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Comparative Effectiveness of Front-Line Ipilimumab and Nivolumab or Axitinib and Pembrolizumab in Metastatic Clear Cell Renal Cell Carcinoma

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Abstract

Background: Treatment of metastatic renal cell carcinoma (mRCC) is rapidly evolving with new combination therapies demonstrating improved response rates and survival. There are no head-to-head prospective trials comparing an immunotherapy doublet with an immunotherapy/tyrosine-kinase inhibitor-based combination. We compare real-world outcomes in patients treated with axitinib/pembrolizumab (axi/pembro) or ipilimumab/nivolumab (ipi/nivo). The primary endpoints were overall-survival (OS) and real-world progression-free survival (rwPFS).

Patients and Methods: We used a de-identified database to select patients diagnosed with clear cell mRCC and treated with front-line axi/pembro or ipi/nivo from 2018 to 2022. Analyses are adjusted using propensity score-based inverse probability of treatment weighting, balancing age, gender, insurance, race, IMDC risk, and nephrectomy status. We compared survival by treatment groups using weighted and unweighted Kaplan–Meier curves with log-rank tests and weighted Cox proportional hazards regressions.

Results: We included a total of 1506 patients with mRCC who received frontline axi/pembro (*n* = 547) or ipi/nivo (*n* = 959). Median follow-up time was 20.0 months (range: 0.2-47.6). Baseline demographics were similar between the 2 cohorts. Adjusted median OS for the full population was 28.9 months for axi/pembro and was 24.3 months for ipi/nivo (*P* = .09). Twenty-four-month survival was 53.8% for axi/pembro treated patients and 50.2% for ipi/nivo treated patients. rwPFS was 10.6 months for axi/pembro treated patients and 6.9 months for ipi/nivo treated patients. Treatment with axi/pembro conferred improved survival in the IMDC favorable risk strata, with no significant difference in survival observed within the full cohort.

Conclusions: In this retrospective, real-world study of patients treated with front-line combination therapy, patients with IMDC favorable risk disease had better survival when treated with axi/pembro compared to ipi/nivo. However, survival for the entire population and the 24-month median overall survival were not statistically different between treatment groups. Longer follow-up is necessary to discern any emerging significant differences.

Key words: metastatic renal cell carcinoma; real-world outcomes; immunotherapy; targeted therapy.

Implications for Practice

There are multiple front-line therapy options for untreated patients with metastatic renal cell carcinoma (mRCC). Unfortunately, the studies that led to their approvals were not designed in a fashion that allows providers to discern which treatment option is best. The authors looked at survival outcomes from a real-world data set of patients with mRCC treated with 2 of the leading treatment options, either axitinib/pembrolizumab or ipilimumab/nivolumab. No clear differences in survival outcomes were found between the 2 combinations, albeit with limited follow-up time.

Introduction

The therapeutic landscape for metastatic renal cell carcinoma (mRCC) has recently undergone rapid advancements.[1] Prior to 2005, the mainstay of treatment was limited to cytokine-based therapies as RCC proved to be resistant to radiotherapy, hormonal therapy, and conventional chemotherapies. In the cytokine era, responses were modest, treatment-associated toxicities were abundant, and outcomes were poor for most patients.[2] The identification of the role of the *VHL* tumor-suppressor gene, and its downstream signaling pathways served

as the foundation for the development for a number of targeted-based therapies which have been successfully integrated into the front-line and salvage mRCC treatment landscape.[3] Specifically, multitarget tyrosine-kinase inhibitors (TKI) targeting VEGF receptors and other growth receptors provided significant improvements to cytokine-based therapies and became the cornerstone of treatment.[4]

Within 8 years of the TKI era, immune checkpoint inhibitors (ICI) became the next class of agents with proven efficacy in mRCC.[5] Soon thereafter, it was observed that combination approaches, whether with ICIICI or TKI/ICI, may be administered safely and with superior outcomes to TKIs alone.[6,7] The rapid development of these novel agents and combination therapies created a level of uncertainty in the treatment paradigm that has yet to be reconciled in the literature or evidence-based guidelines.[8]

