TPS3175 **Poster Session**

A phase 1 study to evaluate the safety, pharmacokinetics, and efficacy of the first-in-class cyclin A/B RxL inhibitor CID-078, an orally bioavailable, cell-permeable macrocycle.

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Background: The cyclin-dependent kinase (CDK)-RB-E2F axis forms the core transcriptional machinery driving cell cycle progression. Alterations in *RB1* or other key components occur in many cancers, resulting in heightened oncogenic E2F activity. E2F activation relies on the interaction between the cyclin's conserved hydrophobic patch (HP) and the RxL motif found on E2F and other cyclin/CDK substrates. Disrupting this cyclin A/E2F RxL interaction leads to hyperactivation of E2F and synthetic lethality in E2F-driven tumors. CID-078 is a novel, orally bioavailable, passively cell-permeable, potent and selective macrocycle that binds to the HP of cyclins A and B, blocking the RxL motif-mediated binding of E2F1 to cyclin A2-CDK2 and Myt1 to cyclin B1-CDK1. Consequently, CID-078 induces cell cycle arrest at the G2/M phase, leading to apoptotic tumor cell death. In preclinical studies including small cell lung cancer (SCLC) and triple negative breast cancer (TNBC) tumor types, CDX and PDX models with high E2F target pathway scores and high E2F1 expression demonstrated tumor regression following single-agent CID-078 treatment. Pre-clinical species demonstrate a well-tolerated safety profile and 20% oral bioavailability. Preclinical to clinical predictions maintain a 20% bioavailability. **Methods:** This is a phase 1, first-in-human, open-label, multicenter, dose escalation and dose expansion study to evaluate the safety, tolerability, pharmacokinetics (PK) pharmacodynamics (PD) and preliminary anti-tumor efficacy of CID-078 in patients (pts) with locally advanced or metastatic solid tumor malignancies (NCT06577987). Pts previously treated with standard of care therapy and for whom no available curative therapy exists are eligible. CID-078 will be administered orally, twice-daily in repeating 21-day cycles and treatment will continue until disease progression, death, unacceptable toxicity or withdrawal from study. Part I dose escalation will be guided by a Backfill-Bayesian Optimal Interval Design (BF-BOIN) based on the incidence of dose-limiting toxicities (DLTs) and all available safety and PK data. Under the BF-BOIN design, additional pts may be enrolled to expand previous cohorts to better characterize the safety, PK, PD and preliminary efficacy activity to support a recommended dose for expansion. A pilot food effect cohort is planned as well. In Part II dose expansion, pts will be enrolled to one or more cohorts defined by histologic tumor type or molecular alteration at the recommended doses of expansion. Based on preclinical data generated to date, the study plans to include patients with SCLC, TNBC, and RB1-mutated tumors with additional tumor types expanded based on observed efficacy. Dose escalation is ongoing with no DLT reported in the initial 3 dose cohorts evaluated. Clinical trial information: NCT06577987. Research Sponsor: None.