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Results of A Randomized Phase 2 Trial of an Anti-Notch 2/3, Tarextumab (OMP-59R5, TRXT, Anti-Notch 2/3), in Combination with Nab-paclitaxel and Gemcitabine (Nab-P+Gem) in Patients (pts) with Untreated Metastatic Pancreatic Cancer (mPC)

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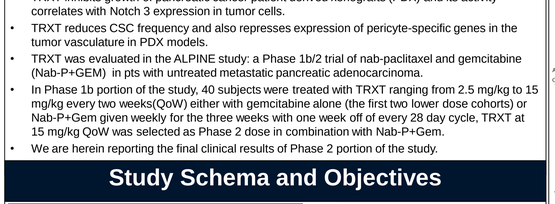
Background

- The Notch pathway plays a central role in embryonic development, the regulation of stem and progenitor cells, and is implicated centrally in many human cancers.
- Pancreatic adenocarcinoma expressing Notch 3 has a poor survival prognosis (Mann, *PloS ONE*, 2012).
- Tarextumab (TRXT) is a fully human IgG2 that inhibits the signaling of both Notch 2 and Notch 3 receptors.
- Cancer Stem Cells (CSCs), the sub-population of cells with increased tumorigenicity, mediate tumor recurrence, metastasis, and resistance to many conventional therapies.
- TRXT inhibits growth of pancreatic cancer patient derived xenografts (PDX) and its activity correlates with Notch 3 expression in tumor cells.
- TRXT reduces CSC frequency and also represses expression of pericyte-specific genes in the tumor vasculature in PDX models.
- TRXT was evaluated in the ALPINE study: a Phase 1b/2 trial of nab-paclitaxel and gemcitabine (Nab-P+GEM) in pts with untreated metastatic pancreatic adenocarcinoma.
- In Phase 1b portion of the study, 40 subjects were treated with TRXT ranging from 2.5 mg/kg to 15 mg/kg every two weeks(QoW) either with gemcitabine alone (the first two lower dose cohorts) or Nab-P+Gem given weekly for the three weeks with one week off of every 28 day cycle, TRXT at 15 mg/kg QoW was selected as Phase 2 dose in combination with Nab-P+Gem.
- We are herein reporting the final clinical results of Phase 2 portion of the study.

Study Schema and Objectives

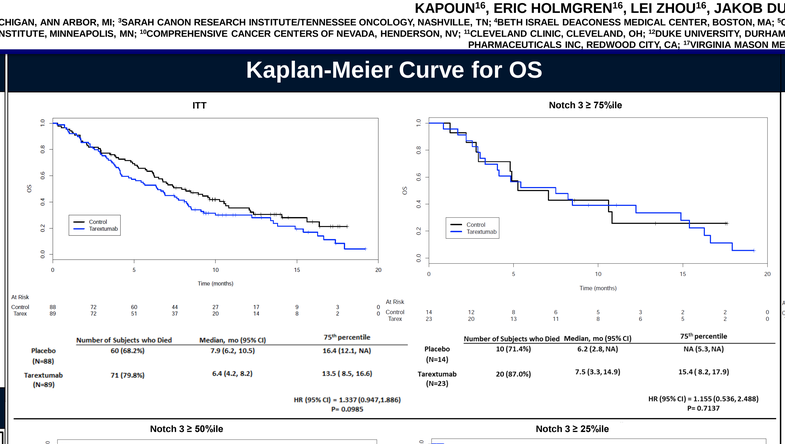


Baseline Characteristics (n=177)*

	Placebo (N=88)	Tarextumab (N=89)	Total (N=177)
Median age, years (range)	66 (40-82)	66 (34-88)	64.1 (34-88)
Female, n (%)	34 (38.6%)	39 (43.8%)	73 (41.2%)
ECOG Score, n (%)			
0	34 (38.6%)	34 (38.2%)	68 (38.4%)
1	54 (61.4%)	55 (61.8%)	109 (61.6%)
CA19-9, n (%)			
0-ULN	18 (20.5%)	19 (21.3%)	37 (20.9%)
>ULN – 59xULN	26 (29.5%)	24 (27.0%)	50 (28.2%)
>59 x ULN	44 (50.0%)	46 (51.7%)	90 (50.8%)
Primary pancreatic tumor location, n (%)			
Head	37 (42.0%)	39 (43.8%)	76 (42.9%)
Body	32 (36.4%)	34 (38.2%)	66 (37.3%)
Tail	32 (36.4%)	29 (32.6%)	61 (34.5%)
Frequent site(s) of metastasis(in >30% of Pts), n (%)			
Liver	78 (88.6%)	76 (85.4%)	154 (87.0%)
Lung	31 (35.2%)	39 (43.8%)	70 (39.5%)
# of metastatic sites, n (%)			
1	1 (1.1%)	1 (1.1%)	2 (1.1%)
2	27 (30.7%)	28 (31.5%)	55 (31.1%)
≥ 3	59 (67.0%)	60 (67.4%)	119 (67.2%)
Prior surgery Yes, n (%)	6 (6.8%)	7 (7.9%)	13 (7.3%)

