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621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Compatibility of Venetoclax and OPN51107 in Treatment of Mantle Cell Lymphoma

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Introduction

Mantle Cell Lymphoma (MCL) is the third most common form of B-Cell lymphoma and patients diagnosed tend to have poor long-term survival when compared to patients of other B-cell lymphoma subtypes. Deregulation of the apoptotic cellular machinery contributes to early acquirement of therapy resistance in MCL and contributes to the poor clinical outcomes observed in relapsed/refractory MCL patients. Developing therapeutic strategies using agents that favor a pro-apoptotic cellular environment are being investigated in pre-clinical and clinical studies. To this end, we evaluated the therapeutic effects of targeting the Bcl-2 related proteins using Venetoclax, a Bcl-2 inhibitor, and OPN51107, a BET inhibitor, in MCL pre-clinical models. OPN51107 targets BRD4 in B-cells, a protein involved in the preinitiation complex for transcription of miRNA inhibit the translation of BIM, a pro-apoptotic initiator in the Bcl-2 family.

Methods

Using a panel of MCL cell lines (HBL-2, Granta, Z-138, Mino, Jeko-1, and Rec-1) along with resistant cells of each cell line made to Cytarabine, we conducted pre-clinical targeting of Bcl-2 and BRD4 with Venetoclax and OPN51107 respectively. Single and double agent exposure experiments were performed at 72 hrs and coefficients of synergy were assessed using CalcuSyn. Synergy was determined from cellular viability using Cell Titer-Glo (Promega) and was read using a BioTek Synergy HTX multimode reader. During *in vivo* experiments, 6-week SCID mice were inoculated with 10×10^6 HBL-2 or Granta cells via tail vein injection. OPN51107 was administered at 5 and 20 mg/kg/dose PO Days (3-7, 10-14. And 17-21). Venetoclax was administered at 50 and 100 mg/kg/dose PO Days (3-7, 10-14, and 17-21). Bcl-2 family member protein expression was determined via western blot. Protein-protein interactions of members of the Bcl-2 family were also studied though Co-immunoprecipitation.

Results

In vitro exposure of MCL cells lines resulted in an up-regulation of BIM levels. Synergistic activity between Venetoclax and OPN51107 was observed in SCID mice bearing the Granta cells but not in animals inoculated with the HBL-2 cell line. The median survival for Granta bearing SCID mice treated with Venetoclax and OPN51107 was longer (26 days) when compared to animals treated with either Venetoclax (24 days) or OPN51107 (25 days) (P values: 0.000383 and 0.089 respectively). Ongoing studies are investigating protein to protein interactions between BIM and other Bcl-2 related proteins to further define the mechanisms responsible for the synergy observed between Venetoclax and OPN51107.

Conclusion

Previous *in vitro* activity presented a synergistic relationship on cell death from combination treatment of OPN51107 and Venetoclax. Our present research suggests that this relationship can also be replicated *in vivo* and further research has been done to help elucidate a possible mechanism of action responsible for the enhancement of activity seen. Continuing these directions to understand the synergy between OPN51107 and Venetoclax is necessary to advance therapies within MCL.

Disclosures Hernandez-Ilizaliturri: *Kite:* Consultancy; *BMS:* Consultancy; *Incyte/Morphosys:* Consultancy; *Epizyme:* Consultancy; *Amgen:* Consultancy; *BioGene:* Consultancy; *AbbVie:* Consultancy; *Gilead:* Consultancy; *Collectar:* Consultancy; *Dava Oncology:* Consultancy; *Novartis:* Consultancy; *ADC Therapeutics:* Consultancy.

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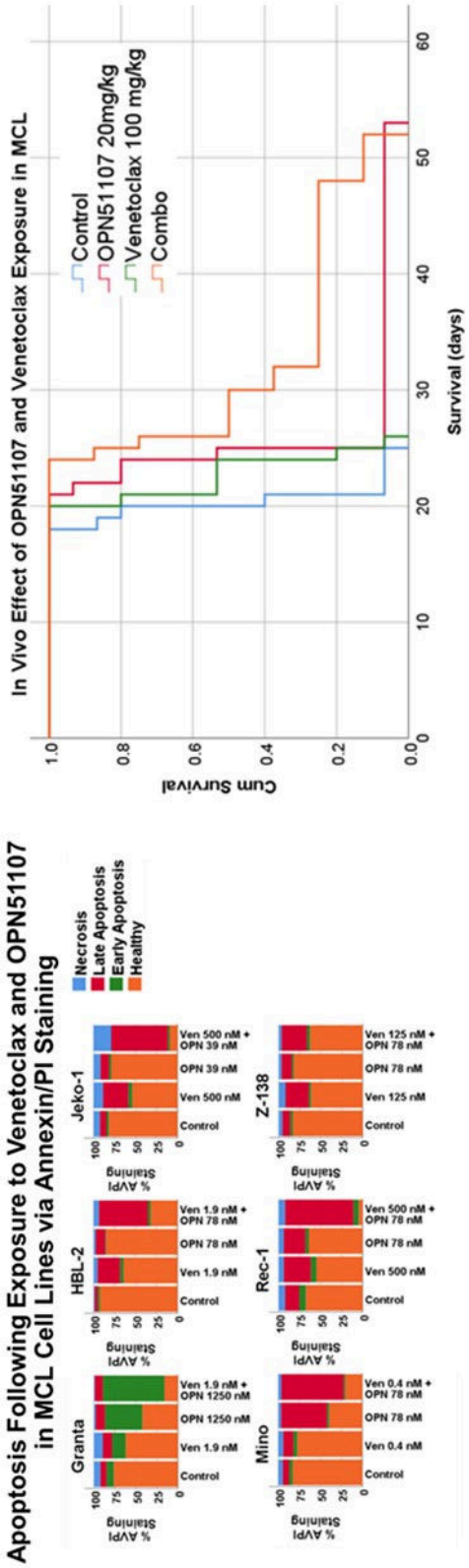

Figure 1