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POSTER ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

A First-in-Human Phase 1 Study of ABBV-525, a Small-Molecule MALT1 Inhibitor, in Patients with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma

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Background and Significance

Many B-cell malignancies are characterized by chronic activation of the B-cell receptor (BCR) and nuclear factor kappa B (NF-κB) signaling pathways. In many non-Hodgkin lymphoma (NHL) subtypes, constitutive NF-κB activation results from genetic mutations and/or auto-antigen stimulation of the BCR pathway. While agents targeting the BCR pathway are effective treatments for many B-cell malignancies, patients (pts) often have progressive disease due to acquired resistance to BCR-targeted agents. Thus, there is an unmet medical need for novel therapeutic targets and treatment approaches. The mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) is an enzymatic and scaffolding node in the BCR pathway and a key mediator of the BCR/NF-κB signal transduction pathway. Its action is downstream, or in some instances parallel to, resistance mechanisms to existing NHL therapies, including *BTK* C481S and *PLCG2* mutations, which are known acquired mechanisms of resistance to covalent Bruton's tyrosine kinase (BTK) inhibitors in pts with chronic lymphocytic leukemia (CLL). MALT1 inhibition represents a novel therapeutic approach for malignancies with chronic activation of NF-κB, including those pts with acquired resistance to upstream targets. ABBV-MALT1 is a small-molecule, tool compound, MALT1 inhibitor. Preclinical studies of ABBV-MALT1 have demonstrated potent activity against MALT1-relevant biomarkers, including inhibition of BCR pathway signal transduction and reduced NF-κB gene activation in non-germinal center B-cell diffuse large B-cell lymphoma (non-GCB DLBCL) cell lines. ABBV-MALT1 has also shown activity in a range of preclinical lymphoma models as both monotherapy and in combination with venetoclax, including robust antitumor activity in malignant B-cell models that are resistant to BTK inhibitors. This phase 1 study evaluates the clinical candidate MALT1 inhibitor ABBV-525 as monotherapy in pts with relapsed or refractory (R/R) B-cell NHL.

Study Design and Methods

This is a first-in-human, phase 1, open-label, multicenter study of single-agent ABBV-525 in pts with R/R B-cell NHL (NCT05618028). Eligibility criteria are listed in Table 1. The primary objectives are to evaluate safety, tolerability, and pharmacokinetics (PK) of ABBV-525 and to determine the recommended phase 2 dose (RP2D). The secondary objective is to assess the preliminary efficacy of ABBV-525 in subsets of pts with R/R B-cell NHL. Exploratory objectives include evaluating biomarkers predictive of response and pharmacodynamic biomarkers, including the effects of ABBV-525 on BCR pathway signal transduction and NF-κB gene activation. This is a 3-part study (Figure 1): dose escalation (part 1), dose optimization (part 2), and dose expansion (part 3). Part 1 aims to establish the maximum administered dose/maximum tolerated dose of ABBV-525 and is primarily guided by a Bayesian optimal interval design. Part 2 aims to identify the RP2D of ABBV-525. Part 3 will further characterize the safety profile of ABBV-525 at the RP2D. Approximately 150 pts are planned for enrollment, including those with various R/R mature B-cell lymphomas in part 1, pts with documented diagnosis of R/R CLL in part 2, and pts with documented diagnosis of non-GCB DLBCL in part 3. ABBV-525 is orally administered until disease progression, intolerable toxicity, or other study discontinuation criteria are met. Safety assessments include dose-limiting toxicities, adverse events (per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0), clinical laboratory parameters, vital signs, and electrocardiogram variables. PK parameters, including maximum observed plasma concentration (C_{max}), time to C_{max}, and area under the concentration-time curve will be analyzed using noncompartmental methods. Efficacy will be assessed through response per disease-specific criteria (including International Workshop on Chronic Lymphocytic Leukemia, International Workshop on Waldenstrom's Macroglobulinemia, and Lugano classification). Duration of response will be evaluated

