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POSTER ABSTRACTS

802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

MALT1 Protease Inhibition Overcomes BTK Inhibitor Resistance and Shows Synergistic Activity with Venetoclax in Models of B Cell Lymphoma and Leukemia

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Background

Specific B cell malignancies, including the aggressive non-germinal center B cell-like (GCB) subtype of diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL), are driven by constitutive activation of the transcription factor NF-kB. Chronic signaling resulting from mutations or antigen-induced activation of the B cell receptor (BCR) pathway drives NF-kB activity in these tumors resulting in sustained proliferation and survival pathways. Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) represents a key mediator of the BCR/NF-kB signal transduction pathway responsible for maintaining survival and driving proliferation of NF-kB-addicted B cell tumors by proteolytically cleaving NF-kB antagonists.

Aims

Pharmacological inhibition of MALT1 protease activity may provide an attractive treatment option for patients with these cancers. Further, as combination therapy is often required for the treatment of aggressive B cell malignancies, the identification of therapies that synergistically combine with MALT1 inhibitors could afford additional and promising treatment options.

Methods

A highly potent and orally bioavailable MALT1 protease inhibitor (ABBV-MALT1) was used to test the hypothesis that MALT1 inhibition will abrogate the proliferation of preclinical models of B cell malignancies in vitro and in vivo. Tumors treated with ABBV-MALT1 were subjected to transcriptomic and functional proteomic assays to elucidate molecular mechanisms of action and rational combination partners.

Results

ABBV-MALT1 potently inhibits MALT1 activity in vitro while showing high selectivity against a panel of proteases, kinases and other types of receptors and enzymes. Mechanistic studies reveal that ABBV-MALT1 effectively inhibits signal transduction of the BCR pathway and reduces NF-kB gene activation in non-GCB DLBCL cell lines resulting in cell cycle arrest and diminished viability. In vivo, oral administration of this compound demonstrates robust tumor growth inhibition in several models of B cell tumors, including non-GCB DLBCL models that are resistant to Bruton's tyrosine kinase (BTK) inhibitors.

NF-kB target genes include the pro-survival family members BCL-XL and BCL2-A1, which aid in regulation of the intrinsic apoptosis pathway. As ABBV-MALT1-induced inhibition of the NF-kB pathway resulted in downregulation of these genes, we hypothesized that the associated tumor models would become increasingly dependent on the pro-survival family member BCL-2. To test this hypothesis, combination studies of ABBV-MALT1 and the selective BCL-2 inhibitor venetoclax were performed in both cell line and patient-derived xenograft models of DLBCL. Herein we show that concomitant administration of ABBV-MALT1 and venetoclax results in dramatic antitumor activity in all models tested in vivo. This efficacy also translates to primary patient CLL cells in vitro where the combination confers greater levels of apoptosis compared to either agent alone.

Summary/Conclusion:

ABBV-MALT1 demonstrates robust single agent anti-tumor activity in malignant B cell models that are resistant to BTK inhibitors. Moreover, combination of ABBV-MALT1 with the BCL-2 inhibitor venetoclax shows synergistic cell killing of B cell tumors in vitro and dramatic tumor regression in vivo. Together, these data indicate that MALT1 inhibition may overcome BTK inhibitor resistance and combine with venetoclax to effectively treat patients with DLBCL, CLL and other B cell malignancies.

Disclosures

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Disclosures Plotnik: *AbbVie:* Current Employment. **Bontcheva:** *AbbVie:* Current Employment. **Dowell:** *AbbVie:* Current Employment. **Will:** *AbbVie Inc.:* Current Employment, Other: may own stock. **Chen:** *AbbVie:* Current Employment. **Richardson:** *AbbVie:* Current Employment. **McClure:** *AbbVie:* Current Employment. **Jung:** *AbbVie:* Current Employment. **Pham:** *AbbVie:* Current Employment. **Souers:** *AbbVie:* Current Employment. **Meulbroek:** *AbbVie:* Current Employment. **Pappano:** *AbbVie Inc.:* Current Employment, Other: may own stock.

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