SITC 2024
1331

BXQ-350: A novel approach to rebalancing the tumor's microenvironment and immune response

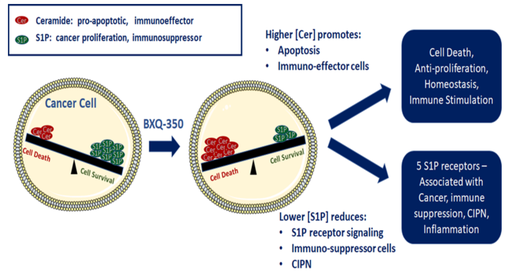
G. Tapolsky, T. Ashad, J. Beach, M. Gazda

Bexion Pharmaceuticals, Covington, KY, USA

gtapolsky@bexionpharma.com

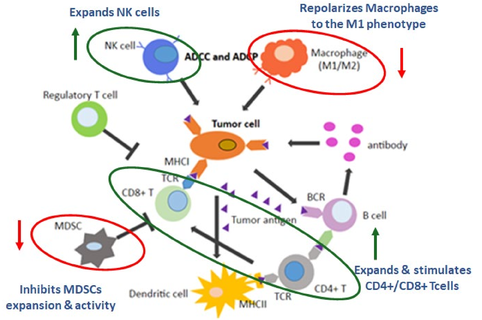
1. BXQ-350 is a nanovesicle formulation of Saposin C, an allosteric activator of sphingolipid metabolism that :

- normalizes dysregulated sphingolipid metabolism, **lowering S1P and increasing ceramides levels**
- **decreases S1P signaling & immunosuppressor cells (1)**
- **increases ceramides that stimulates immunoeffector cells (2)**



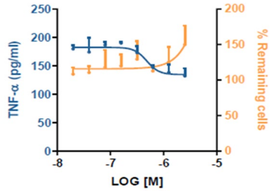
2. BXQ-350 rebalances the tumor microenvironment:

- Sphingolipid metabolism is implicated in the recruitment and function of immuno-effector/suppressor cells
- High S1P concentration / S1P signaling favors immuno-suppressor cells
- Simultaneously increasing ceramides & lowering S1P, activates effector cells and inhibits suppressor cells (3)

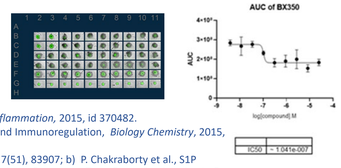


3. BXQ-350 repolarizes macrophages to the M1 phenotype and increases T cells cytotoxicity

- CD14+ macrophages from PBMCs from healthy donors stimulated to induce M2 phenotype for 4 days
- Cell viability and TNFα concentration measured at Day 8



- Tumor spheroids A549 lung cancer cells transfected with Luciferase & T Cells activation with IL-2/anti-CD3+
- Addition of BXQ-350 and viability measurements



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(3) a) A. Darmoise et al., The Immunological Functions of Saposins, *Adv Immunol.*, 2010, 105, 25. b) CM. Reimann et al., S1P in cancer immunity and development., Translational Cancer Research, 2015, 4 (no 5), 460.

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 Phase 1 clinical studies, BXQ-350 was **well-tolerated and showed signs of single agent activity in multiple tumor types**
- BXQ-350 **may reduce Chemotherapy Induced Peripheral Neuropathy (CIPN) symptoms in some cancer patients**

On-going Studies

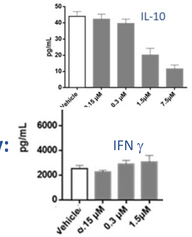
BXQ-350 is clinically being investigated in:

- Phase 1b/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. *Ex vivo*, BXQ-350 inhibits MDSCs differentiation and their immune suppressive function:

- decreases HLA-DR, CD86, CD11b, CD80 expression
- decreases IL-10 secretion



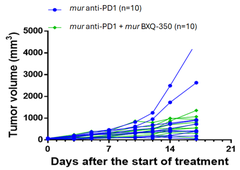
5. *Ex vivo*, BXQ-350 stimulates CD4+/CD8+ T Cells expansion and cytotoxicity:

- increases IFN γ secretion

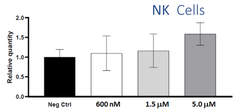
6. *In vivo,* BXQ-350 synergizes with a *mur* anti-PD1, increases CD3+/CD4+/CD8+ TILs and NK cells:

CT-26, a CRC syngeneic murine tumor model

Treatment	# of tumors larger than 1600 mm³ at Day 17 (total number of tumors)	% of tumors larger than 1600 mm3
mur BXQ-350	3 (9)	33.3
mur-anti-PD1	2 (10)	20.0
m BXQ-350 + *m* anti-PD1	0 (10)	0.0

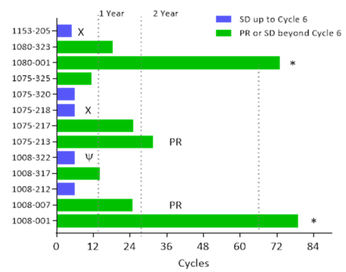


HT-29, a human CRC model in the CAM assay

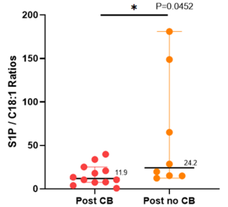


7. *Clinically,* in a safety & dose escalation Phase 1 study in cancer patients with advanced recurrent solid tumors, BXQ-350 :

- Well tolerated (no DLT, no MDT)
- 13 patients with PFS ≥ Cycle 6 (17.8 % of 73 patients)
- 7 patients with PFS ≥ 12 months
- 2 patients with long lasting clinical benefit over 6 years
- Lowers S1P and increases C18:1
- Impacts cytokines and exosomes



S1P/C18:1 Ratios post-BXQ-350 comparing subgroup with clinical benefit CB (n=12) to subgroup with no clinical benefit no CB (n=8)



% Change in CD59+ exosomes in patients experiencing a clinical benefit

		1008-001	1008-007	1075-210	1075-208	1080-01	1153-205
		GBM	Appendi	Pancreatic	GIST	CRC	Ependy
		~ 5y Still SD	24m SD	4cy SD	2 cy PD	~5y Still SD	6cy SD 50% ↓ in 1 tl
% of Exosomes Positive for CD59	% Change Day 1 to Day 29	- 28%	- 95%	-79%	-29%	-24%	-96%