Preliminary Activity in the First in Human Study of the First-In-Class Fatty Acid Synthase (FASN) Inhibitor, TVB-2640

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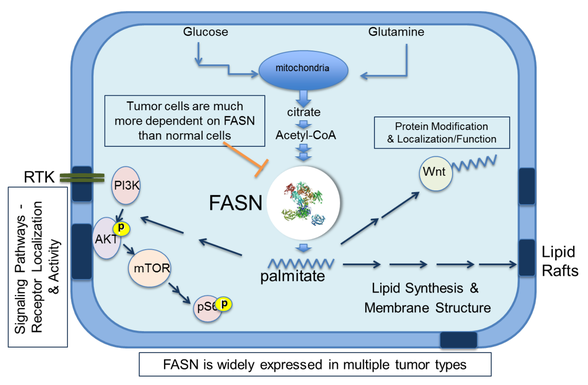
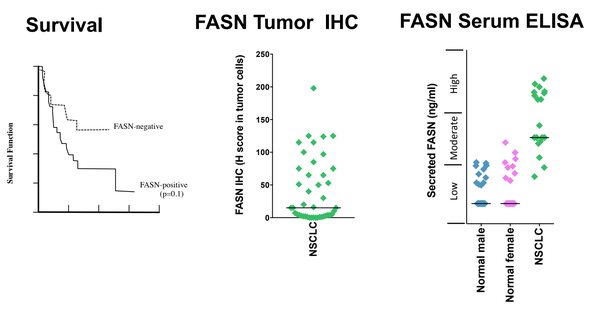
Introduction

- FASN inhibition is a novel approach to cancer treatment.
- Selective disruption of palmitate biosynthesis leads to apoptosis in many tumor cells.
- FASN expression correlates with poor prognosis in certain tumor types including NSCLC (Visca et al., 2004).
- TVB-2640 is the only selective FASN inhibitor in clinical trials.
- Preliminary data show:
  - Broad monotherapy activity in multiple solid tumors, including 75% (6 of 8) NSCLC $KRAS^{Mut}$ patients with > 12 weeks SD.
  - Well tolerated with majority grade 1-2 adverse events at the MTD; even when combined with paclitaxel.

FASN: An Integrated Target in Tumor Biology



FASN Expression in Human NSCLC



- Markedly higher in NSCLC patients compared to normal donors.
- NSCLC serum FASN among the highest expression of >10 tumor types tested.

Archival FFPE sections stained with FASN CST rabbit Ab C20G5 using a validated method. H-score in tumor tissue quantitated by standard pathology review. ELISA for FASN performed on archival human sera using a commercially available ELISA kit (Immtech), log scale.

Objectives

-Safety, MTD, PK, recommended Phase-2 dose (monotherapy and in combination with chemo) and preliminary activity.
-Biomarkers of response and pharmacodynamic biomarkers

Study Design and Key Eligibility

- Oral, once daily; 21 days in monotherapy or 28 days with a taxane; continuous cycles.
- Adult patients (ECOG 0-1), with pathologically confirmed metastatic or advanced-stage solid tumors, standard accepted Ph-1 In/Exclusion criteria.
- Excluded pts with clinically significant ophthalmologic finding, including history of dry eye.
- The RP2D has been defined as 100mg/m^2 with DLTs of palmar plantar erythrodysesthesia and corneal edema. The trial is currently in dose expansion in multiple tumor types as monotherapy and in combination with taxane regimens.
- TVB-2640 plasma exposure increases with dose, has a half life of approx. 16 hr and was unaffected by paclitaxel.

