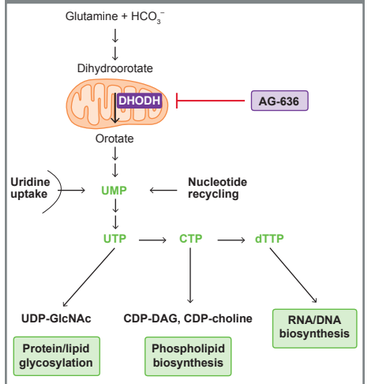
AG-636 for the treatment of adults with advanced lymphoma: Initiation of a phase 1 clinical study

Scott F Huntington[1], Avyakta Kallam[2], Frank G Basile[3], Danielle Ulanet[3], Huansheng Xu[3], Feng Yin[3], Michelle Mobilia[3], Michael Cooper[3], Bijal Shah[4], John P Leonard[5], Gottfried R von Keudell[6], Ajay K Gopal[7]

[1]Yale Cancer Center, New Haven, CT, USA; [2]University of Nebraska Medical Center, Omaha, NE, USA; [3]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [4]Moffitt Cancer Center, Tampa, FL, USA; [5]Weill Cornell Medical College, New York, NY, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Seattle Cancer Care Alliance, Seattle, WA, USA

BACKGROUND

Figure 1. Role of DHODH in *de novo* pyrimidine synthesis: Inhibition by AG-636



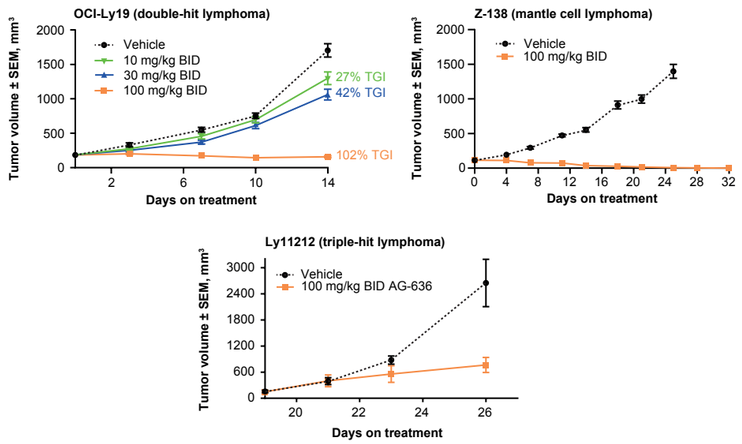
CDP = cytidine diphosphate; CTP = cytidine triphosphate; DAG = diacylglycerol; dTTP = 2'-deoxythymidine 5'-triphosphate; GlcNAc = N-acetylglucosamine; HCO_3^- = bicarbonate; UDP = uridine diphosphate; UMP = uridine monophosphate; UTP = uridine triphosphate

- Dihydroorotate dehydrogenase (DHODH) is a mitochondrial enzyme involved in the *de novo* synthesis of pyrimidines, which are key building blocks for RNA and DNA biosynthesis (**Figure 1**).
- Inhibitors of DHODH are currently in clinical use for the treatment of rheumatoid arthritis (leflunomide)[1] and multiple sclerosis (teriflunomide).[2]
- 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 revived interest in these compounds as potential treatment options for conditions such as lymphoma.[3,4]
- 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 7, 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. double/triple-hit) (**Figure 2**).

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



BID = twice daily; SEM = standard error of the mean; TGI = tumor growth inhibition

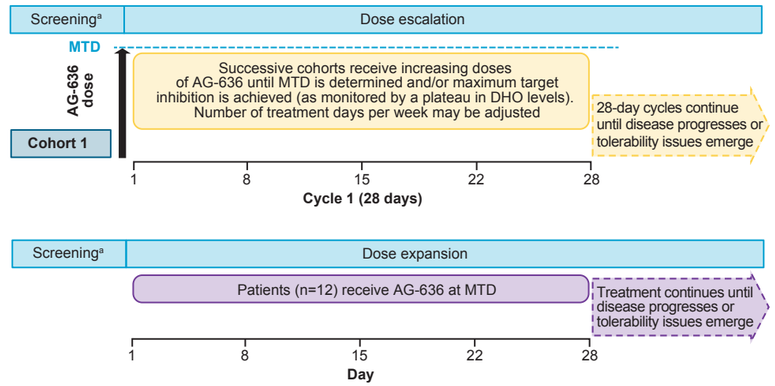
OBJECTIVES

- **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 (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), T-cell lymphomas (peripheral, cutaneous), Hodgkin lymphoma, and less common subtypes as classified by the World Health Organization.[5]
- Primary and key secondary endpoints are shown in **Table 1**.

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 advanced 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
- Alanine aminotransferase and aspartate aminotransferase ≤3.0 × ULN
- Creatinine clearance ≥30 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 CYP2C8, P-glycoprotein (P-gp), or breast cancer resistance protein (BCRP)

[a]Screening takes place up to 28 days before the first dose of AG-636
CNS = central nervous system; CTCL = cutaneous T-cell lymphoma; CYP2C8 = cytochrome P450 2C8; DHO = dihydroorotate; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GI = gastrointestinal; HL = Hodgkin lymphoma; MCL = mantle cell lymphoma; PTCL = peripheral T-cell lymphoma; ULN = upper limit of normal

Table 1. Main endpoints of the study

Primary	• Frequency of DLTs[a] associated with AG-636 administration during the first cycle (first 28 days) of treatment.
Secondary	• AEs and serious AEs; changes in hematology and clinical chemistry values; changes in physical examination, vital signs, electrocardiograms and ECOG Performance Status, and measurements of dose intensity. • PK/PD assessments including: − Plasma concentrations of AG-636 and its metabolite AGI-0045753 and derived PK parameters − Circulating concentrations of DHO. • Disease response as assessed by the 2014 Lugano criteria for lymphoma or the 2011 ISCL/USCLC/EORTC criteria for mycosis fungoides/Sézary syndrome.[6,7]

[a]A DLT is defined as an AE or abnormal laboratory value that meets any of a set of prespecified criteria, and for which a relationship to AG-636 cannot be ruled out
AE = adverse event; EORTC = European Organisation for Research and Treatment of Cancer; ISCL = International Society for Cutaneous Lymphomas; USCLC = United States Cutaneous Lymphoma Consortium

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 ≥33% 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 will 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 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.

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Disclosures
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