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Original Research

Outcomes of patients with metastatic clear-cell renal cell carcinoma treated with second-line VEGFR-TKI after first-line immune checkpoint inhibitors☆

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Abstract ***Background:*** Immune checkpoint inhibitors (ICIs) are being increasingly utilised in the front-line (1L) setting of metastatic clear-cell renal cell carcinoma (mccRCC). Limited data exist on responses and survival on second-line (2L) vascular endothelial growth factor −receptor tyrosine kinase inhibitor (VEGFR-TKI) therapy after 1L ICI therapy.
Patients and methods: This is a retrospective study of mccRCC patients treated with 2L VEGFR-TKI after progressive disease (PD) with 1L ICI. Patients were treated at MD Anderson Cancer Center or Memorial Sloan Kettering Cancer Center between December 2015 and February 2018. Objective response was assessed by blinded radiologists' review using Response Evaluation Criteria in Solid Tumours v1.1. Descriptive statistics and Kaplan −Meier method were used.
Results: Seventy patients were included in the analysis. Median age at mccRCC diagnosis was 59 years; 8 patients (11%) had international metastatic database consortium favourable-risk

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disease, 48 (69%) had intermediate-risk disease and 14 (20%) had poor-risk disease. As 1L therapy, 12 patients (17%) received anti–programmed death ligand-1 (PD-(L)1) monotherapy with nivolumab or atezolizumab, 33 (47%) received nivolumab plus ipilimumab and 25 (36%) received combination anti–PD-(L)1 plus bevacizumab. 2L TKI therapies included pazopanib, sunitinib, axitinib and cabozantinib. On 2L TKI therapy, one patient (1.5%) achieved a complete response, 27 patients (39.7%) a partial response and 36 patients (52.9%) stable disease. Median progression-free survival (mPFS) was 13.2 months (95% confidence interval: 10.1, NA). Forty-five percent of subjects required a dose reduction, and twenty-seven percent of patients discontinued treatment because of toxicity.

Conclusions: In this retrospective study of patients with mccRCC receiving 2L TKI monotherapy after 1L ICI, we observed 2L antitumour activity and tolerance comparable to historical data for 1L TKI.

1. Introduction

The incidence of kidney cancer worldwide in 2018 was greater than 400,000 cases; in the metastatic setting, this disease is typically incurable [1,2]. Clear-cell renal cell carcinoma (ccRCC) is primarily associated with mutations in the *VHL* gene, which has led to the development of vascular endothelial growth factor–receptor tyrosine kinase inhibitors (VEGFR-TKIs) as anticancer therapies in ccRCC [3–6]. From 2006 to 2017, the standard of care in metastatic ccRCC (mccRCC) shifted in the front-line setting to VEGF-targeted therapies [7–9]. In second and subsequent lines of therapy, VEGFR-TKIs, mammalian target of rapamycin (mTOR) inhibitors and immune checkpoint inhibitors (ICIs) have been frequently used [10–12].

Nivolumab, a monoclonal antibody targeting programmed death-1 (PD-1), was the first ICI to be approved in advanced RCC, showing overall survival (OS) benefit over everolimus [13]. More recently, in CheckMate 214, a pivotal randomised phase 3 trial, nivolumab and ipilimumab demonstrated statistically superior median OS and higher objective response rate (ORR), in patients with international metastatic database consortium (IMDC) intermediate- and poor-risk disease compared with sunitinib [14,15]. These results led to the US Food and Drug Administration approval of combination nivolumab and ipilimumab in the front-line setting for treatment of mccRCC.

The mccRCC treatment landscape is further rapidly changing with the exploration of combinations of ICI and anti-VEGF therapies. The results of the IMmotion-151 were recently reported, and the combination of atezolizumab, an anti–PD-L1 antibody, with bevacizumab, an anti-VEGF therapy, was superior to sunitinib in terms of progression-free survival (PFS) (11.2 vs. 7.7 months, hazard ratio [HR] 0.74, $p = 0.02$) and ORR (43% vs. 35%) in PD-L1 positive patients, per investigator assessment [16], opening the possibility of another non-TKI–containing ICI-based regimen in the frontline. The JAVELIN Renal 101 Phase 3 trial has now been reported as a TKI/ICI registration trial meeting (one of) its primary end-points, demonstrating superior PFS for the combination of axitinib and avelumab over sunitinib in PD-L1–positive patients (13.8 vs. 7.2 months, HR 0.61) [17]. In addition, the KEYNOTE-426 trial has demonstrated both PFS and OS advantage of axitinib plus pembrolizumab over sunitinib (median PFS [mPFS] 15.1 months vs. 11.1 months, HR 0.69), which may lead to further approvals in the first-line landscape [18].

