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Avelumab Plus Intermittent Axitinib in Previously Untreated Patients with Metastatic Renal Cell Carcinoma. The Tide-A Phase 2 Study

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Abstract

Background: Combinations of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) plus immune checkpoint inhibitor (ICI) against PD1/PD-L1 are the standard first-line therapy for patients with metastatic renal cell carcinoma (mRCC), irrespective of the prognostic class.
Objective: To investigate the feasibility and safety of withdrawing VEGFR-TKI but continuing anti-PD1/PD-L1 in patients who achieve a response to their combination.
Design, setting, and participants: This was a single-arm phase 2 trial in patients with treatment-naïve mRCC with prior nephrectomy, without symptomatic/bulky disease and no liver metastases.

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Immunotherapy
Renal cell carcinoma
Vascular endothelial growth factor receptor tyrosine kinase inhibitor

Intervention: Enrolled patients received axitinib + avelumab; after 36 wk of therapy those who achieved a tumour response interrupted axitinib and continued avelumab maintenance until disease progression.

Outcome measurements and statistical analysis: The primary endpoint was the rate of patients without progression 8 wk after the axitinib interruption. The secondary endpoints were the median value for progression-free (mPFS) and overall (mOS) survival and the safety in the overall population.

Results and limitations: Seventy-nine patients were enrolled and 75 were evaluated for efficacy. A total of 29 (38%) patients had axitinib withdrawn, as per the study design, with 72% of them having no progression after 8 wk and thus achieving the primary endpoint. The mPFS of the overall population was 24 mo, while the mOS was not reached. The objective response rate was 76% (12% complete response and 64% partial response), with 19% of patients having stable disease. In the patients who discontinued axitinib, the incidence of adverse events of any grade was 59% for grade 3 and 3% for grade 4. This study was limited by the lack of a comparative arm.

Conclusions: The TIDE-A study demonstrates that the withdrawal of VEGFR-TKI with ICI maintenance is feasible for selected mRCC patients with evidence of a response to the VEGFR-TKI + ICI combination employed in first-line therapy. Axitinib interruption with avelumab maintenance leads to decreased side effects and should be investigated further as a new strategy to delay tumour progression.

Patient summary: We evaluated whether certain patients with advanced kidney cancer treated with the fist-line combination of axitinib plus avelumab can interrupt the axitinib in case of a tumour response after 36 wk of therapy. We found that axitinib interruption improved the safety of the combination, while the maintenance with avelumab might delay tumour progression.

1. Introduction

Renal cell carcinoma (RCC) is the most common kidney cancer, constituting about 5% and 3% of all malignant tumours in male and female adults, respectively [1]. Systemic therapy is given to those patients with advanced disease that is not amenable to complete resection or who have a high risk of relapse after surgery. First-line treatment for patients with metastatic RCC (mRCC) has evolved significantly over the past two decades, and current guidelines suggest the use of available immune checkpoint inhibitor (ICI)-based combinations as the first-line option for any patient eligible for immunotherapy. Specifically, all those with intermediate or poor International mRCC Database Consortium prognosis should receive either a combination of a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) + an ICI or a combination of ipilimumab + nivolumab. Otherwise, patients with favourable prognosis should be treated only with a combination of immunotherapy + a VEGFR-TKI [2–4]. Nonetheless, despite the clear improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR), all the ICI-based combinations, especially the VEGFR-TKI + ICI combinations, are also characterised by increased toxicity compared with VEGFR-TKI monotherapy, leading to the interruption or discontinuation of treatment in a noteworthy group of patients. The JAVELIN Renal 101 phase 3 trial reported that of the 442 patients who received axitinib + avelumab in the experimental arm, 42.2% underwent at least one dose reduction and 7.6% a VEGFR-TKI interruption [5]. Similar results have been reported by the combination of lenvatinib and pembrolizumab in the CLEAR study, suggesting class-specific toxicity [6]. The current research thus sought to evaluate whether the interruption of axitinib while maintaining avelumab could lower VEGFR-TKI–related toxicity and delay tumour resistance in mRCC patients who had achieved a tumour response with the combination axitinib + avelumab.

