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PB2096 A PHASE 1B/2 STUDY OF GB5121, A NOVEL, HIGHLY SELECTIVE, POTENT, AND CNS-PENETRANT BTK INHIBITOR FOR RELAPSED/REFRACTORY PRIMARY/SECONDARY CNS LYMPHOMA AND PRIMARY VITREORETINAL LYMPHOMA

Topic: 19. Aggressive Non-Hodgkin lymphoma - Clinical

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Background:

Bruton's tyrosine kinase (BTK) plays an important role in B cell receptor and Toll-like receptor signaling pathways, which are constitutively active in primary CNS lymphoma, and represents an excellent therapeutic target. Ibrutinib, a first-generation BTK inhibitor (BTKi), has been evaluated in two phase 1/2 trials for relapsed/refractory primary/secondary CNS lymphoma (R/R PCNSL, SCNSL) and primary vitreoretinal lymphoma (PVRL) showing limited survival outcomes. Improved BTKis may achieve better therapeutic outcomes. GB5121 is a novel, orally available, covalent BTKi, which has shown superior specificity, CNS penetration, and CNS target occupancy in preclinical testing compared to other BTKis including ibrutinib. It is well-suited for further evaluation in CNS lymphoma. We will therefore conduct a phase 1b/2 open-label, international study of GB5121 in adult subjects with R/R PCNSL, SCNSL, or PVRL (NCT05242146).

Aims: The objective of the phase 1b dose-escalation portion of the study will be to evaluate safety, tolerability, pharmacokinetic/pharmacodynamic profile, dose-limiting toxicity (DLT), maximum tolerated dose, and preliminary therapeutic activity to determine the optimal biological dose that will inform the preliminary recommended phase 2 dose (pRP2D). The phase 1b expansion study will further explore the therapeutic activity and characterize the safety and tolerability of GB5121 at the pRP2D. The efficacy, safety, and tolerability of GB5121 at the pRP2D established in the phase 1b dose escalation study will be investigated in phase 2.

Methods: The study will be conducted in three parts: phase 1b dose-escalation, phase 1b expansion, and phase 2. Eligibility criteria for phase 1b dose-escalation and expansion (N ≈ 30 for each part) include ≥ 18 years of age, ECOG ≤ 2, R/R PCNSL, R/R SCNSL with CNS-only relapse, or R/R PVRL. Patients with newly diagnosed PCNSL who cannot tolerate standard high-dose methotrexate-based therapies are also eligible. Subjects who had prior allogeneic stem cell transplant or previously received a BTKi will be excluded. A Bayesian optimal interval design will be employed to perform dose escalation with the primary objective of determining the preliminary recommended phase 2 dose. In the absence of DLT, subsequent dose levels will increase sequentially according to a modified Fibonacci approach. The phase 2 portion of the study will initiate following the determination of the RP2D based on phase 1 results and is a single-arm, open-label study of GB5121 in subjects with R/R PCNSL. Adverse events will be graded per Common Terminology Criteria for Adverse Events (CTCAE v5.0) to establish a toxicity profile. Therapeutic response (overall response rate, complete response, partial response) will be determined according to the criteria of the International Primary CNS Lymphoma Collaborative Group. Progression-free survival and overall survival will be evaluated. This clinical trial is anticipated to start enrollment in May 2022.

Results: N/A (trial in progress)

Summary/Conclusion: N/A (trial in progress)