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Original Research

Second-line targeted therapies after nivolumab-ipilimumab failure in metastatic renal cell carcinoma

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Abstract ***Background:*** Nivolumab-ipilimumab demonstrated a survival benefit over sunitinib in first-line setting for metastatic renal cell carcinomas (mRCCs) and is becoming a new standard of care for naïve patients with intermediate or poor risk prognosis (International mRCC Database Consortium). The efficacy of subsequent vascular endothelial growth factor

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receptor tyrosine kinase inhibitors (TKIs) after nivolumab-ipilimumab failure remains unclear.

Methods: Medical records of mRCC patients treated with nivolumab-ipilimumab, who received subsequent TKI, as part of Checkmate 214 study were reviewed in 13 institutions. Baseline characteristics, outcome data including progression-free survival (PFS), response, overall survival (OS) and toxicities were retrospectively collected.

Results: Overall 33 patients received subsequent TKI after nivolumab-ipilimumab failure. Median follow-up from start of subsequent TKI is 22 months (19–NR). Best response was assessed in 30 patients: 12 partial responses (36%), 13 stable diseases (39%) and five progressive diseases (15%). Median PFS from start of TKI was 8 months [5–13]. Median PFS with first-generation (sunitinib/pazopanib) and second-generation TKI (axitinib/cabozantinib) was 8 months [5–16] and 7 months (5–NA), respectively. PFS in second line was significantly longer in patients with a long first-line duration of response to the double immune checkpoint blockade ($\geq$6 months) with 8 versus 5 months for short responder (<6 months) ($p = 0.03$). OS rate was 54% at 12 months. Toxicity was as expected: 42% developed at least one toxicity grade $\geq$3.

Conclusion: This is the first report of outcomes with TKI, after first-line nivolumab-ipilimumab failure. Median PFS suggests a sustained benefit of TKI and supports trials investigating the optimal sequence.

1. Introduction

After more than 10 years of supremacy in first-line setting for metastatic renal cell carcinomas (mRCC), vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs), such as sunitinib or pazopanib [1,2], are challenged by the results of the Checkmate 214 study [3], demonstrating an overall survival (OS) benefit of the combination of nivolumab plus ipilimumab over sunitinib in patients with intermediate or poor prognosis by International Metastatic renal cell carcinomas Database Consortium (IMDC) risk criteria [4,5].

Currently, VEGFR TKIs remain the first-line treatment for mRCC recognised by the principal expert committees in Europe and in the United States, although recent approval of nivolumab with ipilimumab combination are likely to change rapidly the landscape [6–8].

RCC have been traditionally known as immunogenic tumours [9], so old-fashioned immunotherapy as interleukin-2 or bevacizumab-interferon alpha were used in the cytokine area with a clinical benefit in a subgroup of patients [10–13]. Because immunotherapy re-appears as a promising alternative, better outcomes were observed underlying a second turn in treatment and care of mRCC: new generation of immuno-targeted therapies such as a programmed death 1 (PD-1) and anti-cytotoxic T lymphocyte-associated antigen 4 antibodies offer a new field of possibilities for our patients. Nivolumab has shown to increase the OS of mRCC patients in second line after VEGFR TKIs failure. The combination of these two checkpoint inhibitors is now a standard of care in metastatic melanoma [14] and was also developed in mRCC in early trial with encouraging results in treatment naïve or previously treated patients. The Checkmate 016 trial [15] reported an objective response rate of 40.4%, a 2-year OS ranging from 67.3% to 69.6%, according to different doses of treatment with the combination. The Checkmate 214 study comparing nivolumab plus ipilimumab over sunitinib as first line in mRCC demonstrated OS benefit in patients with intermediate and poor risk prognosis (IMDC) (OS was not reached with nivolumab plus ipilimumab versus 26.0 months with sunitinib, hazard ratio: 0.63; $p < 0.001$). This combination has now been approved by US Food and Drug Administration (FDA) in first line and is likely to integrate all recommendations [16].