2. Patients and methods

2.1. Study design

The TIDE-A study was a multicentre, single-arm, phase 2 trial conducted to evaluate the feasibility and safety of withdrawing axitinib while continuing avelumab in mRCC patients who had achieved a complete or partial tumour response after 36 wk of combination therapy with axitinib + avelumab. Participants received axitinib 5 mg BID continuously and avelumab 800 mg IV flat dose Q2W until disease progression. In cases where there was a partial/complete response (evaluated using RECIST version 1.1) at week 36 (±2), treatment with axitinib was withdrawn while avelumab was maintained until disease progression. If there was disease progression during avelumab maintenance, treatment with axitinib was resumed for 24 wk at the final dose administered before its initial withdrawal, and was then withdrawn again if there was a new complete or partial tumour response. Patients without a response at week 36 or after the reintroduction of axitinib continued the axitinib + avelumab combination until progression of the disease. Both axitinib and avelumab treatments could be

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discontinued at any time for other reasons, including intolerable toxicity or a decision to bring treatment to an end by the clinician/patient.

2.2. Patients and assessments

Patients aged 18 yr or older were eligible for enrolment in the study if they had histologically confirmed RCC with a predominantly clear-cell histology, locally advanced/unresectable or metastatic disease, Eastern Cooperative Oncology Group performance status of 0–1, not received prior systemic therapy for renal cancer, measurable disease as per RECIST version 1.1 [7], undergone surgery for their primary tumour, and no evidence of hepatic metastases and/or bulky/symptomatic disease. Tumour tissue available for a PD-L1 analysis was required.

Disease extension was assessed using computed tomography or magnetic resonance imaging scanning. Throughout the study, patients underwent the same imaging procedure as employed at baseline (ie, within 28 d prior to the first dose of the trial treatment) and then every 12 wk (±7 d) until disease progression, start of a new anticancer treatment, withdrawal of consent, or death. The patients whose axitinib was withdrawn at week 36 while maintaining avelumab had their first radiological evaluation 8 wk later and every 12 wk thereafter. Imaging was analysed locally using the RECIST version 1.1 criteria [7]. Safety was assessed with version 5.0 of the Common Terminology Criteria for Adverse Events [8] for 30 d after the last dose of avelumab and for 90 d in cases of serious adverse events (AEs).

2.3. Outcome measures

The primary endpoint was to evaluate the rate of patients free of progression 8 wk after the withdrawal of axitinib from the combination with avelumab in the cohort of patients who had achieved a complete/partial response 36 wk after the start of avelumab + axitinib combination treatment. The secondary efficacy endpoints were PFS, OS, overall response rate (ORR), and disease control rate (DCR) in the overall population. Safety was evaluated in both the overall population and those patients whose axitinib was withdrawn, as per protocol. PFS and ORR were determined using RECIST version 1.1, as assessed by local investigators. PFS was evaluated from the date of enrolment in the study until disease progression to the axitinib + avelumab combination or death, whichever occurred first. OS was evaluated from the date of enrolment to death or the last contact. Post hoc analyses were performed based on the PD-L1 expression (described in the Supplementary material) to determine the effect on PFS and OS.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on the Harmonization of Good Clinical Practice guidelines, as well as in compliance with local and institutional regulations. The approval of the ethics committee was obtained for each centre involved in the trial, and all the patients provided their written informed consent. The trial was registered in the EudraCT database (2019-004098-23) and in the ClinicalTrials.gov register (NCT04698213).

2.4. Statistical analysis

The trial aimed to determine whether maintenance with avelumab was able to achieve a 28% absolute improvement (ie, from 20% to 48%) in the rate of patients whose disease had not progressed 8 wk after the withdrawal of axitinib. The power was set at 80% and the two-sided type I error at 0.05. The sample size was calculated using a one-arm binomial study design. A total of 22 patients were required to demonstrate this benefit, with the study regarded as successful if at least nine patients had experienced no progression after 8 wk of avelumab maintenance. Assuming a dropout rate of 10%, the final estimated number of patients required for the study was 25. As the JAVELIN Renal 101 trial reported that around 40% of its participants who had started first-line therapy had experienced tumour progression before week 36, the rate of patients with a response to tumour treatment was expected to be 55% [5]; the total number of patients required for our trial was 75.

All the survivals were estimated with the Kaplan-Meier product-limit methodology. All analyses were exploratory and not adjusted for multiple testing. Significance was set at $p < 0.05$.

SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) and R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) were used for all the statistical evaluations.

3. Results

3.1. Patients

A total of 79 patients from 15 sites across Italy were enrolled in the study from October 2020 to November 2022. Four of them were withdrawn from the analysis, leaving 75 who were ultimately assessed (Fig. 1).

