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ORIGINAL RESEARCH

Outcome of immune checkpoint inhibitors in metastatic renal cell carcinoma across different treatment lines

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Background: Immune checkpoint inhibitors (ICIs) have led to a paradigm change in the management of metastatic renal cell carcinoma (mRCC). Prospective trials have focused on ICI treatment in the first or second line. The aim of this analysis is to evaluate the benefit of ICI across different treatment lines.

Patients and methods: This is a single-center retrospective study that included mRCC patients who received ICIs in various treatment lines. Objective response rates (ORR), progression-free survival (PFS) and overall survival (OS) were evaluated.

Results: Ninety-four patients were eligible for full evaluation. Patients were classified as International mRCC Database Consortium (IMDC) risk group categorization as good, intermediate and poor risk in 26.8%, 61.6% and 14.8% of cases, respectively. They were treated with ICI monotherapy, dual ICI therapy and ICI + tyrosine kinase inhibitor in 59%, 20% and 21% of cases, respectively. ORR, median PFS and OS for the entire cohort was 39.4%, 9.67 months [95% confidence interval (CI) 6.9-12.4 months] and 23.6 months (95% CI 13.3-33.9 months), respectively. The ORR by treatment line was 33% in first, 40.4% in the second, 35% in the third and 43.5% in the fourth line and beyond. Median PFS by treatment line was 8.6, 10.3, 7.9 and 7.23 months, respectively. The median OS was not reached in first-line treatment and was 26.2, 18.1 and 20.7 months in the second, third and fourth line and beyond, respectively.

Conclusions: ICIs or ICI combinations are active in all treatment lines and should also be offered in heavily pretreated patients. Patient selection based on tumor and patient factors allows for maximal benefit from ICI-based therapies.

Key words: renal cell carcinoma, immunotherapy, immune checkpoint inhibitors, tyrosine kinase inhibitors, combination therapy, treatment outcome

INTRODUCTION

The introduction of immune check point inhibitors (ICIs) has changed the therapeutic landscape in metastatic renal cell carcinoma (mRCC). The programmed cell death protein 1 (PD-1) inhibitor nivolumab has been initially studied in the second-line setting comprising patients who are refractory to first-line vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs).[1] When compared with the mechanistic target of rapamycin (m-TOR) inhibitor everolimus, nivolumab significantly improved overall survival (OS) [25 versus 19.6 months, hazard ratio (HR) 0.73, 95% confidence interval (CI) 0.57-0.93, $P = 0.002$] and objective response rates (ORR), (21.5% versus 3.9%). In 2017, the combination of nivolumab with the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab has replaced the former standard of care sunitinib in the first-line treatment setting for mRCC in intermediate and poor risk patients. Dual immune checkpoint (IC) inhibition significantly improved OS (47 versus 26.6 months, HR 0.66, $P < 0.0001$) and ORR (42% versus 26%, $P < 0.0001$) compared with sunitinib.[2,3] The recognition that VEGFR-TKIs have immunomodulatory properties has led to several ICI-TKI combination trials. The KEYNOTE-426 study compared the combination of the PD-1 inhibitor pembrolizumab with the VEGFR-TKI axitinib compared with sunitinib.[4] Patients assigned to the ICI-TKI combination experienced a significantly better OS (24 months, 74% versus 66%; HR 0.68, 95% CI 0.55-0.85, $P < 0.001$), progression-free survival (PFS) (15.4 versus 11.1 months; HR 0.71, 95% CI 0.60-0.84, $P <$

