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Poster P11.03.B

BXQ-350: Increasing Ceramide and Lowering Sphingosine-1-Phosphate May Induce Anti-Tumor Activity and Mitigation of CIPN in Cancer Patients with Advanced Disease

Contact: rtakigiku@bexionpharma.com

R. Wesolowski [4], A. Noonan [4], R. Curry III [1,2], J. Morris [3], C. Muller [7], V.K. Puduvalli [4], O. Rixe [7], J. Villano [6], T. Wise-Draper [3], E. Yilmaz [5], R. Takigiku [1], and G. Tapolsky [1]

[1] Bexion Pharmaceuticals, Covington, KY; [2] CTI, Covington, KY ; [3] University of Cincinnati Cancer Center , Cincinnati, OH; [4] The Ohio State University Comprehensive Cancer Center, Columbus, OH; [5] Cleveland Clinic, Cleveland, OH; [6] University of Kentucky, Lexington, KY; [7] University of New Mexico, Albuquerque, NM

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1. Background:

- **Sphingolipids are a class of bioactive signaling lipids that are essential** for biologic pathways and cellular processes [1]
- **Sphingolipid metabolism and signaling are critically involved in many diseases** and their clinical relevance have been validated in Gaucher disease (Cerezyme® approved in 1994; Cerdelga® approved in 2014), in multiple sclerosis and autoimmune diseases (Gylenia® approved in 2010, Zeposia® approved in 2020, Mayzent® approved in 2019, and Ponvory ® approved in 2021)
- Sphingosine-1-Phosphate (S1P) is a critical sphingolipid that promotes proliferation of cancer cells and resistance to chemotherapies, up-regulates oncogenic pathways and stimulate immuno-suppressor cells, while ceramides are pro-apoptotic and stimulate immuno-effector cells [2]
- S1P signaling is also associated with symptoms of Chemotherapy Induced Peripheral Neuropathy (CIPN) in cancer patients undergoing chemotherapy [3]

(1) B. Ogretmen, Sphingolipid metabolism in cancer signaling and therapy, *Nature Reviews Cancer,* 2018, 18, 33-50.
(2) A. Janneh *et al.* , Targeting Sphingolipid Metabolism as a Therapeutic Strategy in Cancer, *Cancers* 2022, 14, 2183.
(3) M. Langeslag *et al.,* The Ceramide-S1P pathway as a druggable target to alleviate peripheral neuropathic pain, *Expert Opinion On Therapeutic Targets*, 2020, 24:9, 869-884.

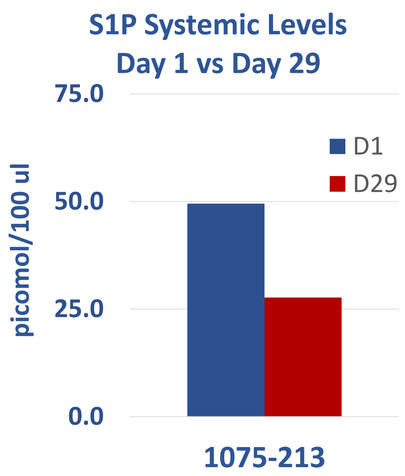
2. BXQ-350 & Clinical Results:

