THELANCET-D-24-04336R2
S0140-6736(24)01758-6
Embargo: September 13, 2024—13:00 (BST)
Doctopic: Primary Research
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Tivozanib plus nivolumab versus tivozanib monotherapy in patients with renal cell carcinoma following an immune checkpoint inhibitor: results of the phase 3 TiNivo-2 Study

Toni K Choueiri, Laurence Albiges, Philippe Barthélémy, Roberto Iacovelli, Sheik Emambux, Javier Molina-Cerrillo, Benjamin Garmezy, Pedro Barata, Arnab Basu, Maria T Bourlon, Helen Moon, Raffaele Ratta, Rana R McKay, Alexander Chehrazi-Raffle, Hans Hammers, Daniel Y C Heng, Edgar Braendle, Kathryn E Beckermann, Bradley A McGregor, Robert J Motzer**

Summary

Background Immune checkpoint inhibitors (ICIs) and vascular endothelial growth factor receptor tyrosine kinase inhibitors are cornerstones of first-line treatment for advanced renal cell carcinoma; however, optimal treatment sequencing after progression is unknown. This study aimed to assess clinical outcomes of tivozanib–nivolumab versus tivozanib monotherapy in patients with metastatic renal cell carcinoma who have progressed following one or two lines of therapy in the post-ICI setting.

Methods TiNivo-2 is a multicentre, randomised, open-label, phase 3 trial at 190 sites across 16 countries, in Australia, Europe, North America, and South America. Patients with advanced renal cell carcinoma and progression during or after one to two previous lines of therapy (including one ICI) were randomised 1:1 to tivozanib (0·89 mg per day, orally) plus nivolumab (480 mg every 4 weeks, intravenously) or tivozanib (1·34 mg per day, orally). Randomisation was stratified by immediate previous therapy (ICI or non-ICI) and International Metastatic Renal Cell Carcinoma Database Consortium risk category. The primary endpoint was progression-free survival (PFS), defined as the time from randomisation to first documentation of objective progressive disease according to RECIST 1·1 or death from any cause, whichever came first, by independent radiology review. Efficacy was evaluated in the intention-to-treat population, and safety was assessed in patients who received one or more doses of the study drug. This trial was registered on ClinicalTrials.gov (NCT04987203) and is active and not recruiting.

Findings From Nov 4, 2021, to June 16, 2023, 343 patients were randomly assigned to tivozanib–nivolumab (n=171) or tivozanib monotherapy (n=172). Median follow-up was 12·0 months. Median PFS was 5·7 months (95% CI 4·0–7·4) with tivozanib–nivolumab and 7·4 months (5·6–9·2) with tivozanib monotherapy (hazard ratio 1·10, 95% CI 0·84–1·43; p=0·49). Among those with an ICI as their immediate previous therapy (n=244), median PFS was 7·4 months (95% CI 5·6–9·6) with tivozanib–nivolumab and 9·2 months (7·4–10·0) with tivozanib monotherapy. With non-ICIs as the most recent therapy, lower median PFS was observed, with no difference between groups (tivozanib–nivolumab 3·7 months [95% CI 2·7–5·4] and with tivozanib monotherapy 3·7 months [1·9–7·2]). Serious adverse events occurred in 54 (32%) of 168 patients receiving tivozanib–nivolumab and 64 (37%) of 171 patients receiving tivozanib monotherapy. One (<1%) treatment-related death occurred (tivozanib group).

Interpretation These data further support that ICI rechallenge should be discouraged in patients with advanced renal cell carcinoma. Furthermore, these data suggest that tivozanib monotherapy has efficacy in the post-ICI setting.

Funding Aveo Pharmaceuticals.

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Lancet 2024; 404: 1309–20
Published Online September 13, 2024 https://doi.org/10.1016/S0140-6736(24)01758-6

This online publication has been corrected. The corrected version first appeared at thelancet.com on October 3 2024

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*Contributed equally.

Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA (Prof T K Choueiri MD, B A McGregor MD); **Institut Gustave Roussy, Villejuif, France** (L Albiges MD); **Institut de Cancerologie Strasbourg Europe, Strasbourg, France** (P Barthélémy MD); **Catholic University of the Sacred Heart, Milan, Italy** (R Iacovelli MD); **Centre Hospitalier Universitaire de Poitiers, Poitiers, France** (S Emambux MD); **Hospital Universitario Ramon y Cajal, Madrid, Spain** (J Molina-Cerrillo MD); **Sarah Cannon Research Institute, Nashville, TN, USA** (B Garmezy MD); **University Hospitals Seidman Cancer Center, Cleveland, OH, USA** (P Barata MD); **Tulane University School of Medicine, New Orleans, LA, USA** (P Barata); **University of Alabama, Birmingham, AL, USA** (A Basu MD); **Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico** (M T Bourlon MD); **Kaiser Permanente Riverside Medical Center, Riverside, CA, USA** (H Moon MD); **Hôpital Foch, Suresnes, France** (R Ratta MD); **University of California, San Diego, CA, USA** (R R McKay MD); **City of Hope, Los Angeles, CA, USA** (A Chehrazi-Raffle MD); **University of Texas Southwestern, Dallas, TX, USA** (H Hammers MD); **Tom Baker**

Introduction

Over the past decade, immune checkpoint inhibitor (ICI) combinations have emerged as a cornerstone of first-line treatment in advanced renal cell carcinoma.[1–5] Their introduction as first-line regimens has created uncertainty in treatment sequencing for patients whose disease has progressed after treatment with ICIs, raising questions about whether rechallenge can improve clinical outcomes: either immediately following treatment or after a treatment interruption (an ICI break), using ICIs in the same class of programmed cell death 1 protein (PD-1) or programmed cell death 1 ligand 1 (PD-L1) inhibitors,[1] or even using the same drug in later lines of therapy.

Evidence exists that vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) have value after the first-line ICI does not work.[6] In the past few years, tivozanib, a selective and potent VEGFR TKI,[7] has shown a clinical benefit in a subgroup of patients with previous ICI treatment.[6] The TIVO-3 phase 3 study compared tivozanib to sorafenib (a multikinase inhibitor) in 350 patients with relapsed or refractory advanced renal

Cancer Centre, Calgary, AB, Canada (D Y C Heng MD); **Aveo Oncology, Boston, MA, USA** (E Braendle MD); **Vanderbilt University Medical Center, Nashville, TN, USA** (K E Beckermann MD); **Memorial Sloan Kettering Cancer Center, New York, NY, USA** (R J Motzer MD)

Correspondence to: Prof Toni K Choueiri, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02215, USA **toni_choueiri@dfci.harvard.edu**

Research in context

Evidence before this study

Immune checkpoint inhibitors (ICIs) are a growing class of therapies that have become standard-of-care, first-line treatments for many cancers. However, questions remain regarding the optimal treatment after progression. One potential strategy is rechallenge with ICIs after progression, but the overall benefit of this strategy is unclear. A search of PubMed and major oncology congresses was conducted to identify articles regarding rechallenge with PD-(L1) inhibitors after previous PD-(L)1 inhibitor therapy in renal cell carcinoma. English language original research articles and meeting abstracts published between May 1, 2014, and May 1, 2024, using the terms "renal cell carcinoma", "programmed death-1", "programmed death-ligand 1", "rechallenge", and "second line" were included. To the best of our knowledge, CONTACT-03 was the only phase 3 study investigating ICI rechallenge in renal cell carcinoma. However, CONTACT-03 assessed rechallenge with a PD-L1 inhibitor and included only patients with an ICI as their immediate previous therapy. Additionally, the vascular endothelial growth factor receptor inhibitor tivozanib has previously shown efficacy following two or more previous systemic therapies, including a predefined subgroup with previous ICI exposure in renal cell carcinoma; however, the efficacy and safety outcomes of tivozanib following ICI combinations (the current standard-of-care for frontline treatment) as monotherapy or in combination with an ICI have not been evaluated in a phase 3 clinical study.

