Efficacy of targeted therapies after PD-1/PD-L1 blockade in metastatic renal cell carcinoma

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Abstract *Background:* Monoclonal antibodies that target the programmed death-1 (PD-1)/programmed death-ligand 1(PD-L1) pathway have shown antitumour activity in metastatic renal cell carcinoma (mRCC) and are currently being developed in first-line (in combination) and in previously treated patients. The efficacy targeted therapy (TT) after PD-1/PD-L1 blockade is still unknown.

Methods: Medical records of mRCC patients treated with investigational PD-1 or PD-L1 inhibitors at 4 academic institutions were reviewed. Patients who received subsequent treatment with TT were selected to collect outcome measures of subsequent TT.

Results: Of 99 patients who received PD-1/PD-L1 blockade as part of clinical trials, 56 patients have received subsequent therapy: 44 patients received vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) inhibitors and 12 received mammalian target of rapamycin (mTOR) inhibitors as first subsequent TT. Median

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follow up, from the start of subsequent TT was 16.1 months (range: 0.2, 30.6 months). TT post PD-1/PD-L1 blockade was administered as second-line, third-line or beyond third-line in 9 (16%), 24 (43%) and 23 patients (41%) respectively. Median time to treatment failure on subsequent TT was 6.6 months (range: 0.2+, 23.0). 1-year and 2 year overall survival from the initiation of subsequent TT was 58% (95% confidence interval (CI): 41–72%) and 36% (95% CI: 18–54%), respectively.

Conclusion: Both VEGF/VEGFR and mTOR inhibitors demonstrate antitumour activity following PD-1/PD-L1 blockade.

1. Introduction

Metastatic renal cell carcinoma (mRCC) accounts for 16,000 deaths in the United States and 37,000 in the European Union in the year of 2015 [1]. Overall, seven targeted therapies have been approved since 2005 and include agents targeting the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, four VEGF receptor tyrosine kinase inhibitors (VEGFR TKI) namely sunitinib, sorafenib, pazopanib and axitinib, and finally, two inhibitors of the mammalian target of rapamycin (mTOR): everolimus and temsirolimus. Efforts to improve patient outcome through combination therapy with approved agents have failed to extend overall survival (OS) [2].

An improved understanding of the immune response to cancer has led to the development of monoclonal antibodies that block immune checkpoints (e.g. CTLA-4 and PD-1). These agents have been shown to restore and enhance the antitumour immune response and have produced promising results in many tumours including mRCC [3,4]. The activity signals of PD-1/PD-L1 inhibitors in mRCC have been reported in phase I and II studies for nivolumab (Bristol-Myers Squibb Company, Princeton, NJ) and MPDL3280A (Genentech, South San Francisco, CA) [5–13]. NCT01668784 recently showed an overall survival benefit for nivolumab over everolimus in patients in the VEGF-refractory setting. In the first line setting, MPDL3280A is being combined with bevacizumab (NCT01984242).

Despite the encouraging results seen in these phase I/II trials of immune checkpoint blockers including response rate in the range of 10–36% [6,10,12,13] and intriguing median overall survival ranging from 18.2 to 25.5 months in the different cohorts of the largest phase II with nivolumab in previously treated patients, it is expected that many patients will require additional systemic therapy after PD-1/PD-L1 pathway blockade. Subsequent therapies are likely to be de facto the 'available' targeted agent that has not been yet used. Whether these changes will impact the efficacy of subsequent therapies including VEGFR TKI or mTOR inhibitors is still unknown. The objective of this work is to assess the efficacy of targeted therapies after PD-1/PD-L1 blockade in patients with mRCC.

2. Patients and methods

2.1. Study population

Ninety-nine mRCC patients enrolled in clinical trials of PD-1 or PD-L1 inhibitors at four institutions (Dana Farber Cancer Center, Boston; Institut Gustave Roussy, Villejuif; Beth Israel Deaconess Medical Center, Boston; and Tom Baker Cancer Center, Calgary) were retrospectively collected. Fifty-six patients who received subsequent treatment with targeted therapies at the same institutions were included in this study.

Baseline patient characteristics including demographic, pathological and prognosis classification according to the International Metastatic RCC Database Consortium (IMDC) criteria [14] were retrospectively collected from medical records. Outcome measures were also retrieved from medical chart reviews including time to treatment failure (TTF), investigator-assessed best response (RECIST 1.1) and OS.

