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BXQ-350: A Novel Biologic that Modulates Sphingolipid Metabolism and Demonstrates Anti-Cancer Activity

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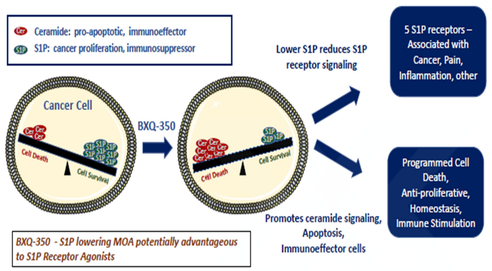
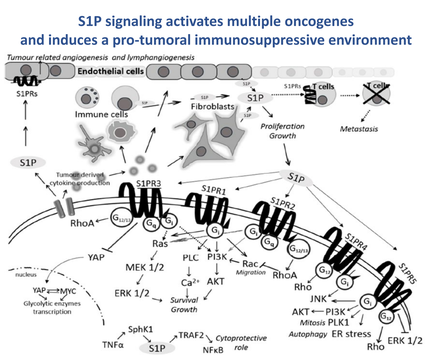
1. BXQ-350 is a nanovesicle formulation of Saposin C, an allosteric activator of sphingolipid metabolism

- normalizes dysregulated sphingolipid metabolism, **lowering S1P and increasing ceramides levels**
- **modulates S1P signaling & stimulates immune response**



2. Sphingolipids are bioactive signaling molecules implicated in cancer

- **Ceramides** are pro-apoptotic, mitigate resistance and promote an anti-tumoral immune environment
- **Sphingosine-1-phosphate** (S1P) promotes cancer cell proliferation, resistance, oncogenic pathways and a pro-tumoral immune environment
- **Several studies have shown elevated ceramide levels** are associated with **improved survival**



Grbcic, P. et al. *S1P Signaling and Metabolism in Colon Cancer*. Molecules, 2020, 25, 2436.

3. Studies: BXQ-350 has been investigated preclinically and clinically

- increases C18 and lowers S1P across cancer cell lines leading to apoptosis and mitophagy
- is additive or synergistic with different classes of antineoplastic agents
- inhibits MDSCs, expands CD8+ T cells, repolarizes macrophages *ex vivo*
- **in a Phase 1 dose escalation safety study** in all-comer cancer patients with recurrent solid malignancies (NCT02859857) **BXQ-350**
  - **was safe and well-tolerated** (no Dose Limiting Toxicity)
  - **had a 17.8% Clinical Benefit Rate** (CR, PR, SD) at Cycle 6 across tumor types including GBM, brain, CRC, appendiceal, pancreatic and rectal cancers; two patients are still on study with no evidence of disease after 6 years of treatment

Summary

- **BXQ-350 is a novel biologic** and a nanovesicle formulation of Saposin C, an allosteric activator of enzymes involved in sphingolipid metabolism
- BXQ-350 modulates sphingolipid metabolism, **lowers S1P and increases ceramide levels**
- BXQ-350 **inhibits S1P signaling and rebalances the tumor microenvironment** towards an anti-tumoral state
- In clinical studies, BXQ-350 is **well-tolerated and showed signs of single agent activity in multiple tumor types**
- Investigating systemic levels of S1P and Cer as **potential biomarkers**
- BXQ-350 **may resolve CIPN symptoms in some cancer patients (see poster 3042)**

On-going Studies

Preclinical studies to illustrate BXQ-350's MOA

BXQ-350 is clinically being investigated in:

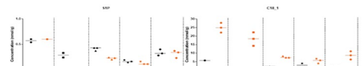
- Phase 1/2 study in combination with SoC in newly diagnosed mCRC patients (NCT05322590)
- PoC and PK/PD study in cancer patients with established CIPN (NCT05291286)
- Phase 2 study in combination with radiation in pediatric DIPG/Diffuse Midline Glioma patients (NCT04771897)

Acknowledgement: Patients who participated in the trials and their families, clinicians and staff at investigational sites, Bexion's personnel

4. Preclinical results; BXQ-350:

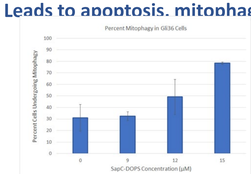
Decreases intracellular S1P & increases C18:1 across cancer cell lines

0.5 µM [BXQ-350] @ up to 144 hrs

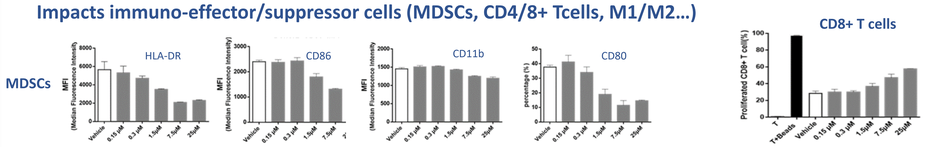


	Control	24 hrs	96 hrs	196 hrs
S1P/C18:1	0.11	0.06	0.03	0.03

Leads to apoptosis, mitophagy …



Impacts immuno-effector/suppressor cells (MDSCs, CD4/8+ Tcells, M1/M2…)

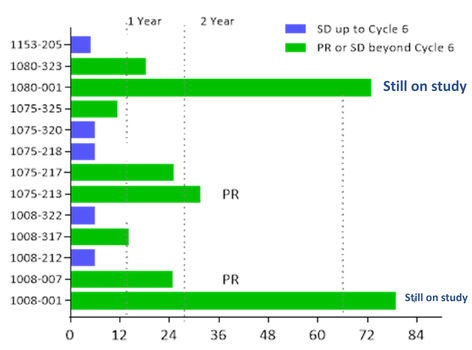


CD8+ T cells

5. Clinical Results:

PFS ≥ 6, 12, 24, 60 months …

- **13 SD / PR patients PFS ≥ Cycle 6** (17.8 % of evaluable pts with clinical benefit) in GBM, CNS, GI and H&N cancers
- **7 patients with PFS ≥ 12 months**
- Changes in systemic levels of S1P or C18 ceramides in most patients with clinical benefit



Long lasting clinical benefit:

- **1 GBM and 1 CRC still on study after 6 years**

Could S1P & C18 systemic levels Post / Pre BXQ-350 biomarkers?

- Further analysis needed in larger and tumor specific studies