Translational Studies of a First-in-class FASN Inhibitor, TVB-2640, Linking Preclinical Studies to Clinical Laboratory Observations in Solid Tumor Patients

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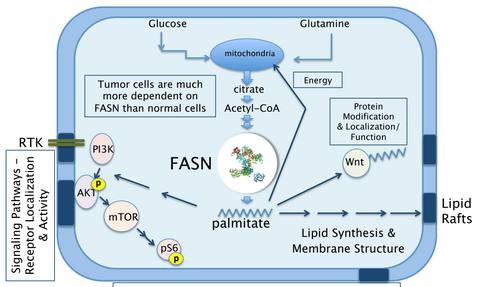
Introduction

- FASN inhibition is a novel approach to cancer treatment involving the selective disruption of palmitate biosynthesis that, in tumor cells, causes changes in cell signaling, induces apoptosis, and enhances sensitivity to other chemotherapeutic agents, in addition to other effects.
- TVB-2640 is an oral, first-in-class, small-molecule reversible inhibitor of FASN that demonstrates *in vitro* and *in vivo* anti-tumor effects with an acceptable non-clinical safety profile.
- This is an update on a dose-escalation study in patients with metastatic or advanced-stage malignant disease refractory to standard therapy and for whom no therapy exists that would be curative or might provide significant benefit.

FASN-Integrated Target in Tumor Biology

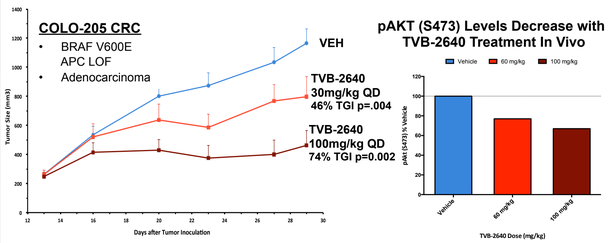


FASN is widely expressed in multiple tumor types

Oral, First-in-Class, Potent FASN Inhibitor

TVB-2640

Inhibits Tumor Growth and AKT Phosphorylation in Rat Xenograft



AACR 2015: #2674. O'Farrell et al. *Biomarker and PK/PD analysis of first in class FASN inhibitor TVB-2640 in a first-in-human phase 1 study in solid tumor patients.* #4446. Heuer et al. *Discovery of tumor types highly susceptible to FASN inhibition and biomarker candidates for clinical analysis.*

O'Farrell et al. Heuer et al.

Objectives

Primary: Safety, MTD, recommended phase 2 dose

Secondary: Pharmacokinetics, preliminary anti-tumor activity (monotherapy and in combination with paclitaxel)

Exploratory: Biomarkers of response

Study Design & Key Eligibility Criteria

- Multicenter, open label, phase 1 study
- Oral, once daily with 21 day monotherapy continuous cycles (or 28 days in combination with paclitaxel)
- Single patient, accelerated titration followed by "3+3" design after ≥ Grade 2 toxicity

Inclusion

- Adult patients with adequate bone marrow, hepatic and renal function and metastatic or advanced-stage solid malignant tumor
- Up to 4 prior chemo regimens
- ECOG 0-1

Exclusion

- History of clinically significant dry eye
- Clinically significant ophthalmologic findings
- History of risk factors for torsade de pointes (e.g., heart failure, hypokalemia)
- Conditions that might interfere with oral absorption

TVB-2640 Monotherapy Dose Levels

240 mg/m² N=4	
120 mg/m² N=6	250 mg flat Ongoing
80 mg/m² N=3	200 mg flat N=5
60 mg/m² N=7	

Monotherapy Planned Expansions

Colorectal Cancer
Non-small Cell Lung Cancer
Hepatocellular Cancer
Diffuse Large B-cell
Endometrial
Prostate Cancer

TVB-2640 + 80 mg/m² Weekly Paclitaxel Dose Levels

	200 mg flat N=7
60 mg/m² N=6	

Combination Planned Expansions

Non-small Cell Lung Cancer
Breast Cancer
Ovarian/Gyn Cancer

Demographics

Monotherapy, N=25		
Age (years)	Median	64
	Range	44–78
Gender	Male	52%
	Female	48%
Race	Caucasian	22
	Asian	3
ECOG Performance Status	0	44%
	1	56%
Number of Previous Regimens	0–2	5
	3–4	12
	5+	8

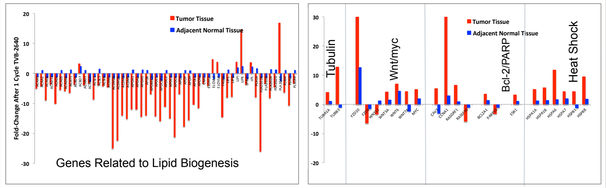
Combo Therapy, N=12		
Age (years)	Median	60
	Range	44-74
Gender	Male	36%
	Female	64%
Race	Caucasian	12
ECOG Performance Status	0	27%
	1	73%
Number of Previous Regimens	0-2	4
	3-4	6
	5+	2

AACR 2015 # CT-203. M. Patel et al. *Report of a First-In-Human Study of the First-In-Class Fatty Acid Synthase (FASN) Inhibitor, TVB-2640.*

Note: All patients to date are enrolled in the US and UK.

