Results of Phase 1b of Tarextumab (TRXT, OMP-59R5, anti-Notch 2/3) in Combination with Etoposide and Platinum Therapy (EP) in Patients (pts) with Untreated Extensive-Stage Small-Cell Lung Cancer (ED-SCLC)

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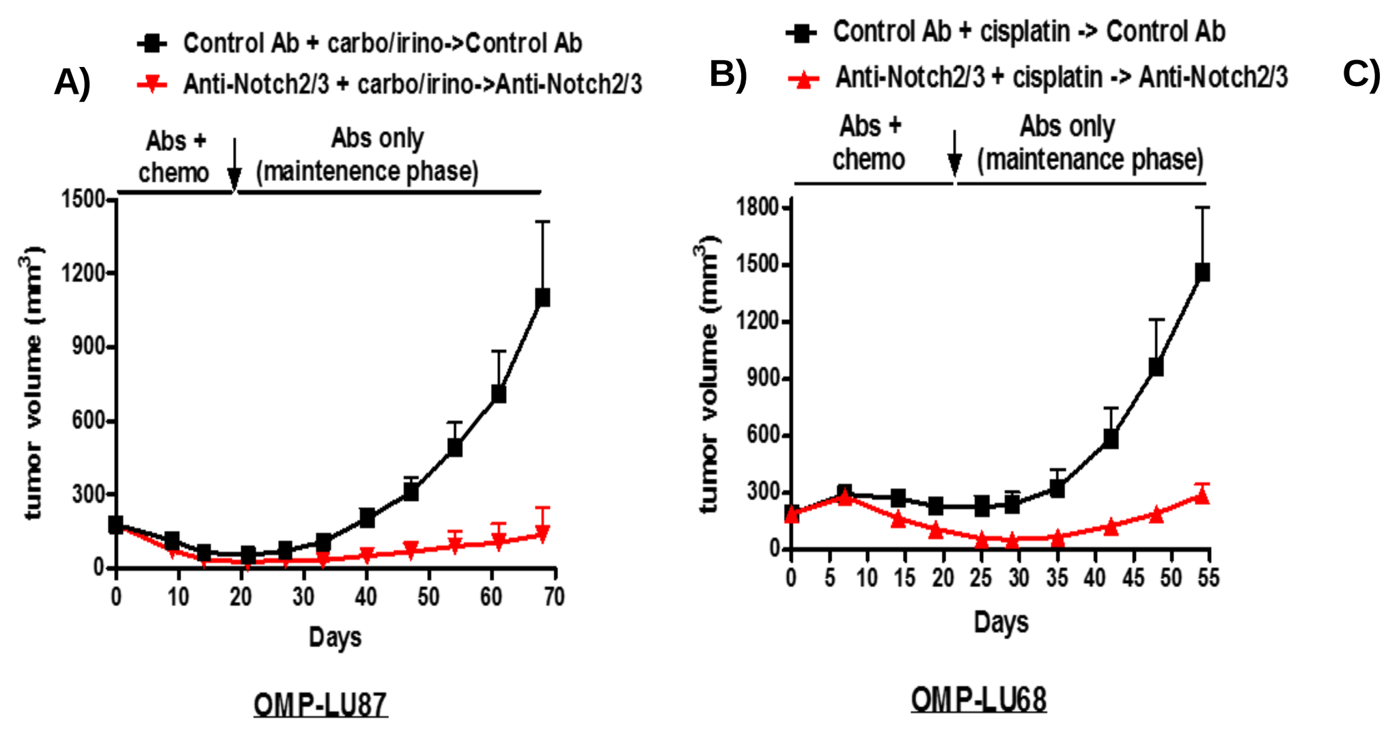
Background

- 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, including small cell lung cancer (SCLC).
- Notch3 overexpression is associated with poor survival and chemo resistance in a number of solid tumors.
- Tarextumab (TRXT, OMP-59R5, anti-Notch2/3) is a fully human IgG2 that was originally identified by binding to Notch2. It inhibits the signaling of both Notch2 and Notch3 receptors.
- TRXT has anti-cancer stem cell (CSC) and anti-vascular pericyte activity.
- The first-in-human Ph1a trial of TRXT in patients (pts) with refractory solid tumors (***Smith, EORTC-NCI-AACR 2013***) showed:
  - The maximum tolerated doses (MTDs) were: 2.5 mg/kg QW, 7.5 mg/kg Q2W and 7.5 mg/kg Q3W
  - Grade 3 diarrhea was the most common dose limiting toxicity (DLT), which was consistent with preclinical findings of diarrhea from goblet cell hyperplasia.
  - Notch and CSC pathways were reduced with TRXT treatment in serial patient tumor and surrogate tissue samples
- TXRT is currently being evaluated in first–line extensive-stage small cell lung cancer (***PINNACLE*** study) and first-line pancreatic cancer (***ALPINE*** study).
- The ***PINNACLE*** study is a Phase 1b/2 trial of TRXT in combination with etoposide and platinum therapy (EP) in pts with untreated extensive stage small cell lung cancer (ED-SCLC).
- Here we report the results of Phase 1b portion of the study.

