POTENTIAL PREDICTIVE BIOMARKERS FOR BXCL701 IN ACUTE MYELOID LEUKEMIA (AML)

Veena Agarwal*, Shubhendu Trivedi, Dimple Bhatia, Zeenia Jagga, Moses Donkor, Vincent O'Neill. BiXcel Therapeutics, New Haven, CT, USA

Background: BXCL701 (talabostat), an oral innate immune activator is currently in a Phase 2 trial in combination with PD-1 checkpoint inhibitor in metastatic castration-resistant prostate cancer patients. In solid tumors, preclinical data suggest that BXCL701 inhibition of dipeptidyl peptidases (DPPs) enhances antitumor immune responses via two mechanisms: (1) DPP4 inhibition increases tumor content of CXCL9/10, which recruits CXCR3+ NK and T cells, and (2) DPP8/9 inhibition activates the inflammasome resulting in immune cell pyroptosis followed by Th1 proinflammatory cytokine release, and dendritic cells (DCs) activation which further enhances the CXCL9/10–CXCR3 axis. Recent studies show that BXCL701 exhibits single agent cytotoxicity against human AML cells through a similar pyroptotic mechanism. Here, we report the identification of potential predictive biomarkers by using BXCL701-responsive and non-responsive human leukemic cell lines.

Methods: The cytotoxic activity of BXCL701 was evaluated in a panel of 170 hematological and non-hematological cell lines and confirmed that mostly but not all the leukemic cells were responsive to BXCL701. Four responding cell lines (KG1, MV4–11, THP1 and EOL-1, IC50 = 100 - 700 nM) and 2 non-responding cell lines (K562 and Kasumi1, IC50 >60 μM) were selected based on the cytotoxicity data and their gene expression profiles were compared to identify predictive biomarkers for BXCL701. Nanostring analysis was performed followed by qRT-PCR using cDNA from the cell lines.

Results: The analysis identified 20 genes as potential predictive biomarkers. These include 5 genes (DPP9, DPP8, caspase 1, CARD8 and PYCARD) involved in the inflammasome – pyroptosis pathway that is activated by BXCL701 and correlate with the BXCL701 cytotoxic activity. Most of the genes have 2-to-1,000-fold higher expression in at least 3 responding cell lines in comparison to non-responding cell lines. On the other hand, EPCAM gene has 7,000-fold higher expression in non-responding cell lines vs responding cell lines. Further, copy number was evaluated for BXCL701 target genes (DPP8, DPP9, DPP4 and FAP) by RT-PCR in 11 responding leukemic cell lines and 6 non-responding cell lines. The DPP9 copy number variation (CNV) was found to be directly correlated with BXCL701 cytotoxicity in BXCL701-responding human leukemic cell lines with correlation coefficient (R^2) of 0.813.

Conclusions: A gene panel consisting of genes involved in BXCL701 mechanism of action has been identified as a potential predictive biomarker for BXCL701 in leukemia, which can help in selecting patients susceptible to respond to BXCL701 treatment.

REFERENCES