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# Safety and Efficacy of Tivozanib in First-Line mRCC: A Multicenter Compassionate-Use Study (Meet-Uro 16)

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**Keywords**
Tivozanib · Metastatic renal cell carcinoma · Toxicity · Progression · Survival · Retrospective · Hypertension

**Abstract**
***Introduction:*** Tivozanib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptor 1 (VEGFR-1), VEGFR-2, and VEGFR-3, recently approved in Europe for the first-line treatment of metastatic renal cell carcinoma (mRCC). ***Methods:*** Retrospective analysis of safety and activity of tivozanib administered at 1.34 mg daily (3 weeks on, 1 week off) within a compassionate-use program to patients with mRCC with no prior systemic treatment in Italy. ***Results:*** From August 2018 to April 2019, 64 patients have started tivozanib in 9 oncology units. The median age was 67.5 years (range 40–85), 62.5% males. According to International Metastatic Renal Cell Carcinoma Database Consortium criteria, 27.1% of patients were good prognosis, 57.6% intermediate, and 15.3% poor. Primary tumor had been removed in 71.9% of patients. Histology was clear cell 89%, papillary 4.7%, and unclassified 6.3%. The response rate was 34.4%, stable disease 40.6%, and progression 15.6%. Grade 3–4 toxicities were 7.8% hypertension, 4.7% anemia, 3.1% mucositis, 3.1% asthenia, 1.6% diarrhea, 1.6% anorexia, 1.6% worsening of renal function, and 3.1% cardiac events. Dose reduction to 0.89 mg was applied to 17.2% of patients, and the discontinuation rate due to toxicity was 5.8%. Median progression-free survival was 12.4 months, with 68.7% of patients alive at 12 months. The developing of hypertension predicted increased progression-free survival at multivariate

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analysis (HR, 0.128; 95% CI, 0.03–0.59; $p = 0.008$). ***Conclusions:*** Tivozanib showed good activity and favorable safety profile in a real-world cohort of unselected patients with mRCC. Predictive biomarkers of response to antiangiogenic therapy are urgently needed in order to identify RCC patients who could still receive a monotherapy with VEGFR inhibitors in the first line. 

## Introduction

Oral tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor families revolutionized the treatment of metastatic renal cell carcinoma (mRCC), with sunitinib and pazopanib being the most frequent TKIs used in the first line. They achieved comparable results in terms of overall response rates (ORRs) (24 and 31%, respectively), progression-free survival (PFS) (9.5 and 8.4 months), and overall survival (OS) (29.1 and 28.3 months) in a randomized trial [1]. Type and incidence of adverse events (AEs) were different among the 2 agents, with 51 and 44% of dose reductions and 20 and 24% of early discontinuation due to toxicities with sunitinib or pazopanib, respectively. In a randomized phase 2 trial, cabozantinib showed improved PFS over sunitinib in the subgroup of International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) [2] intermediate- and poor-risk patients (8.2 vs. 5.6 months, $p = 0.012$), with 46 and 20% of dose reductions and early discontinuation due to toxicity [3].

Tivozanib (formerly known as AV-951 or KRN-951) is a selective inhibitor of vascular endothelial growth factor-induced phosphorylation of intracellular domains of VEGFR-1, VEGFR-2, and VEGFR-3 [4]. Pharmacokinetic studies showed a half-life slightly above 100 h, thus allowing for once-daily administration. Preclinical studies have reported that tivozanib may also have immune modulatory activities by reducing regulatory T cells and myeloid-derived suppressor cell accumulation, and their potential correlation with activity of this drug has recently been reported in a small cohort of patients with hepatocellular carcinoma [5].

A phase 2 study was conducted in 272 patients with mRCC (83% clear-cell histology) who were treated with tivozanib at 1.5 mg/daily for 3 weeks followed by a 1-week break, with an ORR of 24% and a promising median PFS of 11.7 months [6].

The large randomized TIVO-1 trial was therefore planned to compare tivozanib against sorafenib in 517 mRCC patients with a clear-cell component not previously exposed to TKIs or mTOR inhibitors (only 1 prior regimen with chemotherapy, hormonal therapy, or cytokine-based immunotherapy allowed).