*** Data cutoff as of Sept 29, 2016**

Kaplan-Meier Curve for OS



	Number of Subjects who Died	Median, mo (95% CI)	75th percentile
Placebo (N=88)	60 (68.2%)	7.9 (6.2, 10.5)	16.4 (12.1, NA)
Tarextumab (N=89)	71 (79.8%)	6.4 (4.2, 8.2)	13.5 (8.5, 16.6)

HR (95% CI) = 1.337 (0.947,1.886)
P= 0.0985

	Number of Subjects who Died	Median, mo (95% CI)	75th percentile
Placebo (N=14)	10 (71.4%)	6.2 [2.8, NA)	NA (5.3, NA)
Tarextumab (N=23)	20 (87.0%)	7.5 (3.3, 14.9)	15.4 (8.2, 17.9)

HR (95% CI) = 1.155 (0.536, 2.488)
P= 0.7137

	Number of Subjects who Died	Median, mo (95% CI)	75th percentile
Placebo (N=36)	23 (63.9%)	7.2 [4.4, 10.8]	N/A [10.3,N/A]
Tarextumab (N=38)	32 (84.2%)	5.0 [3.3, 8.5]	14.9 [7.5, 17.9]

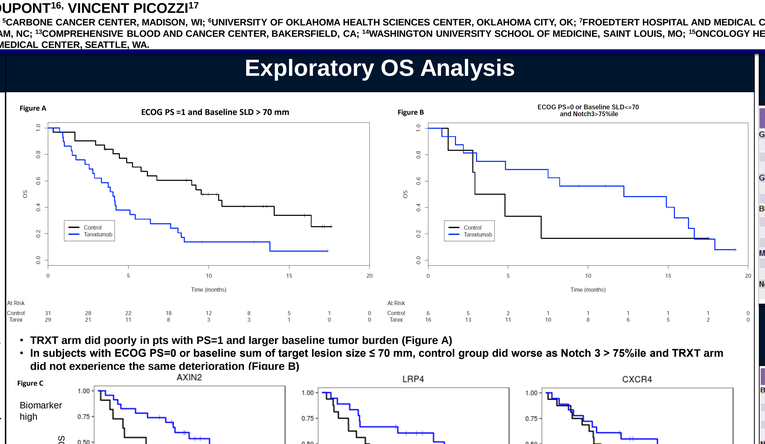
HR (95% CI) = 1.397 [0.817, 2.389]
P= 0.2225

	Number of Subjects who Died	Median, mo (95% CI)	75th percentile
Placebo (N=55)	38 (69.1%)	6.8 [4.8, 10.3]	N/A [10.3, N/A]
Tarextumab (N=55)	45 (81.8%)	5.4 [4.0, 8.3]	13.4 [8.3, 16.6]

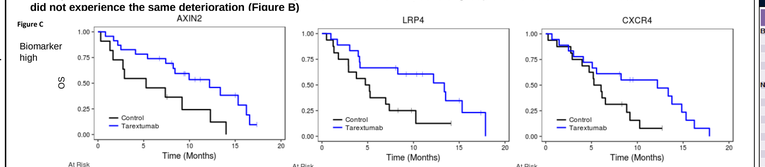
HR (95% CI) = 1.253 [0.813, 1.93]
P= 0.3074

Addition of TRXT to Nab-P+Gem did not provide survival benefit in all treated pts or Notch 3 subsets