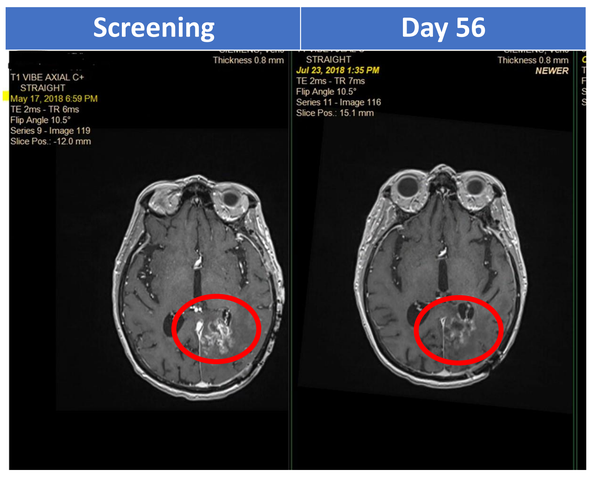
- Nanovesicle formulation of Saposin C, an allosteric activator of sphingolipid metabolism, that decreases S1P levels and increases C18:1 levels
- Characterized in a Phase 1 study in adult all-comers cancer patients with advanced solid malignancies (NCT02859857)
  - BXQ-350 was **safe and well-tolerated** (no Dose Limiting Toxicity) and a **17.8% Clinical Benefit Rate** (CR, PR, SD) was observed at Cycle 6
  - Several patients **reported** an improvement of their pre-existing CIPN symptoms soon after BXQ-350 administration

Efficacy Results

1) Patient 1075-213: PR in Recurrent Glioblastoma

Target lesion (L parietal) 1.4 cm^2 at Screening down to 0.36 cm^2 at Day 56 (-74%).
Progressed after 948 days on BXQ-350 (RANO criteria)

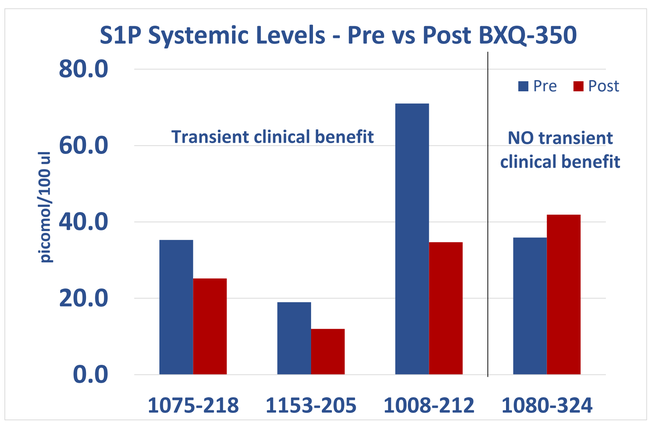




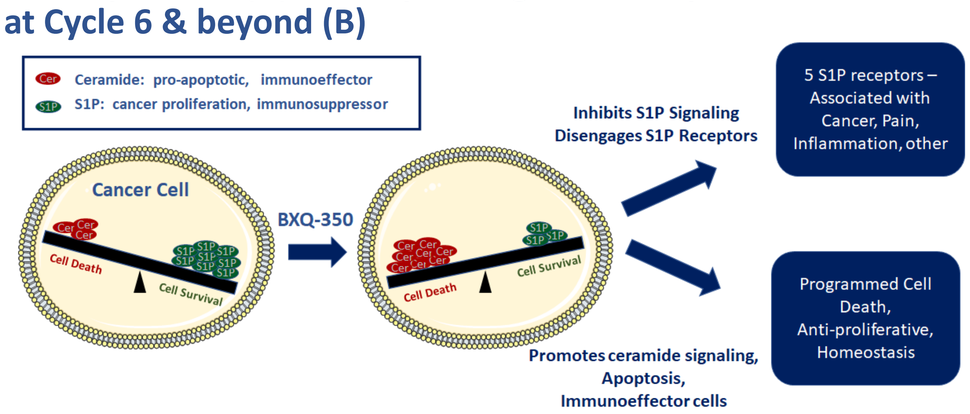
2) 4 Ependymoma patients enrolled in study: 3 had a clinical benefit, one did not

Brain Target Lesion Measurements (RECIST 1.1; cm)

	1075-218	1153-205	1008-212	1080-324
Screening	3.7	9.6	SD up to Cycle 6	PD at Cycle 2
Cycle 1	-	9.0		
Cycle 2	2.9	8.8		
Cycle 3	2.8	-		
Cycle 4	4.4	8.7		



