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Comparing Pazopanib, Sunitinib, Cabozantinib, Axitinib-Pembrolizumab, and Ipilimumab-Nivolumab Therapy For Metastatic Renal Cancer

BY

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Abstract

Metastatic renal cell carcinoma (mRCC) poses significant challenges in treatment. Here, we evaluate the outcomes of patients with metastatic renal cell carcinoma treated with upfront nephrectomy followed by pazopanib, sunitinib, cabozantinib, axitinib-pembrolizumab or ipilimumab-nivolumab as first-line therapy. Using a large federated multi-national network database, we identified patients, in the period from 2008 to 2024, who were diagnosed with metastatic renal cell carcinoma, receiving first-line systemic therapies with tyrosine kinase inhibitors or immunomodulator therapy. Pazopanib demonstrated a 57.7% OS rate (138/239 patients), similar to sunitinib (52.6%, 70/180). Cabozantinib showed a trend towards improved OS (56.7%, 102/180) compared to pazopanib, but this was not statistically significant. Ipilimumab-nivolumab had a 63.3% OS (245/387), while axitinib-pembrolizumab exhibited the highest OS rate (70.0%, 21/30) but with a smaller sample size. Although higher relative risk of mortality was associated with ipilimumab-nivolumab use compared to axitinib-pembrolizumab, log-rank testing was not significant. This study investigated the effectiveness of various treatment regimens for mRCC in a real-world setting.

Keywords: *mRCC (Metastatic Renal Cell Carcinoma), TKI (tyrosine kinase inhibitor), immunomodulator (IO), Ipilimumab-Nivolumab, Axitinib-Pembrolizumab*

INTRODUCTION

Renal cell carcinoma (RCC) is the most prevalent kidney cancer, with one-third of patients treated with curative intent progressing to metastatic disease [1]. The most common sites of metastatic involvement in ccRCC are well characterized and include the lung, lymph nodes, bone, and liver [2]. Clear cell histological subtype is the most prevalent, then papillary and chromophobe [3]. Cytoreductive nephrectomy was historically recommend in patients with more than one International mRCC Database Consortium risk factor and requiring systemic therapy [4]. Although the indications its are debated with the development of more effective systemic therapies, cytoreductive nephrectomy may be offered for patients with low burden of disease, kidney-in-place malignancy, and favorable or intermediate risk profile [5]. Favorable risk patients who fail surveillance post nephrectomy, may consider immune checkpoint (ICI) plus vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) [5]. In intermediate or poor risk, doublet regimen with ICI or ICI-VEGFR TKI is recommended [5].

Real-world data on pazopanib for mRCC includes a subgroup analysis from the COMPARZ trial [6]. Pazopanib demonstrated efficacy, achieving an objective response rate (ORR) of 37.5% and a median PFS of 18.3 months [6]. Favorable risk patients may benefit the most, with a potential median PFS exceeding 18 months [6]. In support of the Category 2A recommendation for pazopanib, the NCCN guidelines cite Sternberg, et al.'s phase III trial comparing pazopanib with placebo, which included patients who had received prior cytokine therapy [7]. In this trial, PFS of patients in the treatment-experienced sub-population was significantly longer with pazopanib than placebo but OS was similar between the two groups [8]. Similarly, a prospective phase II trial studying second-line use of pazopanib after targeted agent (ie, bevacizumab, sunitinib) in advanced mRCC was cited. In this study, OR was 27%, while 49% of patients had stable disease (SD) and regardless of prior treatment regimen, PFS was 7.5 months with OS rate at 24 months estimated to be 43% [9].

Sunitinib use as second-line therapy in advanced mRCC is supported by INMUNOSUN-SOGUG, a multicenter phase II

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trial, and open-label, single-arm, multicenter trial which demonstrated anti-tumor activity in the setting of progression on cytokine therapy. [10].

