with adherence to targeted therapies in mRCC, with increasing age and female gender associated with lower PDC while those who were divorced/widowed/separated had higher odds of being adherent. Similar observations for oral anticancer therapies have been made for age [50–53], and female gender,[54] although the evidence on gender remains inconsistent [55,56]. Our findings on marital status differ with previous findings in diverse cancers, with studies finding those who are married or with greater social support have higher levels of adherence [57–59]. Interestingly, however, perceived burden to family and friends has also been associated with non-adherence [56]. A number of additional factors have also been reported as predictors of oral cancer treatment adherence such as patient-clinician

communication, understanding of disease and treatment, depression and adverse events [60,61]. This is of particular importance in older populations who experience higher toxicities as well as other factors that affect adherence such as polypharmacy and cognitive deficits [62]. Unfortunately, we were unable to capture these factors in our study, thus further investigations to fully elucidate the drivers of treatment non-adherence in mRCC are warranted.

As expected for a population with metastatic cancer, a large proportion of patients died within four months of initiating first-line therapy. Mortality may also be relatively high compared to clinical trial data as our cohort consists of older Medicare patients and those with metastasis at presentation thereby excluding those with more favorable risk disease [31]. Notably, results differed based on the inclusion or exclusion of patients who die in the PDC calculation. To the best of our knowledge there is no clear consensus on the most appropriate methodological approach for calculating adherence in high mortality populations such as this. As such, future methodological research is warranted to develop methods in this area.

The poor adherence to first-line oral targeted therapies observed in this study likely reduces the benefit of these agents in the real world setting and has important implications in current clinical practice. While the treatment landscape for mRCC continues to rapidly evolve with the approval of immunotherapies [63,64], the findings of this study remain particularly important as immunotherapies are often recommended in combination with targeted therapies, including in the first-line setting (e.g. pembrolizumab and axitinib) [65]. Adherence is critical to achieving an optimal clinical response and is not likely to be similar in the real-world setting as in trials. This is of particular importance as costs of treatments continue to increase and suboptimal adherence may lead to reduced survival, increased side effects and

toxicity, increased healthcare utilization and lower patient satisfaction. While future studies are needed to specifically evaluate immunotherapies used in this setting, understanding real life treatment patterns and adherence to oral targeted therapies are imperative to improving clinical care and ensuring an optimal clinical response, for not only for metastatic kidney cancer but also the wider oncology landscape as targeted therapy utilization continues to increase across different cancer types [66–69].

Our results should be interpreted considering some additional limitations. Our study population was limited to those patients aged ≥66 years, with Medicare fee-for-service and Part D coverage, thus our results may not be generalizable to a younger population or those with managed care or the uninsured. Second, while we were able to evaluate the associations of certain patient characteristics with targeted therapy initiation and adherence, these are descriptive analyses. Overall, models had moderate discrimination of who receives and who is adherent to targeted therapies. Remaining variation may be explained by unmeasured factors. Medication adherence is a complex, multifaceted issue that is influenced by a range of factors including patient, health system and condition related factors. Adherence measures determined from administrative claims data, such as the PDC, provide information on medication possession rather than consumption. While claims data represents prescriptions dispensed it is possible that patients may not have used their medications as prescribed. Similarly, it is possible that in some cases failure to refill regular prescriptions may represent purposeful treatment breaks or dose reductions. However notably, results remained similar when extending the grace period. Although the impact is expected to be low, it is possible that patients may also have other sources of medication coverage such as the Veteran's Health Administration or through

pharmaceutical company pharmacy assistance programs, which would not be captured within this study. Finally, it is possible that patients may not have full medication coverage during an inpatient stay. However this method of PDC, accounting for inpatient stays, is incorporated by the Centers for Medicare & Medicaid Services into quality measures for Part D plans and claims data are subject to validation procedures to improve accuracy.

Conclusion

First-line targeted therapy utilization for mRCC has increased over time among older Medicare beneficiaries, while advanced age, increased comorbidity and frailty, and non-clear cell RCC histology were associated with reduced therapy initiation. The proportion of days covered by oral therapies was generally low. As such further research into the mechanisms and impact of low adherence in this older population is warranted.

