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First-line Immuno-Oncology Combination Therapies in Metastatic Renal-cell Carcinoma: Results from the International Metastatic Renal-cell Carcinoma Database Consortium

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Abstract

Background: In metastatic renal-cell carcinoma (mRCC), recent data have shown efficacy of first-line ipilimumab and nivolumab (ipi-nivo) as well as immuno-oncology (IO)/vascular endothelial growth factor (VEGF) inhibitor combinations. Comparative data between these strategies are limited.
Objective: To compare the efficacy of ipi-nivo versus IO-VEGF (IOVE) combinations in mRCC, and describe practice patterns and effectiveness of second-line therapies.
Design, setting, and participants: Using the International Metastatic Renal-cell Carcinoma Database Consortium (IMDC) dataset, patients treated with any first-line IOVE combination were compared with those treated with ipi-nivo.
Intervention: All patients received first-line IO combination therapies.
Outcome measurements and statistical analysis: First- and second-line response rates, time to treatment failure (TTF), time to next treatment (TNT), and overall survival (OS) were analysed. Hazard ratios were adjusted for IMDC risk factors.
Results and limitations: In total, 113 patients received IOVE combinations and 75 received ipi-nivo. For IOVE combinations versus ipi-nivo, first-line response rates were 33% versus 40% (between-group difference 7%, 95% confidence interval [CI] –8% to 22%, $p = 0.4$), TTF was 14.3 versus 10.2 mo ($p = 0.2$), TNT was 19.7 versus 17.9 mo ($p = 0.4$), and median OS was immature but not statistically different ($p = 0.17$). Adjusted hazard ratios for TTF, TNT, and OS were 0.71 (95% CI 0.46–1.12, $p = 0.14$), 0.65 (95% CI 0.38–1.11, $p = 0.11$), and 1.74 (95% CI 0.82–3.68, $p = 0.14$), respectively. Sixty-four (34%) patients received second-line treatment. In patients receiving subsequent VEGF-based therapy, second-line response rates were lower in the IOVE cohort than in the ipi-nivo cohort (15% vs 45%; between-group difference 30%, 95% CI 3–57%, $p = 0.04$; $n = 40$), though second-line TTF was not significantly different (3.7 vs 5.4 mo; $p = 0.4$; $n = 55$). Limitations include the study's retrospective design and sample size.
Conclusions: There were no significant differences in first-line outcomes between IOVE combinations and ipi-nivo. Most patients received VEGF-based therapy in the second line.

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In this group, second-line response rate was greater in patients who received ipi-nivo initially.
Patient summary: There were no significant differences in key first-line outcomes for patients with metastatic renal-cell carcinoma receiving immuno-oncology/vascular endothelial growth factor inhibitor combinations versus ipilimumab and nivolumab.
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1. Introduction

Historically, standard-of-care first-line treatment for most patients with metastatic renal-cell carcinoma (mRCC) has included vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitor (TKI) monotherapy (eg, sunitinib and pazopanib). More recently, several phase III randomised clinical trials (RCTs) have reported improved outcomes with novel immuno-oncology (IO) combination therapies. The first of these to report was the CheckMate-214 trial, which demonstrated superiority of the combination of ipilimumab and nivolumab (ipi-nivo) over sunitinib in patients with intermediate- and poor-risk disease [1], as defined by the International mRCC Database Consortium (IMDC) risk model [2]. A variety of other phase III RCTs investigating novel IO plus VEGF (IOVE) inhibitor combinations versus sunitinib have been initiated [3]. To date, all studies of IOVE combinations that have been reported—including bevacizumab plus atezolizumab, axitinib plus avelumab, and axitinib plus pembrolizumab—have demonstrated improved response rates (RR) and progression-free survival (PFS) versus sunitinib monotherapy across all IMDC risk groups, with the latter combination also demonstrating improved overall survival (OS) [4–6].

While these landmark findings are truly remarkable and practice changing, there remain a number of unanswered questions. Chief among them is how these novel IO-based combination therapies compare against one another and which regimen to select for the first-line treatment of modern-day patients with mRCC. As it stands, there are minimal data comparing ipi-nivo versus IOVE combinations, and randomised trials evaluating each strategy in a head-to-head fashion are unlikely to be performed. In addition, the use and efficacy of subsequent therapies in patients receiving these combinations remains largely unknown.