Nevertheless, the efficacy and tolerability of subsequent targeted therapies that should be offered after this combination of immunotherapy failure is still unclear. This retrospective study aimed to report the outcomes in terms of survival, responses and toxicities of second-line VEGFR TKI after double checkpoint blockade with nivolumab-ipilimumab combination.

2. Material and methods

2.1. Study design and participants

This retrospective study collected medical records of mRCC patients treated with nivolumab-ipilimumab as part of Checkmate 214 study and who received any subsequent treatment with VEGFR TKIs. Baseline clinical characteristics at the time of subsequent therapy were reviewed at 12 institutions in Europe (France,

United Kingdom, Spain and Finland). Data collected included patient characteristics at VEGFR TKI start, treatment duration in first line with doublet immunotherapy, response to subsequent therapy including progression-free survival (PFS), response, OS and toxicities. All participating sites had received local ethics approval for data collections.

2.2. Outcomes

Outcome data including PFS, OS, investigator-assessed best response (overall response rate [ORR], according RECIST 1.1) and adverse events (AEs) were retrospectively collected.

2.3. Statistical analyses

The primary objective of this study was to characterise clinical outcomes (PFS and OS) of mRCC patients treated with VEGFR TKIs after nivolumab-ipilimumab failure as part of Checkmate 214 study. Median (interquartile-range) values and proportions (percentage) were provided for the description of continuous and categorical variables, respectively. OS was defined as time between VEGFR TKI start and death from any cause. PFS was defined by drug cessation due to death, disease progression or censored at last follow-up. OS and PFS were estimated using Kaplan–Meier method and described using median or rate at specific time points with their 95% confidence intervals (95% CI). The analyses were stratified by IMDC risk group (good, intermediate or poor), type of VEGFR TKI (first generation was defined as sunitinib and pazopanib and second generation was defined as cabozantinib and axitinib) and duration of first line.

Follow-up was calculated using a reverse Kaplan–Meier estimation. The optimal cut-point for studying the association of PFS and survival end-points under VEGFR TKI was based on the log rank maximisation method described by Hothorn [17].

3. Results

3.1. Patients characteristics

From February 2015 to January 2018, 33 mRCC patients received subsequent TKI after nivolumab-ipilimumab failure and were included in this analysis. Median age was 61 years (range 40–77), with a sex ratio: 3/1 (Table 1). Prior nephrectomy had been performed in 76% (n = 25). At the time of TKI start, Most of patients were intermediate risk (64%, n = 21), while 21% patients (n = 7) were at poor risk and 15% (n = 5) patients were at good risk according to IMDC prognostic group assessment. Prior treatment duration with doublet immunotherapy was less than 6 months in 17 patients (51%) and over 6 months in 16 patients (49%). Seventy-six percent of patients (n = 25) discontinued immunotherapy because of disease progression and 24% (n = 8) patients were compelled to give up treatment because of toxicity. As second line, most of the patients received sunitinib (51%, n = 17), then other VEGFR TKIs were distributed as follows: axitinib for eight patients (24%), pazopanib for six patients (18%) and cabozantinib for two patients (6%, Table 1).

Table 1
Patients characteristics.

Patient and tumour characteristics	N	%
Median age at diagnosis (median - range)	57	40–77
Median age at 2nd line treatment (median - range)	61	40–77
Gender		
F	10	30.3
M	23	69.7
Nephrectomy		
Yes	25	75.8
No	3	9.1
Unknown	5	15.1
Cause of nivolumab-ipilimumab discontinuation		
Progression	25	75.8
Toxicity	8	24.2
Unknown	0	0
Prognosis Group at first-line treatment (IMDC)		
Favourable	4	12.1
Intermediate	23	69.7
Unfavourable	6	18.2
Nivolumab-ipilimumab best response		
CR	0	0
PR	13	39.4
SD	13	39.4
PD	7	21.2
Prognosis Group at second line treatment (IMDC)		
Favourable	5	15.1
Intermediate	21	63.7
Unfavourable	7	21.2
Type of TKI at 2nd line (n = 33)		
Sunitinib	17	51.5
Axitinib	8	24.2
Pazopanib	6	18.2
Cabozantinib	2	6.1
Cause of TKI discontinuation at 2nd line (n = 22)		
Progression	18	54.6
Toxicity	3	9.1
Unknown	1	3