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0.0001) and ORR (60.2% versus 39.9%, $P < 0.0001$).[5] Similarly, the combination of the programmed death-ligand (PD-L1) inhibitor avelumab with axitinib was shown to improve PFS (13.8 versus 7.2 months, HR 0.61, 95% CI 0.475-0.790, $P < 0.0001$) and ORR (55% versus 26%) when compared with sunitinib in PD-L1-positive patients.[6] In contrast with the KEYNOTE-426 trial, the combination of avelumab and axitinib has not yet demonstrated an OS benefit when compared with sunitinib.[5] The CheckMate-9ER trial investigated the combination of nivolumab and the MET-AXL and VEGFR-TKI cabozantinib. Patients randomized to nivolumab plus cabozantinib experienced a significantly longer PFS (16.6 versus 8.3 months; HR 0.51, 95% CI 0.41-0.64, $P < 0.0001$) and OS (HR 0.60, 95% CI 0.40-0.89, $P = 0.0010$) as well as higher ORR (55.7% versus 27.1%, $P < 0.0001$).[7] Most recently, the combination of the fibroblast growth factor (FGF)-VEGFR-TKI lenvatinib and pembrolizumab was reported to significantly improve OS [median/months: not reached (33.6-not estimable) versus not reached (not estimable), HR 0.66, 95% CI 0.49-0.88; $P = 0.05$], PFS [median/months: 23.9 (20.8-27.7) versus 9.2 (6.0-11.0), HR 0.39, 95% CI 0.32-0.49, $P < 0.001$] and ORR [71% (66.3%-75.7%) versus 36.1% (31.2%-41.19%)] compared with sunitinib; moreover, 16.1% of patients assigned to lenvatinib plus pembrolizumab achieved complete responses (CR).[8]

Based on these trials, ICI combinations clearly dominate the first-line treatment setting of mRCC with single-agent TKI treatment no longer being appropriate if ICI combinations can be given.[9-11] Other combination trials are ongoing, mostly in the first-line setting as well. In contrast, no standard of care exists for patients who have failed an ICI combination in the first-line setting. The ESMO guidelines recommend as optional the use of a TKI that has not been given in first-line treatment (evidence/recommendation level IVC).[9,12] In clinical practice, little is known of the potential benefits of ICIs or ICI combinations when given beyond the first- and second-line setting. The aim of this retrospective single-center analysis is to investigate the outcome of patients who have received single-agent ICI or ICI combinations across different lines of treatment. We hypothesized that ICI-based therapy in well-selected mRCC patients will result in stable efficacy across treatment lines.

PATIENTS AND METHODS

This is a single-center retrospective study of all mRCC patients who received ICIs in various treatment lines. The patient registry was kept prospectively. Patients were treated with single-agent PD-1 ICI, PD-1 ICI combined with the CTLA-4-ICI ipilimumab or PD-1/PD-L1 ICIs in combination with VEGFR-TKIs. Data were collected between January 2014 and October 2019. The institutional review board approved the collection, analysis and publication of the data. The objectives were to assess ORR, PFS and OS for the entire cohort and by treatment line. Toxicity assessment was another endpoint of this study. Safety assessments included adverse events (AEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Tumor imaging was carried out at baseline and then every 12 weeks and tumors were assessed using RECIST 1.1. PFS was calculated from the time of initiation of ICI treatment to disease progression or death from any cause; OS was calculated from time to ICI treatment initiation to death from any cause or censored at the time of last follow-up. The estimated median PFS and OS were calculated using the Kaplan—Meier method. Calculations were done using Statistical Software Package for Social Sciences (SPSS) version 26 (IBM SPSS Statistics for Windows, Version 26.0, IBM Corp, Armonk, NY). This study has been approved by the appropriate ethics committee (ethics committee vote number 1157/2020).

RESULTS

A total of 94 patients with mRCC who were treated with ICIs across different treatment lines were included in this analysis. Patient characteristics are displayed in Table 1. According to the International mRCC Database Consortium (IMDC) risk group classification, 26.8%, 61.6% and 14.8%

Table 1. Patient characteristics

Variable	*N* (%)
All	94 (100)
Male/female	70 (77.8)/24 (22.2)
Median age at diagnosis of mRCC and range	62 years (17-81 years)
IMDC risk at the begin of ICI treatment	
Favorable	25 (26.8)
Intermediate	58 (61.6)
Poor	14 (14.8)
Nephrectomy yes	86 (91.4)
Nephrectomy no	8 (8.6)
History of metastasectomy	52 (55.3)
Complete: *n*	27
Incomplete: *n*	25
History of complete metastasectomy before ICI	42 (80.7)
Timepoint related to start of ICI therapy (median/range)	45.3 months (0.4-173)
History of radiotherapy	39 (41.5)
Clear-cell histology/non-clear-cell histology	78 (83)/16 (17)
Sarcomatoid differentiation	6 (6.4)
Number of metastatic sites at the beginning of ICI treatment	
1	9 (9.6)
2	30 (31.9)
≥3	55 (58.5)
Most common metastatic sites	
Lung	63 (67)
Lymph nodes	39 (41)
Other	53 (56)
Liver	29 (31)
Bone	39 (41)
CNS	13 (14)
Treatment given before ICI-based regimen, *n* (%)	
Sunitinib	47 (55.4)
Pazopanib	3 (3.5)
Axitinib	12 (14.1)
Cabozantinib	9 (10.6)
Lenvatinib + everolimus	3 (3.5)
Other	11 (12.9)

CNS, central nervous system; ICI, immune checkpoint inhibitors; IMDC, International mRCC Database Consortium; mRCC, metastatic renal cell carcinoma.