TRXT with Chemotherapy in Patient-Derived SCLC Xenografts

TRXT treatment significantly delays tumor recurrence when combined with platinum-based chemotherapy compared to controls.



C)

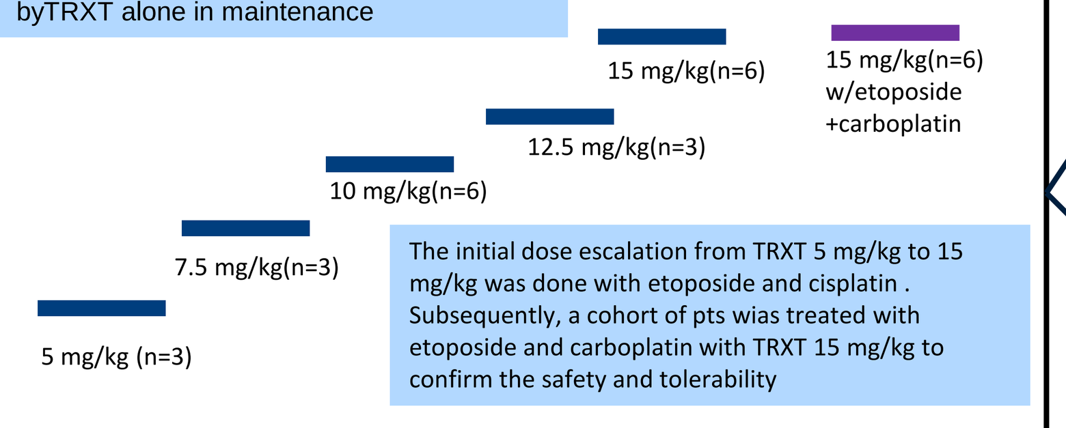
SCLC Tumor	OMP-59R5 Activity
LU40	+
LU61	+
LU65	+
LU66	+
LU67	-
LU68	+
LU87	+
LU90	-

Legend: OMP-LU87 (A) or OMP-LU68 (B) were injected into Nod-Scid mice and allowed to grow until tumors had reached an approximate tumor volume of 180 mm^3. Tumor bearing mice were randomized into two groups (n= 9 -10 mice per group) and treated with either chemotherapeutics plus control antibody or chemotherapeutic agents plus TRXT. Following three weeks of combination treatment (induction phase), the chemotherapeutic agents were discontinued and the antibody treatments were maintained. In the control groups, the tumor growth recurred after cessation of the chemotherapeutic agents, whereas in the TRXT groups, tumor recurrence was delayed. (C) Summary table of TRXT activity in patient-derived SCLC xenografts. A "+" indicates a reduction in tumor growth in combination with chemo relative to the chemo control group ($p < 0.05$). Six out of eight models tested are sensitive on TRXT.

Study Schema and Objectives

Phase 1b Dose escalation: in untreated ED-SCLC, DLT assessed within the first 21 days

TRXT, platinum IV Day 1, etoposide Days 1, 2, 3 of q21 days for 6 cycles, followed byTRXT alone in maintenance



The initial dose escalation from TRXT 5 mg/kg to 15 mg/kg was done with etoposide and cisplatin . Subsequently, a cohort of pts wias treated with etoposide and carboplatin with TRXT 15 mg/kg to confirm the safety and tolerability

Objectives:
Primary: MTD
Secondary:
- PK of TRXT
- Immunogenicity
- Safety and tolerability of the combination

Exploratory:
- PD biomarkers, including Notch pathway related genes and proteins and circulating tumor cells

Randomized Phase 2: in untreated ED-SCLC; N=135; Ph2 dose =15 mg/kg

1:1

- EP x 6 cycles + TRXT → TRXT alone
- EP x 6 cycles + Placebo → Placebo alone

Stratified: 1) platinum Tx; 2) prior brain XRT or PCI

Objectives:
Primary: PFS in all pts and in Notch 3 high
Secondary:
- Overall survival (OS), 12 months OS, overall response rate (ORR) in all pts, and in Notch 3 high
- Safety and tolerability of the combination
- PK of TRXT
- Immunogenicity

Exploratory:
- PD biomarkers, including Notch pathway related genes and proteins and circulating tumor cells

Etoposide 100 mg/m^2 Days 1, 2, 3 and cisplatin 80 mg/m^2 in Phase 1b and 75 mg/m^2 in Phase 2 or carboplatin AUC of 5 mg/mL•min Day 1 of q21 days for 6 cycles. After the completion of 6 cycles of EP, Pts without disease progression who have never received PCI or WBRT may receive PCI at the discretion of the investigators before continuing TRXT/placebo alone as a maintenance therapy.