Tivozanib 1.5 mg/daily (3 weeks on, 1 week off) achieved superior ORR at a blinded independent radiology review (33.1 vs. 23.3%) as well as superior PFS (11.9 vs. 9.1 months; HR, 0.797; 95% CI, 0.639–0.993; $p = 0.042$) compared to sorafenib [7]. However, the final OS analysis showed a trend toward longer survival on the sorafenib arm than on tivozanib (median, 29.3 vs. 28.8 months; HR, 1.245; 95% CI, 0.954–1.624; $p = 0.105$) as a result of 2 factors: the availability of tivozanib (within a separate crossover phase 2 study) just for patients progressing on sorafenib (but not vice versa) and the limited availability of active agents post-progression on tivozanib in Eastern Countries where the majority of patients were enrolled. Indeed, a greater proportion of patients in the sorafenib arm, as compared to those randomized to tivozanib (63 vs. 13%), did receive a subsequent targeted therapy for mRCC, mainly tivozanib itself [8, 9]. The spectrum of AEs was typical of TKIs, with hypertension and dysphonia being more frequent with tivozanib and hand-foot syndrome and diarrhea with sorafenib. The discontinuation rate due to toxicity was low and comparable between the 2 drugs (4% tivozanib and 5% sorafenib), but temporary treatment interruptions due to AEs occurred in 92 patients (36%) treated with sorafenib versus 50 (19%) treated with tivozanib as well as dose reductions occurred in 111 patients (43%) treated with sorafenib versus 37 (14%) treated with tivozanib (Fisher's exact test $p = 0.001$ for both).

The U.S. Food and Drug Administration rejected the approval of tivozanib for mRCC in May 2013, but then European Medicine Agency (EMA) approved it on August 2017 on the basis of both the above considerations regarding TIVO-1 study design, as well as improved side-effect profile and reduced rate of serious AEs with tivozanib [10]. Comparable PFS benefit and less risk of grade 3–4 toxicities were reported with tivozanib in a recent network meta-analysis compared to other TKIs [11].

After EMA registration, a compassionate use of tivozanib was opened in Italy, allowing early access to the drug for first-line mRCC patients. The aim of this analysis was to evaluate the safety and activity of tivozanib administered to a multicenter cohort of real-world patients with mRCC enrolled in the compassionate use.

**Table 1.** Patients' characteristics, *N* = 64

| | Patients, % |
|---|---|
| Age | Median 67.5 years<br>Range 30–85 years<br>25 pts ≥70 years (39.1) |
| Gender | 40 males (62.5)<br>24 females (37.5) |
| ECOG performance status | 22 ECOG 0 (34.4)<br>23 ECOG 1 (35.9)<br>16 ECOG 2 (25.0)<br>3 ECOG 3 (4.7) |
| BMI (59 patients) | 28 <25 kg/m$^2$ (43.8)<br>31 ≥25 kg/m$^2$ (48.4) |
| Creatinine clearance | Median 63 mL/min (range 30–97) |
| Surgery on primary tumor (total or partial nephrectomy) | 46 yes (71.9)<br>18 no (28.1) |
| Histology | 57 clear cell (89)<br>3 papillary (4.7)<br>4 unclassified/specified (6.3) |
| Site of metastases | 46 lung (71.9)<br>24 bone (37.5)<br>35 lymph nodes (54.7)<br>4 brain (6.3)<br>9 liver (14.1)<br>5 pancreas and/or thyroid (7.8) |
| IMDC score (59 patients) | 16 good (27.1)<br>34 intermediate (57.6)<br>9 poor (15.3) |

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ECOG, Eastern Cooperative Collaborative Group; BMI, body mass index.

## Material and Methods

*Inclusion Criteria*

We retrospectively collected the clinical data of all consecutive mRCC patients enrolled in the tivozanib compassionate use (August 2018 to April 2019), treated in 9 oncology centers in Italy.