The use of Ipi-Niv is supported by the phase I trial, CheckMate 016, which included a mix of treatment naïve patients and those treated with multiple agents. Objective response rate results were stratified by treatment status in the analysis. For N3I1 and N1I3 the ORR was around 46% and 39%, respectively. The unstratified OS and PFS data were similar [11]. Kartolo et al's systematic review and meta-analysis of dual ICI (Ipi-Niv) for mRCC reported pooled TFS rates of 35% and 20% at 6 and 12 months, respectively. The TFS was highest for dual ICI treatment [12].

According to a meta-analysis including patients progressing on VEGFR inhibition, cabozantinib was associated with a lower HR for disease progression and death compared to best supportive care [13].

Axitinib-pembrolizumab demonstrated longer overall survival, progression-free survival, and objective response rate compared to sunitinib in the phase 3 key note-426 trial [14]. UK phase 2 trial (PRISM) established no significant difference in progression-free survival for ipilimumab given every 12 weeks versus every 3 weeks with nivolumab for treatment-naive patients with advanced clear cell RCC [15].

A prior retrospective cohort analysis of the GridIron database with patient's stratification by IMDC scoring showed statistically significant survival benefit with axitinib-pembrolizumab compared to ipilimumab-nivolumab [16]. Our results may demonstrate a difference in survival benefit at different time points between the 2 therapies without significant difference in overall survival.

Treatment options for metastatic RCC (mRCC) have expanded, with targeted therapies like pazopanib and sunitinib becoming second-line standards, after the advent of immunotherapies such as Ipi-Niv. These treatments have been shown to extend survival in clinical trials; for example, median overall survival has been shown to be 24 to 30 months among patients receiving targeted therapies compared with less than 1 year in the era before targeted therapy [17]. These advances have been welcome in light of the fact that older treatments for advanced RCC (cytokines such as interleukin 2 and recombinant interferon alfa) were characterized by low response rates, and considerable toxicity [18]. With such a significant change in therapy for mRCC, a need arises for head-to-head comparisons for relevant guidance and benchmark of new therapies.

RESEARCH ELABORATION

A retrospective cohort analysis was performed using the TriNetX network, a global database that provides real-world data of >150 million people [19]. For this study, we used the United States (US) Collaborative Network including 57 healthcare organizations. We selected patients with metastatic RCC aged ≥18 years who received first-line systemic treatment from first available record to current year, between January 1, 2008, and January 1, 2024 (16 years). Cytoreductive nephrectomy needed to be performed 3 months before the initiation of first-line therapy. Patients receiving nephrectomy were identified using ICD-10-CM: Z90.5. The starting date of first-line therapy was set as the index date. Patients with metastases were identified using the International Classification of Diseases, 10th edition, Clinical Modification (ICD-10-CM) codes: ICD-10-CM C64 for malignant neoplasm of kidney, and ICD-10-CM: C78 (lung), ICD-10: C79.7 (adrenal) C78.7 (liver), C79.3 (brain), or C79.5 (bone). Comorbidities were identified using ICD-10-CM: I10-I16 for hypertension, ICD-10-CM: E08-E13 for diabetes mellitus, ICD-10-CM: I50.9 for heart failure, and ICD-10-CM: J44.9 for chronic obstructive pulmonary disease. The primary outcome was overall survival (OS), which was defined as time elapsed between start of first-line therapy to the date of death from any cause or censored at the end of study period.

Patients on pazopanib, sunitinib, cabozantinib, ipilimumab-nivolumab (Ipi-Niv), axitinib-pembrolizumab (Axi-Pem) therapy were reviewed for time on therapy and overall survival. Patients who received first-line therapy with no later anti-neoplastic agents were included for analysis of time on therapy and OS. All analyses were performed on the TriNetX platform. Survival was evaluated using the Kaplan-Meier method for median overall survival (OS) and 95% confidence interval (95% CI), as well as a log-rank test to evaluate inter-group differences in OS. Statistical significance was set at $p < 0.05$.