Exploratory OS Analysis



- **TRXT arm did poorly in pts with PS=1 and larger baseline tumor burden (Figure A)**
- **In subjects with ECOG PS=0 or baseline sum of target lesion size ≤ 70 mm, control group did worse as Notch 3 > 75%ile and TRXT arm did not experience the same deterioration (Figure B)**



Median OS, mo	AXIN2		LRP4		CXCR4	
	Control	TRXT	Control	TRXT	Control	TRXT
Biomarker low	9.19	5.08	9.44	5.99	9.58	6.50
Biomarker high	5.26	12.19	4.97	13.37	5.65	12.19

Affymetrix U133 plus 2 microarrays were analyzed by dichotomizing patients into biomarker high and biomarker low pts (n=136 pts total). Cox proportional hazard model was fitted for OS and treatments in each group. Genes with p-value <0.05 and HR (hazard ratio)<1 in either group while HR>1 in another group were selected. 36 probe sets (out of 32468) were identified including multiple curated Wnt, stem cell, differentiation pathway genes. Improved OS in potential Wnt /stem cell pathway high pts. AXIN2, LRP4 , and CXCR4 are Wnt pathway and stem cell related genes. Representative genes shown; 75% percentile biomarker cut-point.

Related Treatment Emergent Adverse Events Safety Population (≥10% of subjects)

System Organ Class/ Preferred Term	Placebo(N=85)	Tarextumab (N=87)
Gastrointestinal disorders		
Diarrhoea	34 (40.0%)	63 (72.4%)
Nausea	26 (30.6%)	37 (42.5%)
Vomiting	14 (16.5%)	19 (21.8%)
General disorders and administration site conditions		
Fatigue	50 (58.8%)	45 (51.7%)
Pyrexia	10 (11.8%)	8 (9.2%)
Blood and lymphatic system disorders		
Thrombocytopenia	20 (23.5%)	43 (49.4%)
Anemia	22 (25.9%)	25 (28.7%)
Neutropenia	15 (17.6%)	8 (9.2%)
Metabolism and nutrition disorders		
Decreased appetite	11 (12.9%)	15 (17.2%)
Dehydration	10 (11.8%)	8 (9.2%)
Nervous System Disorders		
Dysgeusia	8 (9.4%)	11 (12.6%)

Grade ≥ 3 Treatment Emergent Adverse Events Safety Population (≥5% of subjects)

System Organ Class/ Preferred Term	Placebo(N=85)	Tarextumab (N=87)
Blood and lymphatic system disorders		
Anemia	20 (23.5%)	24 (27.6%)
Thrombocytopenia	11 (12.9%)	32 (36.8%)
Neutropenia	32 (37.6%)	10 (11.5%)
Leukopenia	6 (7.1%)	5 (5.7%)
Febrile neutropenia	4 (4.7%)	0 (0.0%)
Non-hematologic AEs		
Fatigue	12 (14.1%)	15 (17.2%)
Diarrhea	2 (2.4%)	16 (18.4%)
Hypokalemia	5 (5.9%)	9 (10.3%)
Dehydration	7 (8.2%)	8 (9.2%)
Alanine aminotransferase increased	8 (9.4%)	7 (8.0%)
Nausea	3 (3.5%)	7 (8.0%)
Lymphocyte count decreased	7 (8.2%)	4 (4.6%)
Abdominal pain	6 (7.1%)	4 (4.6%)
Gastrointestinal hemorrhage	3 (3.5%)	6 (6.9%)
Vomiting	3 (3.5%)	6 (6.9%)
Sepsis	5 (5.9%)	4 (4.6%)
Aspartate aminotransferase increased	6 (7.1%)	2 (2.3%)
Pulmonary embolism	3 (3.5%)	5 (5.7%)
Hypophosphatemia	5 (5.9%)	2 (2.3%)
Hyponatremia	1 (1.1%)	1 (1.1%)
Hyperglycemia	5 (5.9%)	1 (1.1%)
Neuropathy peripheral	6 (7.1%)	1 (1.1%)

