Inhibition of TLR7 and TLR9 Blocks MYD88 L265P Oncogenic Mutation-mediated Signaling

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INTRODUCTION

- The MYD88 L265P oncogenic mutation is present in various B-cell malignancies, including in 29% of patients with ABC-DLBCL1 and 90% of patients with Waldenström’s macroglobulinemia (WM)2.
- MYD88 is an adaptor molecule in TLR-mediated signaling; the MYD88 L265P oncogenic mutation promotes tumor cell survival by over-activation of the TLR signaling pathway3 which includes IRAK1/IRAK4, TRAF6, BTK, NF-κB and JAK/STAT.
- B-cells express TLR7 and TLR9; inhibition of TLR7 and TLR9 reduces MYD88 L265P-driven signaling and inhibits tumor cell survival3.
- Therefore TLR antagonism is an intriguing novel approach to the treatment of B-cell malignancies harboring the MYD88 L265P mutation.
- In the current study, we evaluated two modalities to suppress MYD88 L265P-driven over-activation of TLR signaling: gene-silencing oligonucleotides (GSOs) targeted to MYD88, TLR7, and TLR9; and IMO-8400, a selective antagonist of TLR7, TLR9, and TLR8.

RESULTS

IMO-8400 INHIBITS MYD88 L265P-DRIVEN SIGNALING AND CELL SURVIVAL

IMO-8400, A TLR ANTAGONIST, AS A THERAPEUTIC APPROACH FOR DLBCL HARBOURING MYD88 L265P

IMO-8400 DECREASES MYD88 L265P MUTATION-DRIVEN SIGNALING PATHWAYS

CONCLUSIONS

- The TLR antagonist IMO-8400 and gene silencing oligonucleotides targeted to TLR7, TLR9, or MYD88 inhibit over-activation of TLR-induced signaling and decrease tumor cell viability in B cell lymphoma cell lines harboring the MYD88 L265P mutation.
- Tumor growth inhibition in xenograft models is correlated to reduced tumor-secreted cytokines and with inhibition of MYD88 L265P mutation-driven signaling pathways including IAK/STAT, NF-κB and p38.
- IMO-8400 and gene silencing oligonucleotides show no impact on a lymphoma cell line lacking the MYD88 L265P mutation.
- Based on promising preclinical data and clinical safety, IMO-8400 is currently being evaluated in a Phase I/2 clinical trials in patients with DLBCL and Waldenström’s macroglobulinemia harboring the MYD88 L265P mutation.

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