BXQ-350: A Novel Approach to Rebalancing the Tumor ’s Immune Response

Background:

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of cancer patients. Clinical results have demonstrated that combining ICIs leads to significant clinical benefits and durable responses across tumor types. These amazing clinical results spurred the investigation of a large number of novel targets, many targeting a specific receptor and immune cell population. These novel compounds typically either inhibited an immunosuppressor cell type or pathway or stimulated a single specific immunoeffector cell type. Results often showed that targeting was effective, but clinical benefits were transient and disappointing. This raises the question of whether a different approach should be considered, one that would positively impact the entire tumor immune environment, inhibiting many immunosuppressor cells and stimulating immunoeffector cells, and potentially result in a synergistic effect that might induce a lasting clinical benefit.

Sphingolipids are bioactive signaling molecules implicated in multiple cellular processes and signaling pathways. Sphingosine-1-phosphate (S1P) is a key sphingolipid that induces cancer cell proliferation, activates multiple oncogenic pathways, is associated with the expression of cytokines and chemokines and stimulates immuno-suppressor cells and inhibits immunoeffector cells. Ceramides, a different class of sphingolipids, induce apoptosis, down regulate oncogenic pathways, and stimulate immuno-effector cells. Therefore, modulating sphingolipids may be an approach to rebalancing the tumor immune microenvironment as a whole.

Methods:

BXQ-350 is a novel biologic that modulates sphingolipid metabolism, lowering S1P and increasing ceramides’ concentration. BXQ-350 was investigated preclinically *(in vitro*, *ex vivo* and *in vivo*) and clinically in a Phase 1 dose-escalation safety study in cancer patients with advanced solid malignancies.

Results:

Preclinical results showed that BXQ-350 modulates many immune cells mildly as it repolarizes macrophages towards the M1 phenotype, it inhibits MDSC proliferation and their suppressive function, and it expands NK cells and CD3+/4+/8+ TILs and enhance their cytotoxicity. Clinically, BXQ-350 was well tolerated in cancer patients and showed signs of single agent activity leading to long term clinical benefits. Analyses of biomarker samples suggest that, in patients experiencing a clinical benefit, systemic S1P/ceramides levels decreased post BXQ-350 treatment.

Conclusion:

Preclinical and clinical results indicate that BXQ-350 modulates sphingolipid metabolism, lowering the immuno-suppressor S1P and simultaneously increasing immuno-effector ceramides. Effects on individual multiple immune cell types are mild, but meaningful and synergistic. Modulating sphingolipids may be an effective strategy to rebalance the tumoral immune system as a whole towards tumor suppression and homeostasis.