Preclinical characterization of LOXO-338, a novel, oral and selective BCL2 inhibitor

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**Background**

- Dysregulation of BCL2 family proteins is implicated in the pathophysiology of various hematologic malignancies.
- Venetoclax is the only BCL2 inhibitor approved for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma and acute myeloid leukemia.
- LOXO-338 is a novel, orally bioavailable BCL2 small molecule inhibitor, designed to achieve selectivity over BCL-xL to avoid dose-limiting thrombocytopenia associated with BCL-xL inhibition.1
- LOXO-338 is being developed for the treatment of lymphocytic lymphoma and acute myeloid leukemia.

**Materials and Methods**

- Homogeneous time-resolved fluorescence (HTRF): Compounds were incubated with the target proteins for 15 min at room temperature. HTRF donor and acceptor (Cisbio binding assay kit) were added for a 2 hr reaction and then fluorescence was measured.
- Co-immunoprecipitation: RS4;11 and Karpas 299 cells were treated with compounds for 4 hrs. Cell lysates were collected for co-immunoprecipitation.
- Mouse xenograft models: Tumors were established by subcutaneous injection of DOHH2 cells into BALB/c nude mice; MV4-11 cells into BALB/c nude mice; RS4;11 cells into NOD-SCID mice; and TMD8 cells into NOD SCID mice. When tumors reached a volume of 100–150 mm3 for DOHH2 and MV4-11, 100–200 mm3 for RS4;11, and 400 mm3 for TMD8, mice were randomized into control and treatment groups.
- In vitro combination: REC-1 and TMD8 cells were treated with compounds for 72 hrs. Cell viability was measured using CellTiter-Fluo (Promega).

**Figure 1. LOXO-338 selectively inhibits BCL2 interaction with pro-apoptotic proteins BAK and BIM**

**Figure 2. LOXO-338 is well-tolerated and inhibits tumor growth in mouse xenograft models**

**Figure 3. In vitro combination of LOXO-338 + pirtobrutinib demonstrates mild synergy in REC-1 human MCL model**

**Figure 4. In vitro combination of LOXO-338 + pirtobrutinib demonstrates additivity in TMD8 human DLBCL model**

**Figure 5. Combination of LOXO-338 + pirtobrutinib in TMD8 xenograft model shows greater tumor growth inhibition**

**Conclusions**

- LOXO-338 is a novel, orally bioavailable BCL2 small molecule inhibitor, with a favorable preclinical pharmacological profile comparable to venetoclax.
- Selectively inhibits BCL2 over other BCL2 family members in biophysical and cellular assays.
- Is well-tolerated in vivo and demonstrates dose-dependent tumor growth inhibition in various murine xenograft models.
- Shows greater efficacy in combination with pirtobrutinib, a BTK inhibitor.
- This preclinical profile of LOXO-338 supports its nomination as a novel BCL2 inhibitor clinical candidate.
- A first-in-human Phase 1 clinical trial is planned for 2021.

**References**


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