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First-line TKI vs IO for Metastatic Renal Cell Carcinoma: IMDC Score Stratified Retrospective Analysis

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Abstract

We evaluate the outcomes of patients with primary metastatic renal cell carcinoma treated with upfront nephrectomy followed by pazopanib, sunitinib, or ipilimumab-nivolumab as first-line therapy. We used a large multinational federated network database to identify 1,956 predominantly elderly Caucasian male patients from January 1, 2010, to January 1, 2024, who were diagnosed with metastatic renal cell carcinoma and received first-line systemic therapies with pazopanib, sunitinib, or ipilimumab-nivolumab. Overall survival was evaluated using the mortality rates, Kaplan-Meier curves, and multivariable analysis. We observed decreasing median survival with increasing International Metastatic Renal Cell Carcinoma Database (IMDC) score. Patients receiving ipilimumab-nivolumab demonstrated the lowest mortality rate, followed by sunitinib and pazopanib. Notably, pazopanib had a significantly higher risk of death compared to ipilimumab-nivolumab in low-risk mRCC (IMDC 0 and 1-2) with higher hazard ratio and significant log-rank testing in patients with IMDC score of 0. No significant difference in overall survival was observed between pazopanib and sunitinib for all IMDC risk cohorts. These findings suggest potential advantages for ipilimumab-nivolumab as first-line therapy in favorable-risk mRCC. Our results agree with previous studies, support guidelines, stratify differences in overall survival by IMDC score, and provide direct evidence comparing pazopanib to ipilimumab-nivolumab. These results may provide guidance for clinical decision-making in patients based on IMDC score, drug affordability, and tolerability.

Keywords: mRCC (Metastatic Renal Cell Carcinoma), TKI (tyrosine kinase inhibitor), immunomodulator (IO), ipilimumab-nivolumab, IMDC (International Metastatic renal cell Carcinoma Database Consortium)

INTRODUCTION

Renal cell carcinoma (RCC) is the most prevalent kidney cancer, with clear cell RCC (ccRCC) being the most common subtype [1]. The most common sites of metastatic involvement in clear cell RCC are well characterized and include the lung, lymph nodes, bone, and liver [1]. While 2% of all cancer diagnoses and mortality worldwide are RCC, it ranks as the 14th and 9th most prevalent cancer overall for women and men respectively [2]. Different international models incorporate myriad variables that have demonstrated a predictive relationship with cancer survivorship and are used collectively to categorize patients. A frequently used model with good validation is the International Metastatic RCC Database Consortium (IMDC) Risk Model for mRCC developed by Heng, et al [3]. Patients can be classified into three different IMDC risk groups—favorable, intermediate, or poor risk [2]. This model was formulated during targeted therapy era but has been found applicable in the current immuno-oncology through validation study by Ernst, et al [3]. Cytoreductive nephrectomy has strong evidence of benefits outweighing harm and is offered to patients who have at least one IMDC risk factor and can have majority of their burden removed through surgery [4].

In version 1.2025, the National Comprehensive Cancer Network (NCCN) updated its guidelines for managing metastatic renal cell carcinoma (mRCC), underscoring ipilimumab-nivolumab as the preferred therapy for favorable-risk patients over pazopanib and sunitinib [5]. This recommendation highlights the regimen's moderate efficacy and toxicity profile. Conversely, for poor- and intermediate-risk patients, ipilimumab-nivolumab is a category 1 preferred regimen in immunomodulator-naïve individuals, with limited usage recommended for those previously exposed to

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immunomodulators [5]. Pazopanib and sunitinib are acceptable alternative agents across all treatment lines [5].

A phase I study evaluating pazopanib compared to placebo in 225 patients reported a 35% response rate at 12 weeks with a median progression-free survival of 52 weeks [6]. Further phase 3 investigations confirmed pazopanib efficacy in both treatment naive and cytokine-pretreated patients [7]. In this study of 435 patients, PFS was 9.2 months compared to 4.2 months in placebo. Overall response rate was 30% with a median duration of response greater than 58 weeks [7]. In the COMPARZ phase 3 randomized trial for first-line therapy in 1,110 patients with clear cell metastatic renal cell carcinoma, pazopanib was non-inferior to sunitinib in terms of progression-free survival [8]. Extended analysis for 1 year showed median OS 21.7 m (adverse events)-36.8 m (no adverse events) with pazopanib and 18.1 (AE)-38.0 (no AE) months with sunitinib [9].

