TPS4619 Poster Session

# A phase 2/3 study of bicycle toxin conjugate zelenectide pevedotin (BT8009) targeting nectin-4 in patients with locally advanced or metastatic urothelial cancer (la/mUC; Duravelo-2).

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**Background:** Zelenectide pevedotin (zele; BT8009) is a Bicycle Toxin Conjugate (BTC), comprising a highly selective bicyclic peptide targeting Nectin-4 linked to the cytotoxin monomethyl auristatin E (MMAE) via a cleavable linker. Nectin-4 is an adhesion molecule commonly expressed in many tumor types, including la/mUC, and is a validated therapeutic target (Hoffman-Censits 2021). Zele has a low molecular weight and short plasma half-life, with potential to rapidly penetrate solid tumors and reduce toxicity by minimizing exposure to normal tissue (Rigby 2022). Results from the ongoing phase 1/2 clinical trial of zele (NCT04561362) indicate preliminary antitumor activity and a tolerable safety profile in patients (pts) with advanced malignancies including UC (Baldini 2023). This global, open label, phase 2/3 multicenter adaptive study aims to evaluate the safety and efficacy of zele as monotherapy, or combined with pembrolizumab (pembro), vs chemotherapy in pts with la/mUC (NCT06225596/BT8009-230; Duravelo-2). **Methods:** The trial will enroll n≤956 adult pts in 2 cohorts. Cohort 1 will include n≤641 previously untreated pts eligible for platinum-based chemotherapy. Cohort 2 will include n≤315 pts with ≥1 prior systemic therapy, excluding enfortumab vedotin or other MMAE-based therapy. Pts must have la/mUC of the renal pelvis, ureter, bladder, or urethra, ECOG performance status ≤2 (Cohort 1) or ≤1 (Cohort 2), and adequate organ function. Cohort 1 will be randomized 1:1:1 to receive: 1) zele 5 mg/m$^2$ on days [D]1, 8, and 15 + pembro 200 mg on D1; 2) zele 6 mg/m$^2$ on D1 and 8 + pembro 200 mg on D1; or 3) chemotherapy (gemcitabine + cisplatin / carboplatin, followed by avelumab maintenance in appropriate patients). Cohort 2 will be randomized 1:1 to receive: 1) zele 5 mg/m$^2$ on D1, 8, and 15 or 2) zele 6 mg/m$^2$ on D1 and 8. Cycle lengths will be 21D (28D for avelumab). After 30 pts in each dose arm have 9 weeks follow up, an interim analysis will determine the optimal dose of zele + pembro (Cohort 1) or zele monotherapy (Cohort 2) to be used for the rest of the study. An additional Cohort 2 arm, optimal dose of zele + pembro, will open after completion of the interim analysis. Treatment discontinuation criteria include planned completion of therapy, progressive disease, and intolerable toxicity. Primary endpoints are progression-free survival (PFS; Cohort 1) and objective response rate (ORR; Cohort 2) assessed by blinded independent central review. Secondary endpoints are ORR (Cohort 1), PFS (Cohort 2), overall survival, duration of response, disease control rate, safety/tolerability, and health-related quality of life (Cohorts 1 and 2). Pharmacokinetics, incidence/titers of antidrug antibodies, and tumor/peripheral biomarkers are exploratory endpoints. Efficacy endpoints will be assessed per RECIST v1.1. This study is actively recruiting. Clinical trial information: NCT06225596. Research Sponsor: BicycleTx Ltd.