Added value of this study

The TiNivo-2 results are the first phase 3 data evaluating PD-1 rechallenge, showing no efficacy in this setting. Tivozanib with or without nivolumab was well tolerated and consistent with the established safety profiles of these agents. In the context of what is known from the TIVO-3 and TiNivo studies, these results showed the clinical activity of tivozanib monotherapy at 1·34 mg once a day as a second-line therapy option in patients following progression on previous ICI combination therapy.

Implications of all the available evidence

These data further support that ICI rechallenge should be discouraged in patients with advanced renal cell carcinoma. Furthermore, these data suggest that tivozanib monotherapy has efficacy in the post-ICI setting and highlight the importance of full dosing to achieve maximal efficacy.

cell carcinoma after two or three previous systemic therapies, including a VEGFR TKI. The TIVO-3 study was the first phase 3 study to prospectively define a study population with previous ICI treatments (26% of patients) and showed an improvement in progression-free survival (PFS) with tivozanib compared with sorafenib (median PFS 7·3 months *vs* 5·1 months, respectively, hazard ratio [HR] 0·55; p=0·028) in the subgroup that received previous ICI treatment.[6]

Tivozanib is approved by the US Food and Drug Administration for relapsed or refractory renal cell carcinoma after two or more previous systemic therapies[8] and in the EU for first-line advanced renal cell carcinoma and for adult patients who are naive to VEGFR and mechanistic target of rapamycin pathway inhibitors following disease progression after one previous treatment with cytokine therapy for advanced renal cell carcinoma.[9]

Tivozanib's selectivity for VEGFR-1, VEGFR-2, and VEGFR -3 was designed to maximise pathway inhibition while minimising off-target toxicities, resulting in improved tolerability and combinability.[10] Nivolumab is a PD-1 inhibitor approved as both monotherapy and in combination with either a VEGFR TKI or a cytotoxic T-lymphocyte associated protein 4 antibody in advanced renal cell carcinoma.[11,12] As single agents, tivozanib and nivolumab have different mechanisms of action, single-agent activity, and differing safety profiles.[6,13] VEGFR inhibitors block angiogenesis but have also been shown to modulate antitumour immunity; VEGF in the tumour inhibits T-cell development and contributes to tumour-induced immune suppression. Thus, an agent that inhibits VEGF can also operate in synergy with an ICI.[14–17]

The combination of tivozanib and nivolumab was first evaluated in the single-group phase 1b/2 TiNivo study in metastatic renal cell carcinoma. 13 previously treated patients with metastatic renal cell carcinoma received tivozanib at the recommended phase 2 dose of 1·5 mg once a day in combination with nivolumab 240 mg every 2 weeks.[10] With a median follow-up of 19 months, the combination showed an overall response rate (ORR) of 62%; the median PFS was not reached. Hypertension was increased with the combination (any grade 68%) compared with tivozanib monotherapy (any grade 47% in TIVO-3).[10]

To the best of our knowledge, the only randomised, phase 3 evidence of ICI rechallenge in metastatic renal cell carcinoma is from the CONTACT-03 trial, which revealed largely negative results. CONTACT-03 compared atezolizumab, a PD-L1 inhibitor, and cabozantinib, a multitargeting VEGFR TKI, to cabozantinib monotherapy in patients with advanced renal cell carcinoma in the second-line or third-line setting whose immediate previous line of therapy was an ICI.[1] The combination of atezolizumab and cabozantinib did not yield any clinical benefit and led to increased toxicity. The negative outcome of CONTACT-03 left several questions unanswered, such as potential differences between anti-PD-1 and anti-PD-L1 therapies in the rechallenge setting, whether outcomes of ICI rechallenge would be affected if a non-ICI were used before subsequent ICI treatment, and whether VEGFR TKI dosing and TKI selectivity would affect tolerability or efficacy of combination therapy.

To further explore retreatment with ICI we conducted a study aimed at comparing tivozanib with or without nivolumab in patients with metastatic renal cell carcinoma who have progressed following one or two lines of therapy in the post-ICI setting.

Methods

Study design and participants

TiNivo-2 was a phase 3, open-label, randomised, controlled, multicentre, parallel-group study performed at 190 study centres in 16 countries in Europe, North America, South America, and Australia based on feasibility data (prevalence of renal cell carcinoma, site engagement and projected enrolment, and start-up timelines), investigator experience with tivozanib clinical trials (TIVO-1 and TIVO-3 studies), and diversity in patient population (appendix pp 2–9); the study protocol and all amendments (appendix pp 19–23) were approved by independent review boards or ethics committees at each study site. Tivozanib was provided by the study sponsor (Aveo Pharmaceuticals, Boston, MA, USA), and nivolumab was provided by Bristol Myers Squibb (Princeton, NJ, USA). In agreeing to conduct this investigation, each investigative facility agreed to follow all applicable local regulatory requirements and to perform the study in accordance with the Good Clinical Practice Guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the Declaration of Helsinki.

The trial enrolled patients with advanced renal cell carcinoma with a clear cell component and disease progression during or following receipt of one or two previous lines of therapy, one of which included an ICI. For the purposes of this study, ICI was defined as an anti-PD-L1 or anti-PD-1 antibody, including atezolizumab, avelumab, pembrolizumab, or nivolumab; combinations of ICIs with CTLA-4 inhibitors were allowed.

Eligible patients were aged 18 years and older, with measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1),[18] Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy 3 months of longer, and an adequate recovery from adverse events related to previous therapy (ie, one or two lines, with one having been an ICI). Key exclusion criteria included receipt of more than two lines of therapy, active autoimmune disease, uncontrolled hypertension, and any condition requiring systemic treatment with corticosteroids within 14 days of the first dose or other immunosuppressive medications within 30 days of randomisation. Full eligibility criteria are available in the protocol (appendix pp 14–18). All patients provided written informed consent before any screening or study procedures took place. The sponsor or its designee reviewed the safety data and protocol deviations on an ongoing basis throughout the study and ensured proper conduct of the study. A Safety Monitoring Committee was responsible for monitoring the safety data from this study on a periodic basis to identify any issues and risks, as well as to provide recommendations regarding the study design and conduct to ensure the integrity of the study. A Scientific Steering Committee was established to provide oversight of the conduct of the trial. These included the oversight of the practical aspects of the study, assistance in the development of the study protocol, review of the results of the trial as they became available, recommendations regarding the monitoring of the trial, and input into the publication plan and decision on submissions to a scientific journal. The Scientific Steering Committee worked in conjunction with the Safety Monitoring Committee.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either tivozanib 0·89 mg plus nivolumab 480 mg (group A) or tivozanib monotherapy 1·34 mg (group B). Randomisation was stratified by previous therapy (previous ICI in the most recent line of treatment *vs* not) and International Metastatic Renal Cell Carcinoma Database Consortium risk category (favourable *vs* intermediate *vs* poor).[19] Randomisation was performed using a randomisation trial supply management system. Once the strata were identified, patients were randomly assigned to a treatment group within the strata using a complete permutated block design in an unblinded fashion (open label). To maintain the integrity of the planned analyses, the sponsor had restricted access to treatment assignment information during the conduct of the study based on a blinding maintenance plan.