With front-line approval of the combination of nivolumab and ipilimumab and upcoming data on anti-VEGF/ICI combination therapy, understanding responses of subsequent therapies is needed. This retrospective study of patients with mccRCC reports on ORR, PFS, safety of second line (2L) VEGFR-TKI and OS after progressive disease (PD) with front-line (1L) ICI-based non-TKI–containing therapy.

2. Patients and methods

We conducted this retrospective, multicenter study after Institutional Review Board (IRB) approval was obtained at the two participating centres. A combined deidentified secure database was constructed of 70 patients with mccRCC treated from December 2015 to February 2018 at MD Anderson Cancer Center and Memorial Sloan Kettering Cancer Center with a 2L VEGFR-TKI after PD with 1L ICI. All patients had previously received 1L ICI in the setting of clinical trials (nivolumab vs. nivolumab-ipilimumab vs. nivolumab-bevacizumab in NCT02210117, nivolumab-ipilimumab in NCT02231749, atezolizumab-bevacizumab in NCT02420821, atezolizumab in NCT01984242 and nivolumab-ipilimumab in NCT01472081).

Baseline demographic and clinical data were collected by individual chart review and included gender, age, IMDC risk score at time of 2L therapy start, nephrectomy status, presence of sarcomatoid dedifferentiation,

metastatic sites, previously received ICI regimen and choice of 2L TKI. Histologic diagnosis of ccRCC was made or confirmed in each case via review of tumour specimens by dedicated genitourinary pathologists at either of the two participating sites. During 2L TKI therapy, patients were managed per best practice established at the participating centres sites. Charts were reviewed for individual treatment courses with dedicated attention to treatment dose adjustments and reasons for treatment discontinuations. Radiographic response assessment was provided by two blinded radiologists, who assessed all cross-sectional scans obtained to evaluate extent of disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 [19].

Continuous variables were summarised using descriptive statistics, and categorical data were tabulated with frequency and percentage. The Kaplan–Meier method was applied to estimate time-to-event outcomes. OS and PFS times were calculated from the start of 2L TKI.

3. Results

3.1. Patient characteristics

Among the 70 patients, 50 (71%) were male. The median age at diagnosis with metastatic involvement of RCC was 59 years (range 44–75). Forty-three patients (61%) initially presented with stage IV disease. At the time of 2L TKI therapy initiation, 8 patients (11%) had IMDC favourable-risk disease, 48 patients (69%) had intermediate-risk disease and 14 patients (20%) had poor-risk disease by IMDC criteria. Sixty patients (86%) had previously undergone nephrectomy. All patients included in this analysis had clear-cell histologic subtype, and 14 patients (20%) had evidence of sarcomatoid dedifferentiation. At the time of 2L treatment with VEGFR-TKI, the most common site of metastatic disease was lung in 61 patients (87%), followed by lymph nodes in 48 patients (69%). Additional details on demographics and presentation are summarised in Table 1.

Table 1
Patient characteristics.

