Pancreatic cancer oral inverse agonist of RORγT receptor targets primary cancer cells as well as altering inflammatory mediators of the tumor micro-environment.

Daniel Johnson MD*, David Bearss PhD, Lynne Kelley MD****
* Ochsner Health New Orleans LA, **Xenthera Inc (now Signalexis™) Salt Lake City UT

Plain Language Summary

Why did we perform this research?

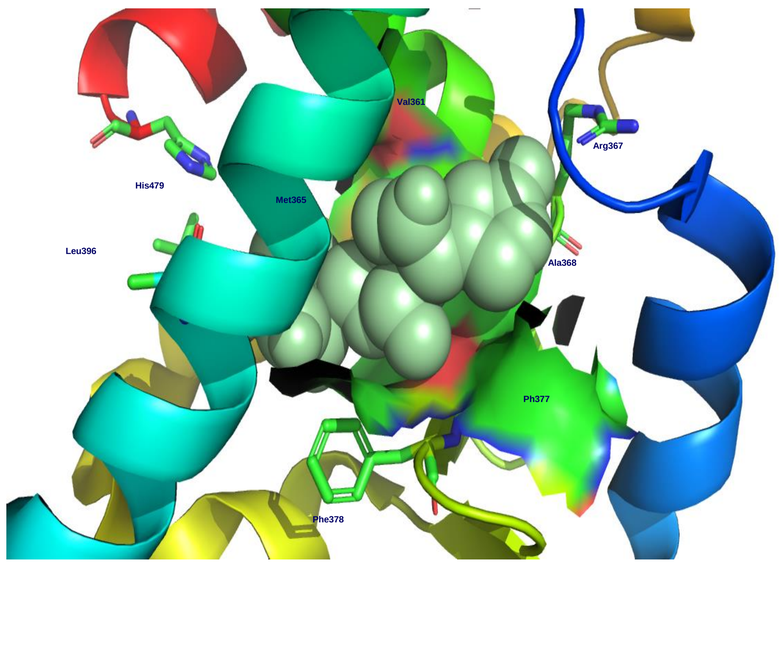
Phase 1 dose finding study has been initiated in oncology patients with the novel RORγT inverse agonist XT-0528. Pre-clinical and healthy human volunteer data demonstrates efficacy signal while maintaining an excellent safety profile. RORγT is an attractive target for pancreatic cancer and other solid tumors.

How did we perform this research?

Standard GLP animal studies in both rats and beagles. Human single and multiple dose studies in healthy human volunteers under GCP and IRB approval.

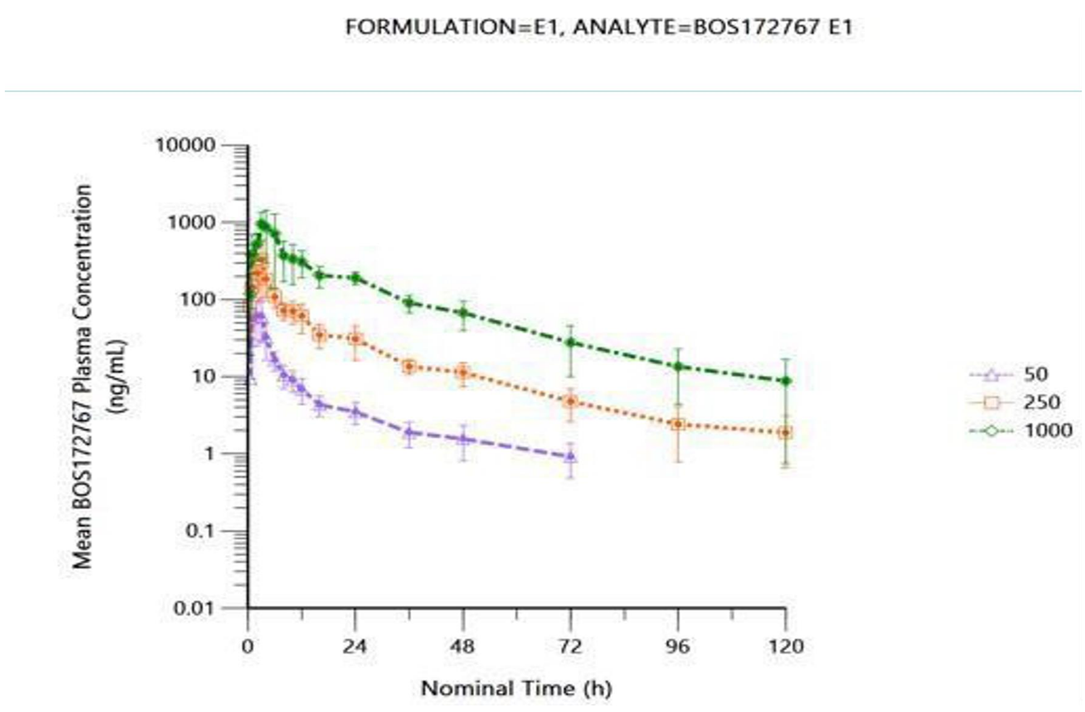
What were the findings and the future implications of this research?

