A Phase 1 Study of Etirinotecan Pegol in Combination with 5-Fluorouracil and Leucovorin in Patients with Advanced Cancer

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BACKGROUND

- Prior Phase I study of EP/SFU/LV established the maximum tolerated dose (MTD) for each dose level of EP 145 mg/m², SFU 75 mg/m², and LV 400 mg/m².
- The current study was intended to repeat prior Phase I study using the population PK model previously developed and validated for EP and SFU.

OBJECTIVES

- To establish the safety profile and recommend a maximum tolerated dose/fractionated dose (MTDFD) of EP in combination with fluorouracil (FU) and leucovorin (LV).
- To evaluate pharmacokinetics (PK) of EP and FU in combination with LV when EP was administered in combination with LV (MTDFD).
- To identify the recommend dose of EP in combination with FU (08-PIR-07) for FU 2400 mg/m² continuous infusion (c.i.) and LV 400 mg/m² c.i.

STUDY DESIGN

- Phase 1, open-label, dose escalation, multicenter study.
- Eligible patients were previously treated advanced metastatic (m) solid tumors that were refractory or unresectable who were candidates for LV/5FU therapy.
- Patients had ECOG ≤1 and 1 evaluable organ and 1 dose limiting toxicity.

DOSE EXPOSURE

- Two Phase 3 studies in metastatic colorectal cancer support the use of 5FU in combination with LV with similar RIs.
- Prior Phase I study of EP/SFU/LV established the MTD for each dose level of EP 145 mg/m², SFU 75 mg/m², and LV 400 mg/m².
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PHARMACOKINETICS

- Observed SFU Concentrations in 20 mg/m² Cohort Led to a Change from Schedule A to Schedule B. Patients in Study 09-PIR-07 with Population Predicted Exposures from Previous Studies Observed Similar Plasma SFU Concentrations at 24Hrs and 180Hrs Using Population PK model previously developed with their individual data.
- SFU concentrations were measured at 0, 24, 48, 72, 120, and 180 hrs post-injection.

SAFETY

- Grade IV Drug-related TEAEs occurring in >10% of patients
- Dose Delays
- Dose Reductions
- Dose-Related

Efficacy

- This study established a recommended dose of 145 mg/m² EP in combination with standard doses of SFU/LV.
- Toxicity of marrow function and function was manageable with dose delays and reductions, as expected.
- This study showed promising clinical activity, including objective response patients with galler cancer (adenocarcinoma colon cancer), clinical benefit (stable disease > 1 year), in 10 patients, to clinically significant improvements in quality of life for patients with metastatic breast cancer.
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