Baseline Characteristics (n=27)*

TRXT Q3Wk dose (mg/kg)	Cisplatin+Etoposide					Carboplatin+Etoposide	Total N, (%), (n=27)
	5 (n=3)	7.5 (n=3)	10 (n=6)	12.5 (n=3)	15 (n=6)	15 (n=6)	
Median ages (yrs) (min, max)	63 (59, 83)	68 (65, 84)	69 (59,72)	69 (51,73)	62 (53, 67)	54 (40,78)	65 (40, 84)
Female, n	1	1	2	-	3	3	10 (37.0)
Race, n							
White	3	3	6	3	6	4	25 (92.6)
Black	-	-	-	-	-	1	1 (3.7)
Other	-	-	-	-	-	1	1 (3.7)
ECOG Score, n							
0	1	1	1	-	1	3	7 (25.9)
1	2	2	5	3	5	3	20 (74.1)
# of met sites, n							
1	1	1	-	-	3	3 (50.0)	8 (29.6)
2	1	1	4	-	1	1 (16.7)	8 (29.6)
≥ 3	1	1	2	3	2	2 (33.3)	11 (40.7)
With brain mets, n	-	1	2	1	-	1 (16.7)	5 (18.5)
Treated brain mets	-	-	2	-	-	-	2 (7.4)
Untreated brain mets	-	1	-	1	-	1 (16.7)	3(11.1)

* Data cutoff as of April 28, 2015

Treatment Exposure (n=27)*

TRXT Q3Wk dose (mg/kg)		Cisplatin+Etoposide					Carboplatin+Etoposide	Total N, (%), (n=27)
		5 (n=3)	7.5 (n=3)	10 (n=6)	12.5 (n=3)	15 (n=6)	15 (n=6)	
Pts with DLTs		-	-	1 (Gr3 N/V)*	-	-	-	1 (3.8%)
Completed 6 cycles of EP, n (%)		3 (100)	1 (33.3)	2 (33.3)	1 (33.3)	5 (83.3)	3 (50)	15 (55.6)
Pts active on treatment		-	-	-	-	1	2	3(11.1)
# of Cycles, median (min, max)	EP	6 (6, 6)	4 (4, 6)	2.5 (1, 6)	4 (3, 6)	6 (1,6)	5.7 (2, 6)	6 (1, 6)
	TRXT	8 (6,8)	6 (4, 21)	2.5 (1, 11)	5 (3, 7)	8 (1, 11)	5.5 (2, 10)	6 (1, 21)
Reasons for TRXT Treatment Discontinuation								
Adverse Events		-	-	-	-	1b	-	2 (7.4)
Progressive Disease		2	2	3	2	4	2	15 (55.6)
Death		-	-	-	1c	-	-	1 (6.3)
Withdrawal by subject		-	-	1	-	-	2	3 (11.1)
Physician's decision a		1	1	2	-	-	-	3 (11.1)

a. Due to subject's poor health condition or physician's decision to switch to carboplatin
b. Elevated creatinine
c. Acute respiratory failure

* Data cutoff as of April 28, 2015

AEs Occurring in >25 % of Pts (n=27)* All Grades Regardless of Relationship

Preferred Term	TRXT (mg/kg) +Cisplatin+Etoposide, n					TRXT (mg/kg) + Carboplatin+Etoposide, n	Total n, (%), (n=27)
	5 (n=3)	7.5 (n=3)	10 (n=6)	12.5 (n=3)	15 (n=6)	15 (n=6)	
Diarrhea	1	2	5	3	5	6	22 (81.5)
Nausea	3	2	4	2	4	4	19 (70.4)
Fatigue	3	3	3	2	5	1	17 (63.0)
Anaemia	3	3	1	1	3	4	15 (55.6)
Decreased Appetite	2	2	3	2	3	2	14 (51.9)
Vomiting	2	1	4	1	3	3	14 (51.9)
Thrombocytopenia	1	2	2	1	4	2	12 (44.4)
Alopecia	3	-	-	2	3	2	10 (37.0)
Hypomagnesaemia	2	2	1	1	3	1	10 (37.0)
Dehydration	1	1	3	1	1	2	9 (33.3)
Edema Peripheral	3	1	1	1	2	1	9 (33.3)
Constipation	1	1	2	1	2	1	8 (29.6)
Increased creatinine	2	2	1	-	2	1	8 (29.6)
Dyspnea	-	1	1	1	2	2	7 (25.9)
Headache	1	1	-	1	3	1	7 (25.9)
Weight Decreased	2	1	3	-	1	-	7 (25.9)

- Incidence of diarrhea was higher at TRXT 15 mg/kg. However, Grade 3 diarrhea occurred only in two pts: 1) 10 mg/kg (unrelated); 2) 12.5 mg/kg (related)
- The incidence of diarrhea was less than expected (based on single agent data). Co-administration of chemotherapy with TRXT may lessen GI tract goblet cell hyperplasia and thus for allow for higher doses of TRXT with chemotherapy.
- No DLT was reported at TRXT 15 mg/kg.
- TXRT 15mg/kg Q3W established as Ph2 dose with EP chemotherapy