Real-world evidence has been proposed as a potential means by which these types of clinical and policy-relevant questions that cannot be answered with data from clinical trials may be approached [7]. The IMDC is a real-world registry of over 10 000 patients with mRCC from over 40 institutions worldwide. Using the IMDC database, we aimed to compare the efficacy of ipi-nivo versus IOVE combinations in the first-line treatment of patients with mRCC, as well as to compare practice patterns and effectiveness of second-line therapies in these cohorts.

2. Patients and methods

2.1. Study design and patient selection

Using the IMDC database, a retrospective analysis was performed using data from 38 international centres involving 10 007 consecutive patients with mRCC. Data were collected from hospital and pharmacy records between 2005 and December 31, 2018, using uniform database software and templates. All participating centres received approval from the local Research Ethics Board prior to initiation of data collection.

All patients with clear-cell or non–clear-cell mRCC treated with first-line ipi-nivo or any IOVE combination were included. Patients treated as part of a clinical trial were permitted for inclusion.

In order to respect the confidentiality of ongoing clinical trials of IOVE combinations not yet reported, outcomes of IOVE combinations are reported in aggregate.

2.2. Outcome measurements

Data regarding patient demographics and baseline characteristics, including IMDC risk factors, tumour/treatment details, and outcomes, were extracted from the IMDC. Outcome measures of interest were first- and second-line RRs, and first- and second-line time to treatment failure (TTF), time to next treatment (TNT), and OS. A preplanned subset analysis included evaluation of these outcomes in patients with IMDC intermediate-/poor-risk disease. RRs were investigator assessed and were reported in all evaluable patients. Best overall response was documented as complete response, partial response (PR), stable disease (SD), or progressive disease (PD) as per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 guidelines, where available [8]. TTF was defined as the time from the initiation of systemic therapy to treatment discontinuation for any reason. TNT was defined as the time from the initiation of systemic therapy to subsequent therapy or death. OS was calculated from the time of initiation of first-line systemic therapy to death from any cause or censored at the time of the last follow-up.

2.3. Statistical analysis

Patient demographics and baseline characteristics were described using proportions (%) for categorical variables and medians (interquartile range) for continuous variables. TTF, TNT, and OS were evaluated using the Kaplan-Meier method. Hazard ratios (HRs) were calculated using multivariate Cox regression analyses including unadjusted and adjusted models to control for imbalances in IMDC risk factors (corrected calcium greater than the upper limit of normal, neutrophils greater than the upper limit of normal, platelets greater than the upper limit of normal, haemoglobin less than the lower limit of normal, Karnofsky performance status <80%, and time from diagnosis to treatment <1 yr) [2]. These dichotomous variables have

previously been externally validated as prognostic criteria in mRCC [9]. All HRs are reported for IOVE versus ipi-nivo.

The case deletion method was used when missing data were encountered. SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA) was used to perform statistical analyses.

3. Results

3.1. Patients and treatments

A total of 188 patients met the eligibility criteria. One hundred and thirteen patients received an IOVE combination and 75 received ipi-nivo. Patient demographics and baseline characteristics are summarised in Table 1. There were no significant differences between the two cohorts in any of the demographic or baseline features examined, including individual IMDC risk factors and overall IMDC risk groups.

VEGF-directed treatment as part of an IOVE combination included axitinib, bevacizumab, cabozantinib, and sunitinib. IO agents as part of an IOVE combination included atezolizumab, avelumab, nivolumab, and pembrolizumab.

Second-line therapy was received in 34 patients (30%) in the IOVE group and 30 patients (40%) in the ipi-nivo group. In both groups, the majority of patients received VEGF-based therapy in the second line, including axitinib, cabozantinib, lenvatinib plus everolimus, pazopanib, and sunitinib. Five and zero patients received second-line IO agents in the IOVE and ipi-nivo groups, respectively. Four patients received "other" second-line treatments, including carboplatin plus gemcitabine, temsirolimus, high-dose interleukin-2, and pazopanib plus radium-223. Second-line treatments are summarised in Table 1.

Table 1 – Baseline characteristics, IMDC risk factors, and second-line treatments.