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CONFLICTS OF INTEREST

Dr. Lund's spouse is a full-time, paid employee of and owns stock in GlaxoSmithKline. She also receives research support from AbbVie, Inc. for an unrelated research study. Ms. Chun is a pre-doctoral fellow at Bristol Meyers Squibb. Dr Tan receives funding from the American Cancer Society. Dr Hicks receives funding from Cancer Research UK.

AUTHOR CONTRIBUTIONS

BH & DC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: BH, JL, DC, RT

Acquisition of data: All authors.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: BH

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: BH & DC.

Obtaining funding: JL

Administrative, technical, or material support: SPH.

Supervision: JL

Other: None

FIGURE LEGENDS

Figure 1 **Timeline of FDA approval for first-line treatment for advanced or metastatic renal cell carcinoma.**

Figure 2 **Flow chart outlining cohort selection**

Figure 3 **Temporal trends of first-line treatment initiation within four months of diagnosis among patients diagnosed with mRCC between 2007 and 2015**

Figure 4 **Figure 4 Temporal trends in the utilization of first-line targeted therapies within four months of mRCC diagnosis, by individual drug type.**
Groups with <11 patients are not included

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Table 1. Baseline characteristics by first-line treatment and their association with targeted therapy initiation.

Characteristic	No therapy (N=1,408) No (%)	Non-Targeted Therapy (N=83) No (%)	Targeted Therapy (N=602) No (%)	Targeted therapy Initiation Adjusted OR (95%CI)
Year of diagnosis				
2007-2008	312 (22.2)	42 (50.6)	112 (18.6)	1.00
2009-2010	300 (21.3)	12 (14.5)	108 (17.9)	1.25 (0.91, 1.72)
2011-2012	293 (20.8)	14 (16.9)	144 (23.9)	1.72 (1.27, 2.34)
2013-2015	503 (35.7)	15 (18.1)	238 (39.5)	1.61 (1.22, 2.12)
Age at diagnosis, median (IQR)	77.3 (71.6-83.8)	72.3 (68.3-76.8)	74.2 (69.7-78.8)	0.95 (0.93, 0.97)
Sex				
Male	763 (54.2)	52 (62.7)	364 (60.5)	1.00
Female	645 (45.8)	31 (37.4)	238 (39.5)	0.99 (0.80, 1.24)
Race/Ethnicity				
White	1,137 (80.8)	70 (84.3)	484 (80.4)	1.00
Non-white	271 (19.2)	13 (15.7)	118 (19.6)	1.27 (0.96, 1.68)
Census Tract % < Poverty[a]				
1st quartile (lowest)	254 (18.0)	20 (24.4)	121 (20.1)	1.00
2nd quartile	322 (22.9)	23 (27.7)	161 (26.7)	0.98 (0.72, 1.32)
3rd quartile	438 (31.1)	21 (25.6)	172 (28.6)	0.70 (0.52, 0.96)
4th quartile (highest)	393 (27.9)	18 (22.0)	148 (24.6)	0.68 (0.49, 0.95)
Low income subsidy				
None	864 (61.4)	58 (69.9)	394 (65.5)	1.00
Partial	68 (4.8)	*	20 (3.3)	0.78 (0.44, 1.30)
Full	476 (33.8)	25 (30.1)*	188 (31.2)	1.18 (0.92, 1.52)
Urbanicity				
Urban	1216 (86.4)	71 (85.5)	516 (85.7)	1.00
Rural	191 (13.6)	12 (14.5)	86 (14.3)	1.03 (0.75, 1.40)
SEER Region				
Northeast	269 (19.1)	14 (16.9)	87 (14.5)	1.00
South	380 (27.0)	31 (37.3)*	160 (26.6)	1.39 (0.98, 1.96)
Midwest	187 (13.3)	*	83 (13.8)	1.40 (0.95, 2.05)
West	572 (40.6)	38 (45.8)	272 (45.2)	1.35 (0.99, 1.83)

