Targeting Homologous Recombination Deficiencies in B-Cell Non-Hodgkin's Lymphomas with the Novel Anti-Tumor Small Molecule LP-284

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Background

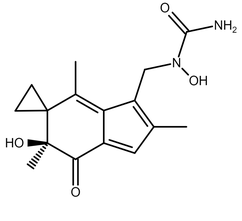
DNA double-strand breaks (DSB) are considered the most deleterious form of DNA damage and failure to correctly repair DSB due to homologous recombination deficiency (HRD) represents a targetable vulnerability in many cancers. The existing clinical HRD tests, which typically include assessment of BRCA mutation and genomic instability, have helped identify subgroups of ovarian and breast cancer patients who may benefit from Poly(ADP-ribose)polymerase inhibitors (PARPi). Although deregulation of DNA damage response (DDR) has been frequently reported in B-cell Non-Hodgkin's lymphomas (B-NHL)[1], neither HRD clinical tests nor agents targeting HRD have been approved for B-NHL patients.

LP-284, a small molecule DNA damaging agent, is being developed for the treatment of relapsed or refractory lymphomas. We previously reported LP-284's strong potency in HRD B-NHL cell line models.

Objectives

- Assess the frequency of HRD in 107 B-NHL patients from the Pan-Cancer Analysis of Whole Genomes (PCAWG) study [2].
- Identify LP-284-induced DNA lesions and cellular responses.
- Evaluate LP-284's in vivo potency in B-NHL xenograft models as a monotherapy and as a combination agent with the anti-CD20 monoclonal antibody rituximab.

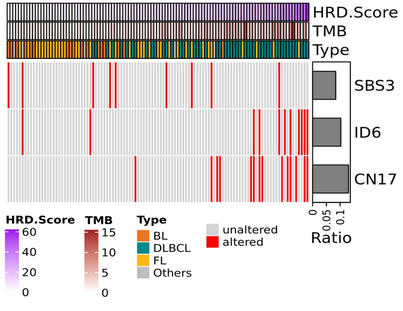
LP-284



- A fully synthetic acylfulvene compound with demonstrated anti-tumor activities in preclinical lymphoma models
- FDA orphan drug designation for the treatment of MCL
- IND application submitted on Aug 18, 2023

Results

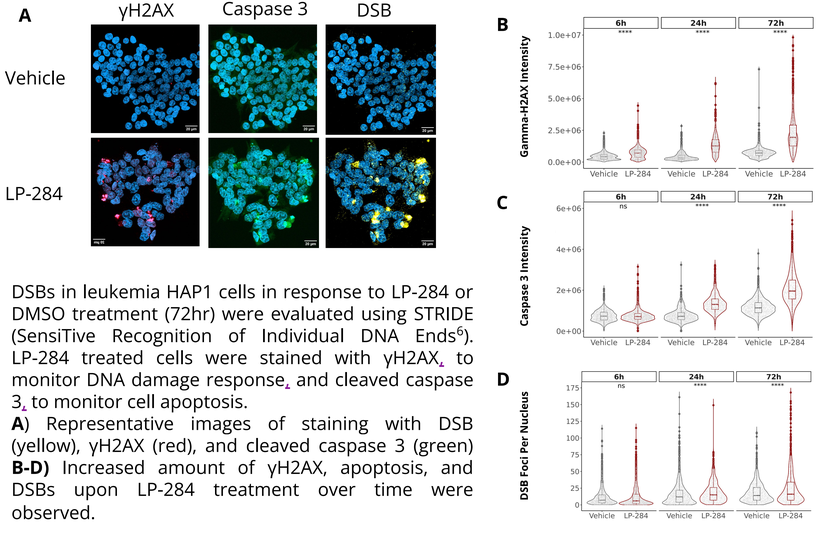
Figure 1. The prevalence of HRD+ in 107 B-NHL patients from the PCAWG study



- High HRD.Score is associated with high TMB (spearman correlation coefficient = 0.67)
- Eleven patients are considered to be HRD+, due to the relatively higher HRD.Score (>=28) and the presence of HRD-associated mutational signatures ID6[4] and CN17[5]
- 91% of the HRD+ patients belong to DLBCL

Fig 1. Legend: TMB, tumor mutation burden; **SBS3**, COSMIC single base substitution signature 3; **ID6**, COSMIC small insertion and deletion signature 6; **CN17**, COSMIC copy number signature 17; **BL**, Burkitt's lymphoma; **DLBCL**, diffuse large B-cell lymphoma; **FL**, follicular lymphoma. Data from the PCAWG study[2] was used to support the analysis.

Figure 2. LP-284 induces DSB, γH2AX, and cell apoptosis

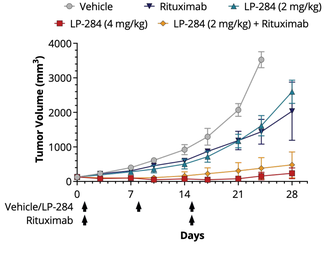


DSBs in leukemia HAP1 cells in response to LP-284 or DMSO treatment (72hr) were evaluated using STRIDE (SensiTive Recognition of Individual DNA Ends[6]). LP-284 treated cells were stained with γH2AX, to monitor DNA damage response, and cleaved caspase 3, to monitor cell apoptosis.
A) Representative images of staining with DSB (yellow), γH2AX (red), and cleaved caspase 3 (green) **B-D)** Increased amount of γH2AX, apoptosis, and DSBs upon LP-284 treatment over time were observed.

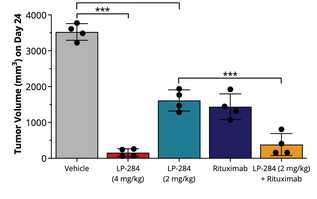
Results Cont.

Figure 3. LP-284 has strong anti-tumor activities in HRD B-NHL xenograft mouse models

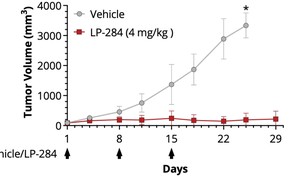
A. OCI-LY1 cell line derived xenograft mice



B.



C. JeKo-1 cell line derived xenograft mice



A/B: IGH/MYC translocation and BCL2 expression are associated with HR inhibition[7,8]. The MYC/BCL2 dual-translocated B-NHL cell line OCI-LY1 derived xenograft mice were treated as shown in the figure. At Day 24 post-treatment initiation, LP-284 (4 mg/kg) resulted in 99% tumor growth inhibition (TGI), and LP-284 (2 mg/kg) resulted in 57% TGI as a monotherapy and 93% TGI in combination with rituximab (N=4 mice/arm).

C: The JeKo-1 MCL cell line has an HRD score of 46. Treatment of JeKo-1 derived xenograft mice with LP-284 (4 mg/kg) led to near complete and sustainable tumor regression (N=3 mice/arm).

Conclusions

- At least 10% of B-NHL patients in the PCAWG study cohort are likely HRD+ and approximately 91% of HRD+ B-NHL cases belong to DLBCL, all of which may be suitable for treatment with DSB-inducing agents.
- LP-284 induces lethal DSBs and shows robust anti-tumor activities in putative HRD+ B-NHL xenograft mouse models, paving the rationale for its clinical development as a targeted therapy for HRD+ B-NHL patients.

References

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