ISPNO 2022
Poster DIPG-30

Trial in Progress:

A Phase 1 Open Label, Multi-Center Study to Evaluate the Safety and Tolerability of BXQ-350 in Children with Newly Diagnosed Diffuse Intrinsic Pontine Glioma (DIPG) and Diffuse Midline Glioma (DMG) with H3K27M alteration

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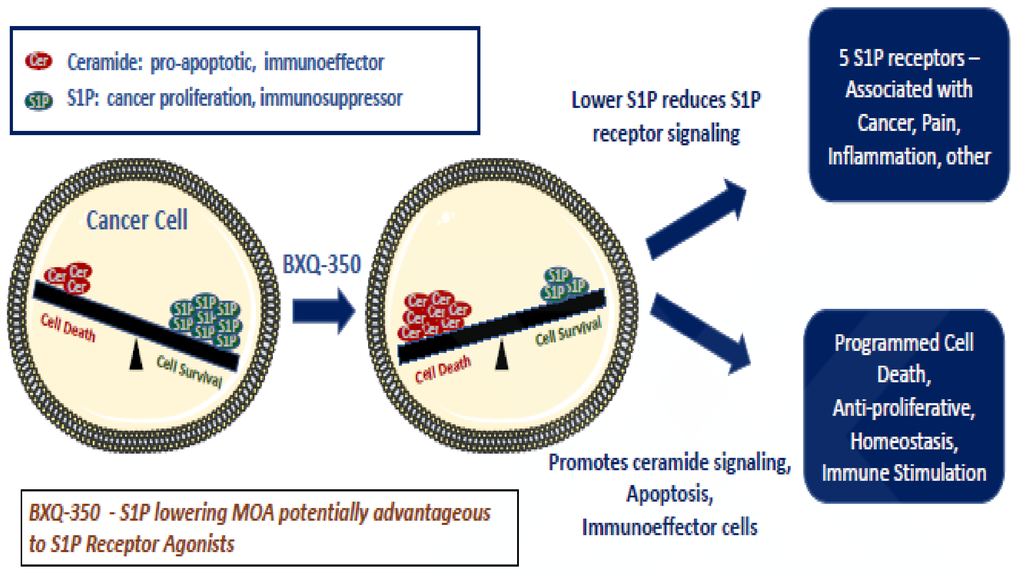
1. Introduction:

- BXQ-350 is a novel biologic agent being investigated in adult and pediatric cancer patients; it modulates sphingolipid metabolism, increasing ceramide concentrations and lowering sphingosine-1-phosphate (S1P) [1]
- Phase 1 adult and pediatric studies indicate that BXQ-350 is well tolerated with potential single agent activity [2]:
  - 11 adult patients (~15% of evaluable patients) had potential clinical benefit across tumor types, including CNS tumors
  - 8 patients demonstrated PFS > 6 months, including 2 GBM and 1 choroid plexus carcinoma
  - 2 patients (GBM, CRC) are still on study >5 years
- Ceramides and S1P are key signaling molecules involved in cancer [3]
- The role of ceramides and S1P in CNS tumors has been recognized and is investigated as a therapeutic target [4], including DIPG / DMG tumors [5]