	IOVE (N = 113)	Ipi-nivo (N = 75)	p value
Age, median (IQR)	63 (57–69)	61 (55–68)	0.13
Male	74/113 (65%)	57/75 (76%)	0.12
nccRCC	13/107 (12%)	9/65 (14%)	0.8
Liver metastases	20/99 (20%)	14/67 (21%)	0.9
Bone metastases	33/99 (33%)	22/68 (32%)	0.8
Brain metastases	4/98 (4%)	3/65 (5%)	0.9
Sarcomatoid features	15/109 (14%)	16/67 (24%)	0.09
>1 site of metastasis	75/100 (75%)	56/69 (81%)	0.4
Nephrectomy	97/112 (87%)	69/75 (92%)	0.3
IMDC risk groups			0.5
Favourable	29/92 (32%)	17/64 (27%)	
Intermediate	49/92 (53%)	33/64 (52%)	
Poor	14/92 (15%)	14/64 (22%)	
IMDC risk factors			
KPS <80	3/105 (3%)	3/73 (4%)	0.7
Diagnosis to therapy <1 yr	65/113 (58%)	39/75 (52%)	0.5
Calcium > ULN	13/109 (12%)	12/69 (17%)	0.3
Haemoglobin < LLN	42/112 (38%)	29/70 (41%)	0.6
Neutrophils > ULN	13/104 (13%)	7/65 (11%)	0.7
Platelets > ULN	12/112 (11%)	11/69 (16%)	0.3
Second-line treatments			
Axitinib	5/34 (15%)	2/30 (7%)	
Cabozantinib	9/34 (26%)	2/30 (7%)	
Lenvatinib + everolimus	2/34 (6%)	0/30 (0%)	
Nivolumab	5/34 (15%)	0/30 (0%)	
Pazopanib	2/34 (6%)	9/30 (30%)	
Sunitinib	9/34 (26%)	15/30 (50%)	
Other	2/34 (6%)	2/30 (7%)	

IOVE = immuno-oncology and vascular endothelial growth factor; Ipi-nivo = ipilimumab and nivolumab; IQR = interquartile range; IMDC = International Metastatic Renal-cell Carcinoma Database Consortium; KPS = Karnofsky performance status; LLN = lower limit of normal; nccRCC = non–clear-cell renal-cell carcinoma; ULN = upper limit of normal.

3.2. Outcomes

At the time of analysis, 99 patients had discontinued first-line treatment, 64 patients had started second-line therapy, and 40 patients had died. The median follow-up time for patients still alive was 11.7 mo.

Among 154 evaluable patients (82%), first-line RRs were 33% and 40% (between-group difference 7%, 95% confidence interval [CI] –8% to 22%, p = 0.4) for IOVE combinations and ipi-nivo, respectively. Complete responses were noted in 2% of patients receiving IOVE combinations and 5% of patients receiving ipi-nivo. When comparing IOVE combinations with ipi-nivo, first-line TTF was 14.3 mo versus 10.2 mo (p = 0.2), TNT was 19.7 versus 17.9 mo (p = 0.4), and median OS was not reached (NR) versus NR (p = 0.17; Figs. 1 and 2). When adjusted for IMDC risk factors, the HRs were 0.71 (95% CI 0.46–1.12, p = 0.14) for TTF, 0.65 (95% CI 0.38–1.11, p = 0.11) for TNT, and 1.74 (95% CI 0.82–3.68, p = 0.14) for death. There were no significant differences in best response between the two cohorts (p = 0.3). Outcomes for first-line treatments are summarised in Table 2.

When restricting the analysis to intermediate- and poor-risk patients, there remained no significant difference in RR between the IOVE and ipi-nivo arms (37% vs 35%, p = 0.16). When comparing IOVE versus ipi-nivo within this group, first-line TTF was 14.7 versus 8.5 mo (p = 0.10), TNT was 15.4 versus 17.2 mo (p = 0.6), and OS was NR versus NR (p = 0.3). Outcomes were similar when restricting the analysis to favourable-risk patients only (data not shown).

In patients receiving second-line VEGF-based therapy who were evaluable for a response (N = 40), second-line RR was lower in the IOVE cohort than in the ipi-nivo cohort (15% vs 45%, between-group difference 30%, 95% CI 3–57%, p = 0.04). However, among all 55 patients who received second-line VEGF-based therapy, there was no significant difference in second-line TTF between those receiving IOVE combinations and those receiving ipi-nivo (3.7 vs 5.4 mo, p = 0.4; Fig. 3). Outcomes for second-line treatments are summarised in Table 3.

