Report of a First-In-Human Study of the First-In-Class Fatty Acid Synthase (FASN) Inhibitor, TVB-2640

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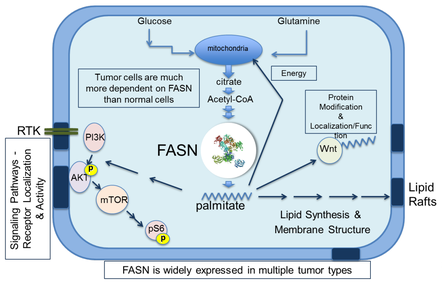
Introduction

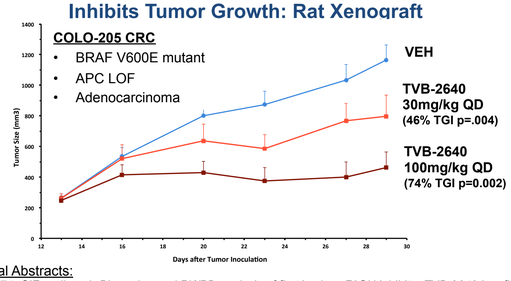
- FASN inhibition is a novel approach to cancer treatment involving the selective disruption of palmitate biosynthesis that, in tumor cells, causes changes in cell signaling, induces apoptosis, and enhances sensitivity to other chemotherapeutic agents, in addition to other effects.
- TVB-2640 is an oral, 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 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



Oral, First-in-Class, Potent FASN Inhibitor TVB-2640

Inhibits Tumor Growth: Rat Xenograft



Preclinical Abstracts:

#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.* Monday April 20, 1:00 PM - 5:00 PM

#4446. Heuer et al. *Discovery of tumor types highly susceptible to FASN inhibition and biomarker candidates for clinical analysis.* Tuesday April 21, 1:00 PM - 5:00 PM

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

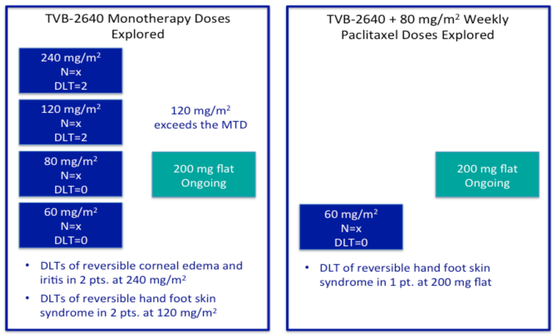
- Multicenter, open label, phase 1 study
- Oral, once daily with 21 day monotherapy continuous cycles (or 28 days in combination with paclitaxel)
- Single patient, accelerated titration followed by "3+3" design after ≥ Grade 2 toxicity

Inclusion

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



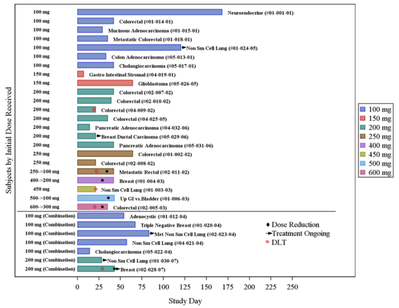
Demographics

Monotherapy, N=22		
Age (years)	Median	63.5
	Range	44-78
Gender	Male	56%
	Female	44%
Race	Caucasian	21
	Asian	1
ECOG Performance Status	0	43%
	1	56%
Number of Previous Regimens	0-2	4
	3-4	10
	5+	8

Combo Therapy, N=7		
Age (years)	Median	59
	Range	44-74
Gender	Male	28%
	Female	72%
Race	Caucasian	7
ECOG Performance Status	0	29%
	1	71%
Number of Previous Regimens	0-2	0
	3-4	5
	5+	2

Note: All patients to date are enrolled in the United States

Time on Study



Grade 1 and 2 Related Adverse Events

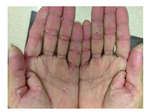
Monotherapy AE Verbatim	Events	Grade 1	Grade 2	N=22
Any Gr 1/Gr 2 Adverse Event				82%
Skin and subcutaneous tissue disorders	15	7	8	68%
General disorders and administration site conditions	11	3	8	50%
Gastrointestinal disorders	9	7	2	41%
Eye disorders	7	5	2	31%
Metabolism and nutrition disorders	4	4	-	18%
Nervous system disorders	3	2	1	14%
Congenital, familial and genetic disorders	1	1	-	4%
Investigations	1	1	-	4%
Respiratory, thoracic and mediastinal disorders	1	1	-	4%

Combo Therapy AE Verbatim	Events	Grade 1	Grade 2	N=7
Any Gr 1/Gr 2 Adverse Event				86%
Gastrointestinal disorders	2	2	-	29%
Metabolism and nutrition disorders	2	2	-	29%
Eye disorders	1	1	-	14%
Skin and subcutaneous tissue disorders	1	1	-	14%

Reversible Adverse Events

Skin

Monotherapy	Grade 1	Grade 2	Grade 3	N=22
Any Skin Toxicity				15 (73%)
Alopecia	10	5	-	15 (68%)
Hand/Foot Skin Reaction	1	4*	1*	6 (27%)
Skin Exfoliation	3	-	-	3 (13%)
Erythema	2	-	-	2 (9%)
Dermatitis	1	-	-	1 (4%)
Nail Disorder	1	-	-	1 (4%)
Pruritus	1	-	-	1 (4%)
Dry Skin	1	-	-	1 (4%)
Dermatitis Exfoliative	1	-	-	1 (4%)
Photosensitivity Reaction	1	-	-	1 (4%)
Rash	1	-	-	1 (4%)
Combo Therapy	**Grade 1**	**Grade 2**	**Grade 3**	**N=7**
Any Skin Toxicity				2 (28%)
Alopecia	1	-	-	1 (14%)
Hand/Foot Skin Reaction	-	-	1*	1 (14%)