In a multicenter retrospective database analysis of 670 patients in Canada, sunitinib demonstrated improved overall survival compared to pazopanib in the first-line setting across heterogeneous disease severities and all risk groups [10]. Notably, 13.8% of the population of interest received pazopanib. In their analysis after stratification by IMDC risk, sunitinib OS was 40.1 months compared to 20.6 for pazopanib in intermediate-risk and the difference in survival was statistically significant [10]. By contrast OS was 46.8 months and 33.8 months in the favorable risk, 12.7 and 9.9 months in the poor risk group for sunitinib and pazopanib respectively, neither of which was statistically significant [10]. In one study, median overall survival was not reached with nivolumab plus ipilimumab versus 26.0 months with sunitinib, resulting in a significant hazard ratio for death of 0.63 (P<0.001) [11]. Furthermore, nivolumab plus ipilimumab led to higher objective response rates (42% vs. 27%, P<0.001) and complete response rates (9% vs. 1%) compared to sunitinib [11]. Median progression-free survival was also favorable with nivolumab plus ipilimumab at 11.6 months versus 8.4 months with sunitinib (HR, 0.82; P = 0.03) [11].

The CheckMate 016 open-label, parallel-cohort, phase I trial, evaluated the efficacy and safety of nivolumab plus ipilimumab combinations in mRCC patients, alongside nivolumab plus a tyrosine kinase inhibitor [12]. Patients received various dosing regimens: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3), or nivolumab 3 mg/kg plus ipilimumab 3 mg/kg (N3I3), followed by nivolumab monotherapy. Both arms demonstrated a confirmed objective response rate of 40.4%, with ongoing responses in 42.1% and 36.8% of patients in the N3I1 and N1I3 arms, respectively, at a median follow-up of 22.3 months [12].

While Tyrosine kinase inhibitors (TKI) are being replaced with newer therapies, there is still value in TKI use. Pazopanib may be more affordable and better tolerated than Ipi-Niv, which can cause immune-related side effects [13]. Previous studies comparing Ipi-Niv to pazopanib had limited small sample size of 97 for sunitinib and 2 patients for pazopanib but also showed better overall response rate in Ipi-Niv cohort compared to TKI therapy (sunitinib, axitinib, sorafenib, pazopanib) [14]. With such a significant change in therapy for metastatic Renal cell carcinoma in the past decade arises a need for head-to-head comparisons for pazopanib and ipilimumab-nivolumab.

RESEARCH ELABORATION

This retrospective analysis collected deidentified patient data from a large federated multi-national database. We included patients with mRCC and aged ≥18 years old. As sunitinib received FDA approval in 2006 and pazopanib in 2009, 2010 was selected as the start of the study period to control for adoption of guideline recommendations. All patients received first-line systemic treatment between January 1, 2010, and January 1, 2024. Patients 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 metastases), C78.7 (liver metastases), C79.3 (brain metastases), C79.7 (adrenal metastases) or C79.5 (bone metastases) to confirm the diagnosis of distant metastases. We recognized patients receiving nephrectomy using ICD-10-CM: Z90.5. Comorbidities were identified using ICD-10-CM: I10-I16 for hypertension, ICD-10-CM: E08-E13 for diabetes mellitus, ICD-10-CM: I50 for heart failure, and ICD-1-CM: J40-44 for chronic obstructive pulmonary disease. The first-line systemic therapies were either TKI (sunitinib, pazopanib) or IO (ipilimumab-nivolumab). The starting date of first-line therapy was set as the index date. Upfront cytoreductive nephrectomy needed to be performed prior to initiation of first-line therapy for all cohorts. The primary outcome was overall survival (OS), which was defined as the duration from the index date to the date of death from any cause, or censored at the end of study, whichever happened first.

Demographic data between cohorts is included in Table 1: Co-morbidities and demographics by treatment cohort after matching. Eastern Cooperative Oncology Group stage or Karnofsky score was not available for more than 50% of patients in the study and not reported for this reason.