All centres obtained local institutional review board approval before data collection in this retrospective study. Uniform data templates were used to ensure consistent data collection at each institution. Patients may have received subsequent targeted therapy as part of clinical trials or with the standard of care according to national cancer guidelines.

2.2. Statistical analysis

The primary objective of this study was to characterise clinical outcomes (TTF and OS) of mRCC patients treated with targeted therapies after progression on PD-1/PD-L1 inhibitors. TTF was defined as the time period between treatment initiation and drug cessation due to progression, toxicity, patient refusal, death, or censored at last follow-up. OS was defined as the time period between the start of the first subsequent targeted therapy initiation and date of death, or censored at last follow-up. Distributions of TTF and OS were estimated using the Kaplan Meier methodology; 1- and 2-year OS

with 95% confidence intervals (CIs) were also reported. The statistical analyses were performed using SAS version 9 (SAS Institute, Cary, NC), and $P < .05$ (two sided) was considered statistically significant.

3. Results

3.1. Baseline characteristics

Of 99 patients who received PD-1/PD-L1 inhibitors on clinical trials at four institutions, 56 patients have received subsequent therapy after PD-1/PD-L1 blockade. Patient's characteristics are reported in Table 1.

Among the 56 patients who received subsequent targeted therapy, 44 patients were treated with VEGF/VEGFR inhibitors and 12 with mTOR inhibitors.

Table 1
Patient characteristics.

Patient and tumour characteristics	N	%
Gender		
Female	17	30.4
Male	39	69.6
Pathology		
Clear cell RCC	46	82.1
Papillary RCC	3	5.4
Chromophobe RCC	1	1.8
Translocation RCC	2	3.6
Unknown	4	7.1
Nephrectomy		
Yes	53	94.6
No	3	5.4
Years from diagnosis to systemic therapy		
<1 year	24	42.9
≥1 year	32	57.1
Baseline characteristics at time of subsequent targeted therapy		
Age (median, range)	61	31–86
IMDC prognosis risk group ($n = 30$)		
Favourable	3	10.0
Intermediate	16	53.3
Poor	11	36.7
Number of prior lines of systemic therapy (including PD-1/PD-L1 inhibition)		
1	9	16.1
2	24	42.9
≥3	23	41.1
Class of targeted therapy		
VEGFR TKI	44	78.6
mTOR	12	21.4
Agent		
Axitinib/Axitinib based combination	20	35.7
Pazopanib	14	25.0
Sorafenib	1	1.8
Sunitinib	4	7.1
Bevacizumab based combination	5	9.0
Everolimus	11	19.6
Temsirolimus	1	1.8

Median follow up from the start of the subsequent targeted therapy is 16.1 months (range: 0.2, 30.6 months). Targeted therapy post PD-1/PD-L1 was administered as 2nd line in nine patients (16%), 3rd line in 24 patients (43%) and in 4th line or more in 23 patients (41%). IMDC risk group classification at the initiation of subsequent targeted therapy was available in 30 patients from three institutions: favourable ($n = 3$, 10%), intermediate ($n = 16$, 53%) and poor ($n = 11$, 37%), respectively.

Out of the 56 patients who received subsequent therapy, 47 patients had been previously pre-treated with targeted therapy prior to PD-1/PD-L1 blockade. The last targeted therapy prior to PD-1/PD-L1 blockade was administered with VEGFR TKI and mTOR inhibitors in 43 and four patients, respectively. Overall, median TTF for the last targeted therapy line prior to PD-1/PD-L1 blockade was 9.3 months (range: 0.6, 32.1).

3.2. Outcomes of subsequent treatment post PD-1/PD-L1 blockade (Table 2)

Overall, median TTF was 6.6 months (range: 0.2 + (patient still on treatment), 23.0) for the first subsequent line of therapy (Fig. 1A). Median TTF was 6.9 months (range: 0.2+, 19.3) and 5.7 months (range: 0.5, 23.0) in patients treated with VEGFR TKI and mTOR inhibitors, respectively.

Overall, median OS after the initiation of subsequent therapy was 17.5 months (95% CI: 10.8 to NR), with 34 (61%) of patients remaining alive at time of analysis (Fig. 1B). One year-OS rate was 58% (95% CI: 41–72%) and 2 year-OS rate was 36% (95% CI: 18–54%). The one year survival rate was 64% (95% CI: 33–83%) in patients with IMDC favourable/intermediate risk and 30% (95% CI: 5–62%) in the poor risk group.