Table 2. Treatment and treatment group characteristics

Treatment lines in which ICIs were given	First line	Second line	Third line	Fourth line and beyond
n (%)	9 (10)	42 (45)	20 (21)	23 (24)
	Median treatment line and range			
	2 (1-7)			
IMDC favorable risk *n* (%)	1 (11.1)	13 (31)	5 (25)	5 (21.7)
IMDC intermediate risk *n* (%)	5 (55.6)	22 (52.3)	14 (70)	16 (69.6)
IMDC poor risk *n* (%)	3 (33.3)	7 (16.7)	1 (5)	2 (8.7)
N met sites by line 1 site, *n* (%)	2 (22.2)	5 (11.9)	2 (10%)	1 (4.3%)
N met sites by line 2 sites, *n* (%)	2(22.2)	13 (30.9)	7 (35)	8 (34.8)
N met sites by line 3+ sites, *n* (%)	5 (55.6)	24 (57.2)	11 (55)	14 (60.9)

ICI-based regimen			
Type	Mono	ICI + ICI	ICI + TKI
n (%)	55 (59)	19 (20)	20 (21)

Addition of TKI during ICI treatment				
Type of TKI	Axitinib	Cabozantinib	Sunitinib	Lenvatinib
n (%)	14 (70)	3 (15)	2 (10)	1 (5)

ICI, immune checkpoint inhibitor; IMDC, International metastatic renal cell carcinoma database consortium; TKI, tyrosine kinase inhibitor.

were favorable, intermediate and poor risk, respectively. The majority of the patients (91.4%) had undergone cytoreductive nephrectomy. Overall, 55.3% and 41.5% of patients had a history of metastasectomy and/or stereotactic radiosurgery (complete resection $n = 27$, incomplete resection $n = 25$). The median time of metastasectomy related to the start of ICI therapy was 45.3 months (0.4-173). Clear-cell and non-clear-cell histology were found in 83% and 17% of patients, respectively, with sarcomatoid features in 6.4%. At the time point of ICI treatment, 9.6%, 31.9% and 58.5% had one, two and three or more metastatic sites, respectively. The most common metastatic site was the lung (67%), followed by lymph nodes (LN) (62%). Prior therapies included sunitinib (55.4%), axitinib (14.1%), other (12.9%), cabozantinib (10.6%) and lenvatinib + everolimus or pazopanib (3.5%). Table 2 outlines treatment groups and treatment group characteristics. Only 10% of patients were treated with ICIs in first-line treatment. The majority of patients received ICIs in the second-line treatment (45%), followed by the fourth line and beyond and the third line (24% and 21%, respectively). The median line of treatment in which ICI-based therapy was given was 2.[1-7] The number of IMDC intermediate risk patients was similar across the different treatment lines; in contrast, the lowest number of IMDC favorable risk and the highest number of IMDC poor risk patients were seen in the group of patients who received ICIs in first-line treatment. ICI-based treatment consisted of single-agent nivolumab (59%), dual IC-inhibition with nivolumab and ipilimumab (20%) and ICI + TKI (21%). The most commonly used TKI in combination with ICI was axitinib (70%). When combined, TKIs were started either together with ICI in 35% of all TKI patients or later in the context of mixed responses (65% of all TKI patients).