Variable	N (%)
Gender	
Male	50 (71)
Female	20 (29)
Median age at mRCC diagnosis	59
Years (range)	(43.6–74.8)
Stage at initial diagnosis of RCC	
Stage I–III	27 (39)
Stage IV	43 (61)
IMDC risk score at time of 2L TKI start	
Favourable	8 (11)
Intermediate	48 (69)
Poor	14 (20)
Nephrectomy status	
Status after nephrectomy	60 (86)
Primary in situ	10 (14)
Histology	
Clear cell	70 (100)
Sarcomatoid dedifferentiation	14 (20)
Sites of metastatic disease at TKI start	
Lung	61 (87)
Bone	35 (50)
Liver	12 (17)
Lymph node	48 (69)
Adrenal	22 (31)
First-line ICI	
Anti–PD-(L)1 single agent	12 (17)
PD-1 + CTLA-4 blockade (followed by maintenance anti-PD-1)	33 (47)
PD-(L)1 + anti-VEGF therapy	25 (36)
Reason for discontinuation of 1L ICI	
Progressive disease	58 (83)
Toxicity	12 (17)
Median duration on ICI, months (range)	5.9 (0.4–25.2)
Choice of second-line TKI and breakdown of IMDC risk score (fav/int/poor)	
Pazopanib	19 (27) [3/14/2]
Sunitinib	6 (9) [0/2/4]
Axitinib	25 (36) [4/16/5]
Cabozantinib	20 (28) [1/16/3]

mRCC, metastatic renal cell carcinoma; 2L, second line; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; PD-1, programmed death-1; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD-(L)1, programmed death ligand-1; VEGF, vascular endothelial growth factor.

3.2. First- and second-line treatment

All patients in this study had previously received 1L ICI therapy in the context of a clinical trial. Twelve patients (17%) received an anti–PD-1/programmed death ligand-1 (PD-(L)1) inhibition antibody monotherapy (nivolumab or atezolizumab) as 1L treatment. Thirty-three patients (47%) received dual immune checkpoint blockade with nivolumab and ipilimumab as 1L treatment, where patients received induction therapy with nivolumab plus ipilimumab followed by single-agent nivolumab maintenance therapy. Twenty-five patients (36%) received 1L treatment with the combination of an anti–PD-(L)1 antibody plus anti-VEGF therapy, with either the combination of nivolumab plus bevacizumab or the combination of atezolizumab plus bevacizumab. Fifty-eight patients (83%) discontinued 1L ICI therapy because of PD, whereas 12 patients (17%) discontinued therapy because of toxicity.

All 70 patients had resolution of prior grade III/IV adverse events (AEs) and evidence of PD at the time of initiation of 2L TKI therapy. The median time from discontinuation of ICI therapy to initiation of TKI therapy was 4.2 weeks (range 0.0–84.9). The selection of 2L TKI therapy was at the discretion of the treating physician. Nineteen patients (27%) received pazopanib,

6 patients (9%) received sunitinib, 25 patients (36%) received axitinib and 20 (28%) received cabozantinib.

3.3. Best response to 2L TKI therapy

Sixty-eight patients had evaluable disease to assess response to 2L TKI. As best overall response (BOR) per RECIST v1.1, 1 patient (1.5%) achieved a complete response (CR), and 27 patients (39.7%) had a partial response, adding to an ORR of 41%. Thirty-six patients (52.9%) had stable disease, for a disease control rate of 94%. Only four patients (6%) had PD as best response to 2L TKI. A waterfall plot of BOR is shown in Fig. 1, broken down by 2L TKI received.

As demonstrated in Table 2, responses to 2L TKIs were noted in patients within all groups categorised. The median time to best response was 3.9 months. Nine patients (12.9%) were treated beyond RECIST v1.1 PD in the setting of ongoing clinical benefit according to the treating physician; in three of these patients, dose escalation of the TKI was offered, and in other patients, local ablative therapy to a painful bone lesion was offered. The patient who achieved a CR was treated with axitinib and maintains this response for over one year despite prolonged treatment breaks due to side effects.

Table 2
Responses.

Variable	n Total = 68	CR/PR (n)	SD (n)	PD (n)
Male	49	18	27	4
Female	19	10	9	0
Stages I-III at presentation	26	14	12	0
Stage IV at presentation	42	14	24	4
IMDC favourable-risk	7	3	4	0
IMDC intermediate-risk	47	22	22	3
IMDC poor-risk	14	3	10	1
Nephrectomy	58	26	29	3
Primary in-situ	10	2	7	1
1L anti-PD-1 single agent	12	6	5	1
1L anti-PD-1 + anti-CTLA-4	32	14	16	2
1L anti-PD-(L)1 + anti-VEGF	24	8	15	1
2L pazopanib	19	8	8	3
2L sunitinib	6	1	4	1
2L axitinib	24	10	14	0
2L cabozantinib	19	9	10	0

CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; IMDC, international metastatic database consortium; PD-1, programmed death-1; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD-(L)1, programmed death ligand-1; VEGF: vascular endothelial growth factor.