The patients' baseline demographic and disease characteristics are reported in Table 1.

3.2. Efficacy

At the time of the data cut-off point (April 14, 2023), 29 (38%) patients had experienced an interruption in the administration of axitinib at week 36, as per the protocol, and were therefore assessed in relation to the study's primary endpoint. Of the first 22 patients who discontinued axitinib, as per the statistical plan, 14 were free of progression at week 8, thus achieving the primary endpoint of the study. In the overall cohort of those who had axitinib withdrawn, 72% were free of progression at week 8. Additionally, 13 patients interrupted axitinib after a tumour response outside the cut-off point of 36 ± 2 wk (median induction-treatment duration of 40 wk: minimum 28; maximum 60) and were therefore not included in the analysis concerning the primary endpoint due to this protocol deviation.

In the overall population, the median follow-up time was 19 mo. At the time of the analysis, 27 patients had progressed to the combination of axitinib + avelumab (irrespective of axitinib interruption) and the median PFS was 23.8 mo (95% confidence interval [CI], 20.0–not reached; Fig. 2A). At the same time point, the median OS was not

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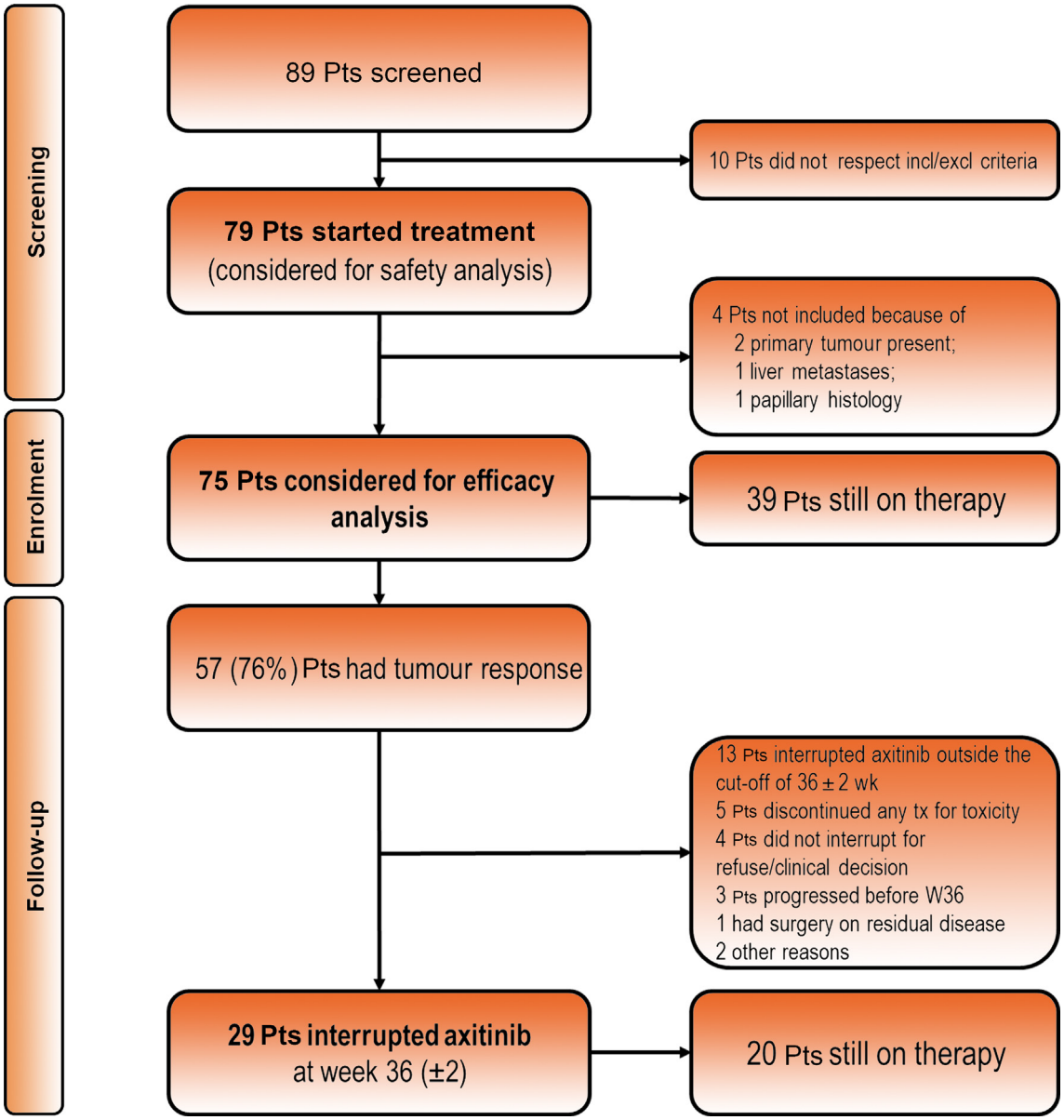