* Data cutoff as of April 28, 2015

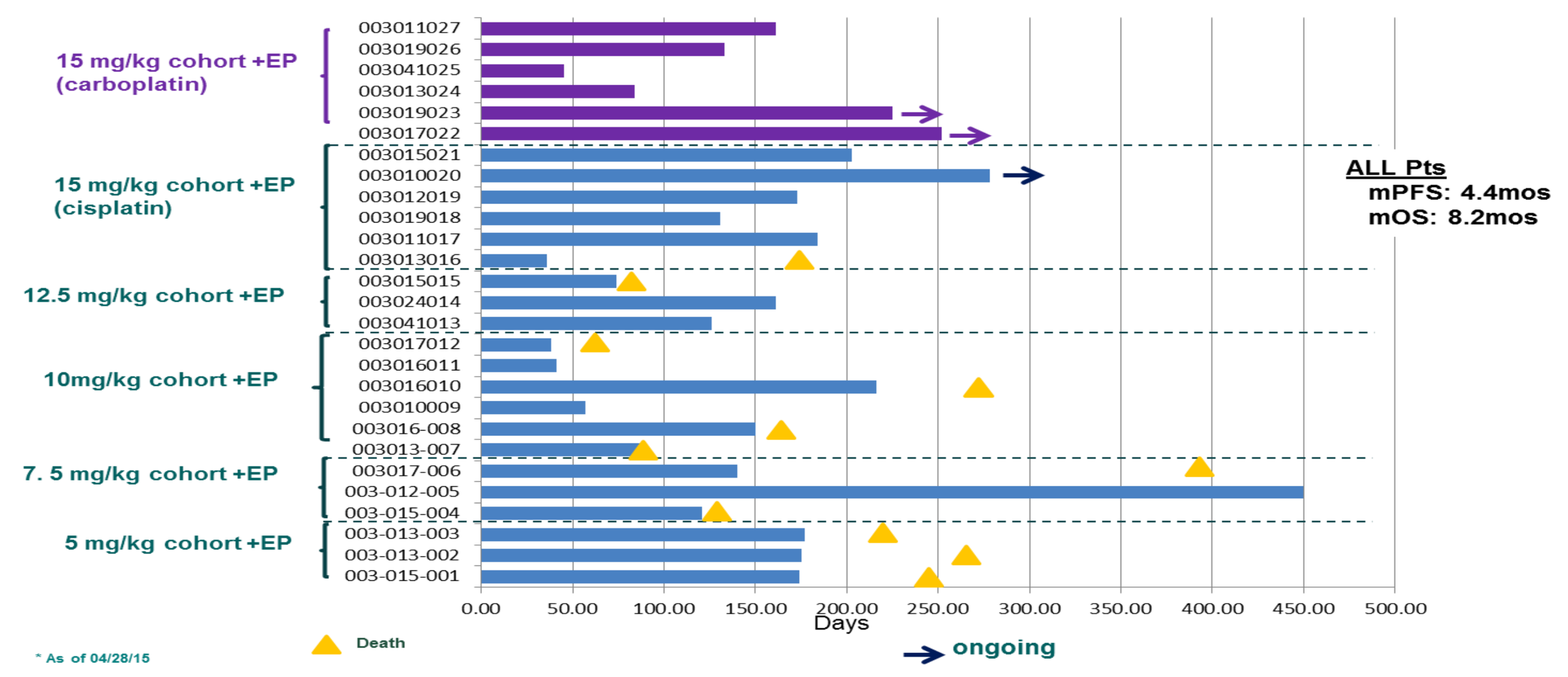
AEs Considered Related to TRXT Occurring in > 10% of Pts (n=27)*

Preferred Term	TRXT (mg/kg) +Cisplatin + Etoposide, n					TRXT (mg/kg) + Carboplatin + Etoposide, n	Total n, (%), (n=27)
	5 (n=3)	7.5 (n=3)	10 (n=6)	12.5 (n=3)	15 (n=6)	15 (n=6)	
Diarrhea	1	1	3	2	5	6	18 (66.7)
Fatigue	3	2	1	1	4	1	12 (44.4)
Nausea	3	-	1	1	3	3	11 (40.7)
Anemia	3	2	-	1	1	2	9 (33.3)
Decreased Appetite	2	1	-	1	2	2	8 (29.6)
Vomiting	1	-	1	1	3	2	8 (29.6)
Alopecia	2	-	-	1	1	1	5 (18.5)
Thrombocytopenia	1	-	1	1	2	-	5 (18.5)
Headache	1	-	-	-	2	1	4 (14.8)
Neutropenia	1	-	-	1	2	-	4 (14.8)
Dehydration	1	-	1	-	1	-	3 (11.1)
Dysgeusia	-	-	1	1	-	1	3 (11.1)
Increased creatinine	1	-	-	-	1	1	3 (11.1)

