BXQ-350: A novel biologic that allosterically activates glucosylcerebrosidase and demonstrates signs of activity in cancer patients

Background:

Ceramides, glucosylceramides and sphingosine-1-phosphate (S1P) are key bioactive signaling molecules. Ceramides are proapoptotic and mitigate chemoresistance while glucosylceramides and S1P promote cancer cell proliferation, activate multiple oncogenic pathways, promote chemoresistance and stimulate a pro-tumoral microenvironment. Many studies have shown a better prognosis and longer survival for patients with high ceramides levels, while high S1P and glucosylceramides levels are associated with shorter survival and worst prognosis. Levels of ceramides, glucosylceramides and S1P are controlled by enzymes involved in sphingolipid metabolism, including glucosylcerebrosidase (Gcase) and sphingosine kinase (Sphk).

Methods: BXQ-350 is a nanovesicle of Saposin C, an allosteric activator of enzymes involved in sphingolipid metabolism; preclinically, BXQ-350 was investigated in different *in vitro* and *in vivo* models. Clinically, BXQ-350 was investigated in a first-in-human Phase 1 safety dose and escalation study in cancer patients with recurrent advanced solid malignancies (NCT02859857).

Results: Preclinical results demonstrated that BXQ-350 allosterically activates Gcase *in vitro*, in cells and *in vivo* in a significant and dose-dependent manner; as expected, *in vivo*, Gcase activation results in lower levels of glucosylceramides, as much as 2/3 lower for picomolar concentrations of BXQ-350. An increase in ceramides and a decrease in S1P are also observed. By impacting glucosylceramides, ceramides and S1P, BXQ-350 rebalances the S1P/ceramide rheostat in favor of an antitumoral state and homeostasis. By lowering S1P and glucosylceramides, BXQ-350 modulates the innate and adaptive immune response and repolarizes macrophages towards the antitumoral M1 phenotype, inhibits differentiation and activity of immunosuppressor of MDSCs, and promotes the proliferation of CD4+ and CD8+ Tcells as well as their activity. Clinical results showed BXQ-350 was safe and well-tolerated (no DLT, no MTD). Also, 13 patients (~17.8% of evaluable patients) had a clinical benefit up to cycle 6 and beyond (PR, SD). Among patients with PFS > 6 months, there were 4 recurrent CRC patients: 1 patient had a PFS of ~12 months, 2 of ~18 months, and 1 is still on study after 6 years. Furthermore, there were signs that BXQ-350 may alleviate symptoms of CIPN as 4 out of 10 patients with chronic CIPN at time of enrollment experienced an improvement of their symptoms.

Conclusions: Preclinical and clinical results demonstrated that BXQ-350 activates Gcase and modulates sphingolipid metabolism leading to a novel anticancer MOA that had not been clinically tested. Additional studies are ongoing to further elucidate BXQ-350’s MOA.