TKI, tyrosine kinase inhibitor; IMDC, International Metastatic renal cell carcinomas Database Consortium; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease.

3.2. Survival end-points

Median follow-up from start of VEGFR TKI was 22 months (95% CI, 19–NR). At time of analysis, 48% patients (n = 16) had died from disease. Median and average time between the end of immunotherapy and start of VEGRF TKI were 36 days (0–805 days) and 93 days, respectively. Most of the patients with a long interval between the two lines discontinued nivolumab-ipilimumab because of toxicity and developed disease progression subsequently. Disease progression was the cause of discontinuation in 55% of patients (n = 18), 9%

discontinued after untolerable AEs and 33% (n = 11) are still ongoing.

Median PFS from start of second line was 8 months (95% CI: 5–13) in overall population (Fig. 1a). According to IMDC prognostic groups, median PFS was 11 months (95% CI, 5-NR), 8 months (95% CI, 7-NR) and 5 months (95% CI, 2-NR), respectively, in good, intermediate and poor IMDC prognostic groups (p = 0.05) (Fig. 1b). Depending on the type of VEGFR TKIs, median PFS was 8 months (95% CI, 3-NR), 7 months (95% CI, 5-NR) and 5 months (95% CI, 1-NR) according to sunitinib, axitinib or other, respectively (p = 0.35) (*Suppl. data*, Fig. A). Median PFS according to first generation TKI (sunitinib/pazopanib) versus second generation (axitinib/cabozantinib) was 8 months (95% CI, 5–16) and 7 months, respectively (95% CI, 5-NA) (p = 0.66) (*Suppl. data*, Fig. B).

Survival rate was 54% at 12 months and 37% at 24 months (Fig. 2a). According to IMDC prognostic groups, median OS was not reached (95% CI, 11-NR), 11 months (95% CI, 11-NR) and 5 months (95% CI, 3-NR), respectively, in good, intermediate and poor IMDC prognostic groups (p = 0.0006) (Fig. 2b). Depending on the type of TKIs, median OS was 11 months (95% CI 5-NR), not reached (95% CI, 11-NR) and 13 months (95% CI, 6-NR) according to sunitinib, axitinib or other, respectively (p = 0.043) (*Suppl. Data*, Fig. C). Median OS according to first-generation TKI (sunitinib/pazopanib) versus second-generation TKI (axitinib/cabozantinib) was 11 months (95% CI, 6-NR) and not reached (95% CI, 11-NR), respectively (p = 0.11) (*Suppl. Data*, Fig. D).

Interestingly, PFS from second line was significantly longer when duration with double immune checkpoint blockade was superior or equal to 6 months with 8 months (95% CI, 8-NR) versus inferior to 6 months with 5 months (95% CI, 3–8) (p = 0.03). There was also a trend favouring the first group of patients in OS with 21 months (95% CI, 8-NR) versus 11 months (95% CI, 5-NR), but significance was not reached (p = 0.74) (Fig. 3). Median PFS from second line depending on the reason of ipilimumab-nivolumab discontinuation was 7.5 months (95% CI, 5-NR) and 8 months (95% CI, 5–13), whether the patient interrupted because of toxicity or progression (p = 0.54). Median OS from second line depending on the reason of ipilimumab-nivolumab discontinuation was not reached (95% CI, NR–NR) and 8 months (95% CI, 6-NR), whether the patient interrupted because of toxicity or progression (p = 0.54).