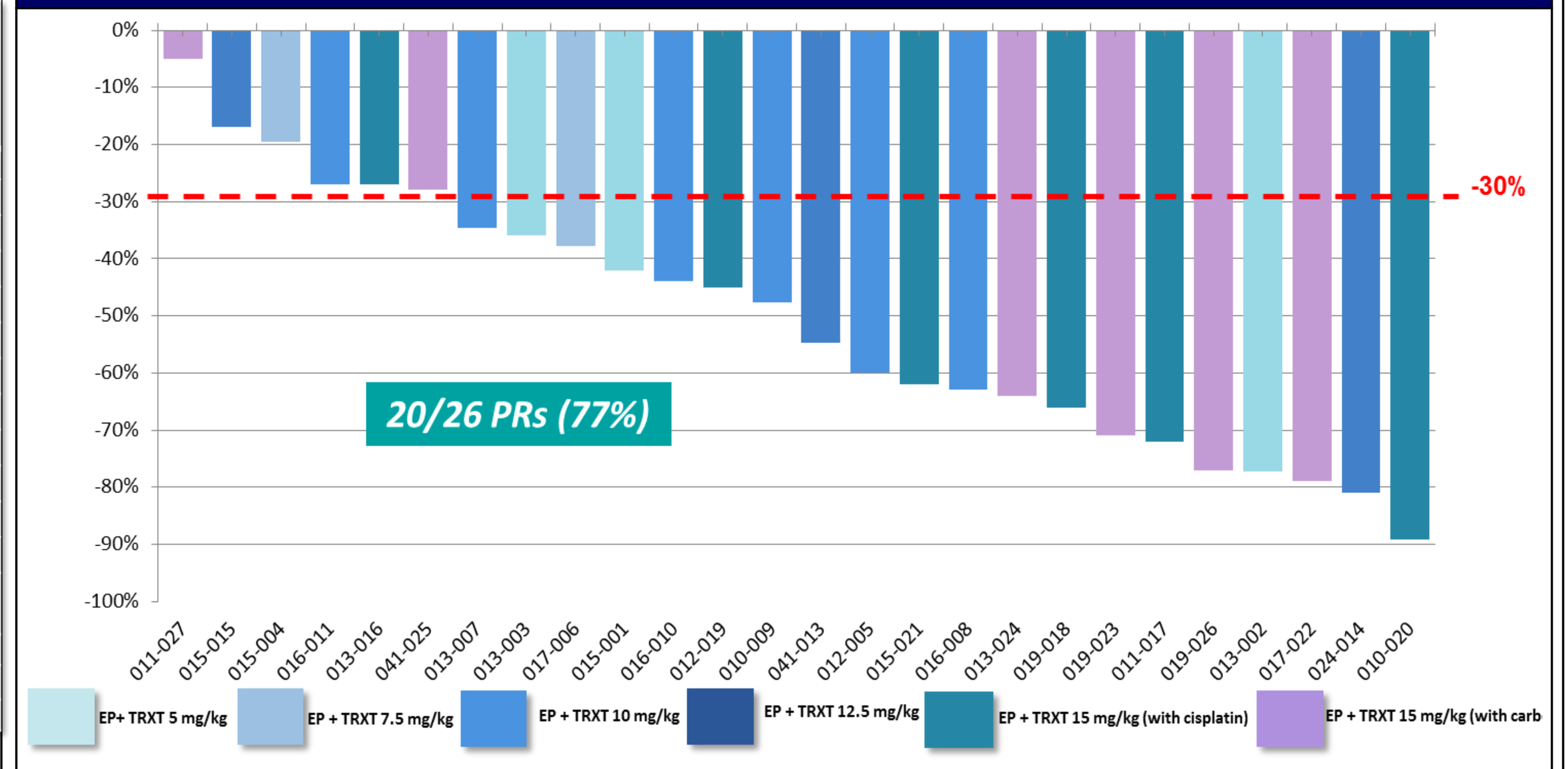
- Consistent with AEs in first-in-man study: diarrhea, fatigue, nausea, decreased appetite and vomiting were commonly reported events that were considered related to TRXT.
- However, the incidence of diarrhea was less than expected in contrast to single agent TRXT trial.
- Grade 3 diarrhea that was considered related to TRXT treatment was only reported in one pt in 12.5 mg/kg.
- The incidence of anemia was not dose dependent and will be continually monitored in the Phase 2 randomized, placebo-controlled trial.