Investigator-assessed best response to subsequent targeted therapy was available for 53 out of 56 patients. Among these 53 patients, 7 (13%) achieved partial response (PR), 33 (62%) achieved stable disease (SD) and 13 (25%) presented progressive disease (PD) as best response.

Out of the 56 patients who received subsequent targeted therapy, 23 further received a second subsequent targeted therapy drug after PD-1/PD-L1 blockade. Median TTF was 5.5 months (range: 0.1+, 20.8+) for the second subsequent targeted agent. Fig. 2 illustrates the time on distinct systemic therapies prior and after PD-1/PD-L1 blockade per patient.

4. Discussion

In a selected population of patients previously enrolled in clinical trials of PD-1/PD-L1 blockade, targeted therapy consisting in VEGF/VEGFR or mTOR inhibitors achieved a median TTF of 6.6 months, and a median OS of 17.5 months.

Table 2
Treatment outcomes of the first subsequent therapy post programmed death-1 (PD-1)/programmed death-ligand 1(PD-L1) blockade.

	Total N	Time to treatment failure		Overall survival		Investigator-assessed best response[*]		
		No. of failure	Median (range), months	No. of failure	1-year rate,% (95% confidence interval (CI))	Partial response (PR)	Stable disease (SD)	Progressive disease (PD)
All	56	42	6.6 (0.2+, 23.0)	22	58 (41,72)	7 (13)	33 (62)	13 (25)
By type of therapy								
VEGF receptor tyrosine kinase inhibitors (VEGFR TKI)	44	32	6.9 (0.2+, 19.3)	16	66 (47,80)	7 (16)	26 (61)	10 (23)
Mammalian target of rapamycin (mTOR)	12	10	5.7 (0.5, 23.0)	6	35 (8,64)	–	7 (70)	3 (30)
By treatment agent[**]								
Axitinib	20	10	10.0 (0.2+, 19.3)	6	69 (34,88)	3 (16)	14 (74)	2(11)
Everolimus	11	9	4.8 (0.5,23.0)	6	27 (4,58)	–	6 (67)	3 (33)
Pazopanib	14	12	4.8 (0.6,11.1)	6	61 (27,84)	–	9 (64)	5 (36)
By line of therapy								
2nd	9	8	5.2 (0.5, 16.5 +)	5	56 (20,84)	–	6 (67)	3 (33)
3rd	24	17	7.1 (0.2+, 23.0)	5	60 (27,82)	3 (14)	13 (62)	5 (24)
≥4th	23	17	6.9 (1.1, 19.3)	12	58 (33,77)	4 (17)	14 (61)	5 (22)

[*] Evaluated in 53 out of 56 patients.
[**] Line of the subsequent therapy: Axitinib: 2nd line ($N = 1$), 3rd line ($N = 8$), ≥4th line ($N = 11$); Everolimus: 3rd line ($N = 8$), ≥4th line ($N = 3$); Pazopanib: 2nd line ($N = 7$), 3rd line ($N = 3$), ≥4th line ($N = 4$).

Nivolumab, MPDL3280A and other PD-1/PD-L1 agents are being actively investigated in mRCC and may represent a major breakthrough to improve clinical benefit [4]. The dose ranging phase II results of nivolumab in 168 patients have reported that overall response rate (ORR) ranged from 20% to 22% and median PFS was 2.7, 4.0 and 4.2 months, respectively for the 0.3-, 2- and 10-mg/kg cohorts [12]. In a phase I study of the immunomodulatory activity of nivolumab, the PFS rate at 24 weeks was 18%, 32% and 49% with nivolumab 0.3-, 2.0- and 10-mg/kg, respectively, in previously