See Online for appendix

Procedures

A treatment cycle was defined as 4 weeks (28 days). In each cycle, patients in group A received tivozanib at an oral dose of 0·89 mg once a day for 21 consecutive days followed by a 7-day rest period; nivolumab was administered on day 1 of each cycle at an intravenous dose of 480 mg. The reduced dose (from the standard dose indicated for treatment of adults with relapsed or refractory advanced renal cell carcinoma) of tivozanib in the combination group was agreed upon with regulatory authorities due to the potential risk of higher rates of grade 3 or 4 hypertension observed in the phase 1b/2 TiNivo study in metastatic renal cell carcinoma.[10] This reduced dose of tivozanib is aligned with the dose reduction recommendation for hypertension in the tivozanib package insert.[8]

Patients in group B received tivozanib monotherapy only at the standard dose (1·34 mg orally once a day) for 21 consecutive days followed by a 7-day rest period. Adverse event information was collected continuously throughout the study period; other safety assessments (including physical examination, haematology, chemistry, coagulation, and thyroid function assessments) were performed twice during cycle 1 and once per cycle thereafter until discontinuation of treatment.

Radiographic assessment of disease using CT or MRI was performed every 8 weeks (plus or minus 3 days) for the first 2 years and every 12 weeks (plus or minus 3 days) thereafter. The investigator or local radiologist performed the collection and assessment of images. The local reader then submitted all images for blinded independent radiology review. As part of the independent radiology review assessment, two radiologists independently reviewed images for each patient; if their findings were discordant, a third radiologist adjudicated the results. Local assessment of scans was used to guide treatment decisions (with independent radiology review confirmation of progressive disease upon request by the investigator or local radiologist). Independent radiology review assessments were used in the prospectively planned analyses of PFS and other endpoints.

All patients were permitted to continue receiving tivozanib in the absence of progression or intolerable toxicity; patients in group A could continue to receive nivolumab for a maximum of 2 years from the first dose. No dose reduction of nivolumab was allowed. Dose reduction of tivozanib and interruption or discontinuation of nivolumab, tivozanib, or both was allowed per study guidelines.

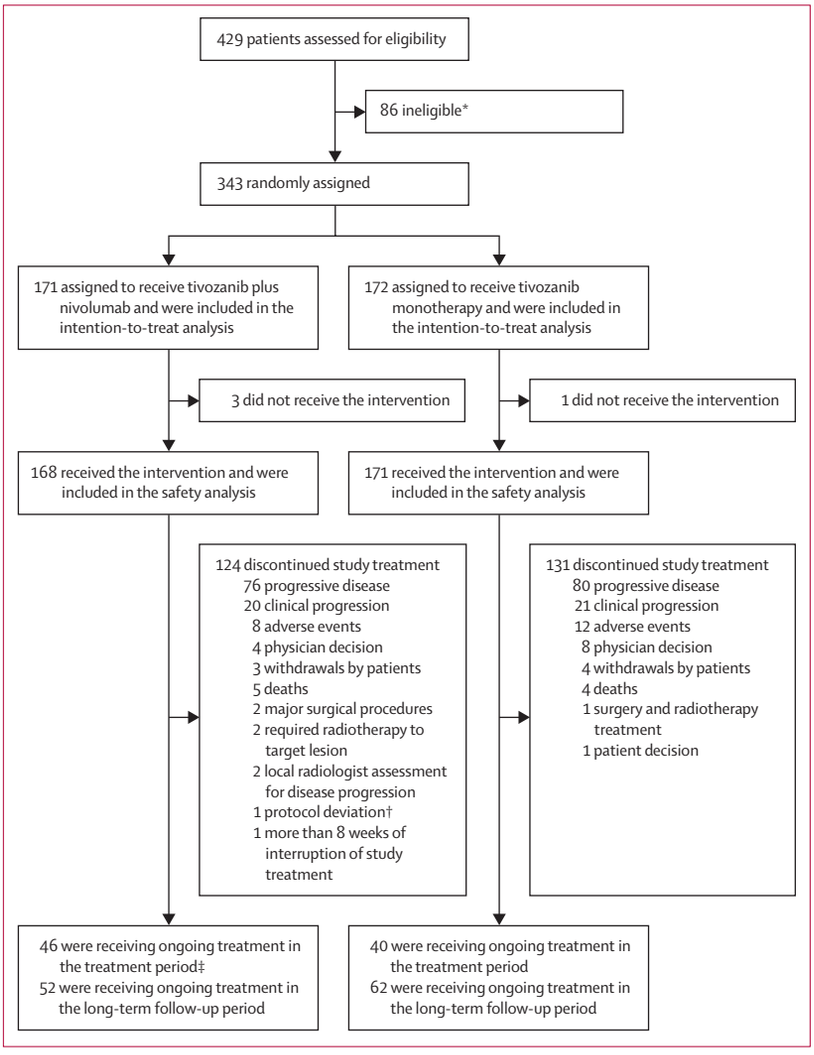

Figure 1: **CONSORT diagram**
*Due to known CNS metastases treated with no stable conditions (n=16), progression longer than 6 months before being randomly assigned (n=12), serum chemistry abnormalities (n=11), more than two previous lines of therapy in the advanced or metastatic setting (n=8), Eastern Cooperative Oncology Group performance status >1 (n=8), without measurable disease per RECIST criteria version 1.1 (n=4), had not recovered from the adverse events of previous therapy to grade ≤1 or baseline (n=4), haematological laboratory abnormalities (n=4), inadequate recovery from any previous surgical procedure or major surgical procedure within 4 weeks before administration of the first dose of the study drug (n=3), life-threatening illness or organ system dysfunction compromising safety evaluation (n=3), active autoimmune disease (n=2), without histologically confirmed renal cell carcinoma with a clear cell component (n=1), condition that required systemic treatment with a corticosteroid (ie, >10 mg daily prednisone equivalent; n=1), serious or active infection (n=1), major bleeding disorders (n=1), previous radiation therapy within 2 weeks of being randomly assigned (n=1), unable to comply with protocol requirements (n=1), life expectancy <3 months (n=1), more than one previous line of therapy with checkpoint inhibitor in the metastatic setting (n=1), psychiatric disorder (n=1), uncontrolled hypertension (n=1), and major cardiovascular disease (n=1). †Started an anticancer therapy before treatment discontinuation. ‡Included participants in the tivozanib plus nivolumab group who could have discontinued one of the medications but could remain on the other treatment.

Outcomes

The primary endpoint of this study was PFS, defined as the time from randomisation to first documentation of objective progressive disease according to RECIST 1.1 (per independent radiology review) or death from any cause, whichever came first. The key secondary endpoint was overall survival (defined as from the date of randomisation to the date of death from any cause). In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive. Other secondary endpoints were PFS per investigator assessment, ORR (defined as the proportion of patients with confirmed complete response or partial response), and duration of response (defined as the time from first documentation of objective tumour response to the first documentation of objective tumour progression or death from any cause) per blinded independent radiology review and investigator. Exploratory endpoints included quality of life (Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease-Related Symptoms [FKSI-DRS]). For a quality-of-life assessment, patients completed a validated FKSI-DRS questionnaire during day 1 of each cycle, before any study treatment administration, and at end of treatment. The FKSI-DRS questionnaire comprises nine symptom-specific questions that address lack of energy, pain, weight loss, bone pain, fatigue, dyspnoea, cough, fevers, and haematuria.

All tumour-response assessments were performed per RECIST 1.1. Complete response was defined as disappearance of all target and non-target lesions. Partial response was defined as a 30% or more decrease in the sum of diameters of target lesions, taking as a reference the baseline sum diameters. Progressive disease was defined as a 20% or more increase in the sum of diameters of target lesions and unequivocal progression of existing non-target lesions or appearance of a new lesion. Stable disease was defined as insufficient increase or decrease to qualify as complete or partial response or

disease progression. Evaluation of the safety and tolerability of the combination was also a secondary objective of the study. Safety was evaluated in patients who received one or more doses of the study drug and according to the Common Terminology Criteria for Adverse Events (version 5.0) of the National Cancer Institute. Additional exploratory endpoints are outlined in the study protocol.

