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Original Research

Efficacy of tivozanib treatment after sorafenib in patients with advanced renal cell carcinoma: crossover of a phase 3 study

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Abstract ***Background:*** Tivozanib is a selective inhibitor of vascular endothelial growth factor receptors 1, 2 and 3 tyrosine kinases. This open-label, crossover clinical study (AV-951-09-902) provided access to tivozanib for patients who progressed on sorafenib in TIVO-1, comparing tivozanib with sorafenib in patients with advanced renal cell carcinoma (RCC).
Methods: Patients enrolled in this single-arm, phase 2 crossover study were previously randomised to sorafenib on TIVO-1, progressed and then crossed over to tivozanib. Patients received tivozanib (1.5 mg/day orally; 3 weeks on/1 week off) within 4 weeks after their last sorafenib dose.
Findings: Crossover patients were exposed to tivozanib for a median of eight cycles. From the start of tivozanib treatment, median progression-free survival was 11.0 months (95%

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confidence interval [CI]: 7.3–12.7) and median overall survival was 21.6 months (95% CI: 17.0–27.6). Best overall response was partial response in 29 (18%) patients and stable disease in 83 (52%) patients, with a median duration of response of 15.2 and 12.7 months, respectively. About 77% of patients experienced adverse events, most frequently hypertension (26%), followed by diarrhoea (14%) and fatigue (13%); 53% of patients had treatment-related adverse events, including 24% grade ≥3. About 9% and 16% of patients had dose reductions and dose interruptions due to adverse events, respectively. A total of 30% of patients had serious adverse events, and 4% had treatment-related serious adverse events.

Interpretation: This crossover study of patients with advanced RCC demonstrated potent tivozanib anti-tumour activity. Safety and tolerability profiles were acceptable and consistent with the established adverse event profile of tivozanib.

1. Introduction

The National Cancer Institute (NCI) estimates that in 2018, approximately 63,300 new cases of renal cell carcinoma (RCC) and 14,900 RCC disease–related deaths will be reported [1,2]. Recent advances in the understanding of the pathophysiologic mechanisms underlying RCC have facilitated the development of therapies that target signalling pathways, in particular, the selective inhibition of vascular endothelial growth factor (VEGF), revolutionising treatment for this disease [3,4]. Small-molecule tyrosine kinase inhibitors (TKIs) including sorafenib, sunitinib, pazopanib and cabozantinib, as well as antibodies like bevacizumab (in combination with interferon alpha), are commonly used for first-line and advanced treatment of RCC [4–8]. However, sorafenib, sunitinib and pazopanib, in particular, demonstrate limitations, including broad-spectrum kinase inhibitory activity and subsequent adverse events (AEs), such as fatigue, diarrhoea, skin rash, hand-foot skin reaction, myelosuppression, liver toxicity and transaminitis [9–12]. Two inhibitors of mammalian target of rapamycin (mTOR), temsirolimus and everolimus, are also approved for treatment of this intractable disease [13,14], as well as a TKI/mTOR combination (lenvatinib and everolimus) [15]. In addition, second-generation TKIs such as axitinib [16] and a monoclonal antibody against the programmed death receptor-1 (PD-1), nivolumab, are approved and used commonly for second-line treatment in patients with RCC [15].

Tivozanib is a TKI recently approved by the European Commission for the treatment of untreated RCC and is currently in further development for the treatment of advanced RCC [17]. Tivozanib has demonstrated a favourable pharmacodynamic profile characterised by highly potent and selective inhibition of VEGF receptors (VEGFRs) 1, 2 and 3 tyrosine kinases, requiring an eight-fold increase in concentration to inhibit other tyrosine kinases, therefore optimising blockade of VEGFRs with minimal toxicities [18–21]. Tivozanib inhibits angiogenesis and vascular permeability in tumour tissues, leading indirectly to inhibition of tumour growth [18]. Furthermore, the half-life ($t_{1/2}$) of tivozanib is approximately 4 days, allowing convenient once-daily dosing at 1.5 mg to maintain effective serum concentrations [19,22]. Clinical study data in the tivozanib programme repeatedly demonstrated the efficacy of tivozanib in the treatment of patients with advanced RCC. In a phase 2 trial of tivozanib in 272 patients with advanced RCC (untreated or following one prior line of therapy), the median progression-free survival (PFS) was 11.7 months, and the objective response rate was 24%, supporting further investigation in a phase 3 study [23].

TIVO-1, a phase 3 trial comparing tivozanib with sorafenib in 517 patients with advanced RCC, either untreated or following progression on a cytokine, met its primary end-point with an improved median PFS of 11.9 months in the tivozanib arm, compared with 9.1 months in the sorafenib arm ($P = 0.042$) [17]. Tivozanib was well tolerated, and patients randomised to tivozanib received 94% of scheduled chemotherapy, compared with 80% in the sorafenib arm. In the protocol-specified final analysis, the median overall survival was 28.8 months (95% confidence interval [CI]: 22.5, NA) in tivozanib-treated patients and 29.3 months (95% CI: 29.3, NA) in sorafenib-treated patients (hazard ratio [HR] 1.245; $P = 0.105$). Of note, 74% of patients randomised to sorafenib on TIVO-1 were treated with next-line therapy (mostly tivozanib) after progressive disease, whereas only 35% of patients in the tivozanib arm received next-line therapy [11,24]. This discrepancy was due to the lack of available second-line therapies in the Eastern European countries, such that many patients randomised to tivozanib had no salvage therapy. The results of overall survival in TIVO-1 were likely confounded by the differential use of subsequent cancer therapy in the two treatment arms, as well as the activity of tivozanib in second line. The current report will