In practice, patients with mRCC are most often stratified by a validated prognostic model known as the International Metastatic RCC Database Consortium (IMDC) criteria, which categorizes patients into 3 risk groups: favorable, intermediate, or poor.[9] These risk criteria have been integrated into recent clinical trials in mRCC, and have aided in the decision-making process for treatment options. Incorporating the IMDC criteria, 2 pivotal trials have led to approval of the most frequently used front-line treatment recommendations.[6,7] CheckMate-214 was a randomized, open-label, phase III study that assessed ipilimumab plus nivolumab (ipi/nivo) versus sunitinib monotherapy.[6] Long-term results demonstrate superiority in all primary endpoints favoring ipi/nivo over sunitinib for patients with IMDC intermediate-and poor-risk disease. KEYNOTE-426 was an open label, phase III trial in patients with previously untreated mRCC who were randomly selected to receive either pembrolizumab plus axitinib (axi/pembro) or sunitinib.[7] The axi/pembro combination demonstrated survival benefits across the IMDC intermediate-and poor-risk risk groups, with no overall survival benefit in the IMDC favorable risk group at ths time. Importantly, with regards to these 2 treatment options, whether in the IMDC intermediate-and poor-risk or favorable-risk patient population, there are no head-to-head comparisons providing level 1 evidence of superiority of either treatment option and no ongoing trials evaluating this question. Thus, there remains an unmet need for data to support clinical decision making in this setting.[10]

Herein, we report real-world outcomes in patients with mRCC treated with either axi/pembro or ipi/nivo combination therapies. Primary endpoints are to assess real-world progression-free survival (rwPFS) and overall survival (OS) of patients with clear-cell mRCC treated with these combination regimens, stratified by IMDC risk group.

Methods

Study Design and Data Source

This is a retrospective, observational analysis of patients with mRCC who received combination ipi/nivo or axi/pembro as their front-line therapy, with data obtained from the Flatiron Health EHR-derived de-identified database.[11,12] This longitudinal database is comprised of de-identified patient-level structured and unstructured variables from approximately 280 community and major academic cancer centers, curated via technology-enabled abstraction.[12,13] This dataset uses pre-specified algorithms, with expert input from oncologists,

to infer lines of therapies based on EMR records. Generally, this rule-based definition for lines of therapy groups together first eligible drugs given within 28 days (ie, all eligible drugs given within 4 weeks of the first eligible drug). We determined IMDC scores via abstraction of the underlying risk criteria.[14] If patients had no known risk factors but has missing variables, they were categorized as unknown risk.

The study objectives include: (1) describe treatment patterns and patient characteristics of this population; (2) determine the rwPFS and OS of the patient population; and (3) determine the relationship between survival outcomes and IMDC risk group. The study period was from April 1, 2018 through April 30, 2022. Institutional Review Board approval of the study protocol was obtained prior to study conduct, and included a waiver of informed consent.

Study Population

Cohort eligibility criteria included adult patients (≥18 years of age) with clear cell mRCC who were treatment naïve and undergoing treatment with ipi/nivo or axi/pembro. The study included patients with or without upfront cytoreductive nephrectomy and/or metastasectomy as well as patients who presented at diagnosis with de novo metastatic disease or those with recurrent metastatic disease. Exclusion criteria included: (1) patients who initiated on TKI or ICI monotherapy, and had a subsequent drug added for dual therapy outside of a 28-day window, (2) patients with predominant non-clear cell histology, and (3) patients who had no structured data entry (ie, vital information, drug encounter) within 90 days of their mRCC diagnosis (Fig. 1).

Outcome Measures

We defined rwPFS as the time in months from the date of initiation of ipi/nivo or axi/pembro to death or disease progression. Dates of real-world progression were retrospectively captured from EHR documentation as part of routine clinical care, curated via technology-enabled abstraction. Technology-enabled abstraction allows for large-scale data review with validated quality and efficiency of the abstraction process.[13] Real-world progression is defined as a distinct episode in which the treating clinician concludes that there has been growth or worsening in the disease of interest.[15] For the rwPFS analysis, patients who were alive and had not progressed at the end of clinical follow-up (date of last clinic visit note) were censored. rwPFS assessment is not affected by treatment interruptions due to toxicity without disease progression.