Table 3. Tumor response according to treatment line and ICI regimen

Objective response by treatment line					
Response	Any line *N* = 94 (100%) *n* (%)	ICI in first line *n* = 9 (10%) *n* (%)	ICI in second line *n* = 42 (45%) *n* (%)	ICI in third line *n* = 20 (21%) *n* (%)	ICI in fourth line and beyond *n* = 23 (24%) *n* (%)
ORR (CR + PR)	37 (39.4)	3 (33)	17 (40.4)	7 (35)	10 (43.5)
DCR (CR + PR + SD)	61 (65)				
CR	7 (7.4)	0 (0)	2 (4.8)	2 (10%)	3 (13)
PR	30 (32)	3 (33)	15 (35.7)	5 (25%)	7 (30.4)
SD	24 (25.5)	4 (44)	11 (26.2)	6 (30%)	3 (13)
PD	33 (35)	2 (22)	14 (33.3)	7 (35%)	10 (43.5)

Objective response rates according to ICI regimen			
Response	ICI monotherapy, *n* (%) 55 (59)	Dual ICI therapy, *n* (%) 19 (20)	ICI + TKI, *n* (%) 20 (21)
ORR (CR + PR)	20 (36.3)	8 (42)	9 (45)
DCR (CR + PR + SD)	31 (56.4)	15 (79)	15 (75)
CR	4 (7.3)	1 (5.2)	2 (10)
PR	16 (29)	7 (36.8)	7(35)
SD	11 (20)	7 (36.8)	6 (30)
PD	24 (43.6)	4 (21)	5 (25)

CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, disease progression, PR, partial response; SD, stable disease.