Of the five patients who received second-line nivolumab following first-line IOVE combination therapy, three had PD as the best response. The remaining two patients had PR and SD as the best response; however, their first-line IOVE exposure was short at <3 mo.

4. Discussion

The treatment of mRCC has been revolutionised twice in the past 2 decades, first with the introduction of targeted

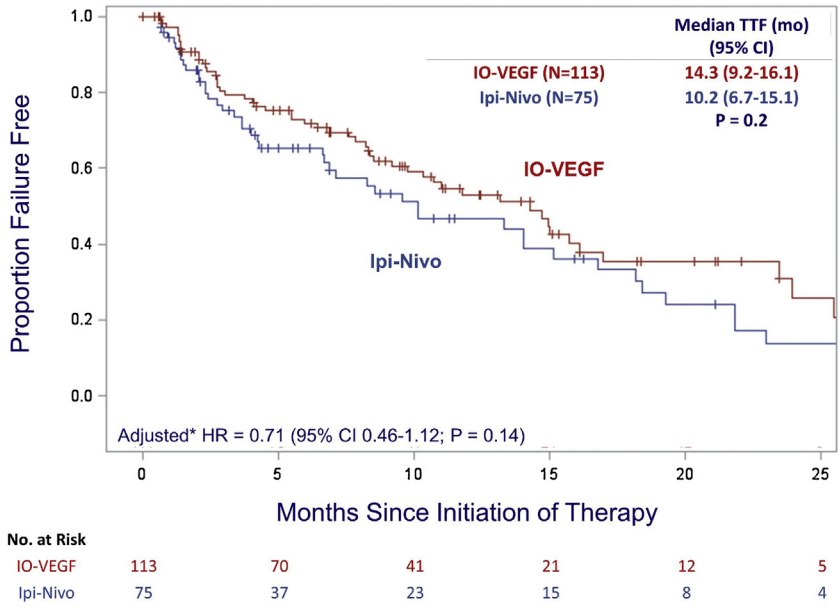

Fig. 1 – Time to treatment failure for first-line IO combination therapies. CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal-cell Carcinoma Database Consortium; Ipi-nivo = ipilimumab and nivolumab; IO = immuno-oncology; TTF = time to treatment failure; VEGF = vascular endothelial growth factor. *Adjusted for IMDC risk factors.

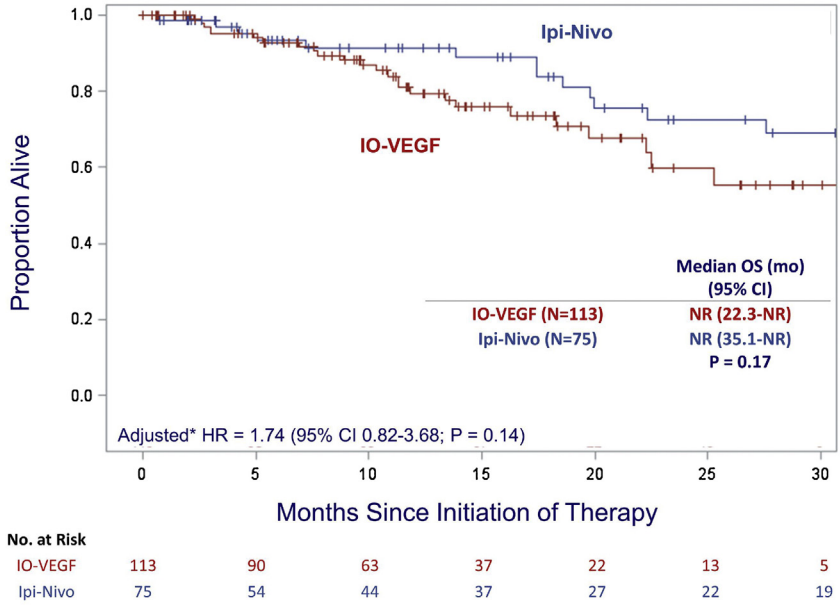

Fig. 2 – Overall survival for first-line IO combination therapies. CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal-cell Carcinoma Database Consortium; Ipi-nivo = ipilimumab and nivolumab; IO = immuno-oncology; NR = not reached; OS = overall survival; VEGF = vascular endothelial growth factor. *Adjusted for IMDC risk factors.

therapies and subsequently IO agents [10]. However, until recently, sequential monotherapy has been the prevailing treatment paradigm in this malignancy. The wave of recently reported phase III RCTs in first-line clear-cell mRCC demonstrating improved outcomes with ipi-nivo and IOVE combinations over standard VEGF-TKI therapy suggests that we are in the midst of a third major transformation, moving towards an era of front-line IO combination therapy.

