



Editorial Commentary: *Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study*

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In the January 2020 edition of *The Lancet Oncology*, Rini and colleagues reported the results of TIVO-3, an open-label phase 3 randomized control trial (RCT) comparing tivozanib with sorafenib in patients with refractory metastatic clear cell renal cell carcinoma (mRCC) (1). Tivozanib is a highly selective vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) which inhibits phosphorylation of VEGFR1, VEGFR2, and VEGFR3 (2). It has a 4–5-day half-life, and ten-fold higher concentrations are required to inhibit cKIT and platelet derived growth factor (PDGF) (2). Compared to earlier generation TKIs, tivozanib was designed to optimize VEGFR blockade while minimizing off-target toxic effects, ultimately resulting in fewer dose interruptions and dose reductions (2,3).

Initially, tivozanib was tested against sorafenib in the first-line setting for mRCC in TIVO-1, an international phase 3 trial (4). Tivozanib demonstrated significantly improved progression-free survival (PFS) compared to sorafenib (11.9 *vs.* 9.1 months; HR, 0.797; 95% CI, 0.639–0.993; $P=0.04$), thus meeting its primary endpoint (4). However, there was a trend towards improved overall survival (OS) in the sorafenib arm (29.3 *vs.* 28.8 months; HR, 1.245; 95% CI, 0.954–1.624; $P=0.11$) (4). Given the improved PFS, tivozanib was approved in Europe for first-line treatment of mRCC, however because of concerns regarding the OS results, it was not approved in the United

Stated (5).

The OS results in TIVO-1 were confounded by geographically driven imbalanced cross-over in second-line treatment. A large proportion of participants were from Eastern Europe with limited access to targeted therapies (4). Under an extension protocol, those who progressed in the sorafenib arm were eligible to receive sponsor-provided tivozanib, while those in the tivozanib arm could only receive best available therapy excluding sorafenib (4). This resulted in 63% of sorafenib patients receiving second-line tivozanib while only 13% of patients in the tivozanib arm received any second-line therapy (4). Notably, subgroup analysis restricted to participants from North America and Europe demonstrated an OS of 35.9 months in the tivozanib arm compared to 31 months for sorafenib (HR, 0.503; 95% CI, 0.174–1.451; $P=0.195$) (4). In addition, patients given tivozanib after progression on sorafenib had a median PFS of 11.0 months and OS of 21.6 months from the start of tivozanib therapy, indicating activity in the second-line setting (6).

Given this potential efficacy in later lines of therapy, TIVO-3 was designed as an open-label phase 3 RCT comparing tivozanib to sorafenib in patients who had received at least two prior lines of therapy (1). Between May 2016 and August 2017, 350 patients were enrolled across 120 sites (1). Randomization was done by permuted blocks with incorporation of two stratification factors—IMDC

risk group and type of previous therapy (1). The primary outcome was PFS as assessed by an independent radiology committee, with numerous secondary endpoints, including OS (1). The authors report a significant difference in PFS at 5.6 months in the tivozanib arm compared to 3.9 months in the sorafenib arm (HR, 0.73; 95% CI, 0.56–0.94; $P=0.016$). Interim OS, assessed 2 years after enrollment of the final patient (10 months after the final PFS analysis) and after 227 (65%) of patients had died, was 16.4 months (95% CI, 13.4–22.2) in the tivozanib arm and 19.7 months (95% CI, 15.0–24.2) in the sorafenib arm (HR, 0.99; 95% CI, 0.76–1.29; log-rank $P=0.95$) (1). A final OS analysis is expected to report in June 2020 (7).

In TIVO-3, better PFS outcomes were seen among favorable (HR, 0.46; 95% CI, 0.25–0.85, $P=0.01$) and intermediate IMDC risk patients (HR, 0.69; 95% CI, 0.49–0.95; $P=0.02$), indicating ongoing responsiveness to VEGFR inhibition (8). These findings are similar to the results from the AXIS trial, in which patients treated with axitinib demonstrated a PFS of 8.3 months (95% CI, 6.7–9.2) compared to 5.7 months (95% CI, 4.7–6.5) for sorafenib (HR, 0.656; 95% CI, 0.552–0.779; one-sided $P<0.0001$) (9). MSKCC favorable risk patients appeared to receive the most benefit (HR, 0.497; 95% CI, 0.326–0.758), implying angiogenesis continued to contribute to tumorigenesis (9,10). Notably, like tivozanib, axitinib is a later generation VEGFR TKI, and despite the improvement in PFS in AXIS, no OS benefit was identified (9,11).

While it is not possible to draw treatment superiority/inferiority inferences by directly comparing effect sizes across clinical trials, prior findings in refractory mRCC trials provide context for interpreting TIVO-3 results. METEOR and CheckMate-025 were large phase three RCTs which evaluated the efficacy of cabozantinib and nivolumab respectively in refractory mRCC populations (12,13). In 2015, both drugs demonstrated significant OS benefit compared to everolimus and were approved for second-line use (12,13). In each study, approximately 30% of patients had received at least two prior VEGFR or anti-angiogenic agents [METEOR: $n=194/658$, (29%); CheckMate-025: $n=230/803$, (29%)], comparable to the TIVO-3 cohort (12,13).