* Data cutoff as of April 28, 2015

Subject Time on Study (n=27)*



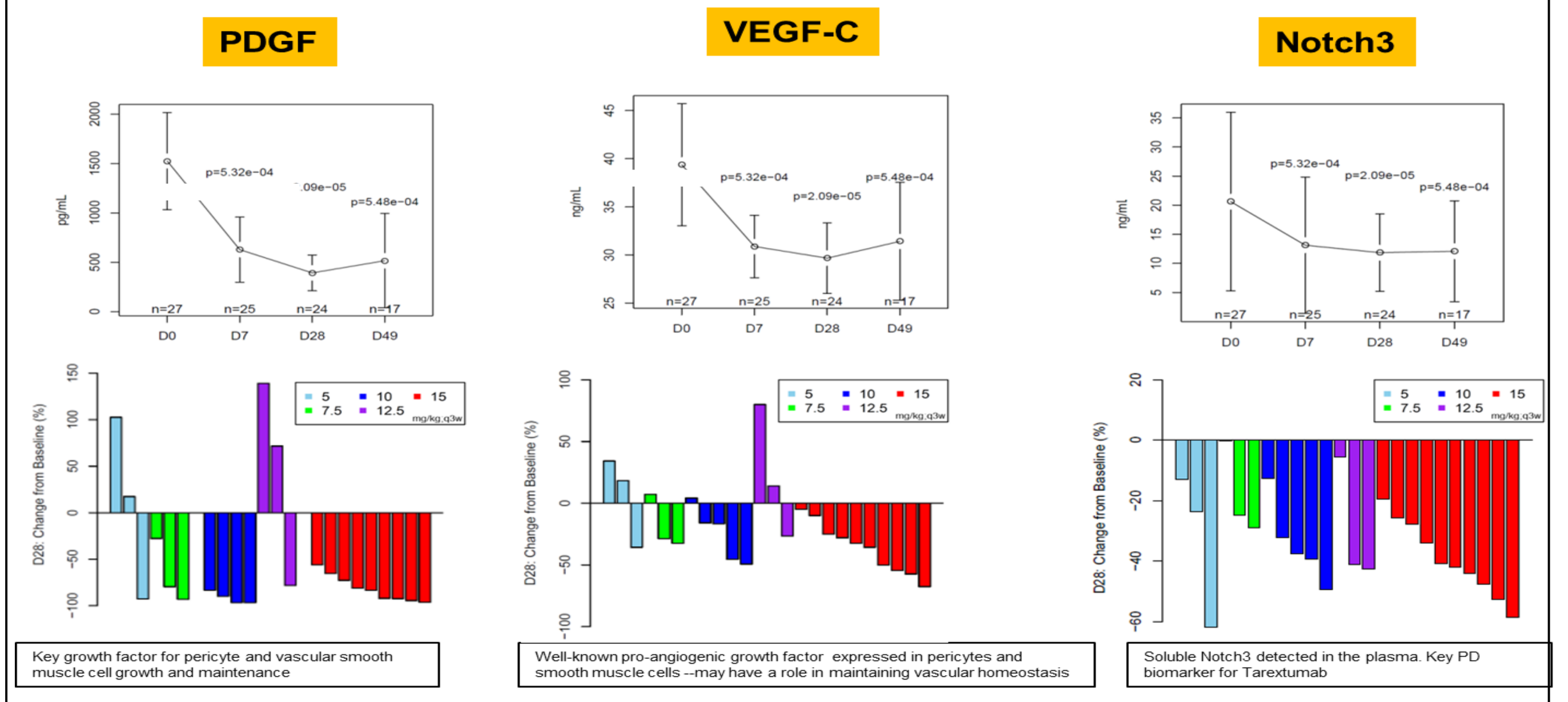
Maximum Change of Radiographic Target Lesions (n=26 Evaluable)*



Greater tumor reductions noted in pts in 15 mg/kg dose cohorts (8/11 pts who had > 60% SLD reduction were from 15 mg/kg dose cohorts), supporting TRXT 15 mg/kg as the selected Phase 2 dose

