Phase 1a/1b clinical trial of LP-284, a highly potent TP53 mutation agnostic DNA damaging agent, in patients with refractory or relapsed lymphomas and solid tumors (NCT06132503)

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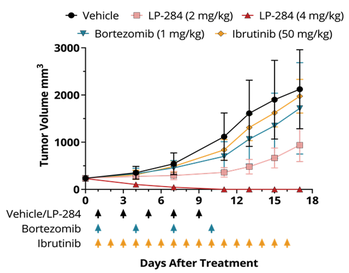
Background and Preclinical Rationale

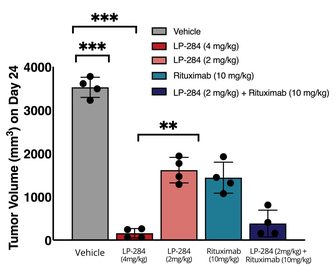
- LP-284 is a next-generation DNA damaging agent that induces double-strand DNA breaks. Deficiency of DNA damage response systems (including ATM alterations) in cancer cells enhances sensitivity to LP-284.
- LP-284 shows nanomolar potency in > 40 hematological and solid cancer cell lines. Presence or absence of TP53 mutations does not impact sensitivity to LP-284.
- LP-284's robust preclinical efficacy in mantle cell lymphoma (MCL) xenograft models suggests superiority to (Figure 1) and the ability to overcome resistance to (Figure 3) ibrutinib and bortezomib. LP-284 is synergistic with rituximab in High-Grade B-cell Lymphoma (HGBL) with MYC and BCL2 rearrangements[2] xenograft models (Figure 2) and prolongs event-free survival in sarcoma xenograft models.

Figure 1. LP-284 inhibited tumor growth at least 3-fold more than ibrutinib and bortezomib



- JeKo-1 (TP53-mutated, MCL) cell line derived xenograft model, n = 8/arm

Figure 2. LP-284 led to 99% TGI when used as a single agent and showed synergy with rituximab



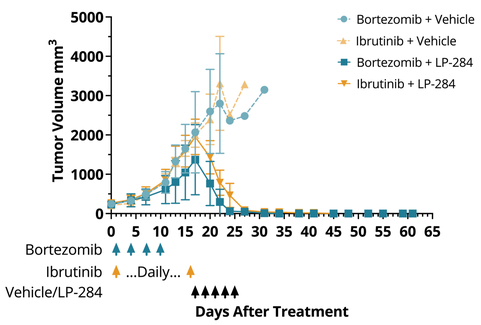
- OCILY-1 (TP53-mutated, HGBL with MYC and BCL2 rearrangements) cell line derived xenograft model, n = 4/arm

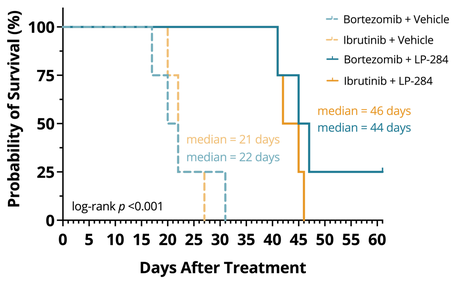
Table 1. Summary of LP-284 Efficacy in Xenograft models

Treatment	TGI* (MCL)	TGI* (HGBL)
LP-284 (4 mg/kg)	113%	99%
LP-284 (2 mg/kg)	63%	57%
LP-284 (2 mg/kg) + Rituximab (10 mg/kg)	NA	93%

*TGI: Tumor Growth Inhibition

Figure 3. LP-284 led to near complete tumor regression and doubled survival in ibrutinib and bortezomib resistant models