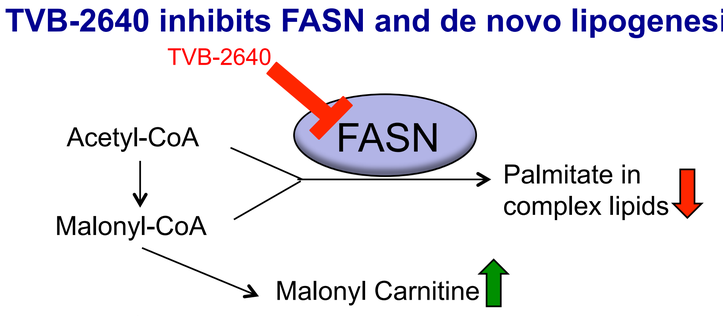
Safety

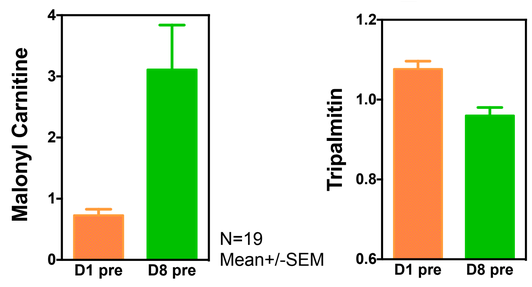
Adverse Event (related)	Monotherapy N=72 all enrolled N=52 ≤ the MTD				Combination w Paclitaxel N=55 all enrolled N= 48 ≤ the MTD			
	G1	G2	G3+	N (%)	G1	G2	G3+	N (%)
Any G1/G2 related AE				68 (94.4)				49 (89.1)
Any G3 or > related AE				17 (23.6)				17 (30.9)
Skin and subcutaneous ≤ the MTD	24 (46.1)	14 (26.9)	6 (14.2)	44 (84.6)	14 (29.1)	14 (32.5)	7 (16.2)	35 (72.9)
All Skin and subcutaneous	30 (41.7)	22 (30.6)	8 (11.1)	60 (83.3)	17 (30.9)	16 (29.1)	9 (16.4)	42 (76.4)
Eye Disorders ≤ the MTD	15 (28.8)	7 (13.4)	-	22 (42.3)	12 (20)	5 (11.6)	-	17 (35.4)
All Eye Disorders	22 (30.6)	9 (12.5)	3 (4.2)	34 (47.2)	13 (23.6)	7 (12.7)	-	20 (36.4)
Gastrointestinal ≤ the MTD	19 (36.5)	6 (11.5)	-	25 (48.0)	21 (43.7)	3 (6.9)	2 (4.6)	27 (56.2)
All Gastrointestinal	27 (37.5)	8 (11.1)	-	35 (48.6)	25 (45.5)	5 (9.1)	3 (5.5)	33 (60.0)
SAE*	**G1**	**G2**	**G3+**	**N (%)**	**G1**	**G2**	**G3+**	**N (%)**
Fatigue	-	-	1 (1.4)	1 (1.4)	-	-	-	-
General disorders	-	-	-	-	-	2 (3.6)	1 (1.8)	3 (5.5)
Infections (Pneumonia, Respiratory)	-	-	-	-	-	1 (1.8)	2 (3.6)	3 (5.5)
Pneumonitis	-	-	-	-	-	2 (3.6)	3** (5.5)	5 (9.0)
Skin and subcutaneous	-	-	-	-	-	1 (1.8)	-	1 (1.8)

*all treatment related SAE's at the MTD of 100mg/m^2 **1 grade 5

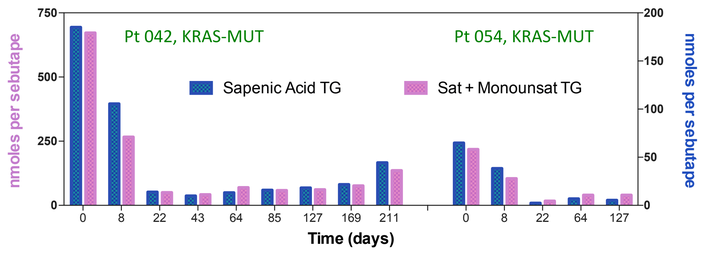
Pharmacodynamics

TVB-2640 inhibits FASN and de novo lipogenesis





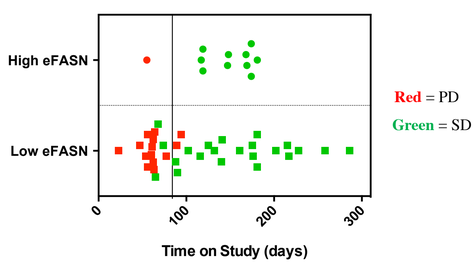
Increased serum malonyl carnitine, and decreased serum tripalmitin were observed in 90% of patients tested, including both KRAS-MUT and KRAS-WT



Sebum was collected using Sebutape® patches on the forehead for 30 minutes, and profiled by GC-MS and MS-flame ionization detection for lipid content at Metabolon. Normal donors were not administered TVB-2640. Similar inhibition of de novo lipogenesis observed across all patients tested (n=19).