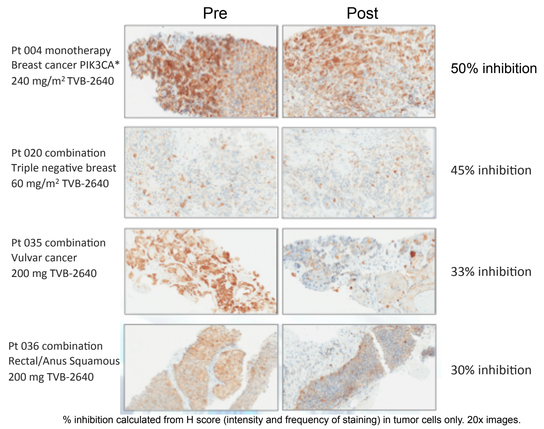
Pharmacodynamics

TVB-2640 Elicits Significant Changes in Mechanism Related Gene Expression *Specifically* in Tumor Tissue



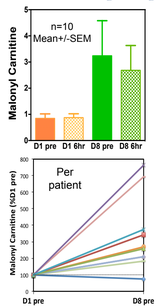
- Pt 004 (240mg/m² monotherapy)
- Breast cancer (PIK3CA E452K, HER2-, PR+, ER+); Matched liver biopsies (pre/post)
- Tumor Tissue Dissected from Adjacent Normal Tissue; RNA extracted and transcripts counted

pAKT S473 Decreases in Tumor Samples from 4/4 Patients

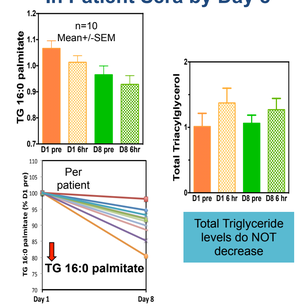


% inhibition calculated from H score (intensity and frequency of staining) in tumor cells only. 20x images.

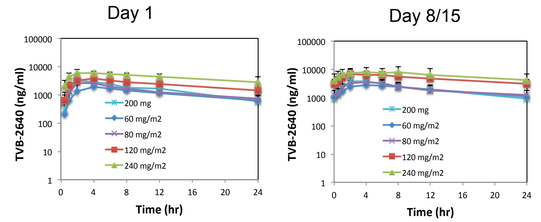
Malonyl Carnitine Increased In Patient Sera by Day 8



Tripalmitin Decreased in In Patient Sera by Day 8

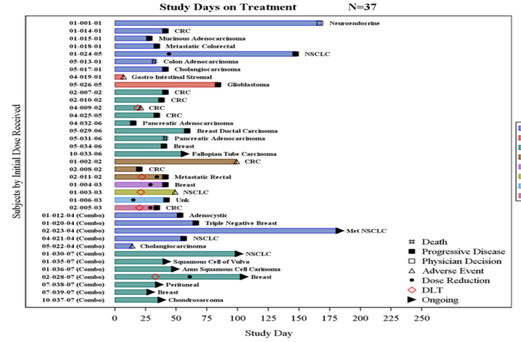


Pharmacokinetic Plasma Levels



Plasma levels of TVB-2640 measured using a validated method. On day 8/15 the predose value is plotted as the 24 hour timepoint. Mean +/- SD for n of 3 to 7 patients per monotherapy cohort.

Time on Study



Conclusions

- TVB-2640 is an oral, selective, potent, reversible FASN inhibitor and is the first FASN inhibitor in clinical trials
- TVB-2640 demonstrates a favorable tolerability profile with no significant GI, hematologic, serum chemistry adverse events
- Exposures of 60 mg/m² and above demonstrate target modulation and are above those associated with efficacy in preclinical models
- Skin and ophthalmological toxicity are on-target and reversible
- Tumor gene expression, tumor AKT phosphorylation and plasma biomarker profiles demonstrate FASN inhibition in patients
- Early data in combination with weekly paclitaxel show expected PK results and no newly emergent toxicities. The combination has been well tolerated to date
- Three patients with NSCLC (one monotherapy and 2 in combination) have evidence of stable disease after >12 weeks of treatment

Thank You to the Patients and Their Families

This poster is available at: 3vbio.com/news-events