Nivolumab-ipilimumab is now FDA approved for intermediate- and poor-risk patients. Our analyses initially included all risk group as enrolled in pivotal trial. However, to match the approved population, we also performed our analysis focusing on patients with an intermediate or poor prognosis at first line (n = 28 patients): from start of subsequent VEGFR TKI, we observed similar median PFS (8 months, 95% CI [5–13] versus 8 months 95% CI [5–16] for the overall population) and similar median OS (11 months, 95% CI [8-NR] versus 13 months, 95% CI [8-NR] in overall population).

Noteworthy, 14 patients out of the 33 subsequently received another TKI as third line, and eight patients received up to four lines. Median PFS was 1.5 months (1-NR) for the second subsequent targeted agent.

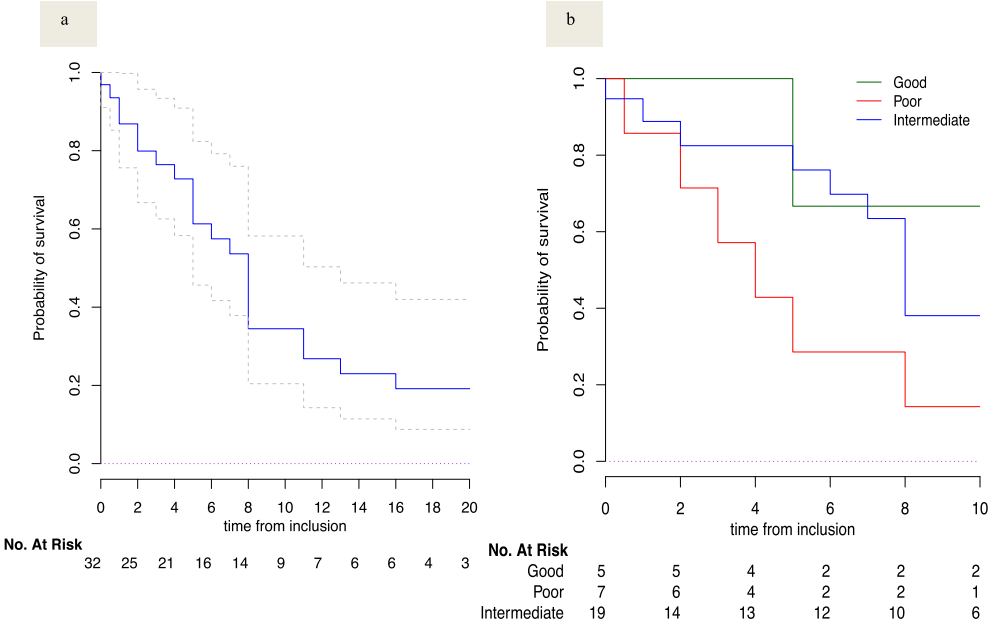

Fig. 1. Progression-free survival on first subsequent targeted therapy after double immune checkpoint blockade for all population (a) and according to IMDC prognostic groups at VEGFR TKI start (b). VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; IMDC, International Metastatic renal cell carcinomas Database Consortium.