Statistical analysis

The planned sample size of 326 patients with 191 events was intended to detect an improvement of 4 months or 50% and an HR of 0·67 with respect to the primary endpoint of PFS per independent radiology review (eg, the median PFS for patients receiving tivozanib in combination with nivolumab and tivozanib monotherapy is 12 months and 8 months, respectively). Based on the final enrolment of 343 patients and the publication of CONTACT-03 results since the development of the original statistical analysis plan, the decision was made on Oct 13, 2023, to increase the number of PFS events for the primary analysis from the original planned 191 to 220 to provide a slight gain in statistical power and ensure that, with a slightly longer follow-up, 64% of patients would experience a PFS event. Treatment groups were compared using a stratified log-rank test with a two-sided 5% significance level. A group-sequential design with an O'Brien–Fleming alpha spending function was used to allow for an interim analysis of overall survival at the time of final PFS analysis and a final analysis of overall survival at the time when 222 overall survival events had occurred, while maintaining the overall type I error below 5% (2-sided). The duration of response was analysed using the same method as for the PFS. The ORR was compared between treatment groups using the Cochran–Mantel–Haenszel test. All statistical analyses of efficacy were performed using the intent-to-treat population. The data cutoff for the primary PFS analysis was April 1, 2024. The trial is registered with ClinicalTrials.gov (NCT04987203).

Role of the funding source

The study protocol, including study design, planned statistical analysis, and other trial elements, was developed by Aveo Pharmaceuticals (Boston, MA, USA), working closely with the study investigators and academic advisors. Aveo (tivozanib) and Bristol Myers Squibb (nivolumab) supplied all study drugs, and Aveo provided administrative oversight throughout the trial via a contract research organisation. Data analyses were also performed by a contract research organisation contracted by the sponsor, then provided to the authors. The first version of the manuscript was written by the first author in collaboration with the sponsor and steering committee leadership. Medical writing and editorial support were provided by Nucleus Global and funded by Aveo.

Results

429 patients were screened for eligibility, and 343 were randomly assigned (from Nov 4, 2021 to June 16, 2023) to receive either tivozanib plus nivolumab (n=171) or tivozanib monotherapy (n=172) and included in the intention-to-treat population (figure 1). The safety population comprised 168 patients in the tivozanib plus

	Tivozanib 0·89 mg plus nivolumab (n=171)	Tivozanib 1·34 mg (n=172)
Age, years	64·0 (37–87)	63·0 (33–82)
Sex		
Male	125 (73%)	134 (78%)
Female	46 (27%)	38 (22%)
Race		
White	112 (65%)	107 (62%)
Asian	1 (1%)	0
Black or African American	2 (1%)	8 (5%)
Not reported, other, or missing	56 (33%)	57 (33%)
Region		
North America	60 (35%)	52 (30%)
Europe	93 (54%)	102 (59%)
Rest of the world	18 (11%)	18 (10%)
Eastern Cooperative Oncology Group performance status		
0	76 (44%)	85 (49%)
1	94 (55%)	87 (51%)
Missing	1 (1%)	0
International Metastatic Renal Cell Carcinoma Database Consortium risk category		
Favourable	30 (18%)	31 (18%)
Intermediate	114 (67%)	113 (66%)
Poor	27 (16%)	28 (16%)
Histology		
Clear cell	157 (92%)	157 (91%)
Clear cell component	13 (8%)	14 (8%)
Missing data	1 (1%)	0
Had previous nephrectomy	108 (63%)	121 (70%)
Had adjuvant therapy	25 (15%)	22 (13%)
Previous lines of therapy		
One	111 (65%)	105 (61%)
Two	60 (35%)	67 (39%)
Previous immune checkpoint inhibitor		
Immune checkpoint inhibitor in the most recent line of therapy	122 (71%)	122 (71%)
Non-immune checkpoint inhibitor in the most recent line of therapy*	49 (29%)	50 (29%)
Previous vascular endothelial growth factor receptor tyrosine kinase inhibitor use		
None	53 (31%)	53 (31%)
One	96 (56%)	101 (59%)
Two	22 (13%)	18 (10%)

Data are n (%) or median (range). *The median time that patients from this group had been off immunotherapy was 10·4 months (IQR 7·4–17·7).

Table 1: **Baseline patient characteristics**

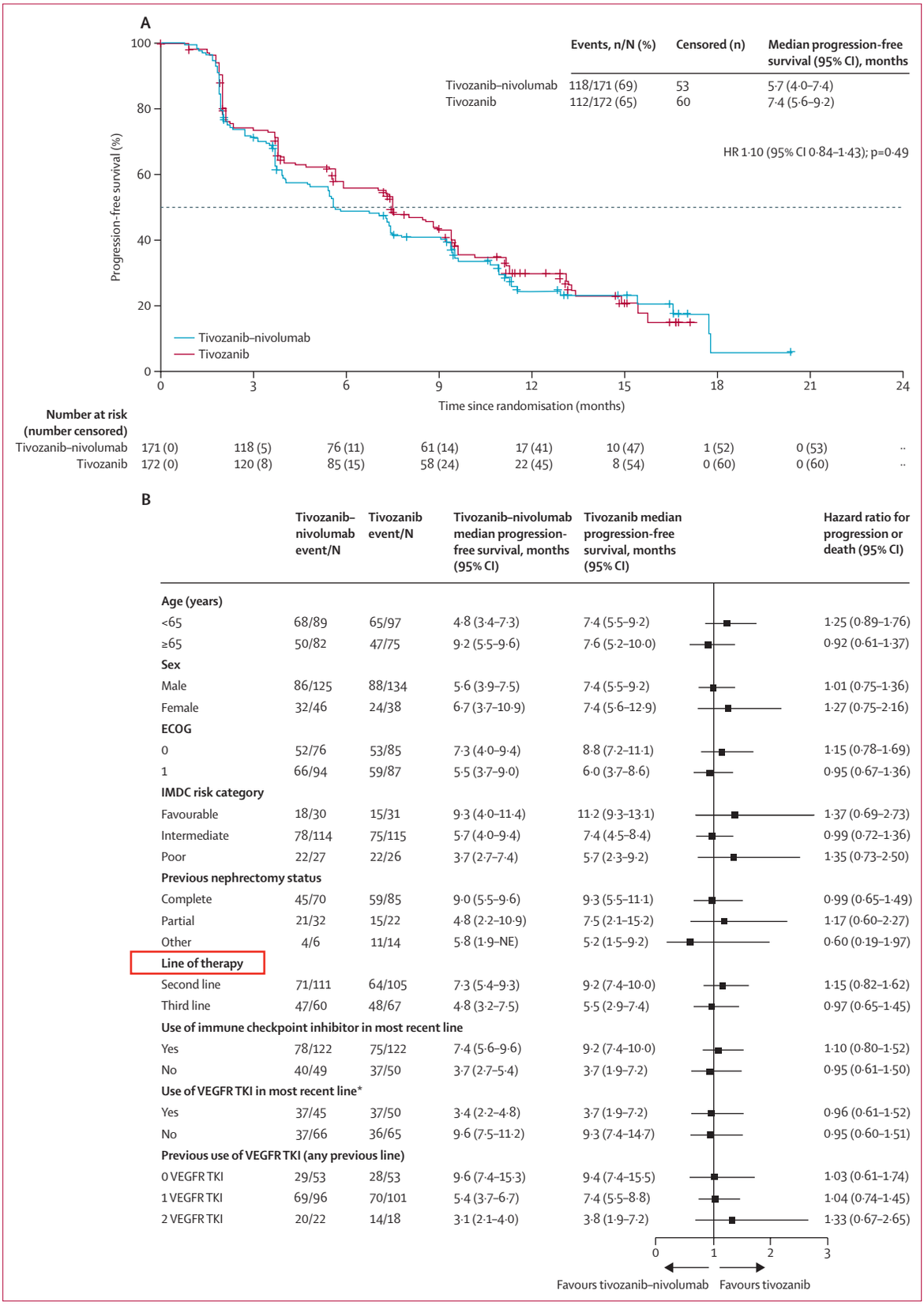

Figure 2: **Kaplan–Meier estimate of progression-free survival based on independent radiology review for intent-to-treat population (A) and prespecified subgroups (B)**
Dotted lines represent 50% marker. ECOG=Eastern Cooperative Oncology Group. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium. TKI=tyrosine kinase inhibitor. VEGFR=vascular endothelial growth factor receptor. *If the most recent regimen contains at least one VEGFR TKI drug but does not contain any immune checkpoint inhibitor drug, then the patient was counted as receiving a VEGFR TKI in the most recent line of treatment.

