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Blood 142 (2023) 6149–6150

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

623.MANTLE CELL, FOLLICULAR, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Preliminary Safety, Pharmacological and Efficacy Data from Patients with Relapsed or Refractory B-Cell Malignancies Treated with the ICP-248, a Next Generation BCL2 Inhibitor

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Background: BCL2, a key protein regulator of the apoptotic pathway, is constitutively expressed in various malignancies, which is a hallmark of cancer cell. BCL2 inhibitors have been shown to be safe and effective and are approved for the treatment of patients with chronic lymphocytic leukemia/small cell lymphoma (CLL/SLL) or acute myeloid leukemia (AML). Venetoclax, the first and only approved BCL2 inhibitor, is associated with gastrointestinal toxicities and tumor lysis syndrome (TLS). Therefore, ICP-248 was developed as a potent and highly selective inhibitor of BCL2 and has shown antitumor activity superior to venetoclax in preclinical studies. Preclinical studies of ICP-248 have demonstrated favorable pharmacokinetics profile, broad safety window and excellent safety profile, as well as synergistic effect in anti-tumor activity in combination with Orelabrutinib, a novel and highly selective BTK inhibitor.
Methods: ICP-CL-1201 is a phase I study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of ICP-248 in patients with relapsed or refractory B-cell malignancies (*ClinicalTrials.gov ID: NCT05728658*). The study will be conducted in 2 parts. Part 1 will evaluate ICP-248 as monotherapy at the target dose of 100mg, 200mg, 300mg, 400mg, 500mg and 600mg (once daily and 28 days per cycle) and will explore different ramp-up dosing strategies. Part 2 will evaluate ICP-248 in selected and proposed indications. The dose escalation in Part 1 will follow the 3+3 design with dose-limiting toxicity (DLT) observation window with 49 days. Eligible patients include those with CLL/SLL and B-cell non-Hodgkin lymphomas (NHLs) who failed on available therapy. Key exclusion criteria include CNS involvement, prior exposure to BCL2 inhibitors and clinically significant cardiovascular disease. Adverse events (AEs) are reported per common terminology criteria for AEs (CTCAE) v5.0. Efficacy was evaluated according to the Lugano 2014 or International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 criteria. Minimal residual disease was evaluated with flow or next generation sequencing.
Results: As of 30 th July, 2023 (data cutoff date) 3 patents (mantle cell lymphoma [MCL], SLL and CLL) had been enrolled at the dose level of 100 mg QD; age ranging from 53 to 68; follow-up ranging from 1.9 to 4.7 months); median of prior regimen numbers was 3 (range, 1-3; 2 out 3 patients failed on zanubrutinib or pirtobrutinib). ICP-248 demonstrated a favorable PK

profile, approximate dose proportionality was observed across the ramp-up stage. No DLTs and SAEs were observed. All the AEs were grade 1 to 2 (mainly neutropenia) without dose interruption and modifications. No TLS including laboratory TLS was observed. Two patients with MCL and SLL were assessed as complete response (CR) at the end of cycle 2, and the CLL patient was assessed as stable disease without sign and symptom of disease and recovering hematology. Undetectable MRD was confirmed in the patient with SLL and MCL.

Conclusions: Preliminary results suggest that ICP-248 is safe and well tolerated in relapsed or refractory B-cell malignancies. The favorable clinical pharmacological and safety profiles support current dose ramp up strategy. Preliminary efficacy data demonstrated good response with deep remission. Further assessment of safety and efficacy with additional dose levels and dosing strategies will be pursued in expanded patient population and in the combination with orelabrutinib.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-182558