Inclusion criteria were as follows:

- adult patients with histological diagnosis of renal cell carcinoma, either clear-cell or alternative histologies
- metastatic disease, any site, without any former systemic treatment with TKIs or immunotherapy
- adequate performance status (Eastern Cooperative Oncology Group-ECOG 0–2), normal hematology, liver, and renal function
- absence of swallowing problems or any other serious comorbidity contraindicating the administration of TKIs

This was an academic study conducted within the Meet-Uro Italian network (Meet-Uro 16 study). EUSA Pharma provided for the supply of tivozanib to each center.

*Treatment*

Patients started tivozanib at 1.34 mg daily (3 weeks on, 1 week off) as per EMA registration. Dosage could be reduced to 0.89 mg daily according to the AEs experienced by the patients, at the discretion of the treating physician.

Patient prognosis was categorized before the start of treatment according to the IMDC prognostic score [2]. Disease was staged and reassessed every 3–4 months mainly with contrast-enhanced computerized tomography or with alternative radiological assessments as per clinical practice of each center. Visits and blood tests were repeated every month or more frequently, according to the toxicities developed by the patients.

We defined dose interruption as a temporary withhold of tivozanib, with the aim of allowing the patient to recover from toxicity. Cause of definitive drug suspension was differentiated as either due to disease progression, unacceptable toxicity, or patient refusal to go on with treatment. AEs were retrospectively collected in the clinical charts as they were registered according to clinical practice, then classified, and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

*Statistical Analysis*

Clinical characteristics were summarized with descriptive statistics. Tumor response and progression were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) ver-

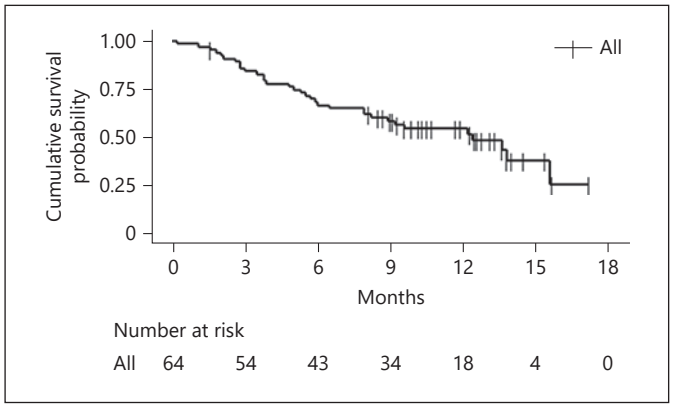


**Fig. 1.** PFS of the whole cohort of 64 patients. PFS, progression-free survival.

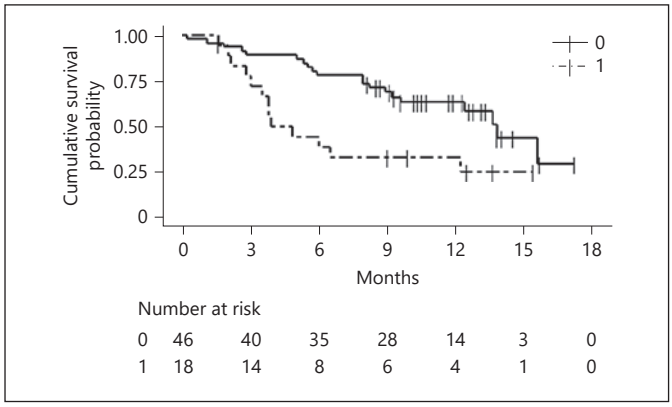


**Fig. 2.** Progression-free survival according to the previous surgery on the kidney (1 – thick line) or none (0 – dotted line), $p = 0.006$. PFS, progression-free survival.

sion 1.1 [12]. PFS was calculated from the start of treatment to disease progression or censored at the last follow-up date known without progression (radiological and/or clinical). OS was calculated from the start of treatment to death for any cause. The survival status of patients lost to follow-up was checked with municipal registries.