Table 1 *Cont'd* **Characteristic**	**No therapy (N=1,408) No (%)**	**Non-Targeted Therapy (N=83) No (%)**	**Targeted Therapy (N=602) No (%)**	**Targeted therapy Initiation Adjusted OR (95%CI)**
Marital Status				
Married/Domestic partner	609 (43.3)	56 (67.5)	349 (58.9)	1.00
Divorced/Widowed/Separated	596 (42.3)	14 (16.9)	172 (29.0)	0.67 (0.53, 0.86)
Unmarried/unknown	203 (14.4)	13 (15.7)	73 (12.1)	0.63 (0.46, 0.86)
Gagne Combined Comorbidity Index				
Low	841 (59.7)	60 (72.3)	416 (69.1)	1.00
Intermediate	326 (23.2)	23 (27.7)[*]	134 (22.3)	0.99 (0.78, 1.28)
High	241 (17.1)	*	52 (8.6)	0.65 (0.46, 0.93)
Faurot frailty prediction	0.05 (0.04-0.11)	0.04 (0.03-0.05)	0.04 (0.03-0.06)	0.78 (0.68, 0.88)[b]
Histology				
Non-clear cell	318 (22.6)	31 (37.4)	99 (16.5)	1.00
Clear Cell	1,090 (77.4)	52 (62.7)	503 (83.6)	1.54 (1.19, 2.00)

Abbreviations: CI confidence interval, IQR interquartile range, OR odds ratio,

[a] Individuals with unknown census tract poverty levels were excluded from multivariable analyses and are not reported here due to numbers <11.

[b] The predicted probability of frailty was scaled to reflect a 0.1-unit change The interpretation of this odds ratio (OR, 0.78) is that an increase in the predicted probability of frailty by 0.1 is associated with a 0.22 decrease in the odds of targeted therapy initiation.

[*] Cells were combined for confidentiality due to numbers <11.

Table 2 Baseline characteristics and their association with adherence (PDC ≥ 80%) to oral targeted therapies in 120 days