OS was calculated using a composite mortality variable aggregated from EHR structured (eg, medication orders, laboratory data) and unstructured information (eg, patient notes, pathology reports), commercial mortality surveillance sources and the social security death index, which delivered data with high sensitivity and specificity.[16] OS was defined as the number of months from the initiation of treatment to death due to any cause. For the OS analysis, patients alive at the end of follow-up (date of last visit) or lost to follow up were censored.

Statistics

We summarized baseline patient characteristics and treatment patterns via standard descriptive statistics. The association between treatment and patient characteristics were assessed via chi-squared tests and *T*-tests. We used multivariable
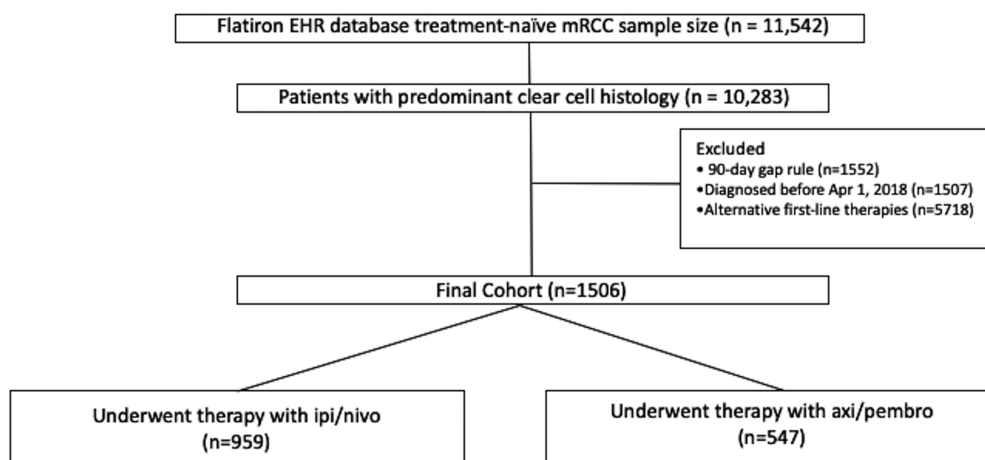
Figure 1. CONSORT plot for patient selection.

logistic regression to simultaneously assess factors associated with a particular treatment. For the survival outcomes of rwPFS, and OS, we characterized survival time via Kaplan-Meier curves, testing for differences using log-rank tests. We created adjusted survival curves using propensity score-based inverse probability of treatment weighting (IPTW). We estimated propensity scores via logistic regression based on all available pre-treatment covariates which could plausibly be associated with treatments or outcomes (age, gender, insurance, race, IMDC, and nephrectomy).[17] We assessed covariate balance by calculating standardized mean differences (differences <0.1 considered adequate balance).[18] We assessed survival by treatment group using weighted Kaplan-Meier curves weighted Cox proportional hazards regressions with robust standard errors and IPTW log-rank tests.[19] We created IPTW survival curves in strata determined by IMDC risk score. We grouped all patients with poor and intermediate IMDC scores together, due to our categorization of IMDC scores with missing data.

Results

Patient Characteristics

We included a total of 1506 patients with mRCC who started front-line axi/pembro (*n* = 547) or ipi/nivo (*n* = 959) between April 1, 2018 through April 30, 2022 (data cut off). Median follow-up time was 20.0 months (range: 0.2-47.6). The majority of patients were male (73.2%). 57.5% of patients had a nephrectomy, 56.2% of patients had metastatic disease at time of initial diagnosis, and the average patient age was 66.0 years (range: 21.0-85.0). Patients were characterized by IMDC risk criteria as follows: 6.4% favorable risk, 82.3% intermediate/poor risk, and 11.4% unknown risk. The median time from (initial) diagnosis of disease to initiation of therapy was 2.5 months (interquartile range: 0.9-25.1). More patients were treated with ipi/nivo in 2018, then the treatment pattern transitioned with increased use of axi/pembro through 2019-2021, although ipi/nivo was more commonly used throughout the study period. Otherwise, patient demographics and baseline characteristics were generally balanced, and are outlined in Table 1.