The association between nominal variables has been analyzed with the $\chi^2$ or Fisher's exact test whenever appropriate according to the size subgroups. PFS and OS have been estimated with the Kaplan-Meier method and compared with log-rank test and Cox proportional hazards method. The effect of different prognostic factors on PFS including age (<70 vs. ≥ 70 years), performance status (0 vs. 1–2), body mass index (<25 vs. ≥ 25 kg/mq), previous surgery on renal tumor (yes vs. not), IMDC risk category (good, intermediate, poor), and dose reduction, hypertension, or hypothyroidism developing during treatment was first assessed by the univariate analysis. The multivariate analysis was performed with covariates affecting patient prognosis at univariate analysis and incorporating IMDC risk category. All statistical analyses have been carried out with the software "R," version 4.0.3.

## Results

*Patients*

We identified 64 patients who received at least 1 dose of tivozanib, median age 67.5 years, more than one-third being ≥70 years (39.1%). Patients' characteristics are outlined in Table 1. Almost 90% of patients had clear-cell histology. Sixteen patients (27.1%) had a good IMDC prognostic score, 34 (57.6%) had an intermediate-risk score, and 9 (15.3%) had a poor-risk score. Twenty-two out of 24 patients with bone metastases received bone-targeted agents (bisphosphonates or denosumab). Fifteen patients received concomitant palliative radiotherapy during tivozanib administration, mainly on bone lesions.

*Response and Second-Line Therapy*

Twenty-two patients achieved a radiological partial response (34.4%) according to the treating oncologist's evaluation, with a median time to response of 3.0 months (range 2.3–4.3 months). Twenty-six patients had stable disease as their best response (40.6%), 10 patients developed early progression (15.6%), and 6 patients were not evaluable.

RR was compared between patients with or without involvement of bone (25.0 vs. 47.0%, respectively, $\chi^2$ test $p = 0.08$), of lymph nodes (39 vs. 37.0%, $p = 0.89$), of liver (33 vs. 38.4%, $p = 0.58$), of lung (45 vs. 22.2%, $p = 0.098$), of brain (33 vs. 38.1%, $p = 0.86$), and of pancreas and/or thyroid (50 vs. 37.0%, $p = 0.98$). At the cutoff date of January 25, 2020, therapy with tivozanib had been definitively stopped in 34 patients (53.1%), while 30 patients were still on treatment. The main reasons for discontinuation were disease progression (31 patients, 91.2%), followed by toxicity (2 patients, 5.8%), and a single case of refusal to continue the treatment despite the absence of severe toxicities (1 patient, 3%). Out of 34 patients discontinued from first-line tivozanib, 16 patients (48.5%) had started a second-line therapy at the cutoff date: nivolumab in 10 patients (62.4%), sunitinib in 1 (6.3%), cabozantinib in 1 (6.3%), while 4 patients (25%) were enrolled onto an experimental trial.

*Progression and Survival*

After a median follow-up of 12.5 months, 33 patients have progressed or died, with an estimated PFS of 12.4 months (95% CI, 8.2 – not reached) (shown in Fig. 1). At univariate analysis, patients with ECOG performance status 0 had a superior PFS compared to the remaining pa-

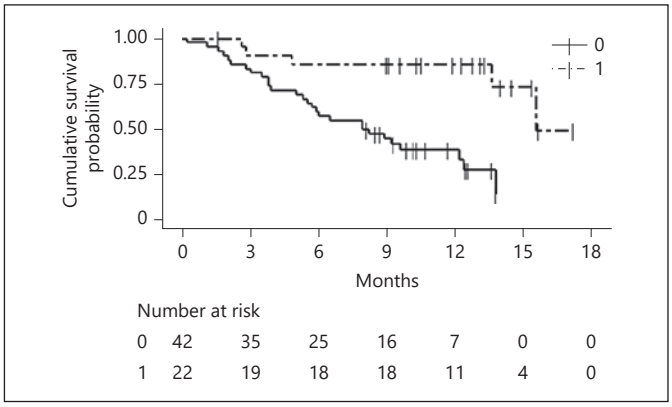


**Fig. 3.** PFS according to the development of hypertension (1 – dotted line) or no hypertension (0 – thick line), $p < 0.001$. PFS, progression-free survival.

