Synergy Between BXCL701, a DPP Inhibitor, and Immune Checkpoint Inhibitors Discovered Using AI and Big Data Analytics

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Background: Using the proprietary artificial Discovery platform Evolvere, BioXcel Therapeutics identified BXCL701, a Dipeptidyl peptidases (DPP) inhibitor previously known as Talabostat/PT-100, as a novel therapeutic approach to neuroendocrine prostate cancer (NEPC). NEPC is an aggressive tumor that appears in about 20-30% of patients progressing after treatment with androgen inhibitors Zytiga and Xtandi (ADT) with limited therapy options. More than 700 humans have received BXCL701 giving a comprehensive overview of safety, PK, target inhibition and downstream PD effect on cytokine increase and immune-cell modulation. Existing data shows that inhibition of DPP8/9 and Fibroblast Activator Protein (FAP) can affect NEPC at multiple levels

1) NPY, a neuroendocrine peptide hormone upregulated in NEPC, is a substrate of DPP8-9. NEPC-like cells use NPY to grow and survive and blocking the processing of NPY results in antitumor activity
2) FAP+ cancer associate fibroblast (CAF) are present in the tumor micro-enviroment and are activated by ADT. Depleting FAP+CAF delay or prevent CRPC development.
3) FAP+CAF together with MDSC block CD8+ T-cell infiltration into the prostate tumor microenvironment, one of the major reason for the poor response to immune-checkpoint inhibitors (ICI) monotherapy in CRPC. BXCL701 not only can deplete FAP+CAF but induces a granulocytic differentiation resulting in less immune suppressive MDSC and neutrophil infiltration, which synergistically increase ICI antitumor activity
4) Finally, BXCL701 triggers the macrophage cell death "pyroptosis" resulting in proinflammatory stimulation of the innate immunity leading to defining DPP88/9 as "novel immune-checkpoints".
5) BXCL701 stimulates the priming, migration and cytotoxicity of T-cells and the formation of memory T-cells

Results: Co-administration of BXCL701 with ICI showed a synergistic inhibition of tumor growth, synergistic up-regulation of cytokine known to have strong antitumor activity like Il-2, IL-12. CXCL9/MIG responsible to attract T-cells into the tumor was also increased. At the cellular level, the combination was shown to mobilize activated tumor killing NK cells, from the blood to the tumor while blocking the relocation to the tumor of immune-suppressive T-regulatory cells that is normally induced by treatment with ICI. In addition, an analysis of genomic alterations in FAP, DPP8 and DPP9 in cancer singled out NEPC with a high level of overexpression and amplification of BXCL701 targets which overlap with overexpression and amplification of PDL1, known to be induced by treatment with ADT

Discussion: Given these strong mechanistic and preclinical data, an open label clinical trial is being planned to test the antitumor activity of BXCL701 either as monotherapy or in combination with Keytruda in patients with NEPC. This POC trial, using Simon-2 stage design and leveraging existing clinical PK/PD and safety data to define upfront a dose and regimen will clarify whether BXCL701 can make a difference for NEPC patients in a fast and efficient way

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