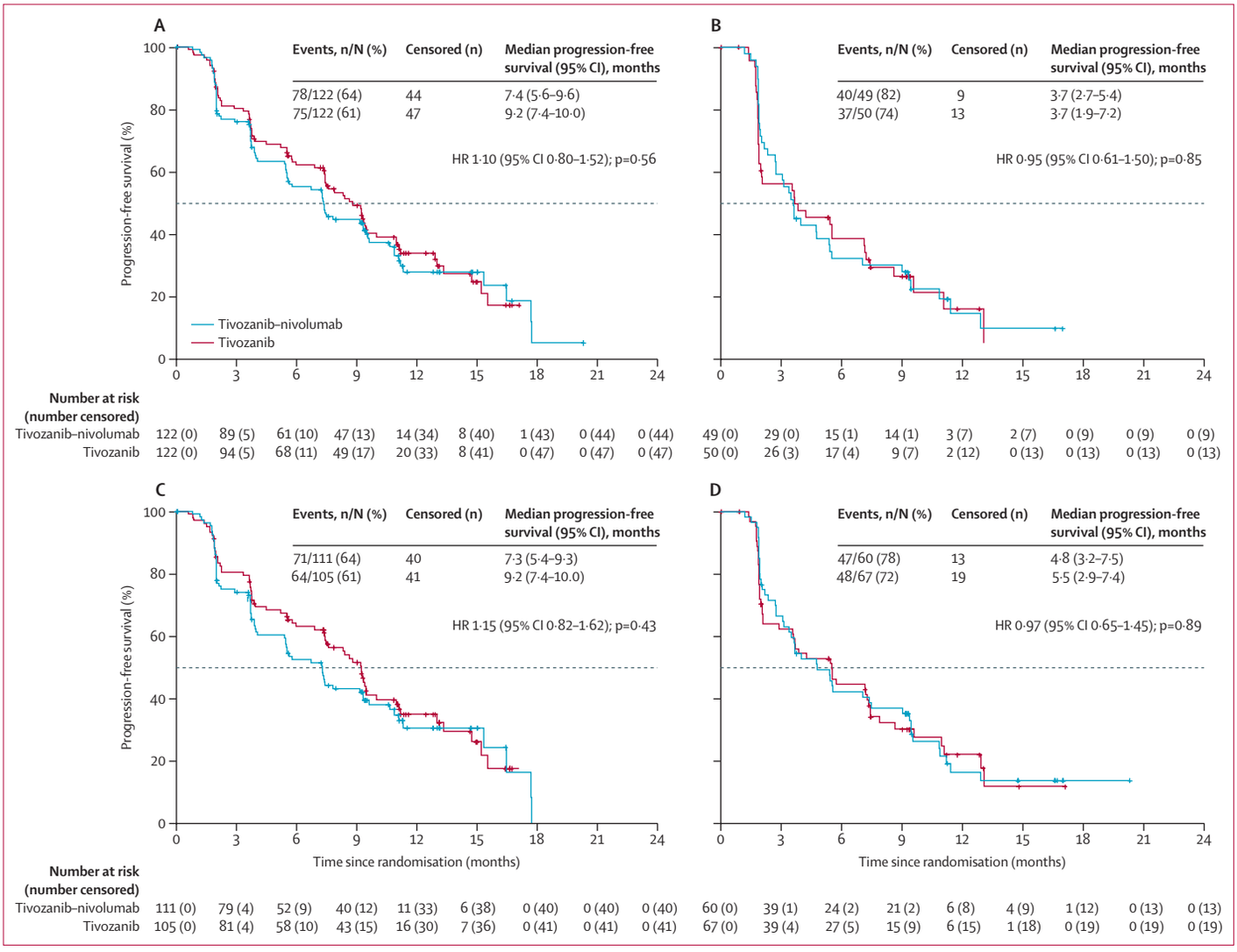

Figure 3: **Kaplan–Meier estimate of (A) progression-free survival for patients with an immune checkpoint inhibitor as the most recent line of therapy, (B) those with a non-immune checkpoint inhibitor as the most recent line of therapy, (C) the study drug as second-line therapy, and (D) the study drug as third-line therapy**
Dotted lines represent 50% marker. HR=hazard ratio.

nivolumab group and 171 patients in the tivozanib monotherapy group. Major protocol deviations are listed in the appendix (p 11). The median age of patients was 64 years (range 37–87) in the tivozanib plus nivolumab group and 63 years (33–82) in the tivozanib monotherapy group; 259 (76%) of 343 were male, 84 (24%) were female, 161 (47%) had an Eastern Cooperative Oncology Group performance status of 0, and 229 (67%) had a previous nephrectomy (table 1). Before entering the study, 216 (63%) patients had received one line of therapy, and 127 (37%) had received two lines.

Overall, 47 (14%) patients had adjuvant therapy; the most recent therapy was ICI in 244 (71%) patients and non-ICI agents in 99 (29%) patients (of which >90% were VEGFR TKI; table 1). The most common previous systemic cancer therapies were ipilimumab–nivolumab and axitinib–pembrolizumab combinations in the first line and single-agent cabozantinib and single-agent nivolumab in the second line (appendix p 10); overall, 204 (60%) of 339 patients had received previous nivolumab either alone or in combination (appendix p 10). At the data cutoff on April 1, 2024, the median follow-up was 12·0 months (95% CI 11·5–12·8) in the overall population, 11·8 months (11·1–12·6) in the tivozanib–nivolumab group, and 12·5 months (11·6–13·6) in the tivozanib monotherapy group (data not shown).

The median independent radiology review-assessed PFS was 5·7 months (95% CI 4·0–7·4) in the tivozanib–nivolumab group and 7·4 months (5·6–9·2) for those receiving tivozanib monotherapy (figure 2). The stratified HR was 1·10 (95% CI 0·84–1·43; p=0·49), indicating that TiNivo-2 did not meet its primary endpoint and that ICI