Multivariable analyses of potential factors that predict choice of therapy are demonstrated in Table 2. A regression model was performed to determine the likelihood of receiving ipi/nivo based on covariates. Categorization as IMDC intermediate/poor risk demonstrated a significantly increased likelihood toward ipi/nivo as choice of therapy (OR of 2.09, 95% CI: 1.27-3.45; *P* = .004).

Progression-Free Survival

In the adjusted model for the full population (*n* = 1506), median rwPFS was 10.6 months (95% CI: 8.9-12.6) in the axi/pembro treated patients, and 6.9 months (95% CI: 5.8-9.1) in ipi/nivo treated patients (P = .04) (Fig. 2a). When risk stratified by IMDC criteria; IMDC favorable risk median rwPFS 25.5 months for axi/pembro treated patients (95% CI: 14.6-NR) and 6.9 months for ipi/nivo (95% CI: 3.7-NR) (*P* = .01) (Fig. 2b). In IMDC intermediate/poor risk, the median rwPFS was 9.5 months (95% CI: 8.2-12.1) for axi/pembro treated patients, and 6.4 months for ipi/nivo treated patients (95% CI: 5.6-7.8; *P* = .2; Fig. 2c).

Overall Survival

In the adjusted analysis for the full population, median OS for patients treated with axi/pembro and ipi/nivo were 28.9 months (95% CI: 23.5-NR) and 24.3 months (95% CI: 22.0-28.5) (*P* = .9), respectively (Fig. 3a). When analyzed per IMDC risk category, median OS was NR for either treatment group in the favorable risk population (*P* = .04; Fig. 3b). In the IMDC intermediate/poor risk patient, median OS was 23.3 (95% CI: 18.4-30.1) for the axi/pembro treated patients, and 23.3 months (95% CI: 20.4-26.0); (*P* = .4) for the patients treated with ipi/nivo (Fig. 3c). At 24-month survival analysis, the OS was 53.8% among patients who received axi/pembro versus 50.2% for patients treated with ipi/nivo (Table 3).

Discussion

In this large, retrospective analysis, we used a real-world data source to compare outcomes in patients with metastatic clear cell RCC. There are no prospective clinical trials comparing recommended front-line therapy options in mRCC. Both the KEYNOTE-426 and CheckMate-214 studies compared their respective combination therapy to sunitinib, which is no longer a category 1 NCCN (National Comprehensive Cancer Network) recommended treatment.[6-8] In our analysis, there is no discernible difference in median or 24-month landmark

Table 1. Patient characteristics of all included patients.

	Axitinib+Pembrolizumab (*n* = 547)	Ipilimumab + Nivolumab (*n* = 959)	*P*-value
Median age (range), years	67.0 (21-85)	65.0 (29-84)	.001
Male, *n* (%)	384 (70.2%)	719 (75.0%)	.044
Race, *n* (%)			
White	361 (66.0%)	610 (63.6%)	.187
Black or AA	26 (4.8%)	68 (7.1%)	
Other or unknown	160 (29.3%)	281 (29.3%)	
IMDC risk group, *n* (%)			
Favorable	47 (8.6%)	49 (5.1%)	.001
Intermediate/poor	422 (77.1%)	817 (85.2%)	
Unknown	78 (14.3%)	93 (9.7%)	
Hx of nephrectomy, *n* (%)	329 (60.1%)	537 (56.0%)	.117
Stage at diagnosis, *n* (%)			
I-III	249 (45.5%)	373 (38.9%)	.04
IV	285 (52.1%)	562 (58.6%)	
Unknown	13 (2.4%)	24 (2.5%)	
Time from diagnosis to treatment (interquartile range), months	3.25 (0.9-34.9)	2.30 (0.09-19.3)	.004
BMI, median (range), kg/m^2	28.9 (17.1-74.4)	28.7 (15.1-67.6)	.692
Prescription patterns by year, *n* (%)			
2018			
2019	9 (1.6%)	238 (24.8%)	<.001
2020	179 (32.7%)	250 (26.1%)	
2021	168 (30.7%)	212 (22.1%)	
2022	177 (32.4%)	232 (24.2%)	
	14 (2.6%)	27 (2.8%)	