3.4. Survival

As noted in Fig. 2, mPFS on 2L TKI was 13.2 months (95% confidence interval [CI] 10.1–NA). The 1-year PFS probability was 52.5%, and the 2-year PFS rate was 34.2%. Twenty-two patients had died of PD by the time of data analysis. The median time for follow-up for surviving patients was 14.9 months. Median overall survival was not reached. As noted in Fig. 3, the 1-year actuarial survival probability was 79.6% (95% CI 70.2–90.3). The 2-year actuarial survival probability was 57.6%.

3.5. Duration of therapy

At the time of data analysis, 25 patients (35.7%) were still on active 2L TKI therapy, whereas 45 patients (64.3%) had discontinued 2L TKI therapy. Of those off

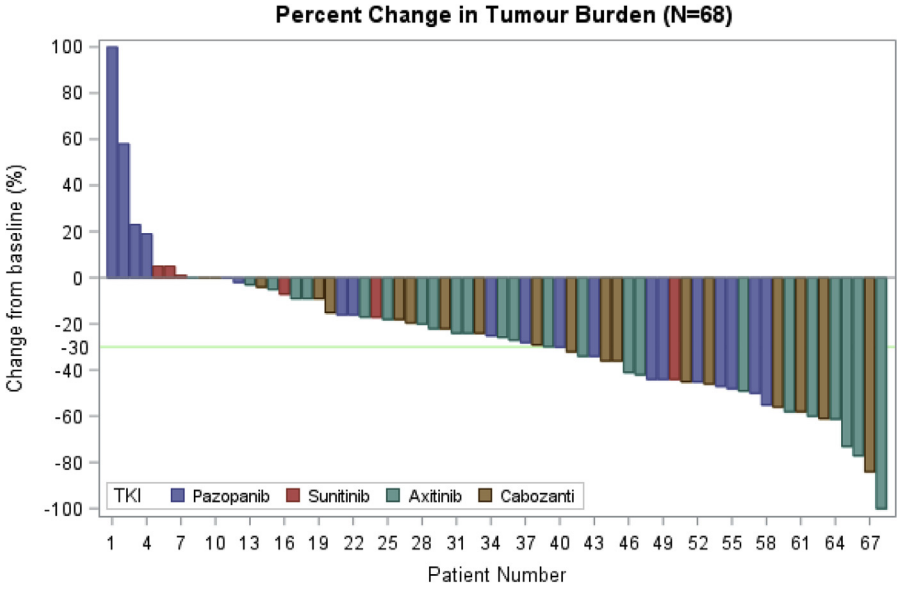

Fig. 1. Waterfall plot of best overall response: 68 patients with evaluable disease included, with overall best responses broken down by choice of 2L TKI. One patient achieved CR, 27 with PR, 36 with SD, 4 with PD. TKI: tyrosine kinase inhibitor. TKI, tyrosine kinase inhibitor; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease.

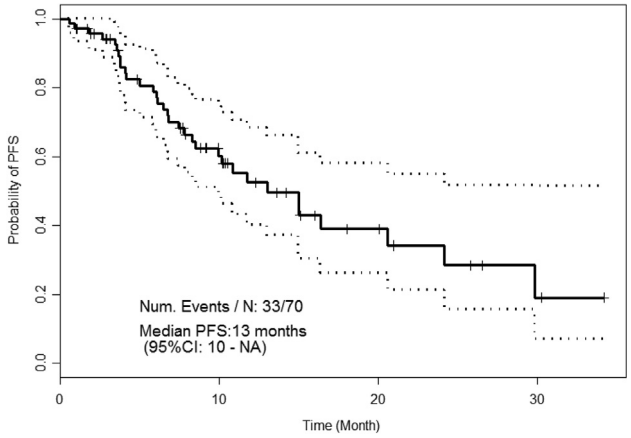

Fig. 2. Median progression-free survival by Kaplan–Meier method was 13.2 months (95% CI 10.1–NA). CI, confidence interval.