	Tivozanib 0·89 mg plus nivolumab (n=168)	Tivozanib 1·34 mg (n=171)
Any-cause TEAE	163 (97%)	167 (98%)
Treatment related	137 (82%)	144 (84%)
Tivozanib related	135 (80%)	144 (84%)
Nivolumab related	119 (71%)	0
Grade ≥3 adverse event*	102 (61%)	103 (60%)
Related	54 (32%)	60 (35%)
Serious adverse event*	54 (32%)	64 (37%)
Related	14 (8%)	15 (9%)
Death due to adverse event	7 (4%)	5 (3%)
Deemed related to study drug	0	1 (1%)
TEAE leading to withdrawal	27 (16%)	33 (19%)
Of tivozanib	19 (11%)	33 (19%)
Of nivolumab	22 (13%)	0
TEAE leading to dose interruption	82 (49%)	93 (54%)
Of tivozanib	79 (47%)	93 (54%)
Of nivolumab	35 (21%)	0
TEAE leading to dose reduction of tivozanib	18 (11%)	38 (22%)
Any-grade TEAE occurring in ≥10% of patients in either group		
Hypertension	62 (37%)	69 (40%)
Fatigue	49 (29%)	68 (40%)
Diarrhoea	51 (30%)	62 (36%)
Nausea	26 (15%)	47 (27%)
Decreased appetite	37 (22%)	46 (27%)
Vomiting	20 (12%)	36 (21%)
Asthenia	39 (23%)	35 (20%)
Proteinuria	16 (10%)	30 (18%)
Constipation	17 (10%)	29 (17%)
Arthralgia	26 (15%)	27 (16%)
Cough	26 (15%)	26 (15%)
Hypothyroidism	15 (9%)	26 (15%)
Back pain	21 (13%)	23 (13%)
Dyspnoea	15 (9%)	22 (13%)
Dysphonia	15 (9%)	22 (13%)
Weight decreased	17 (10%)	21 (12%)
Palmar-plantar erythrodysesthesia	10 (6%)	21 (12%)
Abdominal pain	12 (7%)	20 (12%)
Blood creatinine increased	14 (8%)	19 (11%)
Anaemia	28 (17%)	16 (9%)
Pruritus	26 (15%)	11 (6%)
Headache	23 (14%)	10 (6%)

TEAE=treatment-emergent adverse event. *Grade ≥3 adverse event includes all serious adverse event.

Table 2: **Overview of adverse events**

rechallenge with tivozanib–nivolumab did not improve clinical outcomes. A sensitivity analysis for mis-stratification was consistent with the primary analysis.

Similar results were seen with investigator-assessed PFS 5·7 months (95% CI 4·1–7·4) with tivozanib–nivolumab and 7·4 months (5·5–9·2) with tivozanib monotherapy (stratified HR 1·01, 95% CI 0·78–1·32; p=0·92; data not shown). Subgroup analyses were consistent with the primary analysis (figure 2).

In a predefined analysis per strata in patients who had received an ICI as part of their most recent therapy (predominantely second line), median PFS was 7·4 months (95% CI 5·6–9·6) with tivozanib–nivolumab and 9·2 months (7·4–10·0) with tivozanib monotherapy (HR 1·10, 0·80–1·52; p=0·56; figure 3). In those who received non-ICIs as their most recent line of therapy, median PFS was 3·7 months (95% CI 2·7–5·4) with tivozanib–nivolumab and 3·7 months (1·9–7·2) with tivozanib monotherapy (HR 0·95, 95% CI 0·61–1·50; p=0·85; figure 3). The outcome of the median PFS for the group of patients after a non-ICI as their most recent line of therapy could be due to the fact that those patients were predominately in the third-line setting and potentially due to emerging resistance mechanisms.

An additional predefined strata was the International Metastatic Renal Cell Carcinoma Database Consortium risk categories (ie, favourable, intermediate, and poor) in the intent-to-treat population (figure 2). Patients in the favourable risk category that received tivozanib–nivolumab had a median PFS of 9·3 months (95% CI 4·0–11·4) compared with 11·2 months (9·3–13·1) with tivozanib monotherapy at 1·34 mg (HR 1·37, 95% CI 0·69–2·73; figure 2). For patients with intermediate risk the median PFS was 5·7 months (95% CI 4·0–9·4) with tivozanib–nivolumab and 7·4 months (4·5–8·4) with tivozanib monotherapy at 1·34 mg (HR 0·99, 95% CI 0·72–1·36). For patients in the poor risk category, the median PFS was 3·7 months (95% CI 2·7–7·4) with tivozanib–nivolumab and 5·7 months (2·3–9·2) with tivozanib monotherapy at 1·34 mg (HR 1·35, 95% CI 0·73–2·50).

In patients who received study treatment as second line, median PFS was 7·3 months (95% CI 5·4–9·3) with tivozanib–nivolumab and 9·2 months (7·4–10·0) with tivozanib monotherapy (HR 1·15, 95% CI 0·82–1·62; p=0·43; figure 3). In patients who received study treatment as third line, median PFS was 4·8 months (95% CI 3·2–7·5) with tivozanib–nivolumab and 5·5 months (2·9–7·4) with tivozanib monotherapy (HR 0·97, 95% CI 0·65–1·45; p=0·89; figure 3).

Although overall survival was not yet mature at 33% of events, median overall survival at the time of analysis was 17·7 months (95% CI 15·1–not reached [NR]) with tivozanib–nivolumab (with 53 deaths) and 22·1 months (15·2–NR) with tivozanib monotherapy (with 57 deaths; appendix p 12). Best overall response assessed by RECIST 1·1 by independent radiology review is shown in the appendix (p 10). With tivozanib–nivolumab, the objective response rate was 19% (95% CI 13·7–26·0), with one (<1%) complete response and 32 (19%) partial responses. The objective response rate was 20% (95% CI 14·1–26·5) with tivozanib monotherapy, with one (<1%) complete response and 33 (19%) partial responses.

Duration of response at analysis was 15·8 months (95% CI 9·63–NR) with tivozanib–nivolumab and NR (95% CI 7·39–NR) with tivozanib monotherapy (data not shown).

The safety analysis population consisted of 339 patients who received at least one dose of the study drug. Median duration of treatment was 6·3 months with tivozanib–nivolumab and 7·4 months with tivozanib monotherapy. With tivozanib–nivolumab, the median dose intensity with tivozanib was 4·6 mg per week, and with nivolumab was 120·0 mg per week. In patients receiving tivozanib monotherapy, median dose intensity was 6·8 mg per week. The median relative dose intensity of tivozanib was 100% with tivozanib–nivolumab and 99·5% with tivozanib monotherapy. The most common any-grade treatment-emergent adverse events (TEAEs) occurring in 10% or more of the patients were similar for both groups for hypertension (62 [37%] of 168 patients receiving tivozanib–nivolumab and 69 [40%] of 171 patients receiving tivozanib monotherapy) and diarrhoea (51 [30%] receiving tivozanib–nivolumab and 62 [36%] receiving tivozanib monotherapy; table 2). For certain TEAEs, such as fatigue, nausea, vomiting, proteinuria, and hypothyroidism, the combination group showed lower numerical rates. However, this was not the case for anaemia, pruritus, and headache, which showed the reverse. The lower dose in the combination potentially explains the lower rate of TEAEs associated with VEGF TKIs. The rates of TEAEs in the tivozanib monotherapy group in this study are consistent with the safety profile of tivozanib in the TIVO-3 study (table 2).

205 (60%) patients experienced a grade 3 or higher adverse event. The most common grade 3 or higher TEAE was hypertension, reported equally in both groups (75 patients [22%]). All other grade 3 or higher TEAEs were reported in less than 5% of patients. Serious adverse events occurred in 54 (32%) of 168 patients who received tivozanib–nivolumab and in 64 (37%) of 171 patients who received tivozanib monotherapy. Serious adverse events that occurred in more than 2% of patients in either group were hypertension and pulmonary embolism (four [7%] each) and hypercalcaemia, pleural effusion, and acute respiratory failure (three [5%] each) in the tivozanib–nivolumab group and haematuria (four [7%]), and dyspnoea (three [5%]) in the tivozanib monotherapy group (data not shown). Adverse events leading to death occurred in seven (4%) of 168 patients who received tivozanib–nivolumab and in five (3%) of 171 patients who received tivozanib monotherapy (table 2). Only one death in the tivozanib monotherapy group was deemed treatment related (in a single patient with sepsis, renal failure, haematuria, and hypertension). No deaths in the tivozanib–nivolumab group were deemed treatment related. TEAEs leading to withdrawal occurred in 27 (16%) patients receiving tivozanib–nivolumab and 33 (19%) receiving tivozanib monotherapy. TEAEs leading to dose interruption occurred in 82 (49%) patients receiving tivozanib–nivolumab and 93 (54%) receiving tivozanib monotherapy; TEAEs leading to dose reduction occurred in 18 (11%) patients receiving tivozanib–nivolumab and 38 (22%) receiving tivozanib monotherapy (table 2).