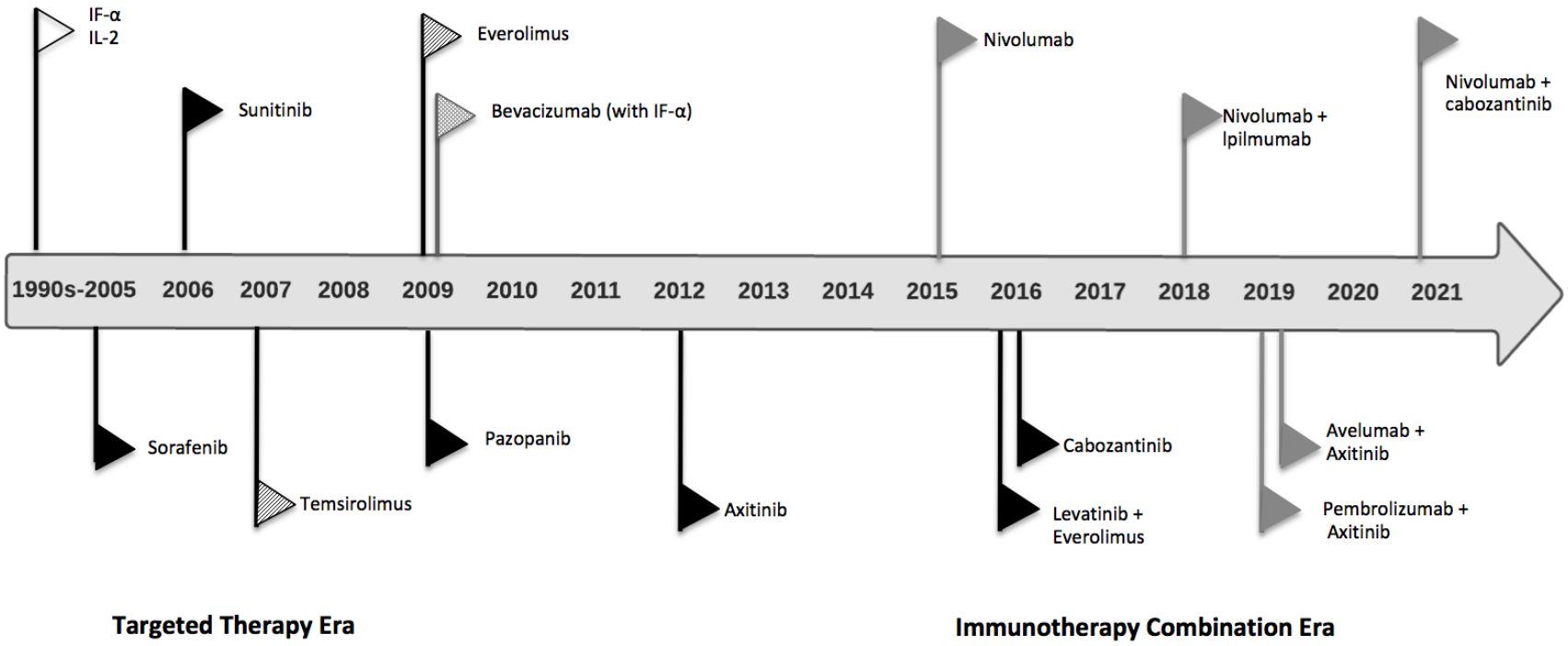
Characteristic, N(%)[a]	Non-adherent PDC<80% (N=171)	Adherent PDC <80% (N=159)	Adherence Adjusted OR (95%CIs)
Year of diagnosis			
2007-2008	31 (18.1)	38 (23.9)	1.00
2009-2010	28 (16.4)	26 (16.4)	0.70 (0.33, 1.51)
2011-2012	44 (25.3)	32 (20.1)	0.54 (0.27, 1.10)
2013-2015	68 (39.8)	63 (39.6)	0.70 (0.37, 1.32)
Age at diagnosis, median (IQR)	74.3 (70.2-79.3)	73.7 (69.1-77.3)	0.96 (0.92, 1.00)
Sex			
Male	92 (53.8)	102 (64.2)	1.00
Female	79 (46.2)	57 (35.9)	0.49 (0.28, 0.83)
Race/Ethnicity			
White	142 (83.0)	126 (79.3)	1.00
Non-White	29 (17.0)	33 (20.8)	0.98 (0.50, 1.94)
Census Tract % < Poverty			
1st quartile (lowest)	38 (22.2)	26 (16.4)	1.00
2nd quartile	42 (24.6)	49 (30.8)	1.52 (0.76, 3.02)
3rd quartile	50 (29.2)	39 (24.5)	1.05 (0.51, 2.16)
4th quartile (highest)	41 (24.0)	45 (28.3)	1.55 (0.71, 3.38)
Low income subsidy			
None	121 (70.8)	94 (59.1)	1.00
Full/Partial	50 (29.2)	65 (40.9)	1.67 (0.94, 2.97)
Urban/Rural			
Urban	147 (86.0)	143 (89.9)	1.00
Rural	24 (14.0)	16 (10.1)	0.62 (0.27, 1.43)
SEER Region			
Northeast	22 (12.9)	20 (12.6)	1.00
South	51 (29.8)	35 (22.0)	0.78 (0.33, 1.85)
Midwest	19 (11.1)	27 (17.0)	2.01 (0.76, 5.31)
West	79 (46.2)	77 (48.4)	1.00 (0.57, 2.11)
Marital Status			
Married/Domestic partner	110 (64.3)	88 (55.4)	1.00
Divorced/widowed/separated	45 (26.3)	51 (32.1)	1.89 (1.02, 3.49)
Unmarried/Unknown	16 (9.4)	20 (12.6)	1.62 (0.74, 3.54)
Gagne Combined Comorbidity Index			
Low	*	147 (92.5)	1.00
Intermediate/high	*	12 (7.6)	1.32 (0.51, 3.39)
Histology Group			
Non-clear cell	22 (12.8)	23 (14.5)	1.00
Clear cell	149 (87.1)	136 (85.5)	0.80 (0.41, 1.56)

Abbreviations: CI confidence intervals, IQR interquartile range, OR odds ratio, PDC proportion of days covered

*values of <11 are suppressed

[a] Faurot frailty prediction score was not included in the model due to sparse data/separation in higher categories of frailty.

Figure 1 Timeline of Food and Drug Administration **approval for first-line treatment for advanced or metastatic renal cell carcinoma.**



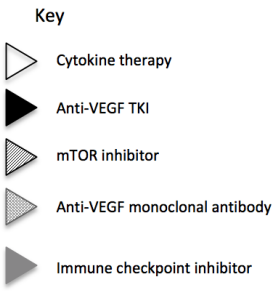

Key
Cytokine therapy
Anti-VEGF TKI
mTOR inhibitor
Anti-VEGF monoclonal antibody
Immune checkpoint inhibitor