Significant reductions in sebum saturated and monounsaturated triglycerides including sapienic acid (primarily de novo) were observed after one week of treatment and generally remained low through subsequent cycles of treatment.

Baseline serum FASN levels for combination patients

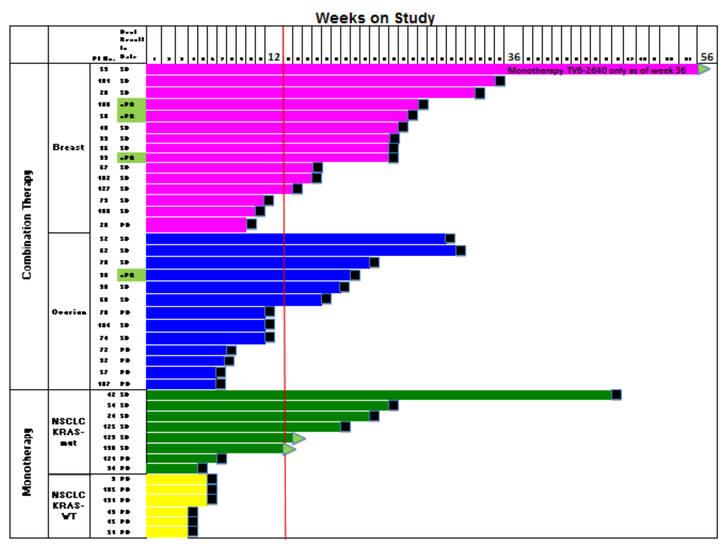


- 91% patients with high serum FASN (≥ 10 ng/mL) have SD and longer duration on study
- To date, approximately 50% breast cancer patients have high serum FASN

Results

Duration on Study

Breast, Ovarian and NSCLC Patients



KRAS-MUT have longer duration on study than KRAS-WT

- 14 NSCLC patients enrolled on monotherapy
  - ➢ 75% KRAS-MUT on study > 12 weeks
  - ➢ 0% KRAS-WT on study > 12 weeks
- Similar plasma TVB-2640 exposure across MUT and WT patients

NSCLC Preliminary Anti-Tumor Activity

Tumor Type	Response	Previous Taxane Treatment*	Notes
TVB-2640 monotherapy			
NSCLC KRAS-MUT	SD > 12 weeks **6 of 8**	N/A	1 KRAS-Mut SD = 56 weeks
NSCLC KRAS-WT	SD > 12 weeks **0 of 5**	N/A	

Tumor Type	Response	Previous Taxane Treatment*	Notes
TVB-2640 + paclitaxel			
NSCLC KRAS-MUT	1 Confirmed PR	None	Confirmed PR at 12 weeks; patient on study for 46 weeks
NSCLC KRAS-MUT	SD > 12 weeks **3 of 5**	**1 of 5**	
NSCLC KRAS-WT	SD > 12 weeks **4 of 6**	**3 of 6**	1 KRAS-WT SD=16 weeks

*** # of average prior regimens (including taxanes)=4**

Conclusion

- TVB-2640 demonstrates a favorable tolerability profile with no significant GI, hematologic or serum chemistry adverse events; no evidence of QTc prolongation by Holter monitoring.
- Biomarker analysis demonstrates target engagement (FASN inhibition), and inhibition of lipogenesis in patients.
- NSCLC KRAS-MUT patients remain on study longer than NSCLC KRAS-WT patients, when treated with TVB-2640 monotherapy.
- Further exploration of biological activity is underway in heavily pretreated ovarian and breast cancer patients in combination with paclitaxel and docetaxel:
  - ➢ Breast: 3 confirmed PRs and 8 SDs ≥ 12 Weeks (in combination w paclitaxel).
  - ➢ Ovarian/Peritoneal: 1 confirmed PR and 58-98% decreases in tumor marker CA-125 in n=6 patients (in combination w paclitaxel).
  - ➢ High baseline serum FASN associated with longest duration on study, a potential patient selection marker.

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Thank You to the Patients and Their Families