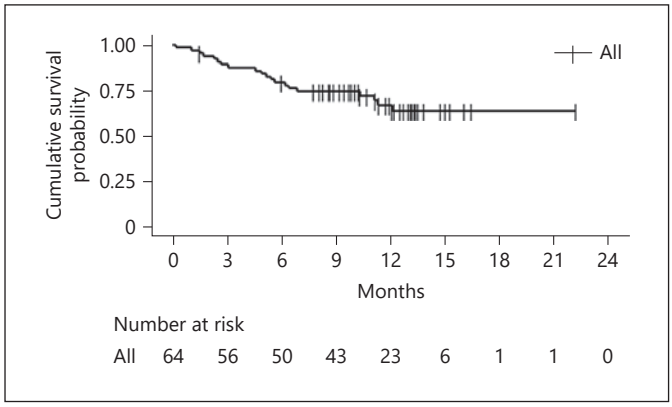


**Fig. 4.** OS of 64 patients (median not reached). OS, overall survival.

**Table 2.** Multivariate analysis for progression-free survival

| Variable | Patients, *n* | Hazard ratio | 95% CI | *p* value |
|---|---|---|---|---|
| ECOG PS >0 versus 0 | 64 | 2.029 | (0.64–6.41) | 0.227 |
| Previous surgery on the kidney no versus yes | 64 | 1.639 | (0.65–4.14) | 0.296 |
| Hypertension yes versus no | 64 | 0.128 | (0.03–0.59) | 0.008 |
| Radiological response no versus yes | 58 | 2.091 | (0.43–10.19) | 0.361 |
| IMDC intermediate versus good | 50 | 3.961 | (0.67–23.51) | 0.129 |
| IMDC poor versus good | 25 | 2.723 | (0.86–7.03) | 0.538 |

ECOG PS, Easter Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; CI, confidence interval.

tients (median PFS 13.8 vs. 7.9 months; $p = 0.004$). Previous surgery on the kidney had been performed on 71.9% of patients and was associated with improved PFS compared to unoperated patients (13.8 vs. 4.4 months; $p = 0.006$) (shown in Fig. 2), as well as the development of hypertension during treatment in 34.4% of patients compared to patients with no hypertension (15.6 vs. 8.1 months; $p < 0.001$) (shown in Fig. 3) and the achievement of radiological response compared to patients with stable disease or progression as their best response (15.6 vs. 12.4 months; $p = 0.04$). Patients in the good IMDC group had a superior PFS compared to intermediate and poor patients (median PFS not reached vs. 12.4 and 6 months, respectively; $p = 0.07$). Age ≥70 years, BMI ≥25 kg/m$^2$, hypothyroidism, and dose reduction were not significant for PFS. At multivariate analysis, only hypertension was independently associated with improved PFS with an HR of 0.128 (95% CI, 0.03–0.59; $p = 0.008$) (Table 2). At the cutoff date, 44 patients were still alive at 12 months (68.7%) and the median survival had not been reached (shown in Fig. 4).

*Toxicity*

Dose reduction to 0.89 mg/daily was reported in 11 patients (17.2%) due to AEs, while temporary interruption of treatment was applied to 11 patients (17.2%). Almost all patients experienced grade 1–2 AEs (92.3%), the most frequent of which are asthenia/fatigue, hypothyroidism, hypertension, and gastrointestinal. The overall incidence of grade 3–4 toxicities was 21.5%, with a nonsignificant trend for increased incidence in patients ≥70 years of age (47%, $\chi^2$ test $p = 0.11$). Interestingly, there were no episodes of skin toxicities >grade 2. Two elderly patients experienced a myocardial infarction (3.1%, 1 fatal). The cumulative incidence of toxicities is reported in Table 3.