Animal studies without evidence of toxicity. Once daily oral dosing in humans demonstrated linear dose response kinetics.



Lead compound in complex with RORγT

Background: Pancreatic cancer is the fourth deadliest cancer for both men and women. Current five-year survival rate is 12% increased to 44% for the 15% with localized disease, and most patients present with advanced or metastatic disease at presentation. The backbone of therapy has been gemcitabine and more recently in combination with Nab-paclitaxel, FOLFIRINOX or NALIRIFOX regimens however the incremental gains in survival range from 2-4.5 months[1,2] with the risk of serious side effects. The use of immune checkpoint inhibitors (ICI) have not been as effective in pancreatic cancer as some other malignancies.[3] This ICI resistance may be due to T cell exclusive tumor associated neutrophils and macrophages that have been shown to be induced by IL-17. New approaches that not only target the primary tumor cells but also alter the tumor immune microenvironment (TIME) could prove beneficial. RORγT receptor is a ligand dependent transcription factor that regulates multiple pro-inflammatory genes including driving the differentiation of T helper cells to Th17 cells. Translational work suggests RORγT receptor is a promising target with patient derived pancreatic cancer xenografts responsive to an inverse agonist. Three healthy human volunteer studies have been conducted with the novel oral inverse agonist XT-0528.



Oral Toxicity - Tabular Summary
28-Day Oral Toxicity Study Followed by a 14-Day Recovery Period in Sprague Dawley Rats

Dose (mg/kg/day)		0 (Control)		200		600		2000	
Number of Animals				Toxicokinetic					
		M: 3	F: 3	M: 9	F: 9	M: 9	F: 9	M: 9	F: 9
	Day 1								
C_{max}	(ng/mL)	--	--	1410	1850	2740	4170	4440	5140
T_{max}	(hr)	--	--	8.00	4.00	8.00	8.00	8.00	8.00
T_{last}	(hr)	--	--	24.00	24.00	24.00	24.00	24.00	24.00
C_{last}	(ng/mL)	--	--	10	53	176	653	425	3070
$AUC_{(last)}$	(hr*ng/mL)	--	--	18100	23700	36800	59500	60800	89400
$AUC_{(All)}$	(hr*ng/mL)	--	--	18100	23700	36800	59500	60800	89400
$AUC_{(0-\infty)}$[a]	(hr*ng/mL)	--	--	NA	NA	NA	NA	NA	NA
$t_{1/2}$[a]	(hr)	--	--	NA	NA	NA	NA	NA	NA

M: Male F: Female NA: Not Applicable
[a]: Because of the limited values in the regression phase of most treated groups, the half-life and AUC (0-∞) could only be determined for female rats receiving 600 mg/kg/day with a half-life of 7.5 hours.

