Targeting cancer with a novel BET bromodomain inhibitor

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Background

Bromodomain and extra-terminal (BET) family proteins are dual bromodomain-containing epigenetic readers that bind to acetylated-lysine residues in histones at gene promoter and enhancer elements and recruit protein complexes to promote transcriptional elongation. Recent evidence demonstrates that BET bromodomain inhibition leads to anti-proliferative activity in pre-clinical models of many hematological malignancies and solid tumors. Selective inhibition of BET bromodomains by small molecule inhibitors has emerged as a promising therapeutic strategy for the treatment of cancer. In this study, we evaluated the antitumor activity of ODM-207, a novel, potent and highly selective BET bromodomain inhibitor.

Methods

Biochemical activity ( binding of ODM-207 to BRD2 BD1, BRD3 BD1, BRD4 BD1, BRDT BD1 and BRD4 full length ) was measured by increasing the displacement of bromodomain-bound fluorescent peptide from bromodomain containing plasmid DNA. Cell viability and apoptosis assays: Cell lines and patient derived cells from pleural effusions or tumor biopsies were plated on multiwell plates and treated with 8-point semi-log dilution series of ODM-207 in duplicate or triplicate for 3 to 4 days. Growth inhibitory effect of ODM-207 in solid tumor cell lines was measured using WST-1 Cell Proliferation Assay (Roche). Cell viability and apoptosis of hematological cancer cell lines using CellTiter-Glo® assay (Promega). Apoptosis in relation to live cells was measured using ApoTox-Glo assay (Promega). Growth inhibitory effect on patient-derived tumor cell cultures (Misvik Biology) was measured either by proliferation assay (ProQinase), immunofluorescence and cell cycle analysis: In situ cell extraction was performed essentially as described by Zhan et al. 2015

Results

1. Biochemical activity of ODM-207

2. In vitro antiproliferative activity of ODM-207 across multiple tumor types

3. ODM-207 inhibits cell growth and induces apoptosis in a subset of prostate and breast cancer cells

4. OTX015 resistant LNCaP prostate cancer cells maintain sensitivity to ODM-207

5. ODM-207 is efficacious as a single agent in xenograft models

Conclusions

ODM-207 is a novel and structurally distinct inhibitor of BET proteins that

 ✓ Induces cell cycle arrest and shows broad and potent antiproliferative activity against a wide range of different hematological and solid tumors in vitro and in vivo. 
 ✓ Inhibits proliferation of patient-derived cancer cells representing various tumor types. 
 ✓ Inhibits proliferation and downregulates Myc levels in prostate cancer cells that have acquired resistance to BET-inhibitor OTX015. 

A clinical trial with ODM-207 is ongoing in patients with solid tumors (NCT03035597).