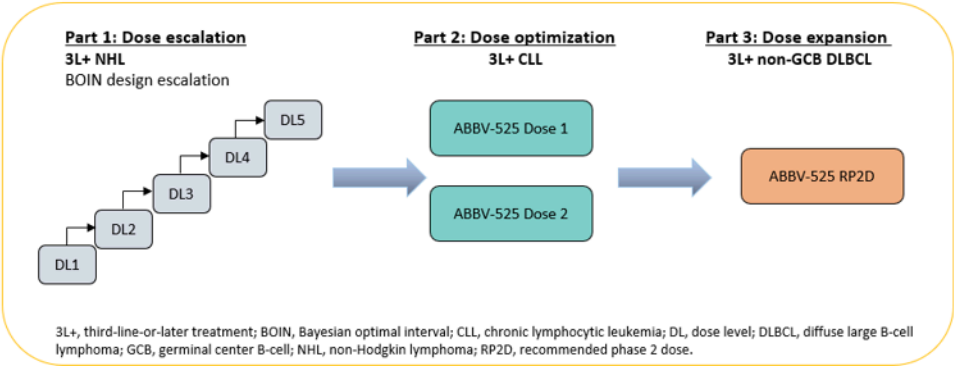
by Kaplan-Meier estimates. Biomarker data will be analyzed as change from baseline and summarized for each scheduled postbaseline visit. Pts are being enrolled in 25 sites across the USA, Australia, Belgium, France, Germany, Israel, Spain, and UK. As of August 1, 2023, 2 pts had been treated.

Disclosures Sochacki: *AbbVie, Shattuck Labs, ALX Oncology, Boehringer Ingelheim, MacroGenics, Regeneron, Incyte:* Other: Research and or Clinical Trial Support. **Burger:** *AstraZeneca, Pharmacyclics:* Other: Advisory Board, Research Funding; *Janssen:* Other: Speaker fees and Travel Support; *Abbvie, Beigene:* Research Funding. **Ludwig:** *AbbVie Inc.:* Current Employment, Other: may own stock. **Assaily:** *AbbVie:* Current Employment. **Munasinghe:** *AbbVie Inc.:* Current Employment, Other: may own stock. **Pappano:** *AbbVie Inc.:* Current Employment, Other: may own stock. **Greenberg:** *AbbVie Inc.:* Current Employment, Other: may own stock. **Will:** *AbbVie Inc.:* Current Employment, Other: may own stock. **Thompson:** *Abbvie:* Research Funding; *Genentech:* Research Funding; *AstraZeneca:* Research Funding; *Nurix Therapeutics:* Research Funding; *Genmab:* Research Funding; *MJH Life Sciences:* Honoraria; *Intellisphere LLC:* Honoraria; *Brazilian Association of Hematology, Hemotherapy and Cellular Therapy (ABHH):* Honoraria; *Dava Oncology:* Other: Travel ; *Curio Science:* Honoraria; *Massachusetts Medical Society:* Honoraria; *VJHemOnc:* Honoraria; *Loxo Oncology at Lilly:* Consultancy; *AstraZeneca:* Consultancy; *Janssen:* Consultancy; *Beigene:* Research Funding.

Table 1. Eligibility criteria
Age ≥18 years
Histology **Part 1:** R/R NHL mature B-cell lymphomas **Part 2:** R/R CLL/SLL with or without mutations in *BTK* C481S **Part 3:** Non-GCB CAR T/HCT R/R and/or ineligible DLBCL
Exposure to ≥2 prior systemic therapies
Measurable disease
Eastern Cooperative Oncology Group performance status of 0 or 1
Life expectancy ≥12 weeks

CAR T, chimeric antigen receptor T cells; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; HCT, hematopoietic cell transplant; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

Figure 1. M23-324 Study Design



3L+, third-line-or-later treatment; BOIN, Bayesian optimal interval; CLL, chronic lymphocytic leukemia; DL, dose level; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; NHL, non-Hodgkin lymphoma; RP2D, recommended phase 2 dose.

Figure 1

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