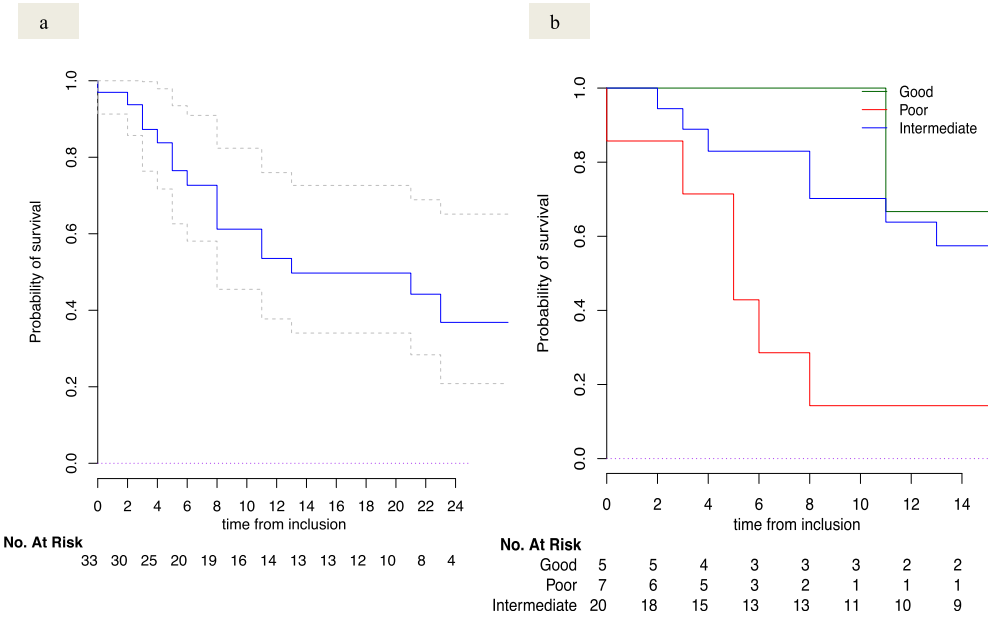

Fig. 2. Overall survival on first subsequent targeted therapy after double immune checkpoint blockade for all population (a) and according to IMDC prognostic groups at VEGFR TKI start (b). VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; IMDC, International Metastatic renal cell carcinomas Database Consortium.

3.3. Response

Response assessment was available for 30 of 33 patients. Objective response rate was 36% with 12 partial response (36%), 13 stable disease (39%) and five progressive disease (15%). Overall disease control rate was 76% (Table 2).

3.4. Toxicity

Adverse events of grade 3 and 4 regardless of causality were recorded for all patients. Fourteen patients developed at least one toxicity superior or equal to grade 3 (42%) as follows: cutaneous AEs represented 12% of AEs with hand foot syndrome for three patients (9%) and one rash, cardiovascular AEs were represented by high blood pressure for two patients (6%), pulmonary embolism for two patients (6%) and one cataclysmal haemorrhage, gastrointestinal AEs were essentially diarrhoea for two patients (6%) patients and hepatitis for one patient. Others grade 3 or 4 AEs counted infections (2 patients), renal failure with interstitial nephritis, thrombocytopoenia and fatigue, respectively, one patient each (Table 3). Overall, safety of TKIs appears to be as expected.

4. Discussion

This study represents the first specific report of outcomes with VEGFR TKI after first-line nivolumab plus ipilimumab failure for mRCC patients. Owing to the changing paradigm in first line for intermediate and poor risk patients, all the subsequent treatment algorithm needs to be redefined.

Response rates, PFS, and survival rates suggest a sustained benefit of VEGFR TKIs after immune checkpoint doublet. Indeed, 36% of patients achieved an objective response, and 80% of our patients derived a clinical benefit. Response rate and clinical benefit are aligned with first line VEGFR TKIs historical registration trials [1,2,18]. Moreover, two previous retrospective studies explored the activity of VEGFR TKIs or mammalian target of rapamycin inhibitors after checkpoints inhibitors [19,20]. These two cohorts included renal clear cell carcinoma patient (and fewer patients with other histology) who received different immune checkpoints blockers, mostly as part of clinical trial as first, second or further lines. Over 44 and 47 patients, ORR to VEGFR TKI after immune checkpoints blockers were 16% and 36%, respectively. Median time to treatment failure on subsequent therapies were respectively 6.6 and 8.4 months, and consistent OS results with median OS after the initiation of subsequent therapy was 17.5 and 16.9 months, respectively. These two cohorts suggested sustained activity of targeted therapy after immunotherapy use in more advanced stages of the disease and are consistent with our findings.