Measures of association were estimated and multi-variate analyses were completed for 101 patients on first-line sunitinib monotherapy, who were matched with 101 patients on pazopanib. Similarly, 88 patients on cabozantinib were matched with 88 patients on pazopanib. Measures of association were also estimated and multi-variate analyses were completed for 85 patients on first-line Axi-Pem, who were matched with 85 patients on Ipi-Niv first-line combination therapy. Variables for matching included age, cancer stage, and co-morbidities, including hypertensive disease, diabetes, heart failure, and chronic obstructive pulmonary disease. The matching was achieved using TriNetX. P-values for difference in proportion was >0.05 for all matching variables. Effect size was measured using risk ratio, significance was assessed using log-rank testing and impact of interventions was evaluated using hazard ratio.

RESULTS

TriNetX identified almost 13,000 patients with mRCC. Of patients who did not receive any second-line therapy, 723 received first-line TKI monotherapy, 517 received first-line combination therapy. In the TKI cohort, 231 (31.9%) received pazopanib, 208 (28.8%) received sunitinib and 284 (39.3) received cabozantinib. In the combination therapy cohort, 432 (50.9%) received Ipi-Niv, 85 (10.0%) Axi-Pem.

	Paz	Sun	Cab	Ipi-Niv	Axi-Pem
Number of patients	219	281	281	429	85

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Age	67.9+-11.4	64.3+-12.1	64.4+-11.3	68+-9.74	65.1+-9.94
Male	163	147	207	290	55
White	172	160	209	328	65
Black	16	19	22	20	<10
Asian	<10	<10	<10	11	<10

Table 1 (above): Demographic data for all cohorts

The study population was predominantly elderly, Caucasian males. The most common site of metastasis for all groups were lungs, followed by BM/bone, liver, adrenal glands, and meninges/brain for all treatment groups with the notable exceptions of Ip-Niv where adrenal metastases were less common than brain.

	Paz	Sun	Cab	Ipi-Niv	Axi-Pem
Lung	141	119	146	229	48
Bone marrow+Bone	93	79	126	146	29
Liver	60	47	57	82	20
Adrenal	46	42	47	56	13
Meninges +Brain	42	34	36	76	13

Table 2 (above): Sites of metastases by cohort

Comorbidities were similar with no statistically significant differences in rates of hypertension, diabetes mellitus, COPD, or heart failure among all treatment groups.

	Pazopanib	Sunitinib	Cabozantinib	Ipi-Niv	Axi-Pem
Essential HTN	140	125	175	326	72
DM	53	48	77	152	31
COPD	25	22	40	64	14
CHF	23	20	26	64	10
	241	215	318	606	127
Chi-square	1.8658			Chi-square	10.7317
p-value	0.931615			p-value	0.294549

	n	Median Time on therapy	Mortalities	Median Survival
Paz	239	371	101	170
Sun	133	572	63	201
Cab	180	296	78	195
Ipi-Niv	387	356	142	138
Axi-Pem	30	575	9	393

Table 3 (above): Prevalence of co-morbidities, time on therapy, mortality and median survival by cohort

Median Time on Therapy was longest for Axi-Pem and sunitinib, followed by pazopanib, Ipi-Niv with shorter times for cabozantinib.

Median time to mortality while on therapy was longest for Axi-Pem at 393 days, followed by sunitinib, cabozantinib around 200 with shorter times for pazopanib around 170 and shortest for Ipi-Niv around 140.