Table 2. Multivariate cox regression of treatment and prognostic variables on choice of therapy.

Covariate	Odds ratio	95% CI	*P*-value
Gender(Ref = female)	1.25	0.97-1.62	.09
Male			
Race (Ref = Caucasian)			
Black	1.40	0.83-2.36	.205
Hispanic/Latinx	0.92	0.57-1.47	.728
Age at diagnosis (continuous)	0.98	0.97–0.99	.05
Hx of nephrectomy (Ref = no nephrectomy)	0.95	0.68–1.33	.785
Insurance (Ref = commercial)			
Medicaid	0.91	0.58–1.43	.685
Medicare	1.11	0.82-1.49	.498
IMDC risk (Ref = favorable)			
Intermediate/poor	2.09	1.27-3.45	.004
Body Mass Index (continuous)	1.00	0.98–1.02	.841

overall survival between the axi/pemrbo (IO/TKI) and the ipi/nivo (ICI/ICI) groups. However, axi/pembro treatment conferred an improved median rwPFS in this study population, although this benefit was not sustained over time with crossing of the curves on Kaplan-Meier analysis. When patients are categorized by IMDC criteria, as they are in clinical practice, axi/pemrbo confers clear benefit over ipi/nivo with respect to

rwPFS and OS in the favorable risk population, although it represented a minority of patients.

These results are concordant with historical trial data and reaffirms current guideline practice recommendation of axi/pembro for IMDC favorable, intermediate, and poor risk groups, with reservation for ipi/nivo for IMDC intermediate/poor risk patients. IMDC risk criteria were originally
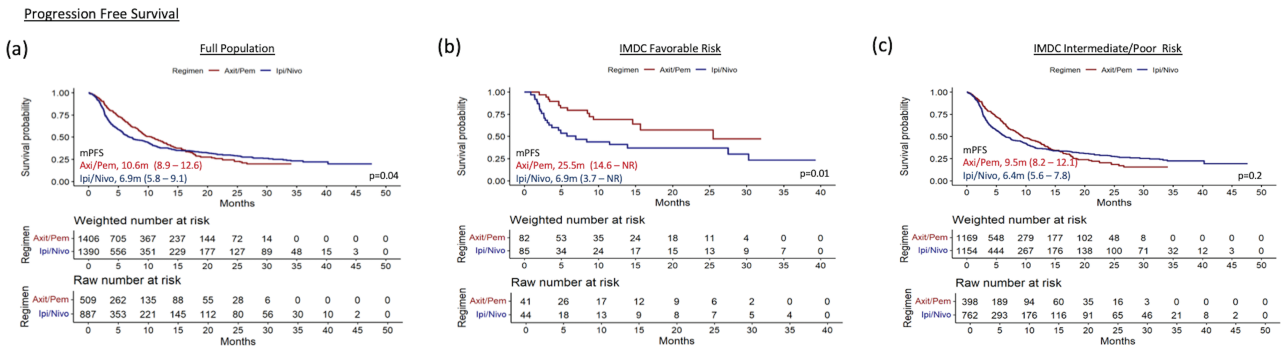
Figure 2. Real-world progression-free survival; Kaplan-Meier estimates for rwPFS in (**a**) full population, (**b**) IMDC favorable risk population, (**c**) IMDC intermediate/poor risk population. KM analyses performed with propensity score weighting.