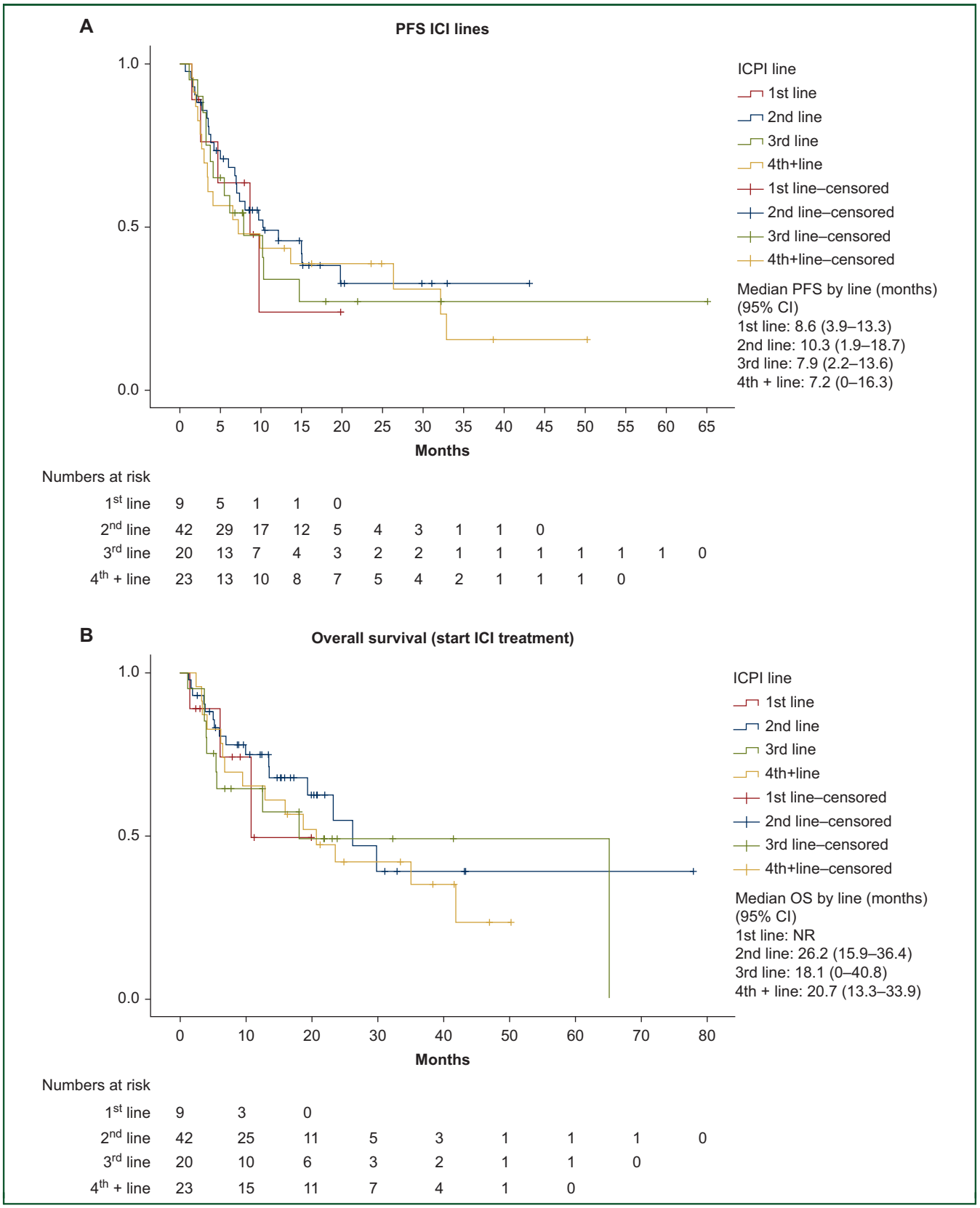

Figure 1. (A) PFS according to treatment lines. (B) Overall survival according to treatment lines.
ICPI, immune checkpoint inhibitors; NR, not reached; PFS, progression-free survival.

Table 4. Adverse events

Adverse event	All grades (AE 1-4) $N = 90$ *n* (%)	Grade 3 + 4 *n* (%)
Fatigue	37 (41.1)	9 (10)
Diarrhea	17 (18.9)	7 (7.9)
Nausea	16 (17.8)	1 (1.1)
Asthenia	15 (16.7)	3 (3.3)
Hypertension	13 (14.4)	2 (2.2)
Renal	11 (12.2)	2 (2.2)
Stomatitis	8 (8.9)	1 (1.1)
Dyspnea	7 (7.8)	0
Musculoskeletal	7 (7.8)	1 (1.1)
Anemia/thrombocytopenia/leukopenia	6 (6.7)	2 (2.2)
Pancreatitis	2 (2.2)	1 (1.1)
Immune-related adverse event		
Rash	13 (14.4)	1 (1.1)
Pruritus	11 (12.2)	0
Increase of AST and/or ALT	8 (8.9)	4 (4.4)
Chills (influenza-like symptoms)	8 (8.9)	1 (1.1)
Pneumonitis	4 (4.4)	0
Thyroiditis	2 (2.2)	2 (2.2)
Colitis	2 (2.2)	2 (2.2)
CNS*	2 (2.2)	2 (2.2)
Grade 3-4 AE per treatment type		
ICI + ICI, $n = 19$	Na	11 (57.9)
ICI + TKI, $n = 20$	Na	10 (50)
ICI single agent, $n = 51$	Na	10 (19.6)
Dose reduction, treatment interruption and treatment discontinuation		
Treatment interruption ICI *n* (%)	13 (13.9)	
Treatment interruption TKI, *n*	6	
Dose reduction TKI, *n*	2	
Discontinuation ICI, *n*	9	
Discontinuation ICI and TKI, *n*	3	
Oral or intravenous corticosteroid use		
All *n* (%)	15 (15.9)	
0.5-1 mg/kg prednisolone *n* (%), oral	8 (8.5)	
1-2 mg methylprednisolone, intravenously *n* (%)	7 (7.4)	

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; ICI, immune checkpoint inhibitor; IRAEs, immune-related adverse events; Na, not available; TKI, tyrosine kinase inhibitor.

* IRAEs occurring in the CNS included one patient with encephalitis and one patient with myoclonia.

Efficacy outcomes

ORR are outlined in Table 3. According to RECIST 1.1 criteria, ORR and disease control rates for all patients were 39.4% and 65%, respectively. Complete responses (CR) were observed in 7.4% of patients and disease progression in 35%. Objective responses including confirmed CR were observed in all lines; the highest CR rate (13%) was achieved in patients who received ICIs in the fourth line and beyond, followed by patients in the third line (10%). The highest rate of disease progression (PD; 43.5%) was also seen in patients who were treated with ICIs in the fourth line and beyond. The highest ORR and CR rates were observed in patients who received ICI + TKI combinations (45% and 10%), followed by dual ICI therapy patients (42% and 5.2% of patients, respectively) and were 36.3% and 7.3% in patients treated with ICI monotherapy. PFS is shown in Figure 1A. The median PFS by treatment line was 8.6 months (95% CI 3.9-13.3 months) in the first, 10.3 months (95% CI 1.9-18.7 months) in the second, 7.9 months (95% CI 2.2-13.6 months) in the third and 7.2 months (95% CI 0-16.3 months) in the fourth and beyond. The median OS (Figure 1B) by treatment line was not reached in the first line; it was 26.2 months (95% CI 15.9-36.4 months) in the second line, 18.1 months (95% CI 0-40.8 months) in the third line; and 20.7 months (95% CI 13.3-33.9 months) in the fourth line and beyond. The global OS for the whole patient cohort calculated from diagnosis of metastasis to death or censoring was 80 months (95% CI 50.5-109.5 months).