	Pazopanib v Sunitinib	**Pazopanib v Cabozantinib**
	101	88
# patients	200	213
Risk	0.505	0.413
95% Confidence Interval	-0.0880,0.108	0.009, 0.198
p-value	0.8415	0.0326
Risk ratio	1.02	1.25
95% Confidence Interval	0.845,1.236	1.017, 1.536
Median survival	911	651
Hazard ratio	1.014	0.955
95% CI	0.771,1.334	0.717,1.272
Log-rank X2 (LR-X2)	0.0101	0.0996
Proportionality p-value	0.92	0.752

Table 4 (above): Summary statistics measures of association, hazard-ratio, and log-rank test comparing cohorts between Pazopanib, Sunitinib, and Cabozantinib

Effect size was measured using risk ratio, significance was assessed using log-rank testing and impact of interventions was evaluated using hazard ratio. No significant differences were seen in overall survival in patients receiving pazopanib compared to sunitinib. Compared to pazopanib, sunitinb was associated with mortality risk ratio of 1.02, hazard ratio 1.014 with log-rank p-value 0.92, and no violation of homoscedasticity on proportionality testing. In contrast, although overall mortality risk was lower in cabozantinib cohort compared to pazopanib cohort with risk 0.413 compared to 0.516 mortality risk (95% CI 0.009, 0.198, p=0.0326), multi-variate analysis did not demonstrate a significant difference. Mortality risk ratio was 1.25 (95% CI 1.017, 1.536) for pazopanib compared to cabozantinib, with hazard ratio 0.955, log-rank test with p-value 0.0996, and proportionality preserved with p-value 0.752.

Axi-Pem v Ipi-

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	Niv
# patients	85
Risk	0.247059
95% Confidence Interval	0.129,-0.008
p-value	0.0686
Risk ratio	1.524
95% Confidence Interval	0.961, 2.416
Median survival	1921
Hazard ratio	1.984
95% CI	1.142, 3.446
Log-rank X2 (LR-X2)	6.146
Proportionality p-value	0.0132

Table 5 (above): Summary statistics measures of association, hazard-ratio, and log-rank test comparing cohorts between Ipi-Niv and Axi-Pem

Significant differences were seen in measures of association and multi-variate analysis of patients by combination therapy. Ipi-Niv had higher mortality risk ratio of 1.524 (95%CI 0.961, 2.416) compared to Axi-Pem, however, multi-variate testing was also not statistically significant with a P value of 0.0686. Proportionality testing demonstrated statistically significant difference between cohorts, at least partly due to sample size.

CONCLUSION

We studied outcomes including time on therapy and overall survival for 1,540 patients treated with pazopanib, sunitinib, cabozantinib, Ipi-Niv, or Axi-Pem. Pazopanib remains useful in the management of mRCC. The COMPARZ trial's insights, alongside supportive data from subsequent studies, affirm its utility, particularly among favorable-risk patients. In our 88 patients treated with cabozantinib matched with patients treated with pazopanib, cabozantinib appears to have better relative risk of overall survival compared to pazopanib, but hazard ratio was not statistically significant on multivariate analysis. This may indicate differences in survival at different time points and needs further elucidation. The evolution of treatment with the introduction of immune checkpoint inhibitors (ICIs), requires further consideration.

Dual immune checkpoint inhibitor Ipi-Nivo has emerged as an alternative for intermediate and poor-risk cohorts, due to enhancement in overall survival (OS). The extended follow-up data from the CheckMate 214 trial reveals not only improved long-term outcomes but also highlights a significant rate of complete responses, thus marking a shift in treatment for mRCC. Previous retrospective studies demonstrated improved OS in Axi-Pem compared to Ipi-Niv, however, our results for Axi-Pem did not have statistically significant log-rank test p-value, likely due to the small sample size of 85 patients. These results support NCCN guidelines for a 2b recommendation for Ipi-Niv for advanced disease.

This study's retrospective design inherently limits causal inferences. Additionally, the relatively small sample size, particularly for the Axi-Pem group, may affect the generalizability of some findings.

Moving forward, larger, prospective studies are necessary to confirm the potential survival benefit of Axi-Pem compared to Ipi-Niv. Additionally, subgroup analyses based on patient characteristics could reveal variations in treatment effectiveness across different patient populations.

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