Conclusions

- The addition of tarextumab to Nab-P+Gem did not improve OS in subjects with untreated metastatic pancreas adenocarcinoma in overall intent to treat population as well as in each of the Notch 3 subgroups. The study was stopped prematurely by OncoMed in consultation with the Data Safety Monitoring Board (DSMB).
- There were more grade 3 and above side effects, e.g., thrombocytopenia, diarrhea, vomiting and hypokalemia in tarextumab treated arms, and more neutropenia, leukopenia, febrile neutropenia in placebo arm.
- No statistical differences observed with subsequent anticancer therapy.
- Addition of tarextumab did not change chemotherapy dose intensity.
- An exploratory analysis identified subjects with ECOG PS=1 and high disease burden (baseline sum of target lesions >70 mm) as those for whom tarextumab was particularly detrimental in reducing OS. In subjects who did not fall into this subgroup, there was a trend of a Notch 3 related treatment benefit with the greatest treatment benefit in subjects with Notch 3 expression > 75%ile.
- Exploratory biomarker analysis of baseline FFPE samples identified potential OS benefit in stem cell/Wnt biomarker high pts.
- No further development of tarextumab is planned in advanced pancreas adenocarcinoma. Further evaluation of the data is underway to try to reconcile the clinical observations with the preclinical and phase 1b observations.

Treatment Exposure-Safety Population

	Study Drug		Gemcitabine		Nab-Paclitaxel	
	Placebo (N=85)	TRXT (N=87)	Placebo (N=85)	TRXT (N=87)	Placebo (N=85)	TRXT (N=87)
Total # of administration per Subject Median 25th 75th Percentile	9 4.0, 15.0	6 3.0, 9.0	12.0 5.0, 20.0	7.0 4.0, 12.0	12.0 5.0, 20.0	7.0 4.0, 11.0
Relative Dose Intensity Median 25th 75th Percentile	1 0.93, 1.00	1 0.93, 1.01	0.80 0.66, 0.99	0.70 0.58, 0.93	0.78 0.66, 0.94	0.75 0.60, 0.93
Duration of Treatment (days) Median 25th 75th Percentile	128.0 43.0, 210.0	78.0 36.0, 126.0	113 43.0, 210.0	85 36.0, 148.0	128 43.0, 210.0	82 36.0, 147.0

Addition of TRXT did not change chemo dose intensity

Subsequent Anti-Cancer Therapies

	Placebo (N=88)	Tarextumab (N=89)
Zero subsequent systemic Tx, n (%)	50 (56.18%)	46 (52.27%)
One line of subsequent Tx, n (%)	32 (35.96%)	39 (44.32%)
Two lines of subsequent Tx, n (%)	6 (6.74%)	3 (3.41%)
Three lines of subsequent Tx, n (%)	1 (1.12%)	0
Type of subsequent Tx received, n (%)		
5-FU	29(33.0%)	31(34.8%)
Nab-paclitaxel	5 (5.7%)	7 (7.9%)
Gemcitabine	10 (11.4%)	10 (11.2%)
Irinotecan	8 (9.1%)	10 (11.2%)
Oxaliplatin	11 (12.5%)	15 (16.9%)
Pembrolizumab	1 (1.1%)	0

PFS and Overall Response Rate

		PFS			ORR	
Pt Subsets	Tx Arms	Median, mo [95% CI]	HR [95% CI]	P value	Best ORR [95% CI]	P value
ITT	Placebo(N=88)	5.5 [3.7, 5.8]	1.426 [1.010, 2.013]	0.0437	31.8% (22.3%, 42.6%)	0.0867
	Tarextumab (N=89)	3.7 [1.9, 4.2]			20.2% (12.4%, 30.1%)	
N3≥75%tile	Placebo (N=14)	4.1[2.2, 9.1]	1.020 [0.398, 2.611]	0.9678	28.6% (8.4%, 58.1%)	0.9258
	Tarextumab (N=23)	5.5 [1.9, 7.5]			26.1% (10.2%, 48.4%)	
N3≥50% tile, but <75% tile	Placebo (N=36)	4.7[2.8, 5.8]	1.197 [0.679, 2.108]	0.5345	30.6% (16.3%, 48.1%)	0.5840
	Tarextumab (N=38)	3.7 [1.7, 5.7]			26.3% (13.4%, 43.1%)	
N3≥25% tile, but <50% tile	Placebo (N=55)	4.9 [3.5, 5.8]	1.164 [0.729, 1.858]	0.5253	29.1% (17.6%, 42.9%)	0.5950
	Tarextumab (N=55)	3.7 [1.9, 5.4]			23.6% (13.2%, 37.0%)	

Addition of TRXT to Nab-P+Gem did not provide progression free benefit or increase in overall response rates in all treated pts or Notch 3 subsets