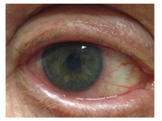


- 120 mg/m²
- Gr. 2 Hand/Foot Skin Reaction
- Onset on Cycle 3, Day 8
- Complete resolution 35 days later

* Dose Limiting Toxicities: one grade 2 and two grade 3 HFSR

Ocular

Monotherapy	Grade 1	Grade 2	Grade 3	N=22
Any Eye Toxicity				9 (41%)
Eye Pain	2	1	-	3 (13%)
Conjunctivitis	1	1	-	2 (9%)
Iritis	-	1	1*	2 (9%)
Lacrimation Increased	2	-	-	2 (9%)
Photophobia	1	1	-	2 (9%)
Dry Eye	2	-	-	2 (9%)
Corneal Edema	-	-	1*	1 (4%)
Discharge	1	-	-	1 (4%)
Corneal Scar	1	-	-	1 (4%)
Pruritus	1	-	-	1 (4%)
Ocular Hyperaemia	1	-	-	1 (4%)
Trichiasis	1	-	-	1 (4%)
Blurred Vision	-	1	-	1 (4%)
Reduced Visual Acuity	1	-	-	1 (4%)
Combo Therapy	**Grade 1**	**Grade 2**	**Grade 3**	**N=7**
Any Eye Toxicity				1 (14%)
Lacrimation Increased	1	-	-	1 (14%)

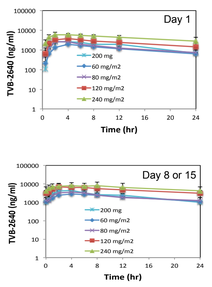


- 240 mg/m²
- DLT of Gr. 3 Corneal Edema
- Onset on Cycle 2, Day 1
- Resolution 5 days later

*Both 120 and 240mg/m2 exceed the MTD

* Dose Limiting Toxicities: one grade 3 Iritis and one grade 3 Corneal Edema

Pharmacokinetic Plasma Levels



Day 1

Cohort (n)	Dose level	T1/2 (hr)	Cmax (ng/ml)	AUC0-24 (hr*ng/ml)
1 (7)	60 mg/m²	12.3 (3.7)	1.96 (0.5)	28560 (8200)
5 (3)	80 mg/m²	14.9 (1.8)	2780 (100)	33010 (13400)
2 (8)	120 mg/m²	16.9 (6.3)	3780 (600)	55870 (15200)
3 (4)	240 mg/m²	15.8 (7.2)	6590 (1700)	102130 (24100)
6 (3)	200 mg	9.8 (2.4)	3070 (1100)	36560 (16700)

Day 8 or 15

Cohort (n)	Dose level	T1/2 (hr)	Cmax (ng/ml)	AUC0-24 (hr*ng/ml)
1 (6)	60 mg/m²	18.3 (12)	3090 (1300)	46390 (22700)
5 (3)	80 mg/m²	8.2 (2.3)	3650 (1100)	46360 (3600)
2 (8)	120 mg/m²	19.6 (10.6)	7310 (2700)	113450 (32690)
3 (4)	240 mg/m²	14.8 (5.8)	8110 (3600)	97730 (11200)
6 (3)	200 mg	7.6 (1.5)	4590 (2500)	50260 (25100)

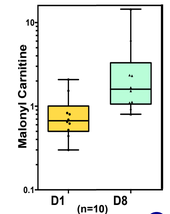
TVB-2740 (60 mg/m²) + paclitaxel	Cohort (n)	Tmax (hr)	T1/2 (hr)	Cmax (ng/ml)	AUC0-24 (hr*ng/ml)
Day 1 (TVB-2640 single agent)	5 (5)	4.0 (2.4)	9.1 (3.2)	2460 (12100)	36960 (12400)
Day 8/15 (TVB-2640 + paclitaxel)	5 (5)	4.0 (2.5)	8.8 (1.8)	2660 (11300)	33460 (15800)

Mean (SD) PK estimates for TVB-2640. Predose plasma levels on day 8/15 used to calculate AUC0-24.

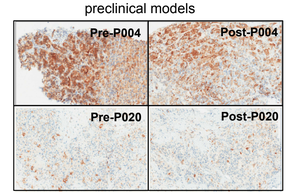
Plasma levels of TVB-2640 measured using a validated method. On day 8 (monotherapy) or 15 (combination) the predose value is plotted as the 24 hour timepoint. Mean +/- SD for n of 3 to 7 patients per monotherapy cohort.

Pharmacodynamics
Evidence of FASN Inhibition in Patients

Increased malonyl carnitine in sera consistent with FASN inhibition



pAkt expression decreased by ~50% in tumor tissue biopsies consistent with preclinical models



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 or evidence of QTc prolongation by Holter monitoring
- Skin and ophthalmological toxicity are on-target and reversible
- Ophthalmological toxicity occurs at doses much higher than the projected MTD
- Exposures of 60 mg/m² and above demonstrate target modulation and are above those associated with efficacy in preclinical models
- Skin toxicity also occurs higher than but close to the MTD
- Biomarker profile demonstrates 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
- Two patients with NSCLC (one monotherapy and 1 in combination) have evidence of stable disease after >12 weeks of treatment

Thank You to the Patients and Their Families