Metastatic RCC remains a VEGF driven disease as highlighted not only in the favourable prognosis group with longer PFS and higher ORR with sunitinib in the pivotal checkmate 214 study [3] but also given the underlying biology of clear cell RCC as well as the identification of angiogenesis driven signature in different

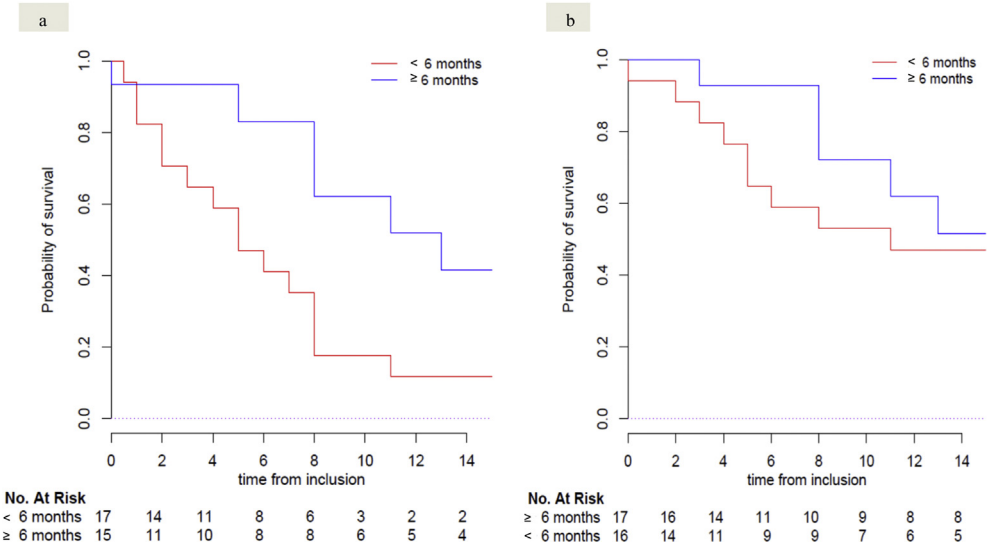

Fig. 3. Progression-free survival (a) and overall survival (b) on first subsequent targeted therapy according to duration with double immune checkpoint blockade.

molecular study [21,22]. Recent reports have further enhanced our understanding of evolutionary patterns to metastatic disease [23]. Furthermore, it is anticipated that the choice of first line may impact on the tumour evolution and therefore could play a role on subsequent treatment activity. A recent report from Pal *et al.* focusing on circulating tumour DNA reported on the growing number of mutations in ctDNA throughout advanced disease progression: among 220 ctDNA collected before and after first line, an increase in genomic alterations frequencies such as TP53, VHL, NF1, EGFR or PIK3CA highlights the therapeutic pressure with vascular endothelial growth factor (VEGF) inhibitor and impact on mutations and genetic variations [24]. Such an analysis would be of interest in patients treated with doublet immunotherapy in first line.

The question of the optimal sequence is yet to be defined. The randomised phase II SUAVE trial (NCT03035630) comparing avelumab (PD-L1 inhibitor) followed by sunitinib on PD versus sunitinib followed by avelumab on PD is an example of trial exploring the question of sequence, with a special interest for biomarkers to guide future development.

