ELSEVIER

Blood 142 (2023) 7143

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

Preclinical Studies Support the Clinical Development of LP-284 in Relapsed and Refractory B-Cell Lymphomas

Jianli Zhou[1], *Drew Sturtevant, PhD*[1], *Aditya Kulkarni, PhD*[1], *Kishor Bhatia, PhD*[1], *Reginald Ewesuedo, MD*[1]

[1] Lantern Pharma Inc., Dallas, TX

Genomic instability, a hallmark of many cancers, often results from corrupted DNA damage response/repair (DDR) pathways. Targeting DDR deficiencies in cancer therapy has been successful in solid tumors with dysfunctional homologous recombination repair (HR). However, while less recognized, lymphomas also carry DDR defects such as HR deficiency (HRD) and can account for approximately 18% of all lymphomas. LP-284 is a fully synthetic DNA-damaging agent that induces double-stranded DNA breaks and displays elevated potency in cancer cells with HRD or transcription-coupled nucleotide excision repair defects, including multiple advanced B-cell lymphomas. In preclinical pharmacology studies, the mantle cell lymphoma (MCL) xenograft tumor mouse model derived from JeKo-1, which has mutated TP53 and checkpoint kinase 2 (CHEK2), an HRD score of 46, and was refractory to ibrutinib and bortezomib, showed near complete response after LP-284 treatment. It is noteworthy that 40~50% of MCL patients may be HRD due to the presence of mutations in the ataxia-telangiectasia mutated (ATM) gene. HRD is also likely to be prevalent in high-grade lymphomas, as IGH/MYC translocation or BCL2 expression has been reported to be associated with HR inhibition. Studies of LP-284 in the MYC/BCL2 dual-translocated OCILY1 tumor xenograft model have shown a robust efficacy profile with an average of 99% tumor growth inhibition.

Key pharmacokinetic studies demonstrated that LP-284 is neither a substrate nor modulator of major CYP-450 enzymes, multi-drug resistance transporters, renal drug transporters, or hepatic drug transporters. Safety pharmacology studies indicated that LP-284 does not inhibit hERG potassium channel and has a low potential to affect cardiovascular functions. Toxicology repeat dose studies of LP-284 in Sprague Dawley rats and Beagle dogs, using intravenous infusion on Days 1, 8, and 15 in a 28-day cycle, were generally well tolerated with notable adverse effects in Beagle dogs consisting mainly of reversible hematologic toxicity and testicular toxicity. The highest non-severely toxic dose (HNSTD) in dogs was considered to be 0.4 mg/kg/dose. Overall, based on its impressive preclinical anti-tumor efficacy profile, low drug-drug interaction liability, and findings from toxicological studies, a Phase 1 study is currently planned with LP-284 to assess its safety, tolerability, pharmacokinetics, and clinical activity in patients with relapsed or refractory B-cell lymphoma. Clinical development will be informed by an emphasis on patient selection strategy based on DDR/HR biomarkers.

Disclosures Zhou: *Lantern Pharma Inc.:* Current Employment. **Sturtevant:** *Lantern Pharma Inc.:* Current Employment. **Kulkarni:** *Lantern Pharma Inc.:* Current Employment. **Bhatia:** *Lantern Pharma Inc.:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties. **Ewesuedo:** *Lantern Pharma Inc.:* Current Employment.

https://doi.org/10.1182/blood-2023-174964