* Data cutoff as of April 28, 2015

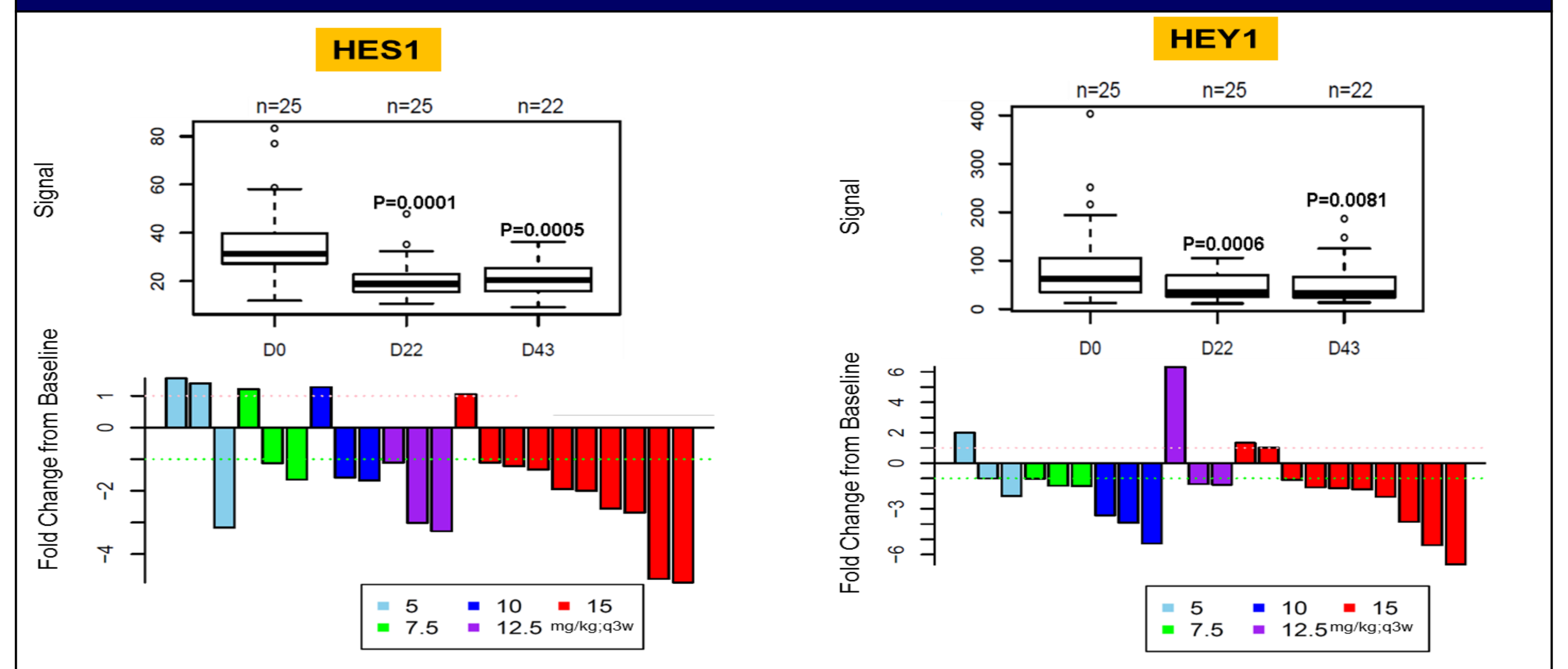
TRXT Pharmacodynamic Biomarkers: Plasma



Dose dependent Notch target genes down-regulation was noted in plasma samples, supporting TRXT 15 mg/kg as the selected Phase 2 dose

* Data cutoff as of April 28, 2015

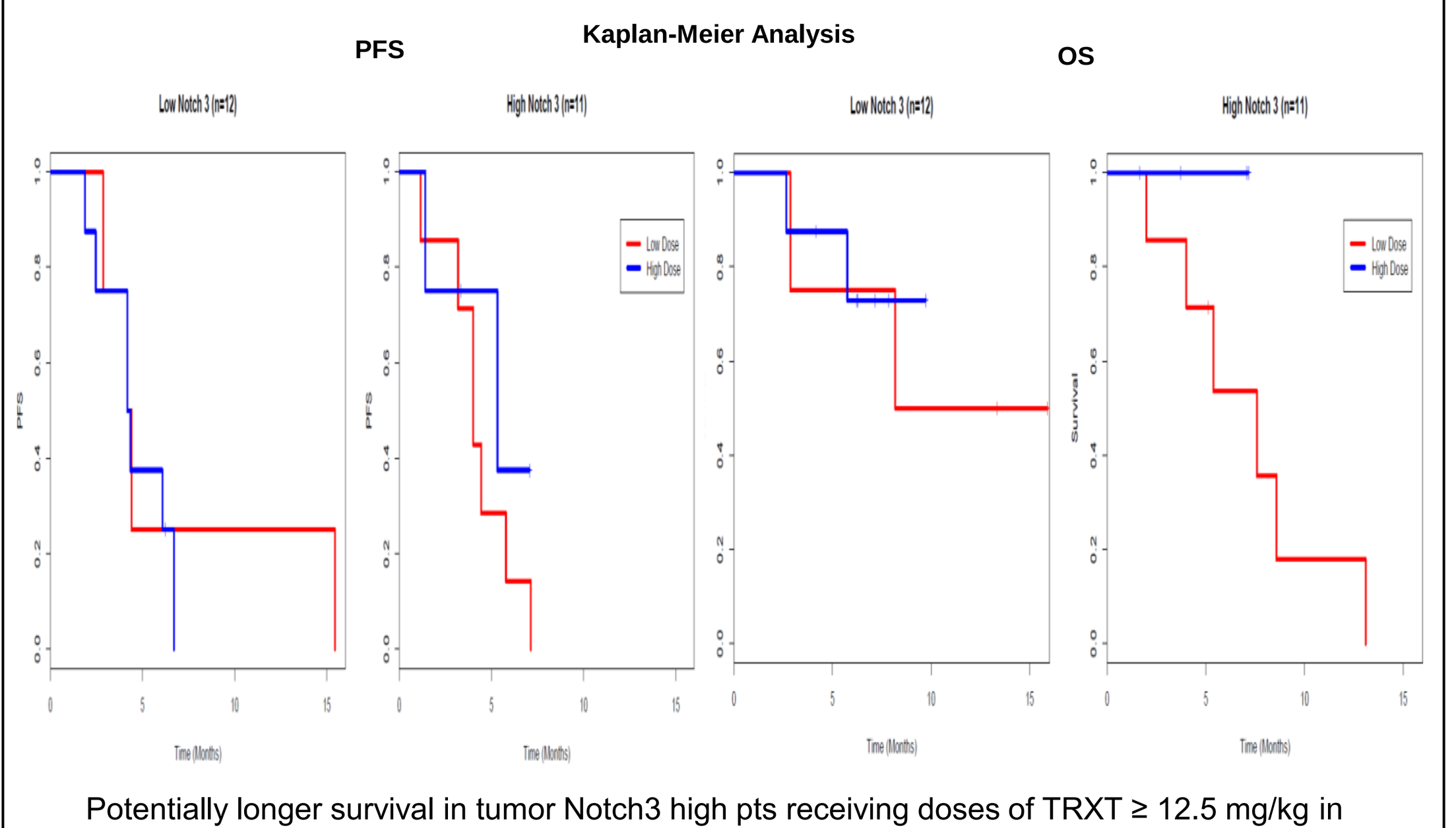
TRXT Pharmacodynamic Biomarkers: Whole Blood



