Study Design

- 2-3 dose-escalation design
- Dose expansion in 6 to determine the maximum tolerated dose (MTD)
- Dose expansion in up to 10 centers
- Objectives

  - Determine the MTD
  - Determine the recommended Phase 2 dose
  - Determine the pharmacokinetics (PK) profile
  - Evaluate the safety and tolerability
  - Detect preliminary evidence of antitumor activity

Key Eligibility Criteria

- Advanced or metastatic solid tumor or lymphoma; refractory to standard therapy
- Eastern Cooperative Oncology Group (ECOG) performance status = 0 to 1
- Serum creatinine and total bilirubin ≤ 1.5 times upper limit of normal (ULN)
- Aspartate amino转nishate (AST) and alanine aminotransferase (ALT) ≤ 1.5 times ULN

Methods

- Plasma concentrations of EZN-2968 were determined by ELISA hybridization assay; lower limit of quantification = 0.05 ng/mL
- PK parameters estimated using nonlinear mixed-effects modeling (Monolix,orphical, Pharmaceutical Systems, Inc.)

Results

- The PK of ezazolimab (EZ-2968) is nonlinear. The drug is eliminated with a saturable process (PK = 2968 (Dose 1)) and a dose range 1-18 mg/kg.

Safety and Tolerability

- To date, 4 patients had dose-limiting toxicity (DLT).

- Two patients had DLT after receiving EZN-2968 administered weekly for 3 weeks per 8-week cycle.

- One patient in the 3.5-mg/kg group had intra-arterial bleeding at a site of metastasis; this patient had a history of breast cancer with no history of signs or symptoms of brain metastasis. This finding led to the discontinuation of drug study, and maximal reduction in current exposure is at this dose level.

- The intracranial bleeding resolved in death within 17 days after the patient’s last dose of EZN-2968.

- One patient in the 5.3-mg/kg group had Grade 3 fatigue.

- Two patients had DLT after receiving the intended EZN-2968 dosage of 16 mg/kg every week for 5 weeks per 8-week cycle.

- One patient had Grade 3 fatigue.

- The patient had a reversible Grade 3 increase in ALT and AST.

- Overall, 48 patients (96%) had at least one treatment-emergent AE. The most commonly reported AEs (≥10% patients) were of grade 1 or 2 severity: nausea (26%), fatigue (21%), pain (21%), and headache (18%).

- Twenty-four (46%) of Grade 3 or 4 AEs, the most common 1 (1 patient) of which was fatigue (1 patient), were considered related to EZN-2968.

- Drug-related adverse events (AEs) were observed in 10% of patients; of these, 10% had grade 1 AEs, 12% had grade 2 AEs, and 6% had grade 3 AEs.

- No drug-related serious AEs were observed in this study.

- No significant changes in blood pressure or ultimate protein were reported.

Pharmacodynamics

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Conclusions

- The MTD of EZN-2968, a novel HIF-1α mriRNA antagonist, is 10 mg/kg given weekly for 4 of 6 weeks every 8 weeks. The drug is well tolerated at doses up to 16 mg/kg, and dose-limiting adverse events were not observed.

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References