## Discussion

In this retrospective study, we analyzed the tolerability and activity of tivozanib administered as a first-line regimen to patients with mRCC within a nationwide compas-

**Table 3.** Toxicity of tivozanib

| | Grade 1–2 | | Grade 3–4 | |
|---|---|---|---|---|
| | patients, *n* | % | patients, *n* | % |
| Asthenia/fatigue | 42 | 65.6 | 2 | 3.1 |
| Hypertension | 22 | 34.4 | 5 | 7.8 |
| Cardiac events | – | | 2* | 3.1 |
| Skin toxicity | 9 | 14.1 | – | |
| Mucositis | 12 | 18.8 | 2 | 3.1 |
| Heartburn/gastritis | 8 | 12.5 | – | |
| Diarrhea | 12 | 18.8 | 1 | 1.6 |
| Nausea/vomiting | 13 | 20.3 | 1 | 1.6 |
| Hoarseness | 1 | 1.6 | – | |
| Anemia | 7 | 10.9 | 3 | 4.7 |
| Erythrocytosis | 2 | 3.1 | – | |
| Thrombocytopenia | 3 | 4.7 | – | |
| Hypothyroidism | 29 | 45.3 | – | |
| Hypercholesterolemia | 2 | 3.1 | – | |
| Worsening of renal function | 4 | 6.3 | 1 | 1.6 |
| Liver toxicity | 3 | 4.7 | – | |

* Two cases of myocardial infarction were reported, 1 fatal.

sionate-use program. Real-world population studies acquire increased relevance whenever a new agent with improved safety profile is approved in order to verify its tolerability in a broader range of patients, less selected compared to registration studies.

Our cohort of 64 patients represent a typical population of every day mRCC patients, with a higher median age of 67.5 years than 59 years of those enrolled into the randomized TIVO-1 trial [7], and a double rate of IMDC poor-risk subgroup (15.3 vs. 7%). Despite this, investigator-assessed RR of 34.4% and median PFS of 12.4 months in our study compare favorably with the centrally reviewed RR and PFS reported in the registration trial (33.1% and 11.9 months, respectively), thus confirming the efficacy of tivozanib as a first-line TKI in the real-world setting. Responses appeared quite early during treatment (median time to response 3.0 months) and were registered more frequently in patients with lung metastases (45%) or lymph nodal disease (39%) than those with bone involvement (25%), but differences were not statistically significant.

At univariate analysis, several clinical parameters predicted prolonged PFS, first of all ECOG performance status which is a well-known prognostic factor in mRCC. Moreover, also the removal of the primary tumor impacted on PFS, as suggested by many other retrospective reports [13] but not in the recent randomized CARMENA trial [14]. Indeed, the role of cytoreductive nephrectomy remains controversial in the current days, but a potential benefit may still be hypothesized for certain subgroups of patients (e.g., good-risk patients with limited burden of metastatic disease).

The development of hypertension impacted on PFS of our patients, as previously reported for other TKIs, because of the close link between intense antiangiogenic activity and constriction of peripheral vasculature with an increase of blood pressure [15]. In our analysis, also the achievement of radiological response (all partial, none complete) impacted on prolonged disease control as reported in other retrospective cohorts treated with different TKIs [16, 17]. Long-term data of a randomized trial recently confirmed that the RECIST response is a predictor of long-term outcome with both TKIs and modern immunotherapy [18].

On the contrary, age ≥70 years did not impact on PFS, suggesting that age does not influence the activity of tivozanib as already demonstrated for other TKIs administered to older mRCC patients [19, 20]. At multivariate analysis, hypertension was the only clinical variable predictive for increased PFS (Table 2).

Considering the brief follow-up of our study, OS analysis can be considered only preliminary. Yet, we report a 12-month survival rate (44/64 patients, 68%) compared to the TIVO-1 study (183/260 patients, 70.4%) [7].

More importantly, the tolerability of tivozanib appears fairly comparable to that previously reported. Grade 3–4 toxicities were retrospectively reported in 21.5% of our cohort, consisting mainly of hypertension (7.8 vs. 27% in the TIVO-1 trial) [7], fatigue (3.1 vs. 5%), anemia (4.7 vs. 2%), and mucositis (3.1 vs. <1%). More than one-third of

our patients had >70 years and showed a superior incidence of grade 3–4 events (45.3%), although not statistically significant. In this setting, multidimensional geriatric parameters may help to identify those patients at an increased incidence of toxicities and guide precautionary dose adjustments [21]. We registered a superimposable rate of temporary treatment interruptions (17.2 vs. 19% of patients), dose reductions (17.2 vs. 14% of patients), and early discontinuation due to toxicity (5.8 vs. 5% of patients) compared to the TIVO-1 study [7], thus proving that the favorable toxicity profile of tivozanib is maintained also in a less selected population of patients. Higher rates of dose reduction of 46 and 42% were reported in real-world cohorts of Italian patients treated with first-line sunitinib [22] or second-line cabozantinib [23], respectively, as an indirect proof of improved manageability of standard-dose tivozanib.

