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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Trial in Progress: A Phase 1b Study of AS-1763, an Oral, Potent and Selective Noncovalent BTK Inhibitor, in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma or Non-Hodgkin Lymphoma

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Background: Covalent Bruton's tyrosine kinase (BTK) inhibitors such as ibrutinib are approved for treating patients with B-cell malignancies, but their long-term efficacy is limited by toxicity related to off-target kinase inhibition and acquired resistance due to BTK C481 mutation. AS-1763 is a potent, highly selective, orally available, and non-covalent BTK inhibitor, equipotent against both wild-type and C481S-mutated BTK with sub-nanomolar IC50 values (Kawahata et al. J Med Chem 2021; 64,14129-14141). In a Phase 1 single-ascending dose study in healthy volunteers, AS-1763 was well tolerated and safe at doses of 5-600 mg and achieved maximum inhibition of B cell activation at doses of 100 mg and above at 1-2 h post-dose and the duration of inhibitory effect increased with dose [Arimura et al. AACR 2022; Cancer Res 2022;82(12_Suppl)]. In preclinical studies, AS-1763 demonstrated a broad spectrum of inhibition against BTK mutations that confer resistance to other non-covalent BTK inhibitors in addition to the C481 mutation.

Study Design and Methods:
This study is an open-label, multi-center, Phase 1b study of oral AS-1763 in patients with advanced chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL) and other B-cell non-Hodgkin lymphomas (NHLs) who have failed or are intolerant to at least two prior lines of systemic therapy. Prior therapy with a covalent BTK inhibitor is permitted; prior use of a noncovalent BTK inhibitor is excluded. This study consists of two parts, i.e., dose escalation and expansion parts. The dose escalation part will follow a 3+3 design with a starting dose of 100 mg BID. Each cycle will be 28 days. Three dose levels will be selected for dose expansion part based on a comprehensive review of data from dose escalation. The dose expansion part consists of 2 cohorts, i.e., Cohort 1 for CLL/SLL and Cohort 2 for B-cell NHL. In each cohort, the first 30 patients will be allocated to the 3 dose levels (10 patients for each), then the same provisional recommended Phase 2 Dose (RP2D) will be selected for Cohort 1 and Cohort 2 after 30 patients have enrolled in either cohort. After the provisional RP2D is selected, up to 28 patients in Cohort 1 and up to 15 patients in Cohort 2 may be treated at the provisional RP2D. In this study, up to 110 patients will be enrolled. Treatment will continue for 24 cycles or until disease progression, occurrence of unacceptable toxicity or discontinuation because of other reasons.

Eligible patients include CLL/SLL, Waldenström macroglobulinemia (WM), marginal zone lymphoma (MZL), mantle cell lymphoma (MCL), and follicular lymphoma (FL). Patients with transformed disease (e.g., Richter's transformation) prior to or during screening are not eligible. Key exclusion criteria include CNS involvement by systemic lymphoma, stem cell transplant or CAR-T therapy <30 days, and clinically significant cardiovascular disease.
The primary objective of the dose escalation part is to determine the maximum tolerated dose/dose-limiting toxicity. Key secondary endpoints include the evaluation of safety profile and tolerability, pharmacokinetics properties, and preliminary anti-tumor activity based on overall response rate (ORR) by investigator according to iwCLL 2018 for CLL, IWW6 for WM, and Lugano Treatment Response Criteria for MCL, MZL, SLL and FL.
The primary objective of the dose expansion part is to assess the preliminary anti-tumor activity based on ORR by the Safety Monitoring Committee (SMC). Key secondary objectives are to investigate safety, tolerability, and pharmacokinetic profiles and to assess the preliminary antitumor activity based on ORR by investigator and best overall response, duration of response, progression-free survival and overall survival by investigator and the SMC. This trial will evaluate several key exploratory objectives including evaluation of minimal residual disease negativity, characterization of patient subsets defined by mutation status of BTK and phospholipase C gamma 2 (PLCG2), and characterize BTK and PLGC2 gene mutation before and after disease progression. Changes in the level of biomarkers such as CCL3 and CCL4 chemokines and B-cell receptor pathway signaling will be evaluated prior to, during therapy, and at time of disease progression. The RP2D will be determined based on all the data generated in the study. The study has been registered on ClinicalTrials.gov (NCT05602363).

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