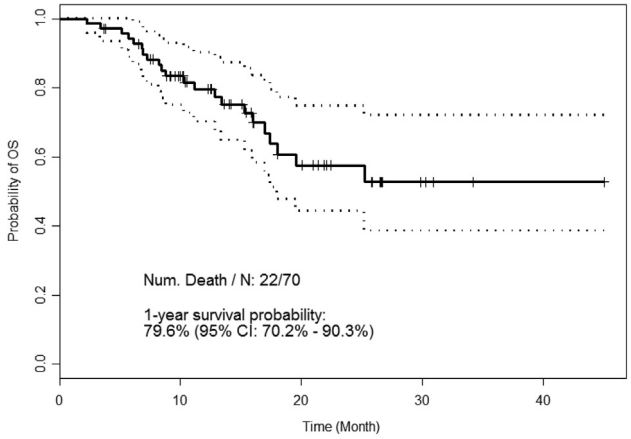

Fig. 3. Overall survival (OS). Median overall survival by Kaplan–Meier was not reached. The 1-year survival probability was 79.6% (95% CI 70.2%–90.3%). CI, confidence interval.

therapy, 33 patients (73%) had discontinued because of PD, whereas 12 patients (27%) had discontinued because of toxicity. The estimated median duration of 2L TKI therapy was 10.1 months (95% CI 6.9–15.2). Fig. 4 shows a swimmer's plot of duration of therapy by 2L TKI received.

3.6. Patient subgroups

Table 3 shows a breakdown of mPFS, OS probability at 1 year and median 2L TKI duration for various patient subgroups defined by baseline clinical characteristics and treatment received. The table provides summary statistics but treatment-subgroup interactions were not tested because of the small sample sizes and the retrospective nature of the study. Patients previously treated with 1L anti-PD-(L)1 monotherapy (n = 12) had mPFS of 7.5 months on 2L TKI, those previously treated with 1L nivolumab-ipilimumab (n = 33) had mPFS of 11.9 months on 2L TKI and those treated with 1L anti–PD-(L)1 + bevacizumab (n = 25) had mPFS of 20.8 months on 2L TKI. Interestingly, while the IMDC good-risk patients had the highest OS rate at 1 year, the longest mPFS and median 2L TKI duration was in the IMDC intermediate-risk group population. There were very few patients treated with 2L sunitinib, but numerically most of these patients had poor-risk disease and had the shortest mPFS and OS rate at 1 year (see Table 3). In the patients with sarcomatoid dedifferentiation, the ORR was 54%.

3.7. Safety

As noted previously, 12 patients (27%) discontinued therapy because of AEs. Three of the 12 patients had previously discontinued ICI therapy because of toxicity. Five of these 12 patients discontinued 2L TKIs because of transaminitis (all on pazopanib), four because of fatigue or anorexia/weight loss, two because of safety concerns of continuing TKIs with radiographic evidence of aortic dissections and one because of gastrointestinal bleeding. Thirty-two patients (45.7%) required at least one dose reduction of 2L TKIs during their course because of AEs. Time from 1L ICI therapy to 2L TKI therapy did not correlate to severity of toxicity; dichotomising the whole population per time between IL IO and 2L TKI as <1 month and >1 month, 17% of patients in each arm had to discontinue 2L TKIs because of toxicity. There were no deaths related to TKI therapy. Further details on the 12 patients requiring 2L TKI discontinuation are provided in Table 4 (supplementary data).

4. Discussion

The landscape of mccRCC treatment has shifted dramatically in the last year with the introduction of ICI therapy in 1L treatment, particularly in intermediate- and poor-risk disease by IMDC [15]. Furthermore, evolving data with ICI-VEGF–directed combination therapies in the 1L setting may well lead to further approvals in this area in the near future [16,20]. With ICI therapy moving up in the treatment paradigm of mccRCC, TKIs previously developed in and approved for the first- and second-line space will now be considered as standard agents following progression on ICI therapy.

