TPS4614 Poster Session

A phase 1b, open-label, safety, tolerability, and efficacy study of HC-7366 in combination with belzutifan in patients with advanced or metastatic renal cell carcinoma (NCT06234605).

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Background: HC-7366 is a novel, highly selective and potent activator of general control nonderepressible 2 (GCN2) kinase, a core regulator of metabolic stress through activation of the integrated stress response (ISR). Prolonged or hyper-activation of GCN2 suppresses general protein synthesis and induces cell cycle arrest, ultimately leading to apoptosis. HC-7366 decreases HIF expression in tumor and immunosuppressive myeloid cells and inhibits glycolysis, oxidative phosphorylation, and TCA cycle function in tumor cells. In CDX RCC xenografts, HC-7366 combined with belzutifan (BLZ) exhibited tumor regression, and in BLZ-resistant PDX models, HC-7366 demonstrated monotherapy (mono) antitumor activity. These preclinical effects of HC-7366 suggest potential therapeutic benefit in clear cell renal cell carcinoma (ccRCC) and rationale for combinations with HIF2α antagonists. Mechanism of action studies identified biomarkers of pathway engagement which may be predictive of efficacy (Stokes, AACR 2024, Abstract 4615). HC-7366 75 mg was determined to be the maximum tolerated dose (MTD) in a previous phase 1a study in patients (pts) with solid tumors which did not include ccRCC (*data on file with sponsor*). **Methods:** This is a multicenter, open-label, phase 1b dose escalation and expansion study evaluating safety, tolerability, MTD, recommended phase 2 dose (RP2D) of HC-7366 + BLZ (combo) in pts with advanced / metastatic RCC, predominantly clear cell histology. Additionally, HC-7366 60 mg mono (up to 20 patients) is assessed in parallel. In dose escalation, HC-7366 (20, 40, 60 mg po qd) + BLZ (120 mg po qd) is evaluated using a modified Toxicity Probability Interval design in up to 20 pts. Dose expansion will evaluate two HC-7366 doses selected from escalation + BLZ (15 pts/dose level). Tumor response will be assessed by CT scans every 8 wks (RECIST v1.1). Secondary endpoints include ORR, DOR, TTR, DCR, PFS, and OS. PK data will be profiled, and exploratory objectives include pharmacodynamic marker evaluation in tumor biopsies and peripheral blood samples. Key eligibility criteria include 1-3 prior therapies for the combo cohorts (naïve to BLZ/ HIF-2α inhibitors) and 1-4 prior therapies for the mono cohort (may include BLZ/ HIF-2α inhibitors), >1 measurable lesion, and willingness to provide biopsy or archival tumor samples at two timepoints. Escalation Dose levels 1 and 2 of the combination cohorts have been cleared and enrollment is ongoing for Dose level 3 (60 mg + BLZ), Expansion Dose Level 1 (40 mg + BLZ) and the mono cohort (60 mg HC-7366) at 20 US sites. The trial is sponsored by HiberCell, Inc. in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Sponsor contact: Paulette Mattson pmattson@hibercell.com, 651.312.5831. Clinical trial information: NCT06234605. Research Sponsor: None.