Of particular note is the very low rate of skin toxicity, the so-called hand-foot skin reaction, which may be particularly frequent with TKIs and impact heavily on the quality of life [24]. Skin toxicity was reported as grade 1–2 by 14.1% of our patients and never grade 3 (vs. 14 and 2%, respectively, in the TIVO-1 study). This event is more troublesome with sunitinib (39% grade 1–2 and 11% grade 3–4) [1] and cabozantinib (34.6% grade 1–2 and 7.7% grade 3–4) [3] and, to less extent, with pazopanib (29% grade 1–2 and 6% grade 3–4) [1], thus representing a potential advantage for the use of tivozanib in the first line.

One patient died of acute myocardial infarction during treatment with tivozanib in our study (1.5%), while in the registration trial 7 deaths occurred due to cardiac events during or within 30 days from the last dose of tivozanib (2.7%). Cardiac toxicity has been described with all TKIs [25] and requires close monitoring of patients, especially those with a previous history of hypertension or ischemic heart disease, who are at increased risk of developing cardiovascular events during treatment.

As a whole, our data confirm the activity and fair tolerability of tivozanib in a real-world population, making tivozanib an attractive alternative to other TKIs for the first-line monotherapy of mRCC, especially in those Counties where the novel immune-based combinations are not available or reimbursed. A recent network meta-analysis confirmed the lower risk of grade 3–4 toxicities induced by tivozanib compared to other TKIs [11], with a potential advantage in terms of quality of life of patients and reduced risk of toxicity-induced discontinuation.

Since the registration of tivozanib in 2017 by EMA [10], the landscape of first-line treatment of mRCC has been revolutionized by immune-based combination regimens such as the association of the anti-CTLA-4 ipilimumab plus the anti-programmed cell death (PD-1) nivolumab [26], the combination of the anti PD-1 pembrolizumab plus the TKI axitinib [27], and the combination of the anti PD-1 ligand avelumab plus axitinib, nivolumab plus cabozantinib, or pembrolizumab plus lenvatinib. The first immunotherapy-only regimen has been approved by EMA only for IMDC intermediate- or poor-risk patients, while the hybrid combinations of immunotherapeutic plus antiangiogenic agent are (or will be) approved for all IMDC risk groups.

Current international guidelines encompass one of these combinations as the preferred choice for the first-line treatment of mRCC [28, 29], although there is a wide debate on whether this should be the choice for all patients, especially those who have a good IMDC risk with low metastatic burden in the lung and/or lymph nodes [30]. The gene expression analysis of the IMMOTION151 trial has given an important hint on how we should ideally proceed in the choice of the first-line regimen [31]. In this study, a specific angiogenic high genetic signature has demonstrated to predict increased benefit from sunitinib compared to the angiogenic low counterpart. This signature was found most frequently in IMDC good-risk patients and was rarer in those with intermediate/poor risk or in tumors with sarcomatoid features, which, on their turn, showed more frequently a T-effector high signature, which was predictive of increased benefit from the association of immunotherapy plus the antiangiogenic agent bevacizumab.

Further prospective randomized trials are necessary to verify if patients with angiogenic high tumors may be managed with a monotherapy with TKI instead of a combination regimen, with the aim of reducing costs and rates of AEs, provided that comparable long-term outcomes are achieved. If that will be the case, tivozanib may be a good option in view of its good activity and favorable tolerability, although only indirect comparisons are available between tivozanib and sunitinib, pazopanib, or cabozantinib [10].