Prospective data on efficacy for previously approved TKI in the post-ICI space is extremely sparse. Choueiri et al [12] noted that the PFS superiority of cabozantinib over everolimus on the phase III METEOR trial extended to the subgroup of patients previously treated with PD-1 or PD-(L)1 therapies with PFS HR 0.22 (95% CI 0.07–0.65), but their findings were limited by small sample size (n = 34), and the authors provided no

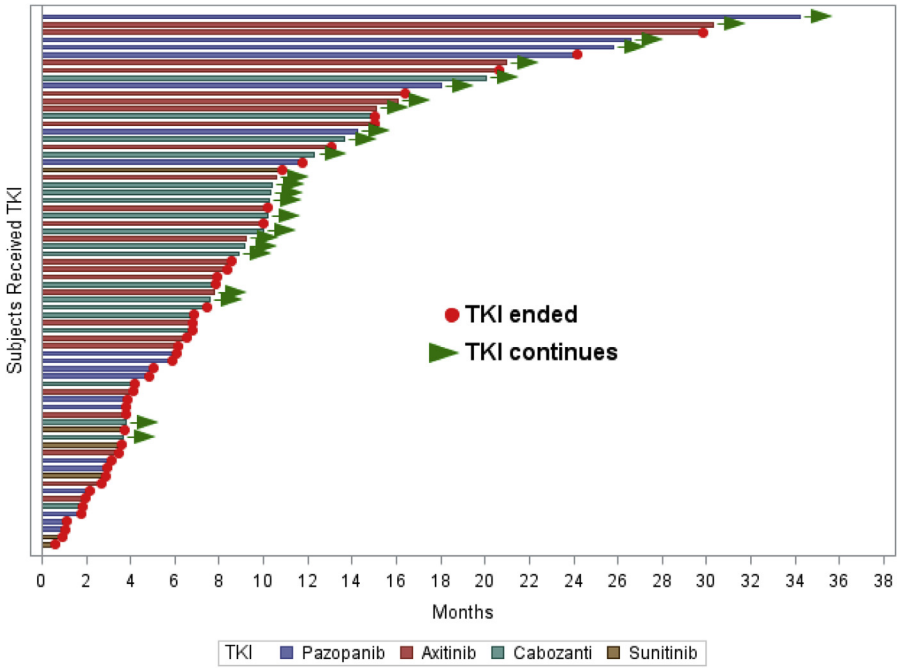

Fig. 4. Duration of 2L TKI Therapy. All 70 patients were included in this swimmer's plot for duration of therapy, broken down by choice of 2L TKI. TKI end denotes that 2L TKI was discontinued either for progressive disease or for toxicity. TKI, tyrosine kinase inhibitor.

Table 3
Subgroup analysis of mPFS, OS rate at 1 year and median duration of TKI.

Variable	n	mPFS (mo) (95% CI)	OS probability 1 yr (95% CI)	Median 2L TKI Duration (mo) (95% CI)
Stages I-III at presentation	27	15.2 (13.2, NA)	0.84 (0.70, 1.0)	13.2 (7.5, NA)
Stage IV at presentation	43	11.0 (6.9, NA)	0.77 (0.65, 0.92)	7.9 (5.1, 16.6)
IMDC favourable-risk	8	8.4 (6.1, NA)	1.0 (1.0, 1.0)	6.2 (6.1, NA)
IMDC intermediate-risk	48	16.6 (13.2, NA)	0.91 (0.83, 1.0)	15.2 (10.1, NA)
IMDC poor-risk	14	4.0 (3.7, NA)	0.31 (0.14, 0.70)	3.8 (3.5, NA)
Nephrectomy	60	15.2 (11.0, NA)	0.83 (0.73, 0.94)	11.0 (6.9, NA)
Primary in situ	10	7.4 (4.2, NA)	0.60 (0.34, 1.0)	6.9 (4.2, NA)
1L anti-PD-(L)1 single agent	12	7.5 (5.9, NA)	0.74 (0.53, 1.0)	6.9 (3.6, NA)
1L anti-PD-1 + anti-CTLA-4	33	11.9 (8.6, NA)	0.81 (0.69, 0.96)	10.3 (6.9, 16.6)
1L anti-PD-(L)1 + anti-VEGF	25	20.8 (10.1, NA)	0.80 (0.63, 1.0)	20.8 (6.2, NA)
2L pazopanib	19	24.4 (6.1, NA)	0.89 (0.75, 1.0)	5.1 (3.8, NA)
2L sunitinib	6	3.6 (0.9, NA)	0.33 (0.11, 1.0)	3.2 (0.9, NA)
2L axitinib	25	13.2 (8.6, NA)	0.87 (0.74, 1.0)	10.3 (8.0, NA)
2L cabozantinib	20	15.2 (7.9, NA)	0.74 (0.54, 1.0)	15.2 (7.9, NA)

