Eradafitinib compared with vinflunine or docetaxel or pembrolizumab in patients (pts) with metastatic or surgically unresetable (M/UR) urothelial carcinoma (UC) and selected fgfr gene alterations (FGFRalt): The phase III THOR study

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Background: Pts with M/UR UC have poor prognoses. Programmed death (ligand)-1 (PD-1) inhibitors have improved outcomes in some pts, but responses vary based on genotypic subtype. FGFRalt are present in 25% of pts with UC, and may reflect an immunologically “cold” tumor that does not respond well to immunotherapy. Norah Siefker-Radtke ASCO GU 2018. In early phase 2 data, the pan-FGFR (1-4) inhibitor erdafitinib (ERDA, 8 mg/d continuous) demonstrated tolerability and a favorable 42% objective response rate (ORR) in pts with M/UR UC and FGFRalt; up titration to 9 mg/d was feasible. Activity of single-agent ERDA will be compared with chemo or pembrolizumab in pts with M/UR UC in this randomized phase 3 study.

Trial design: Adult pts (ECOG performance status ≤ 2 and adequate bone marrow, liver, and renal function; no uncontrolled cardiovascular disease, known HIV, hepatitis B or C, or baseline phosphate persistently above the upper limit of normal allowed) with stage 4 M/UR UC and specific pathogenic FGFRalt (FGFR3 mutations or FGFR2/3 fusions) who have received 1 line of prior systemic therapy are eligible. Pts will be screened for FGFRalt and randomized 1:1 to cohort 1 or 2. In cohort 1 (n ~ 280), pts with prior chemo and PD-1 (1) inhibitor (prior PD-1 (1) inhibitor alone allowed for cisplatin-ineligible pts) in combination or in maintenance setting will receive 8 mg/d continuous ERDA vs chemo (1:1:1) with docetaxel or vinflunine. In cohort 2, pts (n ~ 350) with prior chemo but no prior PD-1 (1) inhibitor will receive 8 mg/d ERDA vs pembrolizumab (1:1). Up titration of ERDA to 9 mg/d is recommended in pts with serum phosphate ≤ 9 mg/dL. Primary end point: overall survival. Secondary end points: progression-free survival, ORR, duration of response, pt-reported outcomes, safety, and pharmacokinetics. PD-L1 expression level per immunohistochemistry and UC subtype per RNA sequencing or other methods are exploratory end points. Pts are being enrolled at sites in 25 countries. For additional information on specific sites/countries: https://clinicaltrials.gov/ct2/show/NCT03390504.

Clinical trial identification: NCT03390504.

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Trial design: Repeated surgical procedures for tumors larger than 3 cm are required to prevent metastasis. Active surveillance until surgery is necessary for management of VHL disease-associated renal tumors. PT2977, a highly selective small molecule inhibitor of HIF-2α, is under investigation for its potential role in the clinical management of ccRCC.

Background: In VHL disease, renal cell carcinomas (RCC) are known to be of clear cell histology. VHL has been established as an oncogenic driver in ccRCC, where VHL gene silencing is associated with upregulation of VEGFA and other downstream angiogenic factors. These findings have led to the exploration of VEGFA inhibitors in the treatment of ccRCC.

In a phase 1 study (EV-101; NCT02091999), single-agent EV at the established recommended phase 2 dose of 1.25 mg/m² weekly was well tolerated and showed antitumor activity in 67% of patients with ccRCC. Moreover, EV demonstrated high levels of clinical benefit in patients with Nectin-4-expressing tumors, which are enriched in tumors with FGFR3 mutations/fusions.

In another study, enfortumab vedotin (EV), a fully humanized monoclonal antibody that delivers the microtubule-disrupting agent monomethyl auristatin E to tumors expressing Nectin-4, was shown to have a confirmed ORR of 40% (n = 46/112) across the overall population of patients with mUC; in patients with prior CPI therapy, no therapies are approved. Enfortumab vedotin (EV) has shown promising activity in patients with mUC, including a confirmed ORR of 36/89 (41%) in patients with prior CPI therapy.

Efficacy endpoints include objective response rate (ORR), duration of response (DOR), and time to response (TTR). Secondary efficacy endpoints include progression-free survival (PFS) and time to progression. The trial will also be evaluated in a phase 2 study (fight-201, NCT02872714) to assess the safety and efficacy of adjuvant INCB054828 in patients with FGFR3 mutations/fusions.

In a single-arm study involving mUC patient samples (Petrylak ASCO 2017), EV demonstrated high levels of clinical benefit in patients with Nectin-4-expressing tumors, which are enriched in tumors with FGFR3 mutations/fusions. In this study, EV was found to be well tolerated and showed antitumor activity in 67% of patients with ccRCC. Moreover, EV demonstrated high levels of clinical benefit in patients with Nectin-4-expressing tumors, which are enriched in tumors with FGFR3 mutations/fusions.

After neoadjuvant chemotherapy (NAC), about 20% of patients with muscle-invasive UC are found to have advanced pT-stage or lymph node involvement and 5-year progression-free survival (PFS) rates are low. The genomic alterations of FGFR3 in tumor tissue are currently being evaluated in an international phase 2 study (fight-201, NCT02872714). Our study aims to assess the safety and efficacy of adjuvant INCB054828 in patients with FGFR3 mutations/fusions.