Method: Pre-clinical data review of a novel high affinity RORγT inverse agonist and the results of three healthy human phase 1 studies

Results: Standard pre-clinical toxicology studies were conducted in Sprague-Dawley rats and beagles with both single and multiple day dosing up to 2000mg/kg dose of XT-0528 with no adverse events in body weight, food consumptions, cardiovascular, clinical, or gross pathology and no dose limiting toxicities identified. The drug demonstrated dose dependent pharmacokinetics and improvement in clinical score and locomotor activity as well as a reduction in IL-17 expression in a recognized autoimmune encephalitis model. Three healthy human volunteer studies have been performed with 78 subjects receiving drug in single and multiple ascending doses. The drug exhibited a linear dose response with 93% bioavailability of the s isomer. Adverse events were limited and mild with complete resolution. The half-life of the drug is 22.5 hours.

Conclusions: RORγT and the IL-17 pathway is a well-recognized target for inflammatory conditions, and increased expression is associated with a worse prognosis for various cancers. XT-0528 is a high-affinity RORγT inverse agonist with a demonstrated reduction in the key inflammatory cytokine IL-17 and a very good safety profile. Translational work demonstrates increased RORγT expression in human pancreatic cancer, and RORγT inhibition led to tumor regression within a human xenograft tumor model.[4]

Pre-clinical and healthy human data suggest that XT-0528 is very well tolerated and effective in blocking RORγT. XT-0528 could decrease Th17 induced inflammation shifting the pool of T cells to Th1 differentiation resulting in a more favorable TIME. A Phase 1 study in an advanced and metastatic solid tumor population will use safety and biomarker activity to define the RP2 dose.

Healthy Human Volunteer Studies

Protocol Design	Study Objectives/Study Population	No of Subjects/Patients Doses Evaluated	Safety Highlights
ARN-CLN-0001: A Phase 1, Single- center, Randomized, Double-blind, Placebo-controlled Safety, Tolerability, and Pharmacokinetic Study of Single Ascending Oral Doses of ARN-6039 in Healthy Adult Subjects	Safety and tolerability of SAD of orally administered ARN-6039 Healthy Volunteers	**51 subjects enrolled** 40 received ARN-6039 11 received placebo ARN-6039 racemate mix Oral administration 50 mg, 100 mg, 150 mg, 200 mg, or 300 mg	**4 AEs (1 Related) 0 SAEs** Related – 1 subject - One Headache, mild (no rx.) - 300mg dose
BOS172767-01: A Phase 1 Study to Determine the Single and Repeat Dose Pharmacokinetics, Food Effect, Drug Interaction, Safety and Tolerability of Oral Prototype Formulations of BOS172767	Single and Repeat Dose Pharmacokinetics, Food Effect, Drug Interaction, Safety and Tolerability Healthy Volunteers	**29 subjects enrolled** all subjects received at least 1 dose of the IMP BOS172767 racemate mix Oral administration 100mg, 200mg, 400mg, 600mg, 800mg	**26 AEs 1 SAEs** **12 Subjects** Possibly Related: 4 AEs in 3 subjects - Headache 1 subject at both 400 and 600 mg - Elevated transaminases at 800 mg grade 2, severe, resolved and no treatment required - Urethritis at 600mg mild no treatment required
BOS172767-02: BOS172767-02: A Phase 1 Study to Determine the Relative Bioavailability of BOS172767 Enantiomer E1 (S) [XT-0528] and E2 (R) and the Single and Repeat Dose Pharmacokinetics, Safety and Tolerability of BOS172767 Selected Enantiomer in Healthy Subjects	Relative Bioavailability, Pharmacokinetics, Safety and Tolerability in Healthy Subjects Healthy Volunteers	**12 subjects enrolled** 9 received BOS172767 3 received placebo BOS172767- tablet for oral administration, 50mg, 250mg, 1000mg	**22 AEs 0 SAEs** **8 Subjects** Related: - Headache mild no rx - R Toe inflammation

References:
1. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-1825
2. Strickler J, Satake H, George T, et al, Sotorabsib in KRAS p.G12C-Mutated Advanced Pancreatic Cancer. N Engl J Med 2023;388:33-43
3. Li, HB., Yang, ZH. & Guo, QQ. Immune checkpoint inhibition for pancreatic ductal adenocarcinoma: limitations and prospects: a systematic review. *Cell Commun Signal* **19**, 117 (2021)
4. Lytle, NK et al, A multiscale map of the stem cell state in pancreatic adenocarcinoma, Cell 2019 April 18