Background: Long-term survival is poor for patients with locally advanced or metastatic urothelial carcinoma (UC) receiving chemotherapy and/or immunotherapy following progression with platinum-containing chemotherapy. Genetic alterations of fibroblast growth factor receptors (FGFR) have been shown to play a role in UC development and progression. Non-genetic and epigenetic activation of FGFR gene expression have also been described. Rogaratinib, an oral pan-FGFR 1-3 inhibitor, has shown promising activity and a manageable safety profile in a phase I study in patients with UC who were selected based on FGFR1-3 mRNA overexpression and/or activating mutations in the FGFR3 gene.

Trial design: This is a randomized, open-label, phase 2/3 study to evaluate the efficacy and safety of rogaratinib compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic UC who have received prior platinum-containing chemotherapy. The primary objective is to show superiority of rogaratinib over chemotherapy in prolonging overall survival (OS) of UC patients with FGFR-positive tumors. Secondary objectives include: objective response rate (ORR), progression-free survival, disease control rate, duration of response, and safety. Testing for FGFR1 and 3 mRNA overexpression will be conducted centrally using an RNA in situ hybridization (RNA-ISH) in archival samples. Eligible patients will be randomized 1:1 to rogaratinib (800 mg po bid) or iv chemotherapy Q3W (docetaxel 75 mg/m²; paclitaxel 175 mg/m²; or 320 mg/m² vinflunine). Randomization will be stratified according to PIK3CA and/or RAS activating mutations, prior immunotherapy, and modified 4-factor Bellmunt risk score. The objective for the phase 2 part of the study is ORR. A total of 116 patients in PIK3CA and RAS WT patients will be enrolled to the phase 2 part of the study to rule out a low difference in ORR between rogaratinib and chemotherapy as futility. The phase 3 portion of the study is powered to detect an increase in median OS in PIK3CA and RAS WT patients. Total patient enrollment expected to be approximately 400 patients.

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