Fig. 1B. Overall survival (OS) from initiation of subsequent targeted therapy post programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade.
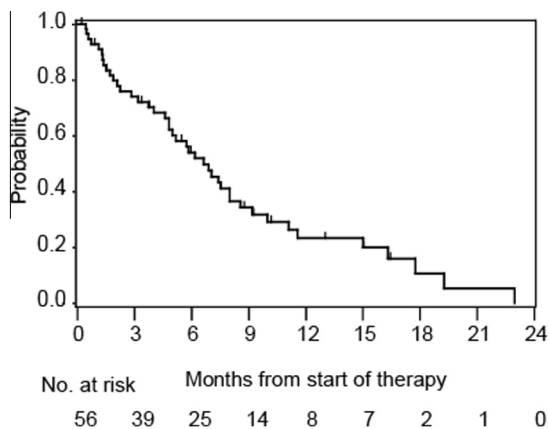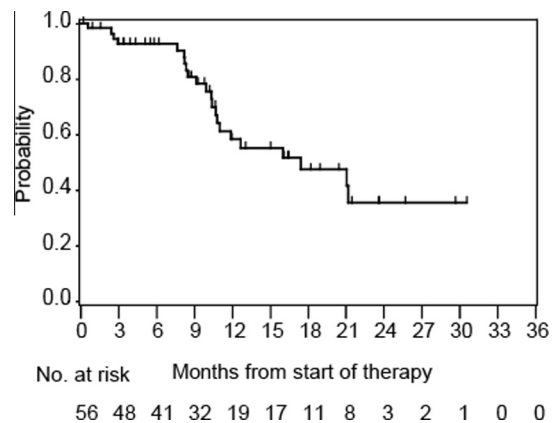

Fig. 1A. Time to treatment failure (TTF) on the first subsequent targeted therapy post programmed death-1 (PD-1)/programmed death-ligand 1(PD-L1) blockade.

treated patients [13]. MPDL3280A phase I expansion cohort in mRCC displayed a 24-week PFS rate of 51% (95% CI: 38–63) and ORR from 9% to 23% [10,11]. The PFS results and the ORR results of PD-1/PD-L1 approach will be further characterised by the pivotal ongoing trials. However, to date, the lack of biomarkers to accurately select the patients that are more likely to benefit from this approach remains a challenge. Pending the availability of a robust predictive biomarker, it is expected that many patients will continue to progress,
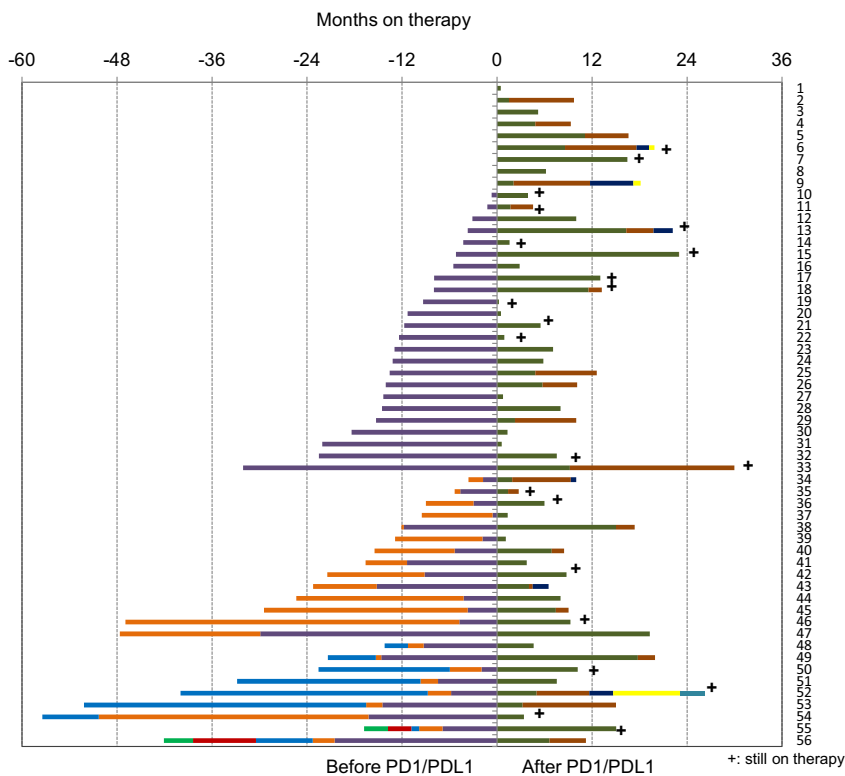
Fig. 2. Time on distinct systemic therapies per patient prior and after programmed death-1 (PD-1)/programmed death-ligand 1(PD-L1) blockade.

even after an initial response. Patients still able to undergo systemic therapy will be offered the currently available agents, VEGF/VEGFR and mTOR inhibitors, and therefore there is a need to report on the efficacy data of these targeted therapies in the post-immune checkpoint blockade setting.