RESULTS

We completed a retrospective database study comparing overall survival in predominantly Caucasian elderly male population from North America. Our study population consisted of 12,655 patients with primary renal cell carcinoma with metastasis to bones, liver, lungs, or adrenal glands who underwent nephrectomy before adjuvant therapy between January 1, 2020, and January 1, 2024. One thousand nine hundred and fifty-six patients were treated with pazopanib (Paz), sunitinib (Sun) or ipilimumab-nivolumab (Ipi-Niv) first-line therapy and had lab testing on file for hemoglobin, platelet count, neutrophil count, and serum calcium. There were 340 patients (Paz 97, Sun 99, Ipi-Niv 144) in the IMDC score 0 group, 732 (Paz 272, Sun 219, Ipi-Niv 241) in the IMDC 1-2 starting treatment within 1 year, 613 (Paz 219, Sun 175, Ipi-Niv 219) in the IMDC 1-2 starting treatment in 1-5 years, 223 (Paz 70, Sun 69, Ipi-Niv 84) in IMDC 3 starting

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treatment within 1 year and 48 patients (Paz 28, Sun 10, Ipi-Niv 10) in IMDC 3 group starting treatment in 1 to 5 years. Due to the small sample sizes of patients with IMDC score 3 starting therapy in 1 to 5 years, they were not included in analysis. Median survival and Kaplan-Meier curve survival had a decreasing trend with increasing IMDC score as outlined in Table 2: Median survival, overall survival, log-rank test p-value, and risk ratio summary by treatment cohort.

Mortality rate and overall survival time were analyzed using built-in measures of association, log-rank test, and Kaplan-Meier curve tools in TriNetX. Effect size was measured using risk ratio, significance was assessed using log-rank, and impact of interventions was evaluated using hazard ratio. There was no significant difference in overall mortality between pazopanib and sunitinib for all subgroups including IMDC score 0, IMDC score 1-2 starting treatment with in 1 year, IMDC score 1-2 starting treatment within 1-5 years or IMDC score 3 starting treatment within 1 year. Significant differences were seen in overall survival for pazopanib relative to ipilimumab-nivolumab in all 3 lowest risk subgroups: IMDC score 0, IMDC score 1-2 starting treatment within 1 year and IMDC score 1-2 starting treatment within 1-5 years. IMDC score 3 starting treatment within 1 year did not show statistically significant differences in survival, which may be due to the smaller sample size. IMDC score 0 patients treated with pazopanib had a higher mortality compared to patients treated with Ipi-Niv with a risk ratio of 3.3 (95% confidence interval 1.727-6.303). On multi-variate analysis, log-rank test was significant with P-value of 0.0005. The hazard ratio was 5.002 (2.198, 11.38). Survival probability on Kaplan-Meier curves was 88.91% for Ipi-Niv compared to 48.68% for pazopanib. In contrast, hazard ratio and log-rank test was not significant for differences between IMDC 1-2 starting treatment within 1 year or 1-5 years when comparing patients treated with pazopanib to patients treated with Ipi-Niv.

CONCLUSION

We examined overall survival with pazopanib, sunitinib, and Ipi-Niv in 1,956 patients. Pazopanib was associated with lower overall survival and shorter median survival compared to Ipi-Niv for patients with low-risk mRCC (IMDC 0) in our study. Compared to COMPARZ trial, the 28.4 month OS for Pazopanib and 29.3 month OS for Sunitinib are closest to IMDC 1-2 score OS seen in our study [9]. We observed slightly longer OS for favorable risk cohort compared to a retrospective study in Lilani, et al's study of the Canadian population. Lilani, et al had unstratified OS of 31.7 months for sunitinib compared to 20.6 for pazopanib [10]. Our intermediate-risk OS was almost identical to Lilani, et al's for Paz (20.6 m vs 19.2-20.4 m for us) but we observed shorter OS with Sun for this cohort (40.1 m vs 20.0-22.8 m for us). These differences may be due the smaller number of patients receiving Paz in the Canadian study, who may not have tolerated alternative therapy. In CheckMate 016, the OS was 67.3% (n=47, 26.7 months) N3I1 and 69.6% (n=47, 26.0 months) N1I3 [12]. As CheckMate was a time-limited phase I trial, we observed comparatively higher survival of 89% with OS of 74.0 months in IMDC-0 and survival of 30% with OS of 22.8 months in IMDC 1-2 starting therapy within 1 year.

Limitations of our study include retrospective design, which can introduce selection bias, and our study population being predominantly Caucasian elderly males restricts generalizability to more diverse patient groups. This study adds evidence to the growing body of research supporting the use of Ipi-Niv as a first-line therapy for favorable-risk mRCC. Treatment decisions should be individualized based on each patient's specific factors, risk profile, and tolerability. Prospective studies may be beneficial to confirm these findings, especially for the high-risk patient group (IMDC 3).