As these novel IO combinations are inevitably carefully transitioned from the realm of clinical trials to the general real-world mRCC population (as evidenced by the recent United States Food and Drug Administration approvals of at least two IOVE combinations [11,12]), selection of the optimal regimen for each patient will be challenging in the absence of randomised or comparative data. Given the low likelihood of phase III RCTs being conducted to directly compare the range of emerging first-line options, real-

Table 2 – Outcomes with first-line IO combination therapy.

	IOVE (*N* = 113)	Ipi-nivo (*N* = 75)	*p* value
Response rate (%)	33	40	0.4
Best response			0.3
CR	2/91 (2%)	3/63 (5%)	
PR	28/91 (31%)	22/63 (35%)	
SD	52/91 (57%)	27/63 (43%)	
PD	9/91 (10%)	11/63 (17%)	
Time to treatment failure (mo)	14.3	10.2	0.2
Time to next treatment (mo)	19.7	17.9	0.4
Overall survival (mo)	NR	NR	0.17
Adjusted[a] hazard ratios (IOVE vs ipi-nivo)			
Time to treatment failure	0.71 (0.46–1.12)		0.14
Time to next treatment	0.65 (0.38–1.11)		0.11
Overall survival	1.74 (0.82–3.68)		0.14

CR = complete response; IMDC = International Metastatic Renal-cell Carcinoma Database Consortium; IO = immuno-oncology; IOVE = immuno-oncology and vascular endothelial growth factor; ipi-nivo = ipilimumab and nivolumab; NR = not reached; PD = progressive disease; PR = partial response; SD = stable disease.
[a] Adjusted for IMDC risk factors.

world evidence will be critical in generating data to inform clinical, policy-related, and funding decisions.

We were unable to demonstrate any significant differences between first-line ipi-nivo and IOVE combinations with respect to RR, TTF, TNT, or OS. Of note, this remained true when restricting the analysis to patients with intermediate- and poor-risk disease, which constitutes the patient population in which true clinical equipoise is most likely to exist, given the absence of noted benefit of ipi-nivo over sunitinib in the favourable-risk subset [1].

Given the novelty of first-line IO combination therapy, there are minimal data regarding the use and efficacy of subsequent lines of treatment. Thus, it was interesting, though not surprising, to observe that the majority (88%) of second-line therapies in this cohort were VEGF based. The higher RR observed in patients receiving second-line VEGF-based treatment following ipi-nivo versus IOVE combinations is noteworthy and thought provoking. Biologically, it is plausible that VEGF-based second-line therapy would be more likely to be effective in the VEGF-naïve ipi-nivo cohort. It remains to be seen whether the numerical difference in TTF observed in this analysis becomes significant with increased sample size and further follow-up, and whether this contributes to differences in OS, which ultimately impacts treatment selection in the first-line setting.

We were particularly interested in qualitatively evaluating the efficacy of second-line IO monotherapy in this population, as the effectiveness of rechallenging with IO agents in mRCC patients who have previously received IO treatment remains unknown. There are emerging reports in other malignancies including non–small-cell lung cancer and melanoma of such strategies being effective for a proportion of patients [13,14]. Within the ipi-nivo cohort, no patients were treated with second-line IO, which was consistent with expectations. Of the five patients in the IOVE cohort treated with second-line nivolumab, three experienced PD as the best response. The remaining two patients experienced PR and SD after discontinuing first-line treatment due to PD. However, it is interesting to note that their length of time on first-line IOVE treatment was only 10.1 and 6.0 wk, respectively, suggesting that perhaps they received an inadequate trial (<3 mo) of first-line IO therapy prior to discontinuation. Overall, though patient numbers are very small, we feel that the rate of primary PD of 60% observed in this study does not support the practice of treatment with IO agents following progression on first-line IOVE combinations.