Fig. 1 – Consort diagram of patients' disposition, showing the total population enrolled in the TIDE-A study and those who withdrew axitinib at week 36. incl/excl = inclusion/exclusion; Pts = patients; tx = treatment; W36 = week 36.

reached (only seven deaths occurred) and the 18-mo OS rate was 94% (Fig. 2B). The ORR in the overall population was 76%. Nine patients (12%) had a confirmed complete response, 48 (64%) a partial response, 14 (19%) stable disease, and three (4%) progressive disease, and one (1%) was not evaluable. The DCR was 95% (Supplementary Fig. 1).

At a median follow-up of 19 mo, nine of the 29 patients whose axitinib was withdrawn at week 36 were continuing with avelumab after the first axitinib interruption, 18 progressed during the first avelumab maintenance period, and two had withdrawn from the study's treatment without evidence of progressive disease. The median PFS of the maintenance therapy with avelumab was 16 wk (95% CI, 11–21), with 36% of patients still under avelumab maintenance after 6 mo from axitinib interruption (Fig. 3). Among the 18 patients who experienced disease progression, 17 restarted axitinib. Thereafter, six had definitive disease progression during the combination therapy, three interrupted axitinib again after 24 wk of reintensification, and the remaining eight were still undergoing the reintensification treatment at the data-analysis cut-off point. One patient refused to restart axitinib (Supplementary Fig. 2). The median overall PFS from the start of axitinib + avelumab until disease progression in the cohort of patients who interrupted axitinib while continuing avelumab maintenance was 23.8 mo, and the 18-mo OS rate was 100%.

3.3. *Outcome by PD-L1 expression*

The analysis of the PD-L1 expression was performed in only 72 of the 75 cases, as three tumour samples were unsuitable. A total of 64 (89%) patients had a combined positive

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Table 1 – Baseline characteristics of the patients

Baseline characteristics	Patients (*N* = 75)
Median age (IQR)	64 (58–70)
Male sex, *n* (%)	49 (65)
Nephrectomy, *n* (%)	75 (100)
Interval from Nx to Tx <1 yr, *n* (%)	31 (41)
Sites of metastases, *n* (%)	
Lung	43 (57)
Lymph nodes	31 (41)
Pancreas	16 (21)
Bone	11 (15)
Kidney area	11 (15)
Soft tissue	11 (15)
Kidney	10 (13)
Adrenal gland	10 (13)
Peritoneum	9 (12)
Other	4 (5)
IMDC prognostic class, *n* (%)	
Favourable	30 (40)
Intermediate	43 (57)
Poor	2 (3)
ECOG performance status, *n* (%)	
0	60 (80)
1	15 (20)

ECOG = Eastern Cooperative Oncology Group; IMDC = International mRCC Database Consortium; IQR = interquartile range; mRCC = metastatic renal cell carcinoma.

score of ≥1, and the median PFS in this group was 23.8 mo (95% CI, 18.5–29.1). The median PFS was not achieved in the subgroup of PD-L1–negative tumours. In the cohort of patients who discontinued axitinib, the durations of avelumab maintenance were 16 wk in both groups based on the PD-L1–positive and PD-L1–negative expression.

3.4. *Safety*

Safety was evaluated in the overall study population of 79 patients who started the combination of axitinib + avelumab. AEs of any grade occurred in 76 of them (96%), with grade 3 or 4 AEs occurring in 32 (41%; Table 2). In 29 patients who discontinued axitinib, the incidence of any-grade AEs was 59%, with only one patient experiencing grade 3 toxicity. No treatment-related deaths have been reported.