The mean FKSI-DRS scores at baseline were similar in the two groups: 28·8 (SD 5·6) with tivozanib–nivolumab and 29·3 (5·3) with tivozanib; 332 (97%) of 343 patients completed the FKSI-DRS questionnaire. A disease-related symptom assessment measured by the FKSI-DRS subscale of mean scores over time showed no differences, with an overall consistent trend of slight improvement in both arms (appendix p 13).

Discussion

To date, the biological mechanisms leading to ICI resistance are a focus of intense research; immunological models have been used to characterise them, and hypotheses have been consequently proposed. Immune checkpoint blockade resistance is thought to be a complex interplay of tumour-intrinsic factors (eg, interferon signalling, antigen presentation, and the canonical cancer signalling path) inducing immune surveillance of the tumour microenvironment.[20,21]

The TiNivo-2 study confirmed and expanded the key conclusion from CONTACT-03 that ICI rechallenge following progression on previous ICI therapy should be discouraged, regardless of treatment sequence (ie, ICI rechallenge following ICI progression or an ICI break with a VEGFR TKI).[1] TiNivo-2 and CONTACT-03 showed differences in their design. In TiNivo-2, 244 (71%) of 343 patients had progressed on ICI as the most recent line of therapy, and 99 (29%) of 343 patients had progressed after an ICI break (with non-ICI agents, mostly VEGFR TKI). The decision to include a population with an ICI break in TiNivo-2 was made to test if the immune system can be reset, improving the outcome of ICI rechallenge. In contrast, all patients in the CONTACT-03 study received ICI as the most recent line of therapy. In our study, the anti-PD-1 inhibitor nivolumab was used in combination with tivozanib for ICI rechallenge, whereas in CONTACT-03, the anti-PD-L1 inhibitor atezolizumab was used for ICI rechallenge. In both studies, TKI monotherapy was used as the control group. In TiNivo-2, no difference was seen in median PFS or ORR in the overall intent-to-treat patient population in either treatment group. By strata for previous therapy (ICI *vs* non-ICI), the addition of tivozanib to nivolumab did not improve median PFS versus tivozanib monotherapy. With a medium follow-up of 12·0 months, the duration of response and overall survival data were too immature to allow a conclusion. No subgroup was identified that benefitted from the addition of nivolumab. Although this study did not meet its primary endpoint, clinically meaningful results were observed in the tivozanib monotherapy group. Tivozanib monotherapy showed clinically meaningful outcomes in

patients on second-line therapy and third-line therapy after progression on ICI as their most recent therapy, with a median PFS of 9·2 months *vs* the median PFS of cabozantinib monotherapy (10·8 months) in CONTACT-03. Cross-study comparisons have recognised limitations and therefore should be taken with caution. Differences in trial design as well as baseline and disease characteristics between both studies should be acknowledged (eg, CONTACT-03 had higher proportions of patients with favourable International Metastatic Renal Cell Carcinoma Database Consortium risk status and allowed the inclusion of non-clear cell histology).

Although not the primary purpose of the study, our results support the use of second-line tivozanib 1·34 mg following progression with ICI combination therapy. Tivozanib monotherapy in third-line therapy showed a median PFS of 5·5 months, which is comparable to the results of TIVO-3 (5·6 months).[6] Of note, the TiNivo-2 data might be more adherent to current clinical practice, as all patients in the TiNivo-2 study received previous ICI while only a small percentage (26%) received previous ICI in the TIVO-3 study.

The type and frequency of safety events in the tivozanib monotherapy group in this study were consistent with those observed in TIVO-3,[6] with no unexpected adverse events, confirming the tolerable safety profile of tivozanib. Serious adverse events occurred in 54 (32%) of 168 patients in the combination group and 64 (37%) of 171 patients in the tivozanib monotherapy group. The lower number of serious adverse events in the combination group could be due to the lower tivozanib dose. The rate of serious adverse events in the tivozanib monotherapy group in this study is lower than was reported in the TIVO-3 study (43%). Overall, adverse events were manageable with supportive-care strategies. In the tivozanib monotherapy group, the rate of adverse events leading to dose interruption or dose reduction was 77%, and the same rate with cabozantinib monotherapy in CONTACT-03 was 87%.

In the combination group, using a tivozanib dose of 0·89 mg, the frequency of TEAEs trended lower than with tivozanib monotherapy (1·34 mg) at 97% and 98%, respectively. For the patient-reported outcome assessment, a disease-related symptom questionnaire (FKSI-DRS subscale) was used, showing no differences in the mean score over time between both groups and indicating a trend towards improvement in patients' quality of life regarding metastatic renal carcinoma-associated symptoms. There are, however, several limitations of the study to be recognised. Firstly, the reduced dose of tivozanib used to manage the potential increased toxicity in the combination group could have impacted the efficacy reflected by the numerically lower median PFS in the combination group. Secondly, the open-label study design is in principle more vulnerable to patient bias and placebo effects due to a lack of blinding for both patients and investigators. Thirdly, due to our study's lack of sarcomatoid tumour data, which are known to have higher PD-L1 expression than other subtypes such as clear cell renal cell carcinoma, the potential benefit of ICI rechallenge remains unknown for this histology.

The results with tivozanib monotherapy in second-line therapy following progression on ICI relative to the lower dose used in the combination group underscored the importance of using the appropriate and optimal dose of VEGFR TKI in maintaining efficacy along with a tolerable safety profile.

Our results suggest that the addition of nivolumab to tivozanib in second-line or third-line treatment does not improve efficacy but potentially increases toxicity from the addition of an ICI. TiNivo-2 is the second prospective, randomised, phase 3 study showing that ICI rechallenge in metastatic renal cell carcinoma does not improve outcomes and should be avoided. In addition, this study showed that neither treatment sequence of ICI rechallenge following an ICI break nor rechallenge with an anti-PD-1 or anti-PD-L1 inhibitor impact outcomes. Tivozanib with or without nivolumab was well tolerated, consistent with the established safety profiles of these agents. These results showed clinical activity of tivozanib monotherapy as a second-line treatment option, and rechallenging with nivolumab in the setting of previous exposure to ICI is not warranted.

Contributors

TKC, LA, and RJM helped draft the initial manuscript and assisted with subsequent revisions. All authors contributed to data collection or analysis. All authors provided approval of the final version of the manuscript for submission and take responsibility for the accuracy and integrity of the data. TKC and EB directly accessed and verified the data. All authors had full access to the data. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