Limitations of our study include its retrospective nature, modest sample size, and limited follow-up duration,

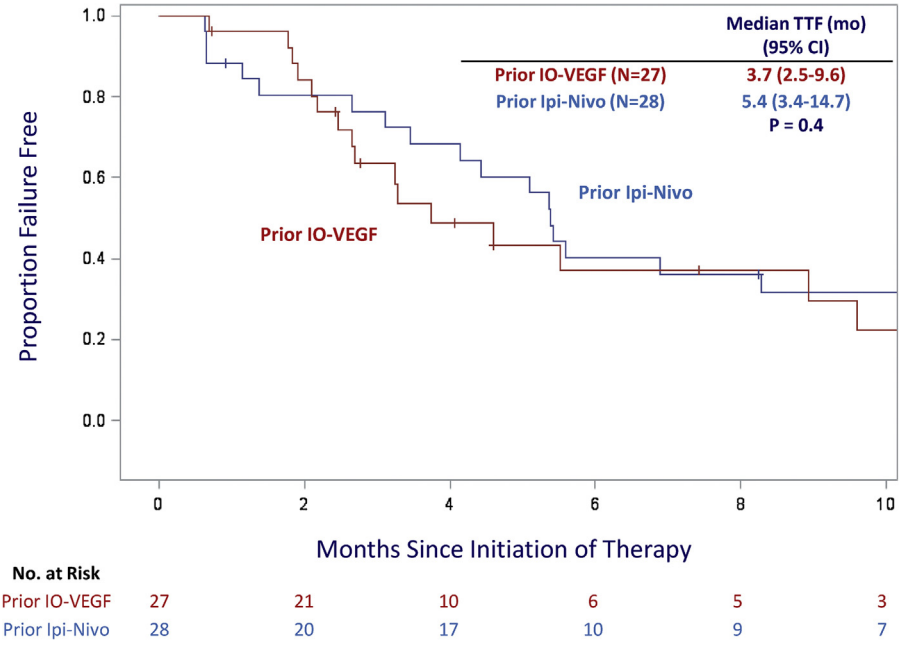

Fig. 3 – Time to treatment failure for second-line VEGF-based therapies. CI = confidence interval; Ipi-nivo = ipilimumab and nivolumab; IO = immuno-oncology; TTF = time to treatment failure; VEGF = vascular endothelial growth factor.

Table 3 – Outcomes with second-line VEGF-based therapy.

	Prior IO-VEGF (*N* = 27)	Prior Ipi-nivo (*N* = 28)	*p* value
Response rate	3/20 (15%)	9/20 (45%)	0.04
Time to treatment failure (mo)	3.7	5.4	0.4

IOVE = immuno-oncology and vascular endothelial growth factor; ipi-nivo = ipilimumab and nivolumab; VEGF = vascular endothelial growth factor.

particularly in the analysis of second-line therapies and OS. As a result, clinically meaningful differences for these outcomes cannot be excluded by the present analysis, and further reports with more mature data are warranted. However, to our knowledge, this is the first analysis to be reported comparing these two strategies, and we look forward to updating the results with greater sample size and follow-up. Additionally, RRs were not available in all patients and were investigator assessed. However, as a result, these data may be more reflective of real-world experience. Another key limitation is that detailed toxicity data were not available. Given that no clearly superior strategy was identified with respect to efficacy, this is an important consideration as differences in side-effect profiles will likely be a key factor for patients and clinicians in deciding between seemingly equally effective treatment strategies. It is also important to note that TTF may not be a robust surrogate endpoint, particularly in patient populations receiving IO-based agents, where treatment discontinuation due to toxicity is not uncommon and patients may continue to experience long-term disease control even after cessation of IO therapy [15,16]. To account for this shortcoming, we calculated and reported outcomes for TNT, which were similarly not significantly different between arms. Furthermore, due to small numbers and in order to respect clinical trial confidentiality, we were unable to report outcomes for each IOVE regimen separately. Finally, though these data were captured through real-world records and resources, the majority of patients included were likely enrolled on clinical trials. As such, as these novel combination regimens become increasingly used as the standard-of-care treatments in the general mRCC population, future studies assessing outcomes in real-world patients would be important to conduct.

Despite the limitations noted above, we believe that this study provides relevant data in a timely manner within the rapidly evolving landscape of first-line IO combination therapies in mRCC. Further strengths of our study include that consecutive mRCC patients were enrolled at each institution, which is important in minimising selection bias in retrospective study designs. In addition, the use of real-world data allowed for reporting of postprogression practice patterns and outcomes, information that is often not well captured in traditional RCTs. The use of individual patient data also facilitated analyses to control for differences in patient populations by adjusting for known prognostic factors (ie, IMDC risk factors). This adjustment aids in overcoming the major limitation of differences in heterogeneous patient populations that generally invalidates cross-trial comparisons [17].