When only the axitinib-related AEs were considered, the incidences of all- and high-grade AEs in the overall population were 34% and 11%, respectively. In the cohort of patients who discontinued axitinib at week 36, the incidences of all- and high-grade axitinib-related AEs during avelumab maintenance were 3.4% and 0%, respectively. The only patient with axitinib-related toxicity after the treatment interruption had grade 1 hand-foot syndrome, but recovered subsequently. In terms of the AEs related to avelumab, the incidences of all- and high-grade toxicity in the overall population were 32% and 11%, respectively. In the cohort of patients who discontinued axitinib at week 36, the incidences of all- and high-grade axitinib-related AEs during avelumab maintenance were 28% and 0%, respectively (Supplementary Fig. 2).

4. Discussion

To the best of our knowledge, the TIDE-A phase 2 trial is the first to evaluate the feasibility of a first-line treatment based on a strategy of withdrawing the VEGFR-TKI while continuing the ICI. The study achieved its primary endpoint (72.4% of patients free of progression at 8 wk after axitinib withdrawal), thus demonstrating that intermittent axitinib with avelumab maintenance is both feasible and associated with a remarkable reduction in treatment-related side effects. Prior to the use of immunotherapy to treat mRCC, VEGFR-TKI interruption had already been investigated in groups of patients similar to those involved in the current trial, with the goals to reduce toxicity, improve quality of life, and delay tumour resistance. In particular, one phase 2 study reported that interrupting sunitinib in cases of tumour reduction ≥10% and reintroducing it in case of disease progression led to median PFS of 22.4 mo and median OS of 34.8 mo, even though the disease of the majority had progressed 2 mo after the sunitinib interruption [9]. Another phase 2/3 trial randomly assigned (1:1) 920 mRCC patients to either a conventional continuation strategy or one with a VEGFR-TKI–free interval. Noninferiority was demonstrated in the intention-to-treat population (adjusted hazard ratio 0.97 [95% CI, 0.83–1.12]), and there were no clinically meaningful differences in life expectancy between the two strategies [10]. Similar to these previous trials, the TIDE-A study has demonstrated that axitinib interruption undeniably leads to reduced all-grade, and particularly high-grade, treatment-related toxicity. Notably, as also recently reported in a major analysis of previous studies involving mRCC, any treatment-related AEs had generally been resolved within a few days of the VEGFR-TKI interruption [11]. The TIDE-A trial reported the longest VEGFR-TKI–free period described to date, reaching 16 wk compared with 12.4 wk of the STAR trial and 8.3 wk of the study by Ornstein et al [9]. Even if direct comparison among trials is not possible, we can presume that the achievement found was more related to the continuation of avelumab maintenance rather than to any differences in the participants' baseline characteristics. Indeed, all three trials involved comparable rates of patients with intermediate or poor prognosis (TIDE-A—60%; STAR—64%; and the study by Ornstein et al [9]—67%). Similar to the Ornstein et al's [9] study, none of the patients included in our trial had the primary tumour in situ, whereas the STAR trial allowed their inclusion (ie, 25%) [10].

From a biological perspective, there are opposing theories on potential interruption of VEGFR-TKI. Specifically, this strategy may be associated with rapid tumour vascular regrowth as a rebound effect after the inhibition of the vascular endothelial growth factor (VEGF) pathway (ie, flare-up). This highlights the reversibility of the VEGFR signalling blockade after the withdrawal of angiogenesis inhibition, which arises from the plasticity of the tumour vasculature. Clinically, this translates into rapid disease growth, which is a possible, although uncommon, phenomenon that is due not to the development of VEGFR-TKI resistance, but to its interruption [12,13]. On the contrary, continuous exposure to VEGFR-TKI may lead to the selection of resistant tumour-cell clones; meanwhile, the temporary interruption of antiangiogenic therapies may be the cause of the persistence of sensitive tumour cells that depend on the VEGF signalling pathway [14,15]. The delicate interplay