Toxicity

AEs are displayed in Table 4. The most common all-grade toxicities were fatigue (41.1%), diarrhea (18.9%), nausea (17.8%), asthenia (16.7%) and hypertension (14.4%), with fatigue and diarrhea being the most common grade 3 or 4 toxicities (10% and 7.9%, respectively). Common all-grade immune-related AEs (IRAEs) included rash and pruritus (14.4% and 12.2%, respectively), followed by liver toxicity and chills (8.9% each). Seven out of 12 patients experienced grade 3 or 4 IRAEs and 15 patients received systemic corticosteroid treatment. The incidence and severity of toxicities did not differ between treatment lines.

DISCUSSION

The aim of this retrospective analysis is to investigate the outcomes of patients treated with ICI-based therapy across

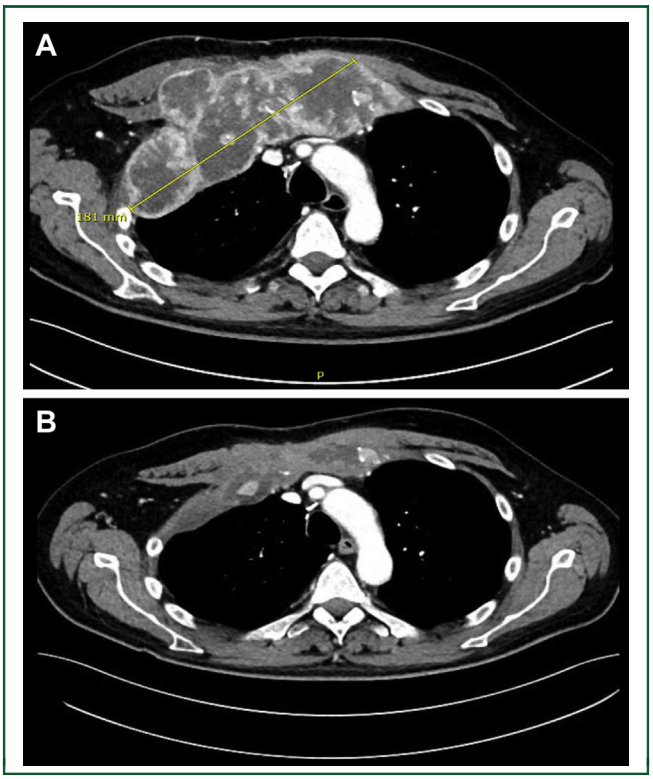

Figure 2. **(A) Large soft tissue metastasis after six lines of treatment. (B) Regression after 3 months of seventh-line treatment.**

different lines of treatment. These treatment strategies are currently approved for first and second-line treatment only; however, we found that both single-agent ICI and ICI combinations provide substantial benefits in later treatment lines as well. When treated in the second, third and fourth lines or beyond, 40.4%, 35% and 43.5% of our patients achieved an OR, respectively. This is consistent with the findings of other authors who reported data on ICI treatment in a real-world scenario. In a retrospective analysis of patients included within the IMDC database,[13] the ORRs for the second, third, fourth line and beyond were 22%, 24% and 26%, respectively. Patients included in this analysis had a median duration of treatment (DOT) of 5.7, 6.2 and 8.3 months, in the second, third and fourth line and beyond, respectively. Although PFS and DOT are two different endpoints, both highlight the activity of the treatment in later lines. We observed a median PFS of 10.3 months (95% CI 1.9-18.7 months) in the second line, 7.9 months (95% CI 2.2-13.6 months) in the third line, and 7.2 months (95% CI 0-16.3 months) in the fourth line and beyond. Similarly, the Italian expanded access program for nivolumab[14] included 389 patients, of whom 43.9% were treated in the third line and beyond. The ORR and PFS for the entire cohort were 23.1% and 4.5 months (95% CI 3.7-6.2 months), respectively. No data were shown for the population who received nivolumab in third-line treatment and beyond. The authors observed a strong association between the occurrence of IRAEs and survival. Hinata et al. reported the results of a non-interventional review study on nivolumab in Japanese patients where 31.7% of 208 eligible patients had received

