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Clinical Trial

Phase 2 trial of dovitinib in patients with progressive *FGFR3*-mutated or *FGFR3* wild-type advanced urothelial carcinoma

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Abstract ***Background:*** Second-line treatment options for patients with advanced urothelial carcinoma (UC) are limited. Fibroblast growth factor receptor 3 (FGFR3) is dysregulated in UC by activating mutations or protein overexpression in non-mutant tumours. In this study, the efficacy, pharmacodynamics and safety of dovitinib—a broad-targeted inhibitor of tyrosine kinases, including FGFR3—were evaluated in patients with previously treated advanced UC with and without FGFR3 mutations.
Methods: Forty-four adults with advanced UC who had progressed after one to three platinum-based and/or combination chemotherapy regimens were classified as having mutant

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(*FGFR3*^{MUT}; $n = 12$), wild-type (*FGFR3*^{WT}; $n = 31$), or unknown ($n = 1$) *FGFR3* status. Patients received 500 mg dovitinib once daily on a 5-days-on/2-days-off schedule. The primary end-point of this two-stage study was the investigator-assessed overall response rate (ORR).

Results: Most of the patients were men (75%) and over half of the patients were aged ⩾65 years (61%). All patients had received ⩾1 prior antineoplastic therapy for UC. The study was terminated at the end of stage 1, when it was determined by investigator review that the ORR of both the *FGFR3*^{MUT} (0%; 95% confidence interval [CI], 0.0–26.5) and *FGFR3*^{WT} (3.2%; 95% CI, 0.1–16.7) groups did not meet the criteria to continue to stage 2. The most common grade 3/4 adverse events, suspected to be study-drug related, included thrombocytopenia (9%), fatigue (9%), and asthenia (9%).

Conclusion: Although generally well tolerated, dovitinib has very limited single-agent activity in patients with previously treated advanced UC, regardless of *FGFR3* mutation status. clinicaltrials.gov NCT00790426.

1. Introduction

Urothelial carcinoma (UC) accounts for ⩾90% of cases of urinary bladder cancer [1]. Despite initial sensitivity to standard first-line combination platinum-based chemotherapy in patients with advanced disease, the overall prognosis is poor; the median survival is approximately 15 months in chemotherapy-treated patients [1,2]. Although taxanes are widely used in cisplatin-refractory patients, efficacy is modest and toxicities are limiting [2]. Vinflunine is registered for relapsed/refractory UC in Europe but is not approved in the United States. Thus, there is a significant need for effective and well-tolerated agents for patients with advanced, previously treated UC.

A promising target in UC is fibroblast growth factor receptor 3 (FGFR3)—one of four highly conserved FGF receptor tyrosine kinases (RTKs) with known regulatory roles in tumour growth and survival [1]. Bladder cancer is associated with FGFR3 protein overexpression in *FGFR3*-mutant (85%) and -non-mutant (42%) tumours, and approximately 70% of low-grade non-invasive and 15% of high-grade UC tumours are associated with 11 different *FGFR3*-activating missense mutations [1,3,4]. Furthermore, transcriptome sequencing of UC tumours revealed recurrent fusion of *FGFR3* with sister chromatid cohesion and segregation component *TACC3* [5]. FGFRs also regulate angiogenesis (along with vascular endothelial growth factor receptor [VEGFR] and platelet-derived growth factor receptor [PDGFR]) [6]. The modest phase 2 clinical activity of sunitinib, a multitargeted inhibitor of RTKs (including VEGFR and PDGFR, but not FGFR), in previously treated metastatic UC suggests that the VEGFR axis may represent a viable target in advanced disease [7]. Therefore, broader inhibition of angiogenesis-associated RTKs, including FGFR, may provide more potent antitumour effects in patients with advanced UC, regardless of *FGFR3* mutation status.

Dovitinib (TKI258; Novartis Pharmaceuticals), an inhibitor of FGFR, VEGFR, PDGFRβ, CSF-1R, CKIT, RET, TrkA, and FLT3, has preclinical activity in *FGFR3*-mutant (*FGFR3*^{MUT}), *FGFR3*-fused and FGFR3-overexpressing bladder cancer cell lines and mouse xenografts [8,9]. This phase 2 study evaluated dovitinib in patients with previously treated advanced *FGFR3*^{MUT} or *FGFR3* wild-type (*FGFR3*^{WT}) UC.

2. Patients and methods

2.1. Patients

Patients aged ⩾18 years with histologically confirmed bladder, urethra, ureter or renal pelvis UC who had progressed after one to three platinum-based and/or combination chemotherapy regimens were eligible for this study. All patients had ⩾1 non-irradiated measurable lesion, archival tumour tissue available for central *FGFR3* mutation analysis, adequate blood chemistry, acceptable cardiac and liver function and a World Health Organisation (WHO) performance status of ⩽2. Patients with known or suspected brain metastases, history of another malignancy within 3 years (except adequately-treated cervical, prostate or non-melanomatous skin cancer), uncontrolled diarrhoea, or those receiving anticoagulant therapy were not eligible. All patients provided written informed consent.

2.2. Study design and treatment

This phase 2, open-label, two-arm, Simon's two-stage design, multicenter study evaluated the safety and efficacy of dovitinib in patients with previously treated advanced *FGFR3*^{MUT} or *FGFR3*^{WT} UC. The protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each study site, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Patients received 500 mg dovitinib orally once daily on a 5-days-on/2-days-off schedule in 28-day cycles until