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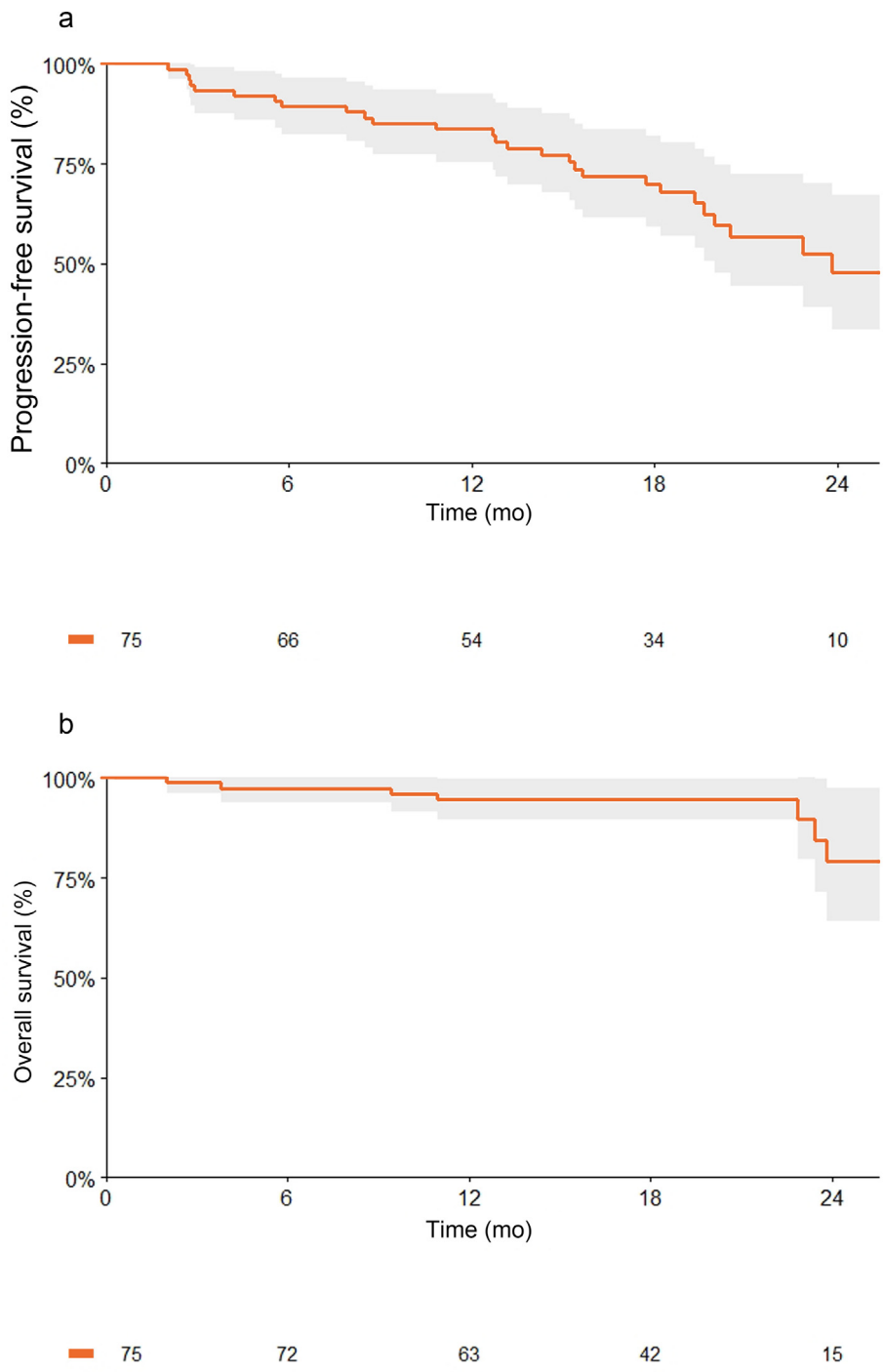

Fig. 2 – (A) Progression-free survival and (B) overall survival in the overall population with 95% CIs. CI = confidence interval.

between angiogenesis and the immune system, and the synergism between anti-PD1/PD-L1 and VEGFR-TKI that is the result, could be exploited in the induction phase by employing a combination of the two different therapies. Meanwhile, the maintenance of immunotherapy may play a role in protecting against flare-ups during VEGFR-TKI interruption, whereas its role after progression and VEGFR-TKI reintroduction has recently been questioned as the results of the CONTACT-03 study reported no benefit for continuing anti–PD-L1 inhibition after progression to anti-PD1–based combination of therapies [16].