Table 5. Dates, treatment types and PFS from first- to seventh-line treatment of one patient

Dates	Treatment	PFS
May 2016	First line: sunitinib	12 months
July 2017	Second line: cabozantinib	3 months
October 2017	Third line: nivolumab + cabozantinib; 2 courses	Discontinued due to thyroiditis
December 2017	Third line: nivolumab rechallenge (mono)	4 months
April 2018	Fourth line: lenvatinib + everolimus	8 months
December 2018	Fifth line: sunitinib	6 months
June 2019	Sixth line: axitinib	2 months
September 2019	Seventh line: nivolumab + ipilimumab + axitinib	

PFS, progression-free survival.

nivolumab in fourth-line treatment or later. The median PFS was 7.1 months and the ORR 22.6%. The ORR in our patients is almost twice as high when compared with the data mentioned above.[15] Several reasons may account for these differences. First, our population is smaller, which may increase the risk of selection bias; second, 4.26% of our patients were treated beyond progression if a clinical benefit was documented; third, 65% of patients had a treatment escalation, i.e. the addition of a TKI in the context of mixed response; fourth, the combination of TKIs and ICIs, which was offered to 21% of patients, may have increased the likelihood of achieving OR. In the KEYNOTE-426 study, the ORR for patients in the pembrolizumab + axitinib arm was 60.2%.[5] Similarly, 55.7% of patients in the CheckMate-9ER study achieved OR.[12] In contrast, single-agent nivolumab resulted in an ORR of 25% in the CheckMate-025 trial.[16]

The limitation of our study is its retrospective nature and the heterogeneity of the treatment. However, data generated in real-world scenarios, where treatment decisions and treatment patterns are based on the individual patient, are important. Our findings may encourage physicians who are hesitant to offer a treatment in a setting that has not been studied in a prospective trial. Moreover, in many countries, access to ICIs or ICI combinations is restricted to first- and second-line treatment scenarios. Such strict treatment approaches may deprive patients of many more months or years of survival. Figures 2A and B display the CT scan of a 43-year-old male patient who has been successfully treated using a triplet therapy with nivolumab, ipilimumab and axitinib in seventh-line treatment. The patient had undergone cytoreductive nephrectomy due to clear-cell renal cell carcinoma in November 2014 and resection of lung metastases in June 2015. In May 2016, the disease progressed with new lung and LN metastases. Table 5 displays the different types of treatment and PFS that the patient received from first-line to sixth-line treatment. At the time point when the triplet was initiated in seventh-line treatment, the patient had progressed on axitinib. The reason to maintain axitinib and to add dual ICIs was based on two factors: first, a smaller proportion of the lesions was still stable and we hypothesized that maintaining the TKI may also optimize the outcome from the ICI; second, although

the patient had already received nivolumab in third-line treatment, we hypothesized that dual ICIs may be more efficacious in preventing cancer immune escape. The patient began triplet therapy with nivolumab, ipilimumab and axitinib in September 2019. The first observation was a considerable improvement of his performance status within 3 weeks. The first computed tomography (CT) scan after 3 months of treatment showed a considerable shrinking of the large sternal metastasis (Figures 2A and B). Dual ICI was maintained for four cycles and subsequently, the patient continued with nivolumab-axitinib. So far, no disease progression has been documented and the current PFS in seventh-line treatment is 16 months. This case is remarkable in many ways, considering both that the most dramatic response was observed in seventh-line treatment and that single-agent nivolumab had already been given in third-line treatment. Diarrhea was the only grade 3 toxicity observed and is meanwhile controlled due to dietary measures. So far, no IRAEs have occurred.

Conclusions

The use of ICI treatment across different lines of treatment is neither supported by prospective evidence nor by the treatment guidelines; however, real-world data suggest that heavily pretreated patients may benefit from ICI or ICI combinations. This may even apply if prior ICI treatment was less effective. The heterogeneity of the tumor with the ongoing course of disease and the potential impact of prior therapies on the tumor microenvironment may contribute to the immunogenicity of the tumor, thus enabling unexpected responses even in late treatment lines.

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