In TIVO-3, 45% of patients ($n=159$) received two prior VEGFR TKIs (1). In this group, median PFS was 5.5 months (95% CI, 3.6–7.4) with tivozanib and 3.7 months (95% CI, 3.6–3.9) with sorafenib (HR, 0.58; 95% CI, 0.4–0.8; $P=0.0032$) (1). In METEOR, median OS was 21.4 months (95% CI, 18.7–not estimable) in the

cabozantinib arm compared to 16.5 months (95% CI, 14.7–18.8) in the everolimus arm (HR, 0.66; 95% CI, 0.53–0.83; $P=0.00026$) (12,14). Notably, while PFS was improved in the subgroup with two prior VEGFR agents (HR, 0.51; 95% CI, 0.35–0.74), there was no OS difference (HR, 0.73; 95% CI, 0.48–1.10) in the final results (14). In CheckMate-025, the median OS was 25 months with nivolumab and 19.6 months with everolimus (HR, 0.73; 95% CI, 0.57–0.93; $P<0.002$) (13). On subgroup analysis, those who had received two or more prior therapies had a statistically significant improvement in OS when given nivolumab compared to everolimus (HR, 0.65; 95% CI, 0.43–0.99) (13,15).

Thus, among patients who have received two prior VEGFR therapies, the clinical relevance of a 55-day improvement in PFS with tivozanib should be critically evaluated given that radiologic progression does not imply symptomatic progression and prior trials have shown OS improvements (16,17). In patients treated with first-line targeted therapy, PFS at 3 and 6 months was found to be predictive of OS; however, PFS may not be a valid surrogate endpoint for OS in later lines of therapy (18). Because of concerns related to OS, the FDA requested that the new drug application (NDA) for tivozanib be held until the final OS results are available from TIVO-3 (19). The company has indicated it will withdraw its NDA if the final OS results in a HR above 1.00 (19).

The second subgroup which benefitted from tivozanib were those previously receiving a checkpoint inhibitor (ICI) and a VEGFR TKI ($n=91$, 26%) (1). Those given tivozanib had a median PFS of 7.3 (95% CI, 4.8–11.1) *vs.* 5.1 months (95% CI, 3.2–7.4) with sorafenib (HR, 0.55; 95% CI, 0.32–0.94; $P=0.02$) (1). Enrollment for TIVO-3 closed in 2017, therefore most patients likely received a VEGFR agent followed by nivolumab monotherapy (13). In 2020, front line combination therapy is standard of care and the optimal sequencing strategy for subsequent agents such a nivolumab is unknown (10). Conclusions about the utility of tivozanib following combination therapy cannot be inferred on the basis of TIVO-3 alone. Trials to evaluate sequencing strategies for advanced RCC are needed, although challenging given the rapidly evolving treatment paradigm.

Finally, much of the interest regarding tivozanib has been due to the specificity of the molecule for VEGFR1, VEGFR2, and VEGFR3, hypothesized to reduce off-target toxicity resulting in fewer dose interruptions and dose reductions (2,3). In a recent study of the real-world use of targeted therapies, Aspinall and colleagues found

that among 220 men with newly diagnosed mRCC treated in the United States Veterans Affairs (VA) system between 2010–2014, 62.3% of patients had one or more doses held or reduced, typically due to an adverse drug event (20). In TIVO-3, adverse events (AEs) were reported in 94% of the sorafenib group and 84% of the tivozanib group (1). Serious AEs occurred in 43.4% of the tivozanib group and 39.4% of the sorafenib group and were considered treatment-related in 11% and 10% respectively (1,7). There were fewer dose interruptions and dose reductions due to AE in the tivozanib group compared to sorafenib group (48% and 24% *vs.* 63% and 38%, respectively) (1). However, because the study was not blinded the authors note there is possible bias in toxicity assessments, potentially resulting in more dose alterations in the sorafenib group (1). In addition, there was no quality of life assessment performed, thus drawing conclusions about patient quality of life or treatment preference is not feasible (1). Notably, in TIVO-1 health related quality of life was measured and no differences between tivozanib and sorafenib were seen (4).

Ultimately, it is hard to know where tivozanib fits in the current mRCC treatment landscape. Outside of clinical trials, Aspinall found that the average number of targeted therapies received by patients with newly diagnosed mRCC was 1.9 and the median time from therapy initiation to death was 13 months (20). This sobering real-world data is a reminder we have a long way to go in the treatment of patients with mRCC. Tivozanib may be beneficial to a subset of patients, but without better methods to identify those patients the overall results from TIVO-3 do little to move the needle.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm.2020.03.217>). The authors have no conflicts of interest to declare.

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