This trial is the first to investigate the interruption of VEGFR-TKI in patients treated with a VEGFR-TKI + ICI combination. However, the study has some limitations. First, as a single-arm design, it is unable to change the current standard of care. Furthermore, PFS and OS remain the most important clinical endpoints, which cannot be replaced by the well-demonstrated toxicity benefit. Consequently, only a randomised study could validate this intermittent strategy. Moreover, such a methodology might increase our understanding of whether the longer PFS and OS outcomes achieved with the first-line combinations in the TIDE-A

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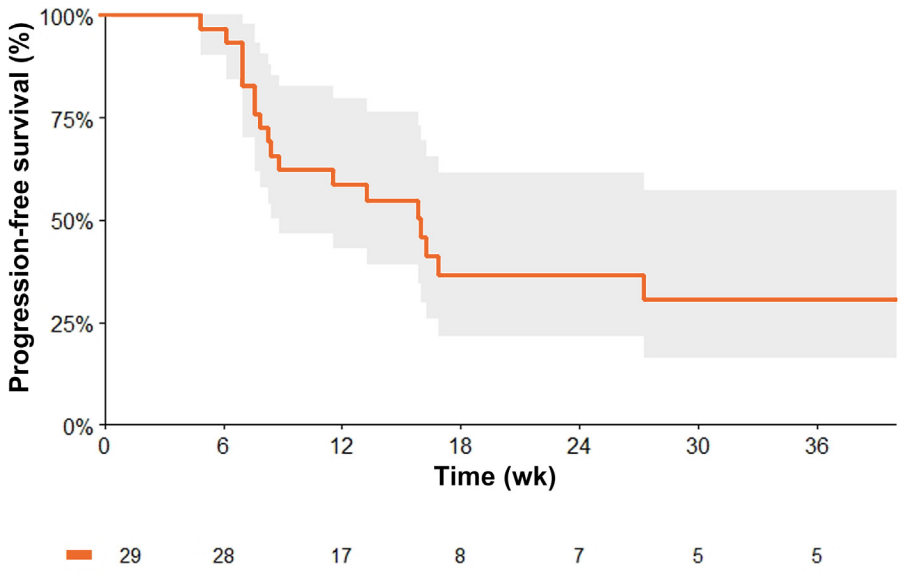

Fig. 3 – Duration of avelumab maintenance in patients who withdrew axitinib at week 36 with 95% CIs. CI = confidence interval.

Table 2 – Incidence of adverse events reported in at least 10% of patients

Toxicity	Any grade *N* = 79 (%)	Grade ≥3 *N* = 79 (%)
Any event	76 (96)	32 (41)
Diarrhoea	45 (57)	2 (2.5)
Hypertension	44 (56)	12 (15)
Fatigue	32 (41)	1 (1.3)
Hand foot syndrome	22 (28)	0
Stomatitis	22 (28)	0
Nausea	20 (25)	0
Cough	19 (24)	0
Fever	18 (22)	0
Hypothyroidism	18 (23)	0
Transaminase increase	17 (22)	6 (7.6)
Dysphonia	16 (20)	0
Anorexia	14 (18)	0
Vomiting	13(17)	1 (1.3)
Back pain	12 (15)	0
Itch	12 (15)	0
Constipation	11 (14)	0
Dyspnoea	10 (13)	0
Rash maculopapular	10 (13)	1 (1.3)
Arthralgia	9 (11)	0
Creatinine increase	9 (11)	0
Flu-like syndrome	8 (10)	0

study are mainly due to the interruption strategy or the selection of patients. This selection is well evident with the 40% of patients with favourable and few patients with poor prognosis. Additionally, this trial investigated the combination of axitinib and avelumab, which, despite the improvement in PFS and ORR reported over sunitinib, was not able to improve OS significantly in the JAVELIN Renal 101 trial [17]. Future studies should attempt to account for this by testing different, more recommended, ICI-based combinations.

5. Conclusions

The TIDE-A trial has demonstrated that the deintensification of therapy by withdrawing the VEGFR-TKI while continuing the ICI is a feasible option for patients who have achieved a disease response to the initial VEGFR-TKI + ICI combination. Consequently, it is a tailored strategy that is worthy of further investigation.

***Author contributions*:** Roberto Iacovelli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Iacovelli, Ciccarese, Giannarelli, Tortora.
Acquisition of data: All authors.
Analysis and interpretation of data: Iacovelli, Ciccarese, Giannarelli.
Drafting of the manuscript: Iacovelli, Ciccarese.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Giannarelli.
Obtaining funding: Iacovelli.
Administrative, technical, or material support: None.
Supervision: Procopio, Tortora.
Other: None.

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Supplementary data

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