Figure 3. Overall survival; Kaplan-Meier estimates for OS in (**a**) full population, (**b**) IMDC favorable risk population, (**c**) IMDC intermediate/poor risk population. KM analyses performed with propensity score weighting.
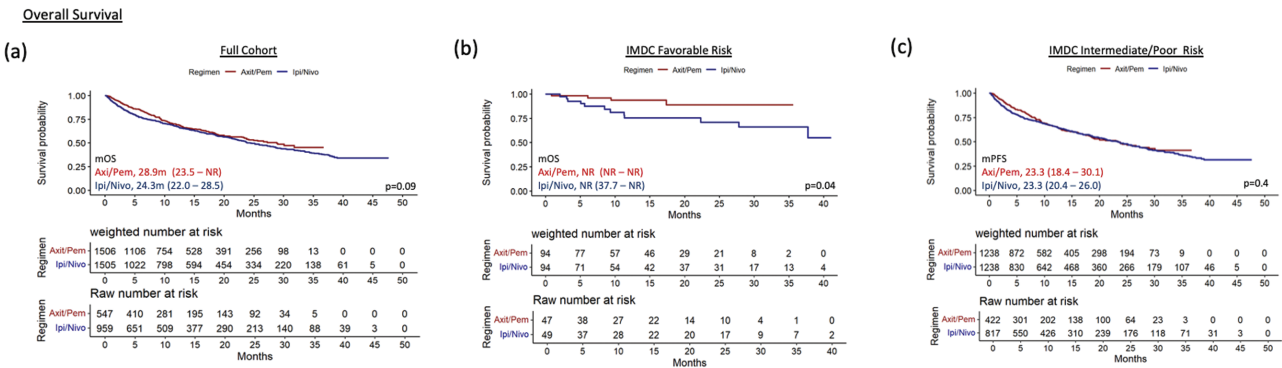
Table 3. Propensity score-weighted adjusted 24-month survival, PFS, OS

IMDC score	Axi/Pembro (*n* = 547)	Ipi/Nivo (*n* = 959)	*P*-value
Favorable (*n* = 96)			
24m survival	86.7%	72.3%	.045
HR for PFS		2.30 (95% CI 1.20-4.43)	
HR for OS		3.28 (95% CI 1.04-10.3)	
Intermediate/poor (*n* = 1239)[a]			
24m survival	48.0%	48.5%	.45
Intermediate	56.6%	57.6%	.86
Poor	33.2%	27.4%	.15
HR for PFS		1.11 (95% CI 0.944-1.32)	
HR for OS		1.07 (95% CI 0.89-1.29)	
Unknown (*n* = 171)[b]			
24m survival	75.8%	51.8%	.045
HR for PFS		1.14 (95% CI 0.72-1.81)	
HR for OS		1.87 (95% CI 1.01-3.47)	
Full cohort (*n* = 1506)			
24m survival	53.8%	50.2%	.09
HR for PFS		1.17 (95% CI 1.00-1.36)	
HR for OS		1.16 (95% CI 0.97-1.39)	

[a]Includes any patient with at least 1 known risk criteria.
[b]No known risk criteria, 1 or more criteria unknown.

developed in the TKI era prior to common use of immune checkpoint inhibitors. As such, its validation as a prognostic tool nests in angiogenesis-driven tumor biology. Our data support the rationale that VEGF-targeted therapies should be used in front-line therapy for favorable risk patients. Importantly, the IMDC model was originally intended as a prognostic model, whereas its current use in prospective studies uses the model as a predictive tool. This utilization has been widely accepted and has been adopted by standard guideline recommendations, but underscores the need for novel predictive biomarkers to further advance optimal patient treatment selection. There are multiple ongoing studies which may assist in clinical-decision making in this regard. The BIONIKK trial is a phase II biomarker-driven study with ipi/nivo or VEGF-TKI in treatment-naïve mRCC patients. Patients were assigned to treatment based on a 35-gene expression mRNA signature to tailor therapy based on tumor characteristics. Recently reported results support the hypothesis that immune and angiogenesis gene signature profiles have predictive value in patient treatment selection.[20] While not necessarily practice changing, such trials serve as a proof of principle that tumor molecular phenotype may 1 day combine with, or replace, IMDC risk stratification in the modern era of mRCC trial design.

