Exposure-Response of Idelalisib, a Novel PI3Kδ Inhibitor, in the Combination Therapy of Chronic Lymphocytic Leukemia

Feng Jin*, Huafeng Zhou, Xiaoming Li, Terry Newcomb, and Srini Ramanathan

Gilead Sciences, Inc, Foster City, CA 94404

Objectives: Idelalisib is a potent PI3Kδ inhibitor that is approved in combination with rituximab in relapsed CLL and as monotherapy in refractory FL and SLL. The relationships between idelalisib and GS-563117 (the major inactive metabolite) plasma exposures vs its efficacy/safety in the treatment for patients with CLL were evaluated.

Methods: Idelalisib and GS-563117 plasma exposures were generated using population pharmacokinetic (PK) models previously established for idelalisib and GS-563117 based on data from several phase 1/2 clinical studies. The relationships between idelalisib and GS-563117 exposures from an efficacy/safety dose ranging study (101-02; 50 mg to 350 mg BID, 150 mg and 300 mg QD), a Phase 2 study (101-07), and a Phase 3 study (GS-US-312-0116) were determined. Efficacy endpoints included best overall response rate (BOR), duration of response (DOR), progression free survival (PFS), sum of products of the greatest perpendicular diameters (SPD) of index lesions, and lymph node response (LNR) and safety endpoints included neutropenia, diarrhea, skin rash, infection, and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation.

Results: Over a wide dose/exposure range in dose-ranging study 101-02, median SPD response increased with idelalisib exposure (C\text{trough}) quartiles, reaching a plateau at the 3\textsuperscript{rd} quartile (Q3: range ~295-437 ng/mL), which encompassed the median C\text{trough} (349 ng/mL) at 150 mg BID, supporting the selection of 150 mg BID for further development. In study 101-07 and GS-US-312-0116, where idelalisib was evaluated as a combination therapy (with anti-CD20 agents rituximab or ofatumumab) in subjects with relapsed CLL, no relationship was observed between idelalisib exposure vs. any of the efficacy or safety endpoints evaluated based on analyses including logistic regression and Cox regression, indicating the absence of exposure-efficacy/safety relationships at 150 mg BID.

Conclusions: There were no exposure-response relationships observed for efficacy or safety endpoints at idelalisib 150 mg BID supporting this dose to be used in combination therapy in the treatment of CLL patients.