mPFS: median progression-free survival; OS: overall survival; TKI: tyrosine kinase inhibitor; IMDC: international metastatic database consortium; PD-1: programmed death-1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; PD-(L)1: Programmed death ligand-1; VEGF: vascular endothelial growth factor

details on rate of radiographic response, extent of prior therapies or TKI safety in this particular subgroup of patients. Further prospective data will be forthcoming from Ornstein et al. [21] on responses with 2L axitinib dose titration after 1L ICI.

Prior publications of multicenter retrospective reports have suggested that TKIs have safety and efficacy after checkpoint inhibitor therapy. Albiges et al. [22] previously reported on 44 patients from 4 academic centres in the United States (US) and Europe who received VEGF-directed therapy subsequent to prior PD-1/PD-(L)1 directed treatments. Overall extent of prior therapies varied with <20% of patients having received ICI therapy in the first line and a significant proportion of subjects with 3 or more lines prior to post-ICI TKI. Median time to treatment failure on post-ICI TKIs was reported at 6.9 months in this mixed population. Auvray et al. reported recently on 33 patients who received 2L TKI after 1L nivolumab plus ipilimumab. mPFS was reported at 8 months with first-generation TKIs and 7 months with second-generation TKIs; interestingly, patients with duration of response

Table 4
Supplementary data: discontinuation of 2L TKI due to toxicity.

Pt requiring 2L TKI discontinuation due to toxicity	1L regimen	1L ICI discontinued for PD or toxicity?	Time from 1L ICI to 2L TKI (weeks)	2L TKI	Toxicity leading to 2L TKI discontinuation	Time to initial toxicity onset (weeks)	Dose modification utilised (Y/N)
1	PD-1 + CTLA-4 blockade	PD	3.7	Pazopanib	Transaminitis	2.0	N
2	PD-1 + CTLA-4 blockade	PD	5.1	Pazopanib	Fatigue, anorexia	0.3	Y
3	PD-1 + CTLA-4 blockade	PD	2.9	Axitinib	Fatigue, anorexia	0.3	Y
4	PD-1 blockade	PD	2.1	Axitinib	Aortic Dissection	31.9	Y
5	PD-1 blockade	PD	12.1	Pazopanib	Transaminitis	7.6	N
6	PD-1 blockade + bevacizumab	Toxicity	0.0	Pazopanib	Transaminitis	14.3	Y
7	PD-1 blockade + bevacizumab	Toxicity	3.0	Axitinib	Fatigue, rash	2.2	Y
8	PD-1 blockade	PD	11.6	Pazopanib	Anorexia, weight loss	1.2	Y
9	PD-L1 blockade + bevacizumab	PD	3.0	Pazopanib	Transaminitis	4.7	N
10	PD-L1 blockade	PD	4.6	Sunitinib	GI bleed	10.0	N
11	PD-1 + CTLA-4 blockade	PD	8.3	Pazopanib	Transaminitis	12.9	Y
12	PD-1 + CTLA-4 blockade	PD	4.7	Pazopanib	Aortic Dissection	8.3	N

TKI, tyrosine kinase inhibitor; PD-1, programmed death-1; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD-(L)1, programmed death ligand-1.

greater than 6 months on 1L ICI appeared to have longer durations of response to 2L TKI [23].