Direct cross-trial comparisons are potentially misleading, and conclusions from such comparisons should be considered with caution.[10] Survival data in patients treated with ipi/nivo are more mature, as its clinical use and FDA-approval predates that of axi/pembro by 1 year. In the CheckMate-214 study, the 18-month overall survival rate with ipi/nivo was 75% in intermediate- and poor-risk patients (95% CI: 70-78). The median progression-free survival (mPFS) was 11.6 months.[6] At 60-month follow-up, mPFS and OS for intermediate- and poor-risk patient were 12.0 and 47.0 months, respectively.[21] With regards to axi/pembro clinical trial data, landmark 18-month survival in the ITT population was 82.3%. Extended follow-up at 24 months revealed 74.4% survival in this population.[22] Both study groups retained the survival benefit with long-term remissions (Table 4). Although our data grossly aligns with survival benefits observed from the respective treatment groups, the treatment benefit is blunted in our retrospective dataset.

Discrepancies in outcomes are typical of comparative analyses of observational data with historic clinical trial data. An efficacy-effectiveness gap is apparent, which is an increasingly appreciated entity in evaluation of oncologic therapies.[23] Randomized control trials take measures to minimize potential bias affecting the internal validity of an intervention's effects on outcome.[24] This attempt to control undesired outcome variability reflects a fundamental tradeoff between internal validity and external utility of the studies.[25] Effectiveness of a therapeutic intervention may be best assessed through observational studies such as this one, that have external validity and provide evidence that is generalizable and may inform day-to-day clinical decision making bedside, future clinical trial design, and healthcare policy.[24,26] Our cohort includes patients who would have been excluded from entering the trials (eg, due to co-morbid conditions) and treatment of these patients relies on subjective judgment rather than protocol-based decisions. It is important to note that our dataset rwPFS analyses are not equivalent to PFS from historical trial data. Historic prospective studies used RECIST-based progression, whereas our progression variable is drawn from the real-world clinical setting without formal evaluations for progression.

Our study underscores that real-world clinical outcomes differ from outcomes from clinical trials, and that the proportion of favorable risk patients encountered in practice may be smaller than in clinical trials. Exploration of our database of community and academic centers revealed that 6.4% of patients which met our study criteria were IMDC favorable risk. This is in contrast to the CheckMate-214 and KEYNOTE-426 study populations which enrolled 22% and 31% IMDC favorable risk patients, respectively. It is expected that our study excludes many IMDC favorable risk patients as many were likely started on TKI monotherapy or started on active surveillance, and our population is underrepresenting the true incidence of patients in this risk group. However, the landmark trials had a larger proportion of favorable risk patients and are not reflective of real-world populations in

Table 4. Real-world and historical survival data with cross-trial comparisons.

IMDC risk category	Ipilimumab + nivolumab			Axitinib + pembrolizumab		
	Real-world dataset	CheckMate-214	CheckMate-214 (extended 60 months)	Real-world dataset	KEYNOTE-426	KEYNOTE-426 (extended 30 months)
ITT/full cohort						
PFS	6.9m	12.4m	12.0m	10.6m	15.1m	15.4m
OS	24.3m	NR	56.0m	28.9m	NR	NR
Favorable risk						
PFS	6.9m	15.3m	12.0m	25.5m	20.8m	—
OS	NR	NR	74.0m	NR	NR	—
Intermediate/ poor risk						
PFS	6.4m	11.6m	12.0m	9.5m	12.6m	—
OS	23.3m	NR	47.0m	23.3m	NR	—
ITT/full cohort						
24-month landmark survival	50.2%	78%	—	53.8%	82.3%	74.4%

this regard, as large and widely accepted database analyses estimate the favorable risk incidence to be closer to ~17%.[9] Similarly, our dataset identified that 56.2% of patients which met our study criteria had de novo metastatic disease at diagnosis. Considerably higher than the historically accepted 30%-40%. It is very probable that our data abstraction and inclusion/exclusion criteria led to overrepresentation of this group as many patients with slow-growing, indolent, recurrent metastatic tumors are IMDC favorable risk and for the above-noted reasons were not captured.