Dose dependent Notch target genes down-regulation was noted in whole blood samples, supporting TRXT 15 mg/kg as the selected Phase 2 dose

Tumor Notch 3 Biomarker and Timed Endpoints

- Tumor Notch 3 gene expression is a potential predictive biomarker for TRXT in PINNACLE Phase 2
- Baseline tumor tissue required for study entry
- 23 of 27 (85%) of subjects (dose levels 5-15mg/kg TRXT) had tumor assessable for Notch3 RUO-validated RT-PCR assay, Almac Diagnostics
- All 23 subjects with Notch3 assessable tumor had progression free survival (PFS) & overall survival (OS) data
- Notch3 gene expression cut-off tested: ≤50%,>50% of Notch 3 expression at baseline, high dose is TRXT ≥ 12.5 mg/kg
- Kaplan-Meier Analysis was performed for PFS and OS based on Notch3 gene expression level

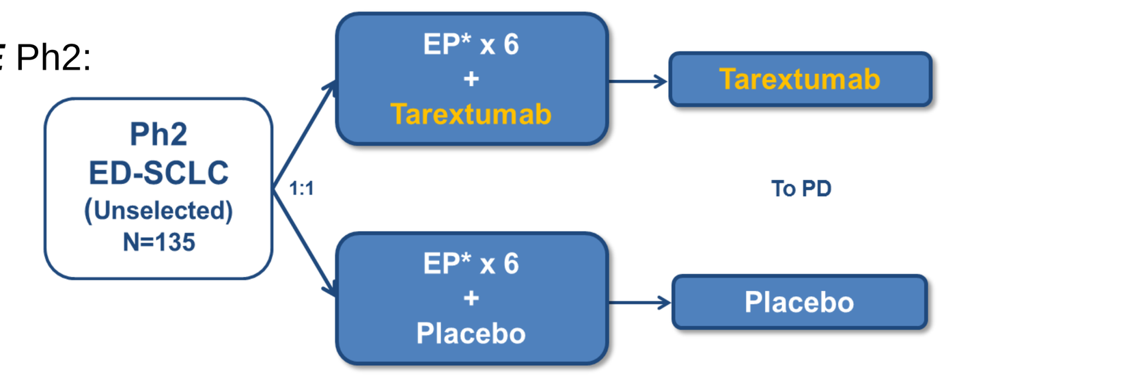


Potentially longer survival in tumor Notch3 high pts receiving doses of TRXT ≥ 12.5 mg/kg in combination with EP. More follow-up is needed .

Summary

- TRXT in combination with EP was well tolerated up to 15 mg/kg Q3W. One DLT of Grade 3 nausea was observed in one pt (10 mg/kg Q3W)
- Diarrhea, fatigue, nausea, decreased appetite and vomiting were the most common TRXT associated AEs (mostly Grade 1 or 2 events, and manageable with supportive care)
- The incidences of chemotherapy associated myelosuppression was not exacerbated by TRXT
- RECIST response (unconfirmed) to EP + TRXT(all dose cohorts) was 77%; greater tumor reduction at high dose TRXT (≥12.5mg/kg Q3W)
- The median PFS and OS values were 4.4 mos and 8.2 mos for all 27 pts, respectively
- There was a potential trend of longer survival in higher dose (TRXT≥ 12.5 mg/kg) cohorts, particularly in subjects with tumors with high Notch3 tumor levels. More follow-up is needed and this will be verified in the Ph 2 randomized portion of the trial
- The Ph2 dose of TXRT with EP selected was 15mg/kg Q3W based on acceptable safety, pharmacodynamic Notch pathway regulations, radiographic tumor reduction and potentially longer survival in Notch 3 biomarker high pts
- The randomized, double blinded Ph2 portion of the ***PINNACLE*** study is currently enrolling at 40 clinical sites in the United States and the efficacy endpoints of PFS, OS and ORR will be evaluated in all pts, as well as, in biomarker (tumor Notch3 high) positive pts; results are expected in 2016/17

PINNACLE Ph2:



* EP: Etoposide + cisplatin or carboplatin (physician choice in Ph2: Cis or Carbo)

Primary Endpoint	Secondary Endpoints	Exploratory Endpoints
PFS (All / Notch3+)	Survival Response Safety	Biomarkers

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