A Multicenter Open-Label Phase 1 Study Evaluating the Safety and Tolerability of HMPL-306 in Patients with Locally Advanced or Metastatic Solid Tumors with IDH Mutations

TPS3159

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BACKGROUND

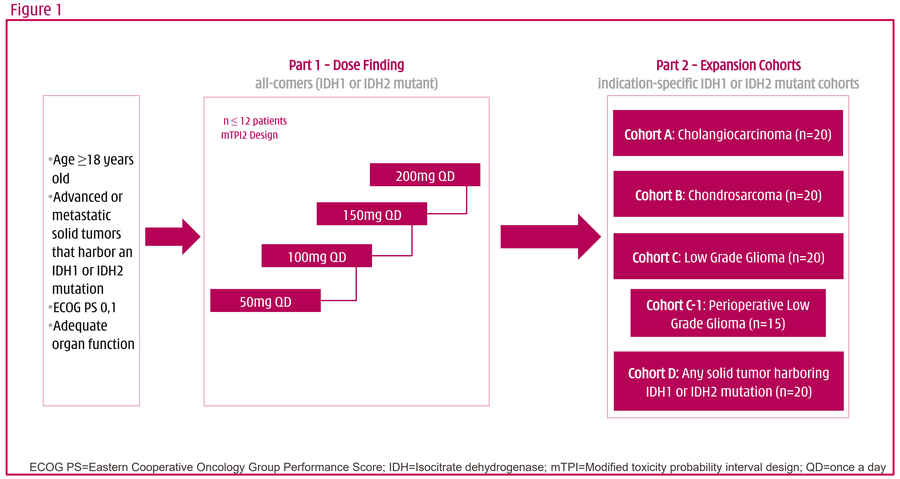
- Isocitrate dehydrogenase (IDH) is a rate-limiting enzyme in the tricarboxylic acid cycle, with 3 isoforms[1,2]
- Mutations in IDH1 and IDH2 result in gain-of-function activity that can cause tumor formation and/or progression and have been associated with various tumor types[3-6]
- Single mutant IDH (mIDH) isotype inhibitors (mIDH1 or mIDH2) can lead to insufficient efficacy and the potential for tumor resistance
- HMPL-306 is an innovative, small-molecule, orally available, highly selective, potent inhibitor of both mIDH1 and mIDH2
- Clinical development of a compound that concurrently targets, inhibits, and suppresses multiple mIDHs could lead to significant and durable clinical benefit for patients with solid tumors harboring IDH mutations

METHODS

- An ongoing phase 1, open-label, dose escalation (Part 1) and dose expansion (Part 2) study (NCT04764474) to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of HMPL-306 in patients ≥18 years with locally advanced or metastatic solid tumors with any IDH mutations
- HMPL-306 will be administered orally, once daily in a 28-day continuous dosing treatment cycle
- Part 1 will be conducted according to the modified toxicity probability interval-2 (mTPI-2) design in 4 cohorts in approximately 15-20 patients: 50, 100, 150, and 200 mg
- Part 2 will enroll approximately 95 patients at the recommended phase 2 dose (RP2D) for 5 dose expansion cohorts (Figures 1 and 2)
- All patients will continue receiving study drug until disease progression, unacceptable toxicity, withdrawal of consent, or at the investigator's discretion
- Disease progression and tumor response will be assessed in accordance with RECIST v1.1 and/or RANO for gliomas
- For inclusion and exclusion criteria, please see clinicaltrials.gov NCT04764474

OVERALL STUDY DESIGN

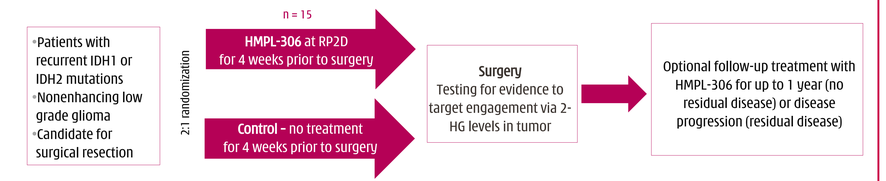
Figure 1



ECOG PS=Eastern Cooperative Oncology Group Performance Score; IDH=Isocitrate dehydrogenase; mTPI=Modified toxicity probability interval design; QD=once a day

COHORT C-1 STUDY DESIGN

Figure 2



2-HG=2-hydroxyglutarate; IDH=Isocitrate dehydrogenase; RP2D= recommended phase 2 dose

- Patients with recurrent Grades 2 and 3 gliomas who are candidates for clinical resection but for whom surgery is not urgently indicated
- Patients will be randomized in a 2:1 fashion to receive either open-label HMPL-306 at the RP2D for 4 weeks prior to surgery or no treatment (control) for 4 weeks prior to surgery

OBJECTIVES AND ENDPOINTS

Primary Objectives	Primary Endpoints
Part 1 – Dose Escalation: Evaluate the safety and tolerability of HMPL-306, and determine the RP2D and/or the MTD of HMPL-306	▪ MTD and/or RP2D ▪ Dose-limiting toxicities ▪ Occurrence and severity of adverse events (AEs) ▪ Electrocardiogram (ECG) and clinical laboratory abnormalities
Part 2 – Dose Expansion: Characterize the safety and tolerability of HMPL-306	▪ Occurrence and severity of AEs ▪ ECG and clinical laboratory abnormalities
Part 2 – Cohort C-1 Only: Determine the 2-hydroxyglutarate (2-HG) concentration in surgically resected tumors following pre surgical treatment with HMPL-306 when compared to untreated tumors	▪ Plasma and tumor concentrations of 2-HG
Secondary Objectives	**Secondary Endpoints**
Assess the preliminary antitumor activity of HMPL-306	▪ Objective response rate (ORR), ▪ Disease control rate (DCR) ▪ Duration of objective response (DoR) ▪ Time to objective response (ToR) ▪ Progression-free survival (PFS)
Assess the PK profile of HMPL-306	▪ Plasma concentrations and PK parameters of HMPL-306
Assess the PD of HMPL-306	▪ Plasma concentrations of 2-HG
Part 2 Cohort C-1: Characterize the safety and tolerability of HMPL-306	▪ Occurrence and severity of AEs ▪ ECG and clinical laboratory abnormalities

STATISTICAL ANALYSIS

- Safety analysis set includes all patients who receive at least one dose of HMPL-306 and will be used for analysis of safety and efficacy endpoints
- All data will be summarized descriptively by dose level, subtype of malignancy, and for overall as appropriate with no formal hypothesis testing
- ORR and DCR and the corresponding 95% confidence interval (CI) will be calculated based on Clopper-Pearson method
- For time-to-event endpoints such as DoR, ToR, and PFS, the median and 25% and 75% percentile will be estimated using Kaplan-Meier method along with their corresponding 95% CI
- No interim analysis is planned; however, the accrued data from any cohort may be analyzed for internal decision-making, for example, to provide information for a future study design

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