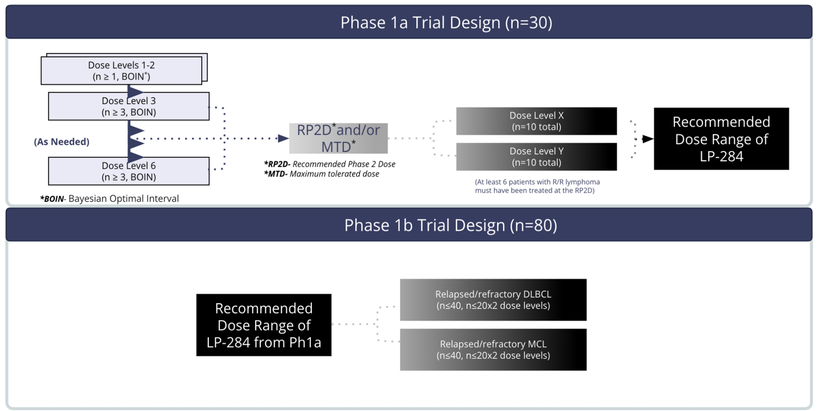


- The JeKo-1 xenograft model was resistant to Ibrutinib and Bortezomib
- When Ibrutinib or Bortezomib was replaced with LP-284 or Vehicle, tumors in the Vehicle group continued to progress, whereas one cycle of 4 mg/kg LP-284 led to near complete tumor regression and approximately two times longer survival (p<0.001)

- The FDA has granted **orphan drug designations** to LP-284 for the treatment of **MCL** and diffuse large B-cell lymphoma/high-grade B-cell lymphoma with MYC and BCL2 rearrangements (**DLBCL/HGBL-MYC/BCL2**)

Clinical Study Design

- NCT06132503 is a First-in-Human, open label, multi-center, Phase 1a/1b dose escalation and expansion study in patients with relapsed/refractory (R/R) lymphomas and solid tumors (**Phase 1a is open to accural**)



Phase 1a Dose Escalation

- The dose escalation study is being conducted using a Bayesian Optimal Interval (BOIN) design with a targeted dose-limiting toxicity (DLT) probability of 0.25.
- The dose escalation involves a minimum of 1 patient/cohort for the first two dose levels (DLs) and of 3 patients/cohort for subsequent DLs. After determination of the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D), additional patients eligible for Phase 1a will be randomized into 2 backfill cohorts at dose levels that were previously evaluated during the dose escalation. Up to 30 patients will be enrolled in Phase 1a.
- LP-284 is administered intravenously on days 1, 8, and 15 of a 28-day cycle.
- Enrollment in dose level 1 (0.04 mg/kg) commenced in March 2024.

Phase 1a Enrollment Criteria

Major Inclusion Criteria:

- Male or non-pregnant female ≥ 18 years of age.
- Confirmed **B-cell NHL** that has relapsed from or is refractory to at least two prior standard of care treatments, or for which no standard treatment is available.
- Histologically or cytologically documented **advanced solid tumor** that has relapsed from or is refractory to standard treatment, or for which no standard treatment is available.
- Patients have not been exposed to anti-cancer therapy within 2 weeks or within at least 5 half-lives whichever is shorter; or 4 weeks from any biologics/immunotherapies or any investigational therapy prior to the first dose of LP-284.

Phase 1a Objectives/Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of escalating doses of LP-284 and to determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) in patients with relapsed or refractory (R/R) lymphomas and solid tumors	Incidence and severity of adverse events (AEs) graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, clinical laboratory, and electrocardiogram (ECG) abnormalities defined as dose-limiting toxicities (DLTs)
Secondary	
To characterize the pharmacokinetics (PK) of LP-284	PK parameters for LP-284 and metabolite(s) derived from plasma concentrations
To assess clinical activity of LP-284	For Lymphoma: Overall Response Rate (ORR) based on Investigator's assessment as per Lugano Criteria and Duration of Response (DOR) For solid tumors: RECIST 1.1 to determine ORR (based on Investigator's assessment), complete response (CR), partial response (PR), DOR
Exploratory	
To evaluate the association between tumor response and changes in circulating tumor DNA (ctDNA)	Comparison of ctDNA in pre-, and post-treatment (at intervals of disease assessment)
To identify the genomic signature of response to LP-284	Somatic alterations and gene expression analysis of tumor tissue and alterations analysis of ctDNA

Phase 1b Dose Expansion

After the completion of Phase 1a, up to 80 additional adult patients with R/R DLBCL and MCL will be enrolled at the recommended dose(s) for further clinical evaluation. A Simon's two-stage design will be adopted. The primary objectives of Phase 1b are to obtain preliminary estimates of clinical activity in adult patients with R/R DLBCL and MCL, and to determine the dose of LP-284 for further development based on exposure-response/safety relationships derived from the totality of the data obtained from both Phase 1a and 1b.

References and Contacts

1. Oncotarget (2023); 14, 597-611
2. Clinical Lymphoma Myeloma Leukemia (2023); 23 (Supp 1), S423

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