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A phase I study of CPI-613 (devimistat) in combination with chemoradiation in patients with pancreatic adenocarcinoma

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TPS760 **Trials in Progress Poster Session**

A phase I study of CPI-613 (devimistat) in combination with chemoradiation in patients with pancreatic adenocarcinoma.

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Background: Local tumor progression is a cause of significant mortality and morbidity in patients with unresectable pancreatic ductal adenocarcinoma (PDAC). Effective approaches to achieve durable local control are urgently needed. Metabolic reprogramming and enhanced mitochondrial function, both hallmarks of PDAC, are known contributors to chemo- and radio-resistance. CPI-613, a lipoic acid analog that selectively inhibits components of the Krebs cycle in tumors, showed promising preclinical synergy in combination with gemcitabine and radiation therapy (gem-RT). **Methods:** We describe a single-arm, single-center, open-label, phase I study designed to determine the maximum tolerated dose of CPI-613 when used concomitantly with gemcitabine and intensity modulated radiation therapy (IMRT) for local control of PDAC. CPI-613 will be administered once weekly by intravenous infusion over approximately 2 hours at a starting dose of 500 mg/m2 and dose-escalated/de-escalated using a Bayesian optimal interval design. Gemcitabine will be given once weekly at 400 mg/m2 dosage and IMRT as 54 Gray (Gy) in 30 fractions (1.8 Gy per fraction) with five fractions given per week. Up to 24 patients will be enrolled for the study after meeting the following main eligibility criteria, which include: pathologically confirmed PDAC; inoperable disease that by institutional pancreatic multidisciplinary tumor board or multidisciplinary review are considered to benefit from definitive local control of the primary tumor; ECOG of 0-2; and adequate organ and marrow function after completion of intended systemic chemotherapy. The secondary objectives are to determine the recommended phase II dose of CPI-613 when used with gem-RT, safety and tolerability of CPI-613-gem-RT, overall survival, local progression-free survival (PFS), overall PFS, patient-reported quality of life after treatment, and late gastrointestinal toxicities following treatment with CPI-613-gem-RT. Clinical trial information: NCT05325281. Support: Cornerstone Pharmaceuticals. Research Sponsor: Cornerstone Pharmaceuticals.

Summary of dose escalation/de-escalation of CPI-613 along with standard gem-RT.

CPI-613 Dose Level	CPI-613*
-1 (Dose De-escalation)	250 mg/m^2
1 (Starting Dose)	500 mg/m^2
2 (Dose Escalation)	1,000 mg/m^2
3 (Dose Escalation)	1,500 mg/m^2

*Once per week by IV infusion.