Our study has several weaknesses, the most important of which is its retrospective nature. Since tivozanib is perceived to be better tolerated than sunitinib or cabozantinib, there could have been a sort of negative selection bias, favoring its use in patients with worse performance status or with more comorbidities, in those not eligible for clinical trials. In fact, the proportion of poor-risk patients in this study is increased compared to clinical trials, but the favorable RR and PFS rates obtained, although not centrally reviewed, do not support a strong negative selection bias of our cohort.

Moreover, some AEs not impacting on dose reduction or treatment interruption may have gone underreported in the clinical charts, especially if we consider that patients were usually seen after 1 week of rest from the treatment, so we may assume that some of the peaks of toxicities (e.g., hypertension) may have been missed. For these reasons, prospective studies are needed to confirm these findings and explore more in depth the potential use of tivozanib monotherapy in patients with mRCC.

Moreover, a very recent trial explored the association of tivozanib (1.5 mg daily for 3 weeks followed by 1-week rest) with nivolumab in 25 mRCC patients (52% pretreated) and reported a promising RR of 56% (including 1 complete response) and a PFS of 18.9 months [32]. Further clinical development of the association of tivozanib with checkpoint inhibitors is therefore warranted in view of the improved tolerability of this TKI and of its immune modulatory properties [5].

## Conclusions

This real-world study confirms the favorable risk-benefit balance of tivozanib in the first-line treatment of mRCC, with RR and PFS results comparable to the registration trial and very limited rates of dose reductions and discontinuation due to toxicity. Validation of predictive biomarkers of response to antiangiogenic therapy is urgently needed in order to identify mRCC patients who could still receive a monotherapy of VEGFR inhibitors in the first line with the aim of maximizing cost-effectiveness and prolong disease control with a limited incidence of AEs and improved quality of life. Trials combining tivozanib with immunotherapy are ongoing.


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## Statement of Ethics

This retrospective research followed the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All patients have given their written informed consent to the compassionate use of TIVOZANIB and to the use of personal data according to General Data Protection Regulation (European Union 2016/679). Approval by Ethics Committee of Istituto Oncologico Veneto of Padova was obtained on October 18, 2018 (No. 17590) and then by all participating centers.

## Conflict of Interest Statement

U.B. plays an advisory role for Bristol Myers Squibb, MSD, and Janssen; receives speaker's fees from Bristol Myers Squibb, Astellas, Janssen, Ipsen, Novartis, and Sanofi Aventis and research funds from Ipsen. G.P. plays an advisory role and/or receives speakers' fees from Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen, Ipsen, Merck, MSD, Novartis, and Pfizer. F.M. has no conflicts of interest to declareA.B. plays an Advisory board role for Takeda, Boehringer Ingelheim, Pfizer, Roche, MSD, and AstraZeneca; receives speaker's fees from Takeda, Boehringer Ingelheim, and AstraZeneca and grant from AstraZeneca. L.F. has no conflicts of interest to declare. M.M. has no conflicts of interest to declare. M.B. has no conflicts of interest to declare. P.E has no conflicts of interest to declare. D.B. has no conflicts of interest to declare. E.V. plays an advisory role for Janssen and receives speaker's fees from Pfizer, MSD, Astellas, Janssen, Novartis, and Ipsen. M.R. plays an advisory role and receives speaker's fees from Pfizer. C.P. receives consultant or speaker's fees from Angelini, AstraZeneca, BMS, Eisai, EUSA, General Electric, Ipsen, Janssen, Merck, MSD, Novartis, and Pfizer; receives expert testimony for EUSA and Pfizer; serves as a protocol steering committee member for BMS, Eisai, and EUSA Pharma; and receives travel support from Roche.


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## Author Contributions

U.B., G.P., and C.P. involved in conceptualization; U.B., G.P., G.F., F.M., A.B., L.F., M.M., M.B., P.E., D.B., E.V., M.R., and C.P. involved in data curation and collection; U.B. involved in formal analysis; U.B., G.P., and C.P. involved in supervision and validation of data; U.B. involved in writing – original draft; and U.B., G.P., E.V. and C.P. involved in writing – review and editing.

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