TKC reports institutional and personal paid or unpaid support for research, advisory board participation, consultancy, and honoraria within the past 5 years from Alkermes, Arcus Bio, AstraZeneca, Aravive, Aveo, Bayer, Bristol Myers Squibb, Calithera, Circle Pharma, Deciphera Pharmaceuticals, Eisai, EMD Serono, Exelixis, GlaxoSmithKline, Gilead, HiberCell, IQVIA, Infinity, Ipsen, Jansen, Kanaph, Lilly, Merck, Nikang, Neomorph, Nuscan and Precede Bio, Novartis, Oncohost, Pfizer, Roche, Sanofi Aventis, Scholar Rock, Surface Oncology, Takeda, and Tempest and equity in Tempest, Pionyr, Osel, Precede Bio, CureResponse, InnDura Therapeutics, and Primium. LA reports consulting fees from Bristol Myers Squibb, Ipsen, Roche, Novartis, Pfizer, Astellas, Merck, MSD, Janssen, Eisai, and Amgen and support for travel expenses from Bristol Myers Squibb, MSD, Ipsen, and Pfizer. PB reports grants or contracts from Roche, Bristol Myers Squibb, MSD, AstraZeneca, Pfizer, Exelixis, Ipsen, Merck, Gilead, Janssen, AAA Pharmaceutical, and Bayer; consulting fees from Astellas, Bayer, Bristol Myers Squibb, Ipsen, Janssen, MSD, Novartis, Pfizer, Merck, Gilead, AAA Pharmaceutical, Eisai, and AstraZeneca; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astellas, Bayer, Bristol Myers Squibb, Ipsen, Janssen, MSD, Novartis, Pfizer, Merck, Gilead, AAA Pharmaceutical, Eisai, and AstraZeneca; and reports participation on a data safety monitoring board or advisory board for Astellas, Bayer, Bristol Myers Squibb, Ipsen, Janssen, MSD, Novartis, Pfizer, Merck, Gilead, AAA Pharmaceutical, Eisai, and AstraZeneca. SE reports consulting fees from MSD, AstraZeneca, Eisai, Janssen, Bristol Myers Squibb, and Kephren and support for attending meetings and travel from MSD, Chugai, Pfizer, and Janssen. JM-C reports payment or honoraria for lectures,

presentations, speakers bureaus, manuscript writing, or educational events from Ipsen, Pfizer, Roche, Bayer, Sanofi, Janssen, Astellas, Eisai, Adacap, Lilly, Novartis, Bristol Myers Squibb, MSD, Adium, and Asofarma; support for attending meetings and travel from Ipsen, Pfizer, Bristol Myers Squibb, and MSD; and participation on a data safety monitoring board or advisory board for Ipsen, Pfizer, Astellas, Eisai, Bristol Myers Squibb, and MSD. BG reports research funding grants from AbbVie, Accutar Biotechnology, Arcus Biosciences, Arvinas, AstraZeneca, AVEO Oncology, CRISPR Therapeutics, Eikon Therapeutics, Exelixis, Roche and Genentech, Flare Therapeutics, Harbour BioMed, IDEAYA Biosciences, Janssen, Janux Therapeutics, Jubilant Therapeutics, Kineta, Kinnate BioPharma, Loxo, Mink Therapeutics, Nuvation Bio, Profound Bio, Takeda Therapeutics, Teon Therapeutics, Tmunity Therapeutics, Xencor, and Zenshine and consulting fees from AbbVie, Adaptimmune, Adicent Therapeutics, AIQ Global, Amgen, Arcus Biosciences, Arvinas, AstraZeneca, AVEO Oncology, Bayer, Bicycle Therapeutics, Eisai, EMD Serono, Exelixis, Janssen, Merck, Novartis, Pfizer, Rondo Therapeutics, Sanofi–Aventis, Seagen, and Xencor. PB reports honoraria from UroToday; consulting or advising fees from Bayer, Bristol Myers Squibb, Pfizer, EMD Serono, Eisai, Caris Life Sciences, AstraZeneca, Exelixis, Aveo, Merck, Ipson, and Dendreon; speakers bureau funding from AstraZeneca, Caris Life Sciences, Bayer, Pfizer and Astellas, and Merck; and research funding from Exelixis, Aveo, Blue Earth, Pfizer, and Merck. AB reports honoraria from Gilead Sciences, Cardinal Health, Eisai, and Natera; consulting or advising fees from EMD Serono, Seattle Genetics, and Bristol Myers Squibb and Pfizer; speakers bureau funds from Eisai; and research funding from Merck, EMD Serono, Natera, Astellas Pharma, Bristol Myers Squibb and Celgene, Genentech and Roche, and Aveo. MTB reports consulting fees, payment or honoraria, and participation on a data safety monitoring board or advisory board from Bristol Myers Squibb. HM reports honoraria from EMD Serono and Pfizer; research funding from Bristol Myers Squibb, Amgen, Genentech, Seattle Genetics, Arcus Bioscience, Apollomics, Nektar, RevImmune, HUYA Bioscience International, Aveo, Xencor, and Pfizer; and travel accommodations or expenses from Aveo, Seagen, Bayer, and Genentech. RR reports honoraria from Ipsen, MSD Oncology, AstraZeneca, Bristol Myers Squibb, Pfizer, Advanced Accelerator Applications, and Eisai; consulting or advisory fees from Astellas Pharma, Pfizer, Ipsen, and MSD; and travel accommodations or expenses from Ipsen, MSD Oncology, and Janssen. RRM reports consulting or advisory roles for Janssen, Novartis, Tempus, Exelixis, Pfizer, Bristol Myers Squibb, Astellas Medivation, Dendreon, Bayer, Sanofi, Merck, Vividion, Calithera, AstraZeneca, Myovant, Caris Life Sciences, Sorrento Therapeutics, Aveo, Seattle Genetics, Telix, Eli Lilly, Blue Earth Diagnostics, Ambrx, Arcus Biosciences, Sumitomo Pharma Oncology, Eisai, and NeoMorph and research funding from Bayer, Tempus, AstraZeneca, Exelixis, Bristol Myers Squibb, Oncternal Therapeutics, and Artera. AC-R reports honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from OncLive and MJH Life Sciences, ASCO Direct, Exelixis, Medical Oncology Association of Southern California, EPG Health, Eisai Co, Aveo, and Seagen. HH reports grants or contracts for clinical trial support from Merck, Bristol Myers Squibb, Eisai, Agenus, Hoosier, and Aveo and advisory consulting fees from Eisai, Aveo, Pfizer, and Bristol Myers Squibb. DYCH reports consultancy fees from Pfizer, Novartis, Bristol Myers Squibb, Janssen, Astellas Pharma, Ipsen, Eisai, and Merck and research funding from Pfizer, Novartis, Exelixis, Bristol Myers Squibb, and Ipsen. EB reports funding for the provision of study materials, medical writing, or article processing charges from Aveo Oncology and stock or stock options from Autolus. KEB reports grants funding from Bristol Myers Squibb–Lung Cancer Foundation of America–International Association for the Study of Lung Cancer, Aravive, Pionyr, and Arsenal Bio; consulting fees from Aravive, Aveo, Alpine Bioscience, Arcus, AstraZeneca, Adicet, Bristol Myers Squibb, Exelixis, Eisai, Merck, Nimbus, and Xencor; and honoraria funding from Merck. BAM reports grants to his institution from Aveo, Bristol Myers Squibb, Exelixis, Gilead, and Pfizer; consulting fees from Arcus, Bristol Myers Squibb, Exelixis, Gilead, Lily, and Pfizer; payments or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Targeted Oncology, Dava Oncology, Aptitude Health, and Curio; and patents planned, issued, or pending with Gilead. RJM reports consulting fees from Aveo, Merck, Exelixis, and Takeda, grants or contracts from Pfizer, Genentech and Roche, Eisai, Merck, Bristol Myers Squibb, and Exelixis; and data safety monitoring and advisory board participation fees from Incyte. RI reports no competing interests.

Data sharing

For eligible studies, qualified researchers can request access to individual patient-level clinical data through the Aveo Pharmaceuticals website portal (medical information inquiries).

Acknowledgments

Editorial support was provided by Bonisile Luthuli at Nucleus Global and funded by Aveo Oncology. TKC is supported in part by the Dana-Farber and Harvard Cancer Center Kidney SPORE (2P50CA101942-16) and Program (5P30CA006516-56), the Kohlberg Chair at Harvard Medical School and the Trust Family, Michael Brigham, Pan Mass Challenge, the Hinda and Arthur Marcus Fund, and the Loker Pinard Funds for Kidney Cancer Research at the Dana-Farber Cancer Institute. Patients treated at the Memorial Sloan Kettering Cancer Center were supported in part by the Memorial Sloan Kettering Cancer Center Support Grant and Core Grant (P30 CA008748). We thank Claudia Lebedinsky for her valuable insight during analysis and understanding of the data.

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