Synergistic Blockade of ABC DLBCL Proliferation with a Selective Inhibitor of IRAK4 in Combination with Inhibition of the B-Cell Receptor Signaling Network

Combination with Other Tumor Signaling Inhibitors: may provide benefit for patients with ABC DLBCL.

ND-2158, a potent (Ki of 1.2 nM) and highly selective IRAK4 inhibitor has been previously shown to be efficacious in a proof-of-concept study demonstrating a selective IRAK4 inhibitor, ND-2158, with BTK, SYK and PI3Kδ inhibitors. Results with kinase inhibitors strongly support a role for signaling through the B-cell receptor (BCR) pathway in the activation of ABC DLBCL. TLR and IL-1 family ligands activate NF-κB via Toll-Like Receptor (TLR) and IL-1 signaling is mediated by the adaptor protein MyD88 through IRAK4 activation. Therefore, inhibition of IRAK4 may be therapeutic in hematologic malignancies containing MyD88 mutations. Recent clinical results with disease-staging strongly support a role for signaling through the B-cell receptor (BCR) pathway in the progression of hematologic malignancies including ABC DLBCL. There is currently a significant interest in the therapeutic application of combining a selective IRAK4 inhibitor, ND-2158, with BTK, SYK and PI3Kδ inhibitors.

ND-2158, a potent (Ki of 1.2 nM) and highly selective IRAK4 inhibitor has been previously shown to be efficacious in reducing the proliferation of ABC DLBCL cell lines expressing MYD88 L265P resistant but lacks activity on cell lines that are not dependent on MYD88/MAL activation (GBM, DLBCL).

Here we show:

- Synergistic blockade of ABC DLBCL OCI-LY10 proliferation when ND-2158 is used in combination with inhibitors of either BTK (dorotinib), PI3Kδ (GS-1101), or SYK (P505-15, BMS-986548).
- Combination of ND-2158 with BCR signaling inhibitors such as ibrutinib is more potent than the single agent, yielding a decrease in the IC50 of 2 to 10 fold in cell lines expressing the BCR signaling pathway.
- In contrast to combinations with BCR signaling inhibition, ND-2158 in combination with lenalidomide failed to demonstrate synergistic activity due to low single agent activity of lenalidomide.

We conclude that ND-2158, in addition to its potent BCR signaling, contributes to the proliferative capacity of ABC-DLBCL. We propose that combination therapeutic approaches, including inhibition of IRAK4, may provide benefit for patients with ABC DLBCL.

Combination with Other Tumor Signaling Inhibitors: Potential for Improved Response Durability,

In Vivo Proof-of-Mechanism: Potent Inhibition of LPS-induced Serum Cytokine Production in Lewis Rats

ND-2158 is Highly Selective Across 334 Kinases

ND-2158 Blocks IRAK4 Induced IκBα Degradation in Monocytes from Whole Blood

Evaluation of Synergism in Cross-Over Combination Study

ND-2158 Demonstrates Synergistic Blockade of ABC DLBCL Proliferation in Combination with BCR Signaling Inhibitors

Summary

- ND-2158 is a highly potent and selective IRAK4 inhibitor that blocks IRAK4 mediated signaling in cells and in vivo as measured by inhibition of IκBα degradation and cytokine expression in response to TLR stimulation.
- ND-2158 is effective in blocking proliferation of ABC-DLBCL but not GCB (BCL6+ BCL2-) cell lines, suggesting that survival of ABC-DLBCL is more dependent on IRAK4 in this BCR signaling network.
- ND-2158 demonstrates synergistic blockade of ABC DLBCL proliferation in combination with BCR signaling inhibitors (BTK inhibitoribrutinib, PI3Kδ inhibitor GS-1101, and Syk inhibitor P505-15), but shows no significant combination effect with Lenalidomide.

Conclusions

- Inhibition of IRAK4, along with blockade of selected BCR signaling, will likely prove efficacious in treating ABC DLBCL.

ABSTRACT

Toll-like receptor (TLR) and interleukin-1 (IL-1) signaling is mediated by the adaptor protein MYD88 through the B-cell receptor (BCR) pathway, which is a critical pathway in the pathogenesis and chemoresistance of B-cell lymphomas. Myeloma and CD20+ B-cell lymphomas (ABC DLBCL) are characterized by high levels of MyD88, NF-κB activation and cytokine production. Therefore, inhibition of IRAK4 may be therapeutic in hematologic malignancies containing MyD88 mutations. Recent clinical results with disease-staging strongly support a role for signaling through the B-cell receptor (BCR) pathway in the progression of hematologic malignancies including ABC DLBCL. There is currently a significant interest in the therapeutic application of combining a selective IRAK4 inhibitor, ND-2158, with BTK, SYK and PI3Kδ inhibitors. Here we show:

- Synergistic blockade of ABC DLBCL OCI-LY10 proliferation when ND-2158 is used in combination with inhibitors of either BTK (dorotinib), PI3Kδ (GS-1101), or SYK (P505-15, BMS-986548).
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We conclude that ND-2158, in addition to its potent BCR signaling, contributes to the proliferative capacity of ABC-DLBCL. We propose that combination therapeutic approaches, including inhibition of IRAK4, may provide benefit for patients with ABC DLBCL.

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