Figure 2 Flow chart outlining cohort selection

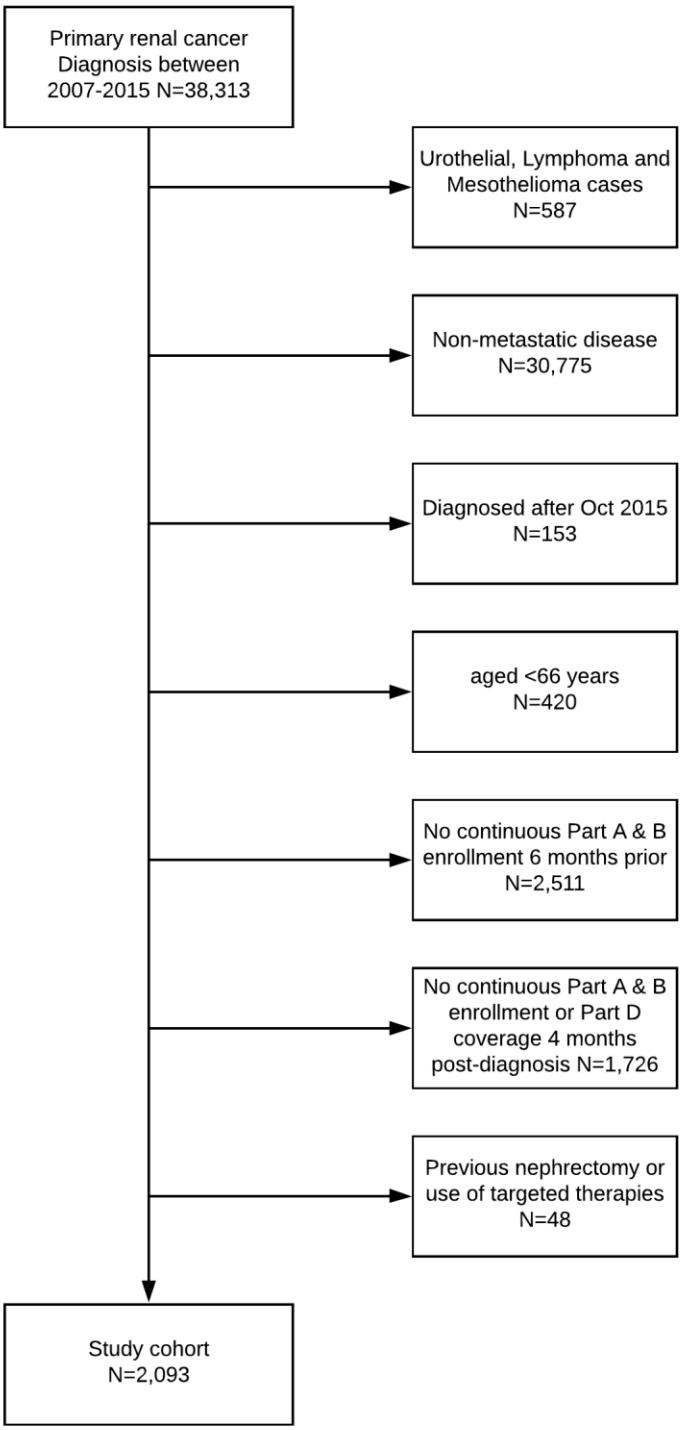


Figure 3. Temporal trends of first-line treatment initiation within four months of diagnosis among patients diagnosed with metastatic renal cell carcinoma between 2007 and 2015