(1) a) Bexion Pharmaceuticals, *manuscript in preparation; b)* See Poster EPEN-14
(2) M. Abdelkabi *et all.,* An Open-label Multi Center Phase 1 Safety Study of BXQ-350 in Children and Young Adults with Relapsed Solid Tumors , Including Recurrent Malignant Brain Tumors, *submitted for publication*.
(3) B. Ogretmen, Sphingolipid metabolism in cancer signaling and therapy, *Nat Rev Cancer 2018, January, 18(1), 33-50.*
(4) a) S. Grassi et al., S1P Receptors and Metabolic Enzymes as Druggable Targets for Brain Diseases, *Front . Pharmacol Review,* Jul 2019, 10, 807; b) S. Mahajan-Thakur *et al*., S1P Signaling in Glioblastoma Multiforme – A Systematic Review, Int Jour of Mol Sciences, 2017, 18, 2448; c) L. Riboni *et al.*, S1P in the Tumor Microenvironment: A Signaling Hub Regulating Cancer Hallmarks, Cells Review, 2020, 9, 337.
(5) a) L. Dai *et al*., Targeting Sphingosine Kinase against Diffuse Intrinsic Pontine Glioma (DIPG), Journal of Cancer, 2020, vol 11(16), 4683; b) E. Hayden *et al.*, Therapeutic Targets In Diffuse Midline Gliomas – AN Emerging Landscape, *Cancers Review,* 2021, 13, 6251; c) A. Wingerter *et al*., Exploiting Gangliosides for the Therapy of H3K27M Mutant Diffuse Midline Glioma, *Cancers*, 2021, 13, 520; d) C Mount *et al.*, Potent antitumor efficacy of anti-GD2 Car T-cells in H3K27M+ diffuse midline gliomas., *Nat Med* 2018 May, 24(5), 572.

2. BXQ-350: BXQ-350 is a nanovesicle formulation of Saposin C, an allosteric activator of sphingolipid metabolism, and dioleoyl-phosphatidylserine (DOPS):

- Ceramides are pro-apoptotic, down regulate oncogenic pathways, and stimulate immuno-effector cells
- S1P promotes proliferation of cancer cells, activates oncogenic pathways, and stimulates immuno-suppressor cells.
- The balance between S1P and ceramides is critical [4]



3. Study Design (NCT04771897): Phase 1 dose-escalation safety study in DIPG/DMG patients with BXQ-350 in combination with radiation at 3 US sites:

- 54 Gy fractionated radiation concurrent with BXQ-350
- Accelerated dose escalation from 2.4 to 3.2 mg/kg
- Disease assessment every 8 weeks
- Dosing up to 12 cycles or unacceptable toxicity or disease progression
- Multiple secondary parameters: Efficacy, PK, biomarkers

Radiation & Once daily BXQ-350 IV Infusion over 60 ± 15 min			
Cycle 1 Week 1	Cycle 1 Week 2	Cycle 1 Week 3 & 4	Cycle 2 & After
Days 1-5 (5 consecut. days)	Days 1-3-5 (every other day)	Once weekly	Once every 28 days

4. Enrollment Status:

- Cohort 1 (2.4 mg/kg) N=1
- Cohort 2 (3.2 mg/kg) N=4

Patients	1-01	1-02	1-03	2-01	3-01
Diagnosis	DMG	DMG	DIPG	DIPG	DMG
Age (years)	19	25	6	14	6
Gender	M	M	F	M	M
Race/Ethnicity [1, 2]	W[2]	W[2]	H[2]	W[2]	W[2]
Disposition	Withdrawn	Cycle 9	Cycle 1	Withdrawn	Cycle 2
Disease Assessment [3]	PD	SD	-	PR / SAE	-

1 W: white / H: Hawaii
2 Not Hispanic or Latino
3 PD: Progressive Disease; SD: Stable Disease; PR: Partial Response; SAE: Significant Adverse Event of hypersensitivity infusion reaction

5. Safety / Adverse Events:

- In the previous pediatric study (NCT03967093), results showed that BXQ-350 was well-tolerated and safety profile warranted further clinical investigations at the maximum administered dose (3.2 mg/kg).
- In this trial in-progress, BXQ-350 in combination with radiation has been thus far well tolerated, however one patient experienced a Grade 4 infusion reaction that was treated on site and resolved without sequalae. Infusion time was increased, and pretreatment medications have been implemented. As summarized in the juxtaposed table, 191 Grade 1-4 adverse events (AE) have been overall observed (unaudited results) and only 1 is believed to be related to BXQ-350.

	Total AEs	Related [1]	Likely & Probably Related [2]	Unlikely & Unrelated [3]
Grade 1	154	-	10	144
Grade 2	24	-	3	21
Grade 3	11	-	-	11
Grade 4	1	1	-	-

1 Related to BXQ-350
2 Sum of Likely and Probably Related to BXQ-350
3 Sum of Unlikely Related and Unrelated to BXQ-350

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