The sequence approach raises the question of the wash-out period after immune agent before TKI use. Indeed, plasma half-lives of ipilimumab and nivolumab are 15.4 and 25.0 days, respectively, and patients receiving oral tyrosine kinase inhibitors should be considered receiving, at least for a while, a combination of TKIs and immunotherapy. A strong rational for associating immunotherapy and VEGF-targeted therapies has previously been demonstrated [25], the latter potentiating the first by modifying the tumour environment into an immune favourable landscape [26]. Promising results had emerged from early trials [27] and ongoing phase 3 trials evaluating different combinations over sunitinib: axitinib plus pembrolizumab, axitinib plus avelumab [28,29], lenvatinib plus pembrolizumab (NCT02811861) or cabozantinib plus nivolumab (NCT02496208) will raise the issue of optimal later lines. For now, no definitive results are published, and these combinations are not yet validated. An alternative combination of atezolizumab (PD-L1 inhibitor) and bevacizumab was also explored [30]. In correlative work from this study, intratumoural CD8+ T cells were found to increase following combination treatment, confirming that the anti-VEGF and anti-PD-L1 combination improves antigen-specific T-cell migration.

Our study is not without limitations; these include a small number of patients retrospectively analysed and a relatively short follow-up. To limit this risk and to prevent selection biases, we collected the subsequent therapy data of all patients included in the randomised phase III across all French institution as well as in four centres in United Kingdom, Spain and Finland.

Table 2
Treatment outcomes of the first subsequent therapy after double immune-checkpoint blockade.

Patients	Total	Best investigator assessment			
		N° of assessment	Partial response (%)	Stable disease (%)	Progressive disease (%)
All	33	30	12 (36)	13 (39)	5 (15)

Table 3
Adverse events of the first subsequent therapy after double immune-checkpoint blockade.

Type of adverse event	Grade 3 and 4	
	N	%
All	14	42.4
Cardio-vascular	5	15.1
High-blood-pressure	2	6.1
Pulmonary embolism	2	6.1
Haemorrhage	1	3
Cutaneous	4	12.1
Hand-foot syndrome	3	9.1
Rash	1	3
Gastro-intestinal	3	9.1
Diarrhoea	2	6.1
Hepatitis	1	3
Others	5	15.1
Infections	2	6.1
Renal (interstitial nephritis)	1	3
Haematological (thrombocytopoenia)	1	3
General (fatigue)	1	3

Additionally, we decided to focus on the ipilimumab and nivolumab combination to provide a homogenous cohort without immunotherapy, VEGFR TKI doublet.

Two other cohorts studied efficacy of VEGFR TKIs after immunotherapy combination in the United States. The first, recently published, mixed patients who had previously received atezolizumab/bevacizumab (64%), ipilimumab/nivolumab (33%) and axitinib/avelumab (3%). With a shorter follow-up of 13 months, the median PFS for first subsequent therapy was 6.4 months (95% CI, 4.4–8.4), and no estimation of OS was provided. Rate of responses were comparable with 29% of partial response, 54% of stable disease and 18% progressive disease [31]. The second cohort was presented in poster session at ESMO 2017 and updated at the ASCO 2018 meeting [32]. The authors reported results for 43 patients in which 20 patients received nivolumab with ipilimumab, 14 received nivolumab with bevacizumab, and nine received nivolumab alone, and it is to note that none of the patient received sunitinib as first-line VEGFR TKI. Median PFS was 10.0 months (95% CI: 7.4, NA); and estimated 1-year OS was 87.5% (95% CI: 74.6–100) without specifying if it was from first or second line. To conclude, these two studies are concordant with our findings and highlight same conclusions about survival and response outcomes, but the main advantage of our cohort is the homogeneity of our population with only ipilimumab/nivolumab doublet as first line.

5. Conclusion

In selected patients, our cohort suggests a sustained benefit of VEGFR TKIs after nivolumab plus ipilimumab failure and supports trials investigating the optimal sequence. The multiplicity of the combinations trials undertaken in first line arises the challenge of testing and confronting all possibilities, enhancing the need of biomarkers to define the best tolerable sequence for each patient. In this context, results from the ongoing French BIONIKK phase II trial (NCT02960906), where first line treatment (nivolumab alone or plus ipilimumab versus TKI) is assigned according to tumour molecular group, will provide crucial insights on the better predictors of single agent nivolumab or double IO combination efficacy.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.11.031.

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