In the dose ranging phase II study reported by Motzer and colleagues, OS was calculated from the time of nivolumab start. Median OS was 18.2 months (80% CI: 16.2–24.0 months), 25.5 months (80% CI: 19.8–28.8 months) and 24.7 months (80% CI: 15.3–26.0 months), for the nivolumab 0.3-, 2- and 10-mg/kg cohorts, respectively. These OS numbers are encouraging when compared to investigational and control arms of the phase III trials in the post VEGFR TKI settings, where median OS survival ranged between 12 and 17 months for targeted therapy agents such as axitinib, sorafenib, everolimus and temsirolimus [15–17]. In our series we report, for the first time, the OS of patients receiving subsequent therapy after PD-1/PD-L1 blockade. A 17.5 month OS is very encouraging. Similarly, TTF, another efficacy endpoint, was 6.6 months which again compared favorably to the 4–5 months PFS from everolimus and axitinib in patients pre-treated with VEGF/VEGFR inhibitors in the RECORD-1 and AXIS trials [18]. If PD-1/PD-L1 demonstrate activity against standard of care in mRCC, a prospective trial design assessing the questions of sequence of PD-1/PD-L1 and VEGF/VEGFR inhibitions would address

both the optimal clinical activity and help to understand the underlying biology associated with the distinct sequences.

The impact of VEGFR TKI on tumour immune environment and potential immunomodulatory properties of sunitinib, in particular, have been investigated, providing some rationale for a VEGFR TKI-PD-1/PD-L1 combined inhibition. Sunitinib is able to reduce the infiltration by MDSC [19] and T regulator lymphocytes [20]. Preclinical work on mRCC models [20–22], as well as other tumour models [23] suggest that sunitinib can be used to reverse immune suppression and as a potentially useful adjunct for enhancing the efficacy of immune-based cancer therapy for advanced malignancies.

Conversely, the current work would potentially support the hypothesis that the front line use of PD-1/PD-L1 blockade may impact the response to subsequent lines with currently approved agents. In fact, the phase 1 study of the immunomodulatory activity of nivolumab showed that nivolumab in vivo has the ability to reactivate T cells, resulting in an expansion and tumour-directed migration as well as triggering serum-cytokine changes [13]. Another potential hypothesis to explain these findings is the fact that PD-1/PD-L1 blockade may actually impact response to subsequent therapy, by modulating tumour microenvironment beyond actual 'progression by imaging', making subsequent targeting therapy active.

This study has several limitations. First, the retrospective nature of this analysis leads to selection bias. However, this is the largest reported study to date showing that in the right clinical scenario, targeted agents with VEGF/VEGFR and mTOR inhibitors can be active after progression on immune checkpoint blockers. Second, although we have designed this analysis based on collaboration among four high volume cancer centres, we acknowledge that the size of the cohort remains a major limitation; preventing drawing any firm conclusions on the sequence of targeted therapies after immune checkpoint blockade.

5. Conclusion

To our knowledge, this is the first report to address the efficacy of subsequent therapies after PD-1/PD-L1 blockade in mRCC. In a selected population, median TTF suggests a sustained benefit of both VEGFR TKI and mTOR inhibitors after PD-1/PD-L1 blockade. If immunotherapies are approved for mRCC treatment, their use in first- and second-line may challenge the frontline use of VEGF/VEGFR TKI or mTOR inhibitors and move the currently available agents to later lines in the management of advanced disease. Furthermore, the potential sustained effect of PD-1/PD-L1 after discontinuation needs to be characterised.

Conflict of interest statement

Laurence Albiges disclosed: consulting or advisory role to Pfizer, Novartis, Sanofi, Amgen; Research funding: Pfizer, Novartis. André P. Fay: No disclosures. Wanling Xie: No disclosures. Katherine Krajewski: No disclosures. David F. McDermott: Consulting or advisory role to Genentech, Merck, BMS, Pfizer; research funding: Prometheus Labs. Daniel Y.C. Heng disclosed consultancies with Bayer Novartis and Pfizer. Charles Dariane: No disclosures. Guillermo DeVelasco has served on advisory boards for Pierre Fabre. Renee Lester: No disclosures. Bernard Escudier disclosed: consulting or advisory role to Bayer, Pfizer, Novartis, Honoraria: Bayer AG, Roche, Pfizer, Genentech, Novartis, AVEO, Pharmaceuticals, GlaxoSmithKline. Toni K. Choueiri disclosed: consulting or advisory role to Pfizer, GSK, Novartis, Merck and Bayer; Research funding: Pfizer, GSK, Novartis, BMS, Merck, Exelixis, Roche, Astra Zeneca, Tracon.

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