5. Conclusions

Our analysis was unable to demonstrate a significant difference in key first-line outcomes between IOVE combinations and ipi-nivo, including first-line RR, TTF, TNT, and OS. Second-line treatments were primarily VEGF based, for which activity was demonstrated. Within this cohort, second-line RRs favoured patients who received ipi-nivo in the first-line setting, though there was no statistically significant difference in second-line TTF.

Given the current lack of evidence to suggest a difference in efficacy between treatment strategies, patients, clinicians, policy makers, and funding bodies are likely to take into account other considerations such as toxicity, cost, logistics, prognostic categories, and patient preferences in deciding between the various front-line IO combination regimens. In addition, intensive research efforts towards identifying predictive biomarkers in mRCC are ongoing and, if successful, may provide additional means by which these treatment strategies may be differentiated [18].

Finally, given the preliminary nature of these results, further analyses with greater sample size and follow-up are warranted to confirm or refute the present findings, and to investigate the effectiveness of these therapies in specific subgroups of interest, including across different sites of metastases, prognostic groups, and variant histologies.

Author contributions: Daniel Y.C. Heng had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Analysis and interpretation of data: Dudani, Heng.
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Critical revision of the manuscript for important intellectual content: Dudani, Graham, Wells, Bakouny, Pal, Dizman, Donskov, Porta, de Velasco, Hansen, Iafolla, Beuselinck, Vaishampayan, Wood, Liow, Yan, Yuasa, Bjarnason, Choueiri, Heng.
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References

[1] Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277–90.

[2] Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27:5794–9.

[3] Lalani AA, McGregor BA, Albiges L, Choueiri TK, Motzer R, Powles T, et al. Systemic treatment of metastatic clear cell renal cell carcinoma in 2018: current paradigms, use of immunotherapy, and future directions. Eur Urol 2019;75:100–10.

[4] Rini BI, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Lancet 2019;393:2404–15.

[5] Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1103–15.

[6] Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1116–27.

[7] Booth CM, Karim S, Mackillop WJ. Real-world data: towards achieving the achievable in cancer care. Nat Rev Clin Oncol 2019;16:312–25.

[8] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

[9] Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14:141–8.

[10] Escudier B. Combination therapy as first-line treatment in metastatic renal-cell carcinoma. N Engl J Med 2019;380:1176–8.

[11] FDA. FDA approves avelumab plus axitinib for renal cell carcinoma. (press release). May 15 2019.

[12] FDA. FDA approves pembrolizumab plus axitinib for advanced renal cell carcinoma.(press release). April 22 2019.

[13] Fujita K, Uchida N, Kanai O, Okamura M, Nakatani K, Mio T, et al. Retreatment with pembrolizumab in advanced non-small cell lung cancer patients previously treated with nivolumab: emerging reports of 12 cases. Cancer Chemother Pharmacol 2018;81:1105–9.

[14] Mohamed AA, Faust G, Zhang S. 57PThe efficacy and safety of rechallenge with an alternative immune checkpoint inhibitor in metastatic malignant melanoma. Ann Oncol 2018;29(suppl_10), mdy486.009.

[15] Tannir NM, Motzer RJ, Plimack ER, McDermott DF, Barthelemy P, Porta C, et al. Outcomes in patients (pts) with advanced renal cell carcinoma (aRCC) who discontinued (DC) first-line nivolumab + ipilimumab (N+I) or sunitinib (S) due to treatment-related adverse events (TRAEs) in CheckMate 214. J Clin Oncol 2019;37 (7_suppl):581.

[16] Elias R, Yan F, Singla N, Levonyack N, Formella J, Christie A, et al. Immune-related adverse events are associated with improved outcomes in ICI-treated renal cell carcinoma patients. J Clin Oncol 2019;37(7_suppl):645.

[17] Markman M. Cross-trial comparisons in the oncology arena: when is this justified? Oncology 2011;80:151–2.

[18] Dudani S, Savard MF, Heng DYC. An update on predictive biomarkers in metastatic renal cell carcinoma. Eur Urol Focus. In press. https://doi.org/10.1016/j.euf.2019.04.004.