AG-636 for the treatment of adults with advanced lymphoma: Initiation of a Phase 1 clinical study

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BACKGROUND

- AG-636 was designed as a DHODH inhibitor and its effects on hematologic cancer cell lines were studied.
- Inhibitors of DHODH are currently in clinical use for the treatment of hematologic diseases (leukemia and multiple sclerosis).
- Brequinar is a specific and potent DHODH inhibitor that was evaluated in several phase 1 and 2 trials in patients with advanced solid tumors in the 1990s and demonstrated little evidence of antitumor activity, however, patients with hematologic malignancies were not evaluated in those studies.
- Recent preclinical research has demonstrated that cell lines and in vivo models derived from hematologic malignancies are highly sensitive to inhibition of DHODH, prompting a renewed interest in this compound as potential treatment options for conditions such as lymphoma.

OBJECTIVES

- Primary: to determine the maximum tolerated dose (MTD) of AG-636 and to characterize its dose-limiting toxicities (DLTs) when given to patients with advanced lymphoma.
- Key secondary: to characterize the safety and tolerability of AG-636, its pharmacokinetic (PK) and pharmacodynamic (PD) parameters, and any antilymphoma activity that may be associated with AG-636 treatment.

TRIAL DESIGN

- Phase 1, multicenter, open-label study investigating AG-636 for the treatment of adult patients with advanced lymphoma refractory to standard treatment (NCT03383458).
- Includes a dose escalation phase followed by an expansion phase (Figure 3).
- Eligible patients include those with B-cell lymphomas (follicular, mantle cell, diffuse large B-cell).
- All patients who either have a DLT during Cycle 1 or complete ≥75% of their planned Cycle 1 doses are eligible for Cycle 2.
- Each cohort may initially include up to six patients who can be evaluated for DLT.
- Patients are being recruited from six sites in the United States.
- Dose escalation phase:
  - Approximately 12 additional patients will receive AG-636 at the MTD to better characterize the safety, PK, and PD of AG-636.
  - Further expansion may be undertaken if AG-636 shows high activity in specific subtypes of lymphoma, either in the clinic or in preclinical models.
- Duration of treatment:
  - Patients whose disease is stable or improved may be allowed to continue treatment with AG-636, if they are tolerating AG-636 treatment well.
- Dose expansion phase:
  - Approximately 12 additional patients will receive AG-636 at the MTD to better characterize the safety, PK, and PD of AG-636, and enable the selection of a dose for future clinical studies.
- Statistics:
  - For MTD estimation: an adaptive Bayesian logistic regression model with two parameters guided by the escalation with overdose control principle.
  - Corresponding primary endpoint: incidence of DLTs in Cycle 1.
  - The Dose-Determining Set will be used to calculate the incidence of DLTs:
    - All patients who either have a DLT during Cycle 1 or complete ≥75% of their planned Cycle 1 doses and have sufficient safety data available to conclude that a DLT did not occur during Cycle 1.
  - Other endpoints will be summarized using descriptive statistics.

SUMMARY AND CURRENT STATUS

- The experience in this study with the PK, PD, and safety of AG-636 will inform the optimal starting dose and regimen for evaluation in subsequent studies.
- This phase 1 study in patients with advanced lymphoma began enrollment on May 31, 2019.
- Patients are being recruited from six sites in the United States.