Tables:

Comparison group	Cohorts	n	Essential (primary) hypertension (%)	Diabetes mellitus (%)	Heart failure	Chronic obstructive pulmonary disease	Age (years)	Male (%)	White (%)	Black (%)
1	**IMDC 0 Paz**	81	74	31	<10*	<10*	69	66	74	<10*
1	**IMDC 0 Sun**	81	74	31	<10*	<10*	64	77	77	<10*
2	**IMDC 0 Paz**	94	77	34	12	<10*	67	67	74	<10*
2	**IMDC 0 Ipi-Niv**	94	77	34	<10*	12	64	76	80	<10*
3	**IMDC 1-2 <1 yr Paz**	206	69	29	11	11	64	68	77	9
3	**IMDC 1-2 <1 yr Sun**	206	69	29	11	11	63	73	82	7
4	**IMDC 1-2 <1 yr Paz**	233	69	29	11	11	64	68	77	8

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4	**IMDC 1-2 <1 yr Ipi-Niv**	233	69	29	11	11	66	51	74	7
5	**IMDC 1-2 1-5 yr Paz**	162	66	27	9	7	63	68	79	10
5	**IMDC 1-2 1-5 yr Sun**	162	66	28	9	7	63	72	80	7
6	**IMDC 1-2 1-5 yr Paz**	203	75	36	11	9	63	68	79	9
6	**IMDC 1-2 1-5 yr Ipi-Niv**	203	75	36	11	9	66	76	73	8
7	**IMDC 3 <1 yr Paz**	53	75	30	19	19	64	71	80	<10*
7	**IMDC 3 <1 yr Sun**	53	75	30	19	19	62	74	78	<10*
8	**IMDC 3 <1 yr Paz**	66	82	39	<10*	<10*	64	71	79	<10*
8	**IMDC 3 <1 yr Ipi-Niv**	66	82	39	<10*	<10*	68	51	73	<10*

Table 1 (above): Co-morbidities and demographics by treatment cohort after matching. Paz = Pazopanib, Sun = Sunitinib, Ipi-Niv = Ipilimumab-Nivolumab, IMDC = International mRCC Database Consortium. * Less than 10 patients, percentage not reported. In comparison 1, IMDC 0 Paz was compared to IMDC 0 Sun, and so on.

IMDC Score	**Agent**	**Overall Survival (%)**	**Median Survival (days)**	**Agent**	**Median Survival (days)**	**Overall Survival (%)**	**Number of patients**	**Log-rank p-value**	**Risk Ratio**	**95 % Confidence Interval**
0	Paz	48	2251	Sun	>4228**	57	81	0.47183	1.153846	0.754059, 1.765593
0	Paz	49	2251	Ipi-Niv	>2175**	89	94	**0.0005**	3.3	**1.727624, 6.303455**
1-2 tw <1 yr	Paz	17	588	Sun	622	18	206	0.312319	1.07438	0.920182, 1.254417
1-2 tw <1 yr	Paz	15	611	Ipi-Niv	695	30*	233	0.308981	1.342342	**1.137505, 1.584066**
1-2 1-5 yr	Paz	19	584	Sun	607	21	162	0.233798	1.117021	0.939301, 1.328367
1-2 1-5 yr	Paz	15	588	Ipi-Niv	661	21	203	0.28178	1.35	**1.138533, 1.600745**
3 <1 yr	Paz	23	148	Sun	275	9	53	0.690601	0.972222	0.744103, 1.270275
3 <1 yr	Paz	17	167	Ipi-Niv	206	16	66	0.749097	1.071429	0.837932, 1.369992

Table 2 (above): Median survival, overall survival, log-rank test p-value, and risk ratio summary by treatment cohort. Statistically significant values are bolded. Cohort 1 was compared to cohort 2 for all statistical analyses. IMDC = International mRCC Database Consortium, Ipi-Niv = Ipilimumab-Nivolumab, Paz = Pazopanib, Sun = Sunitinib, tw = treated within, yr = year. *Survival probability

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at 2180 days, overall survival not reported at end of period by TriNetX for unclear reasons. Median mortality not reached, latest data available in study period.

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