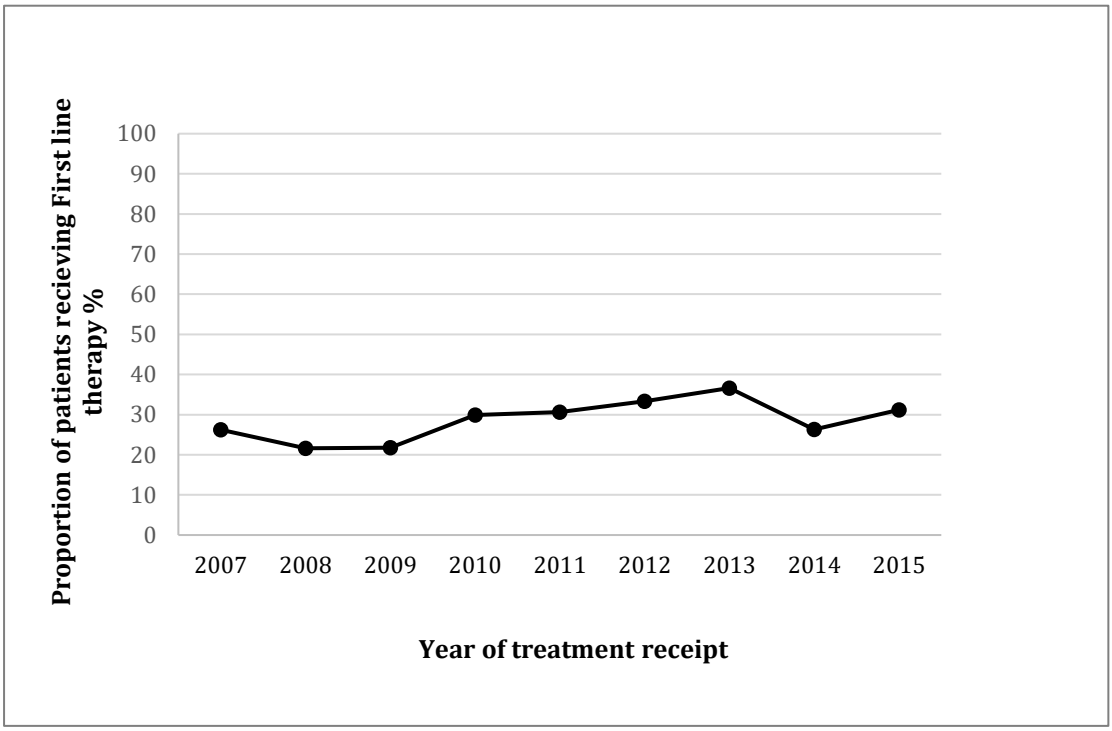
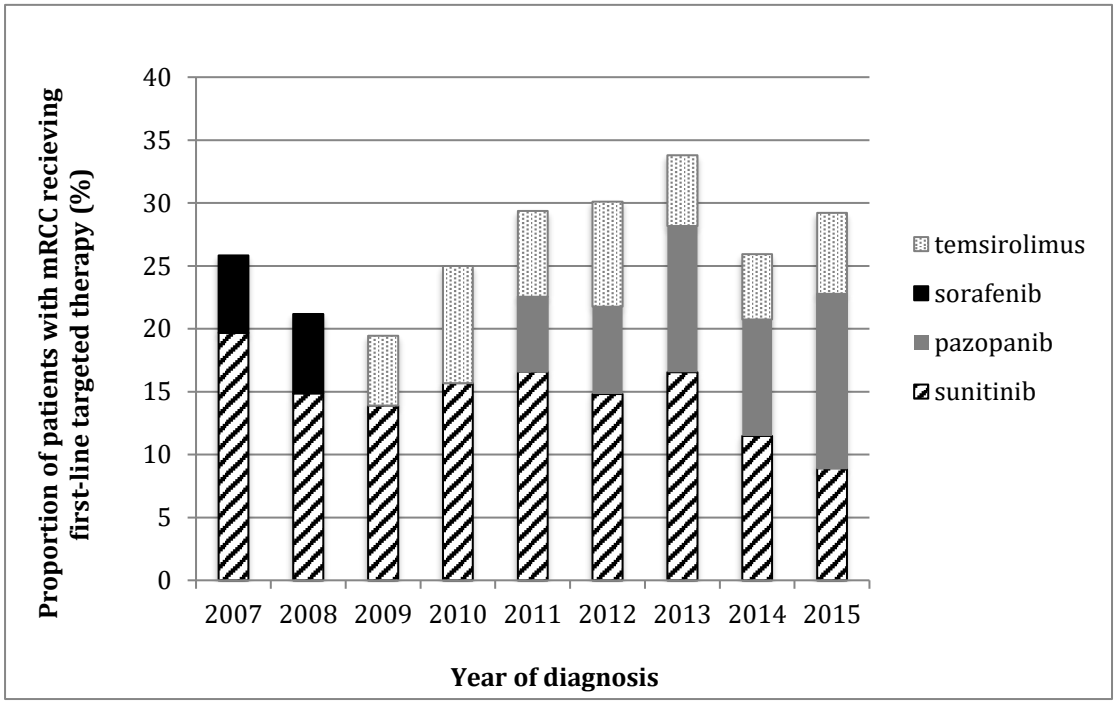


Figure 4 Temporal trends in the utilization of first-line targeted therapies within four months of metastatic renal cell carcinoma diagnosis, by individual drug type.



Abbreviations: mRCC metastatic renal cell carcinoma