BXQ-350: a Novel Biologic with an Innovative Mechanism of Action Targeting Sphingolipid Metabolism that Induces Cancer Cell Death and Repolarizes the Tumor Microenvironment

Background

Antineoplastic agents seem to affect tumors by targeting cancer cells via cytotoxic mechanism (traditional cytotoxic agents), an oncogenic pathway that promotes cancer cells proliferation (targeted agents), or immune pathways that are dysregulated in the tumor microenvironment (immune checkpoint inhibitors -ICI-). Clinical results have demonstrated that ICIs led to significant clinical benefits and durable responses in patients that previously had no or limited therapeutic options. Clinical results also demonstrated that combining ICIs or ICI with cytotoxic / targeted agents improved response rate and duration of response.

BXQ-350 is a novel biologic simultaneously leading to cancer cells death and rebalancing the tumor microenvironment by targeting sphingolipid metabolism that is dysregulated in cancer cells. Sphingosine-1-phosphate (S1P) is a signaling metabolite known to promote cancer cell survival and proliferation and to favor an immunosuppressor environment; ceramide is a metabolite known to induce cancer cell apoptosis, mitophagy or necrosis and to favor an immunoeffector environment.

Methods

BXQ-350 was investigated preclinically in different *in vitro* and *in vivo* models and clinically in a first-in-human Phase 1 safety dose and escalation study in cancer patients with recurrent advanced solid tumors.

Results

Preclinical results demonstrated that BXQ-350 targets sphingolipid metabolism, decreases S1P levels while it simultaneously increases ceramide levels, leading to cancer cells death across multiple cancer cell lines. By impacting S1P and ceramide, BXQ-350 is additive or synergistic with different classes of antineoplastic agents. In addition, *ex vivo* experiments demonstrated BXQ-350 modulates many of immune-effector / suppressor cells as it 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 revealed that BXQ-350 was well tolerated in cancer patients and showed signs of single agent activity. Analyses of biomarker samples showed that in patients experiencing a clinical benefit, systemic S1P plasma levels decreased significantly, and ceramide levels increased. Analysis of circulating cytokines revealed that BXQ-350 seemed to induce an increase of antitumoral cytokines (IFNg, TNFa, IL-2) and a decrease in protumoral ones (IL-6, IL-8, IL-10).

Conclusions

Preclinical and clinical results demonstrated that BXQ-350 modulates sphingolipid metabolism leading to cancer cell death and stimulating the tumor microenvironment. Additional studies are ongoing to further understand BXQ-350's MOA.