Three previously reported meta-analyses have examined efficacy of front-line combination therapies, and results vary between studies.[27-29] In a network meta-analysis combining data from trials, survival benefit and efficacy was assessed between front-line TKI monotherapy, ICI/ICI, and ICI/TKI combination therapies. No difference was found in OS between ipi/nivo and axi/pembro in the full populations (HR, 1.34; 95% CI: 0.92-1.97). There was also no difference in PFS among the treatment groups.[30] In a subsequent network meta-analysis, axi/pembro demonstrated a superior PFS and OS compared to ipi/nivo in the full population, with no significant difference seen in the IMDC intermediate/poor risk population.[31] Together, these network analyses include highly heterogeneous populations, with variable numbers of treatment groups, various TKI agents included, and various comparator arms. Moreover, they represent trial populations which do not accurately reflect patient populations encountered in clinical practice, and the included studies do not all account for IMDC subgroups. An abstract from the ASCO 2021 meeting similarly assessed clinical outcomes in 723 patients with data from the IMDC database and specifically evaluated intermediate/poor risk patients treated with ipi/nivo or ICI/TKI combination therapies. The study did not detect any differences in OS between treatment groups.[32] Our study represents the largest real-world population dataset in the literature to date, and the only study that is inclusive of patients undergoing care in community-based practices.

Our analysis has several limitations. As an EHR-based observational study, the dataset has incomplete patient characteristics and is subject to missing or miscoded data. Further, the study's ascertainment strategy results in a cohort with some clinical or demographic differences from the full population of US mRCC cases; however, these differences are relatively modest.[12] We are also unable to ascertain elements such as tumor burden, symptom burden from disease, and toxicity profiles from therapy which invariably will affect choice of therapy. Depth of response and PFS2 were not assessed due to limitations of data points available. There are no biomarker analyses. Further, the study is limited by the rapid rate of clinical advances in mRCC, as there have been multiple front-line combination therapy options that have recently gained FDA-approval. These include cabozantinib/nivolumab and lenvatinib/pembrolizumab combinations. This report would also benefit from longer patient follow-up.

Conclusion

In the absence of prospective studies, retrospective analyses may provide guidance for clinicians in choosing front-line treatments. Our study reveals no discernible difference in survival at 24-month survival between patients treated with ipi/nivo or axi/pembro. Within the IMDC favorable risk sub-group, treatment with axi/pembro confers an improved

rwPFS and OS. Clinicians may have comfort in knowing that real-world data are concordant with the historical trial data, and align with guideline recommendations. The decision of treatment remains patient centered, accounting for known toxicities, patient co-morbidities, and patient goals of care. Future studies are needed to prospectively compare front-line treatment options, and with biomarker analyses to better inform patient selection.

Conflict of Interest

Elizabeth A. Handorf: NCCN/Lilly, Pfizer (RF [institutional]); **Matthew R. Zibelman:** Pfizer (H), EMD Serono (C/A), Exelixis, Horizon Pharma, Janssen, Pfizer (RF), Bristol-Myers Squibb, Exelixis, Horizon Pharma, Pfizer (RF [institutional]); **Elizabeth R. Plimack:** AstraZeneca, Bristol-Myers Squibb, Flatiron Health, Genentech/Roche, Infinity Pharmaceuticals, Janssen, MEI Pharma, Merck, Pfizer, Seattle Genetics (C/A), Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Genentech/Roche, Merck Sharp & Dohme, Pfizer (RF [institutional]); **Daniel M. Geynisman:** AstraZeneca, Eisai, Exelixis, Merck, Myovant Sciences, Pfizer, Seattle Genetics/Astellas (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

Conception/design: K.K.Z., E.H., D.M.G. Provision of study material or patients: K.K.Z., E.H., D.M.G. Collection and/or assembly of data: K.K.Z., E.H., D.M.G. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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