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 investigated in a phase 1 multicenter, open-label study. The study evaluates AG-636 for the treatment of adult patients with advanced lymphoma. Patients are being recruited from six sites in the United States.

OBJECTIVES

- Primary: to determine the maximum tolerated dose (MTD) of AG-636 and to characterize its anti-tumor activity.
- 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 (NCT03834584).
- 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), which was evaluated in several phase 1 and 2 trials in the 1990s and demonstrated little evidence of antilymphoma 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 revised interest in these compounds as potential treatment options for conditions such as lymphoma.
- AG-636 is a novel, oral, small-molecule DHODH inhibitor that has shown strong in vitro and in vivo activity across diverse models of hematologic malignancy (see Poster 1570 at this congress, December 9, 2019, 5:30–7:30 pm).

AG-636 preclinical studies

- AG-636 was designed as a DHODH inhibitor and its effects on hematologic cancer cell lines were revealed in a chemical biology screen. AG-636 showed potent growth inhibition in cell lines of hematologic origin, whereas its effect on cell lines derived from solid tumors was relatively poor.
- AG-636 inhibits proliferation across many lymphoma cell lines, including those derived from subtypes with a poor prognosis (e.g., doublet-hit) (Figure 2).

Figure 2. Efficacy of AG-636 in xenograft models of lymphoma

Figure 3. Design of a phase 1 open-label study investigating AG-636 for the treatment of patients with advanced lymphoma

Key inclusion criteria

- Age ≥18 years
- Pathologically confirmed lymphoma refractory to standard treatment (such as DLBCL, PTCL, CTCL, MCL, HL)
- ECOG performance status ≤2
- Absolute neutrophil count ≥1.0 × 10^9/L
- Platelet count ≥75 × 10^9/L
- Bilirubin ≤1.5 × ULN
- Creatinine clearance ≥50 mL/min (Cockcroft-Gault formula)

Key exclusion criteria

- Primary CNS lymphoma
- Lymphomatous involvement of the CNS that is symptomatic or requires therapy
- Requirement for immediate cytoreductive therapy
- Impairment of GI function or GI disease that may significantly alter AG-636 absorption
- Ongoing treatment with medications that are sensitive substrates of CYP3A4, P-glycoprotein (P-gp), or breast cancer resistance protein (BCRP)

Dose escalation phase

- Patients will receive oral AG-636 at a starting dose of 50 mg once daily on an intermittent basis, with one cycle of therapy defined as 4 consecutive weeks of treatment.
- Increasing or decreasing the number of days of treatment each week is allowed per protocol, depending on the experience with the initial dosing regimen.
- Dosing regimen may be changed from once- to twice-daily administration, as appropriate.
- Successive cohorts will be treated with increasing doses of AG-636 to estimate the MTD.
- MTD: highest dose unlikely (<25% posterior probability) to cause DLTs in ≥23% of patients during Cycle 1.
- Approximately six dose escalation steps (seven cohorts) are expected to be necessary to estimate the MTD.
- Each cohort may initially include up to six patients who can be evaluated for DLT.
- As many as 42 patients may be enrolled in the dose escalation phase.

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.
- 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.

Statistics

- For MTD estimation: an adaptive Bayesian logistic regression model with two parameters guided by PKPD assessments including:
- Plasma concentrations of AG-636 and its metabolite AG-004753 and derived PK parameters
- Circulating concentrations of DHO.
- Disease response as assessed by the 2014 Lugano criteria for lymphoma or the 2011 ISCL/USCI/CERT criteria for mycosis fungoides/Sézary syndrome.

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.

Table 1. Main endpoints of the study

Primary
- Frequency of DLTs associated with AG-636 administration during the first cycle (first 28 days) of treatment.
- AE and serious AEs; changes in hematologic and clinical chemistry values; changes in physical examination, vital signs, electrocardiograms and ECOG Performance Status, and measurements of dose intensity.

Secondary
- PK/PD assessments including:
- Plasma concentrations of AG-636 and its metabolite AG-004753 and derived PK parameters.
- Circulating concentrations of DHO.
- Disease response as assessed by the 2014 Lugano criteria for lymphoma or the 2011 ISCL/USCI/CERT criteria for mycosis fungoides/Sézary syndrome.

Figure 1. Role of DHODH in de novo nucleotide synthesis; inhibition by AG-636

Figure 2. Efficacy of AG-636 in xenograft models of lymphoma

Figure 3. Design of a phase 1 open-label study investigating AG-636 for the treatment of patients with advanced lymphoma

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