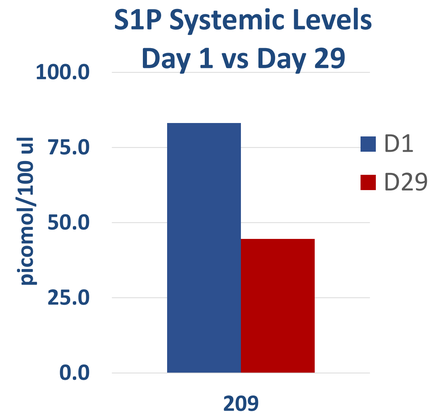
3) The S1P / Ceramide Rheostat and analyzing S1P/C18:1 ratios in Ependymoma patients (A) and expanding to the 12 patients that had a clinical benefit at Cycle 6 & beyond (B)



Potential CIPN Mitigation

A) Patient 1075-209: Resolution of CIPN Symptoms

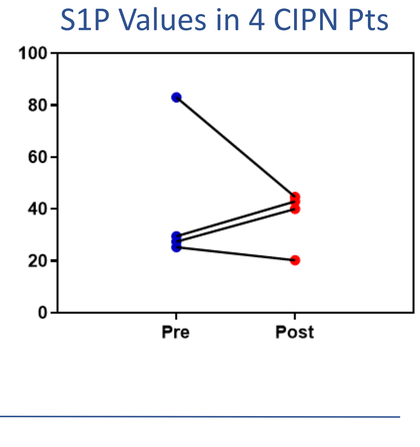
Pancreatic cancer patient with history of CIPN spontaneously reported resolution of her symptoms by Cycle 2



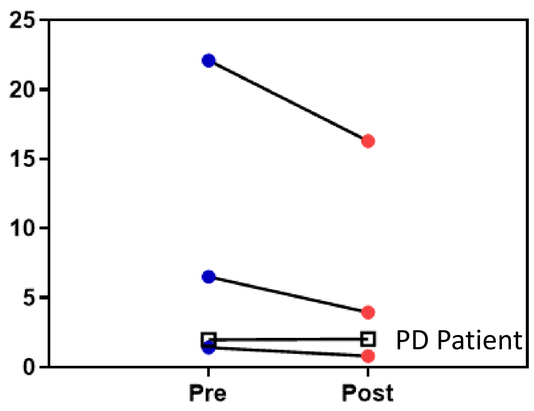
B) Patients with known CIPN symptoms at enrollment were asked about their symptoms after receiving BXQ-350 (CIPN assessment questionnaire).

4 out 10 patients appeared to have improvements of their symptoms following BXQ-350 administration.

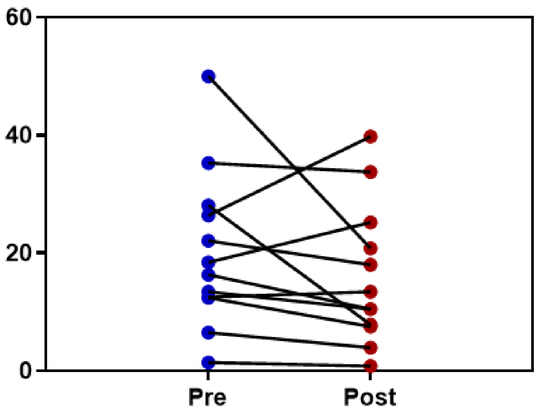
S1P Values in 4 CIPN Pts



A : S1P/C18:1 Values in Ependymomas Decrease between Pe & Post Values for the 3 patients with transient clinical benefit



B: S1P/C18:1 Values in 12 Patients with some clinical benefit; Decrease between Pre & Post for 8 of the 12



Conclusion: Lowering S1P and increasing C18:1 systemic levels may lead to both anticancer activity and mitigation of CIPN but larger and cancer specific studies are needed. BXQ-350 is currently in clinical trials in newly diagnosed DIPG / DMG pediatric cancer patients, newly diagnosed mCRC patients and for the treatment of CIPN.