Nadal et al [24] reported on a heterogeneous cohort of 70 patients receiving TKI treatment subsequent to ICI monotherapy (n = 49) or ICI-based combinations (n = 29). Again, >70% of patients were previously exposed to antiangiogenic therapy, some having received prior mTOR or cytokine therapy as well. Some had received a prior TKI in combination with ICI therapy; these patients had numerically lower response to TKI monotherapy than those treated with single-agent checkpoint inhibitors (ORR 10% vs. 36%). The study further suggested TKI therapy could be safely applied with AE profile similar to historic comparisons.

Here, we retrospectively report on a cohort of 70 patients with a well-defined clinical scenario: all had received only one prior ICI-containing regimen that was delivered in the first-line space, and all patients were VEGFR-TKI naïve. There is some heterogeneity in our population, given that 45 patients (64%) were exposed to ICI only in 1L, whereas 25 patients (36%) where exposed to ICI + bevacizumab in 1L; however, both of these front-line approaches are relevant in the current treatment landscape. In the US, the systemic therapy options for mccRCC have changed over the past year, particularly with the introduction of nivolumab plus ipilimumab therapy as 1L therapy for patients with IMDC intermediate- and poor-risk disease [15]. Furthermore, evolving data with ICI–anti-VEGF combination therapies in the 1L setting will likely lead to future approvals in this setting [16]. With ICI therapy moving upfront in the treatment paradigm of mccRCC, the data from this study suggest that patients have a robust response to 2L TKI. The ORR of 41%, a mPFS of 13.2 months and a 1-year OS probability of 80% nearly parallel the historical comparison for 1L TKI treatment [8].

Appreciating notable differences in efficacy with single-agent versus combination ICI therapy in the first-line setting [15,25] as well as the fact that TKIs have varying efficacy when directly compared [26,27], one should not attempt to draw conclusions regarding associations between 2L TKI outcomes and prior ICI regimen in this data set. Acknowledging such limitations to retrospective data review and the small sample size of subgroup analyses, we noted some interesting trends. We noted responses to 2L TKIs regardless of frontline ICI choice. Interestingly, the IMDC intermediate group population had the longest mPFS and longest median TKI duration. This could reflect the fact that these patients have more disease modification and benefit from upfront ICI therapy than those in the favourable risk group, or this could be related to the small number of favourable risk group patients in this cohort. The pazopanib cohort demonstrated the longest mPFS and OS rate at 1 year, whereas the cabozantinib cohort had the longest median duration of TKI therapy. Whether this is a reflection of differences in mechanism of action/

kinome profile and lingering effects of prior ICI therapy on the tumour microenvironment or simply artefactual (i.e. reflecting small numbers in each subgroup) is not clear and could only be addressed in larger cohorts.

Another limitation of retrospective studies is the limited ability to accurately capture all side effects, leading to an underestimation of AEs, particularly Gr 1/2 events. Powles et al. [28] have previously demonstrated that there can be more VEGFR-TKI–related side effects after prior PD-(L)1 exposure, and it is likely that low-grade toxicities such a fatigue and other quality-of-life measures were not fully reflected in this retrospective cohort.

Our data provide estimates for efficacy outcomes when designing trials with 2L TKI after 1L ICI therapy such as nivolumab + ipilimumab which is now the standard of care for patients with advanced or metastatic ccRCC with intermediate- or poor-risk disease. These data may inform the design of trials testing novel agents in combination with VEGFR-TKI in the 2L or 3L setting after 1L ICI + ICI or 1L ICI monotherapy or 1L ICI + bevacizumab therapy.

We are witnessing the introduction of unprecedented numbers of treatment options for the treatment of patients with mRCC, but much remains to be discovered about patient selection, optimal combinations and treatment sequencing. Although it is encouraging that responses to 2L TKI after 1L ICI are robust, ideally, further such questions should be addressed on prospective trials.

5. Conclusion

In this retrospective study, we observed a high ORR of 41%, mPFS of 13.2 months and 1-yr survival probability of 79.6% in patients with mccRCC treated with 2L TKI after 1L ICI. Very few patients had outright PD on 2L TKI after 1L ICI. Tolerance was comparable with prior experience with these approved agents. Further studies are needed to evaluate optimal combination strategies and sequencing of therapies in mccRCC.

Disclaimers

None.

Research support

None

Conflict of interest statement

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