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

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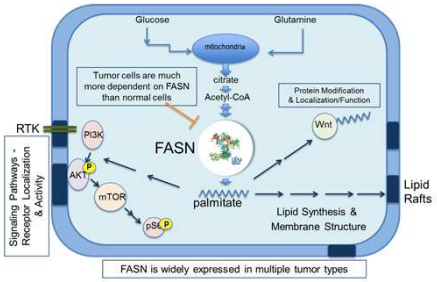
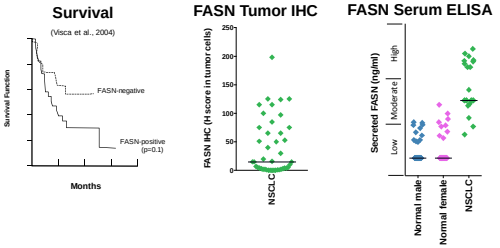
Introduction

- 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 60% (3 of 5) 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 & Key Eligibility Criteria

- 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.
- Clinically significant ophthalmologic finding, including history of dry eye, excluded.
- 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.

More information regarding study design:

Treatment Related Adverse Events

Monotherapy AE Verbatim	Events	Grade 1	Grade 2	Grade 3	N=57
Any Gr 1/Gr 2 Related Adverse Event					32 (55%)
Any 3 Gr 3 Related Adverse Event					10 (24%)
Skin and subcutaneous tissue	53	20	19	6	74%
Gastrointestinal	32	20	7	-	44%
Eye	30	19	8	3	44%
General disorders and administration site	25	8	13	4	37%
Nervous system	17	15	2	-	25%
Metabolism and nutrition	13	8	5	2	19%
Respiratory, thoracic and mediastinal	10	8	1	-	15%
Investigations	6	3	1	1	9%
Blood and lymphatic system	4	2	1	1	6%
Infections	3	1	2	-	5%
Congenital, familial and genetic	1	1	-	-	2%
Vascular	1	1	-	-	2%

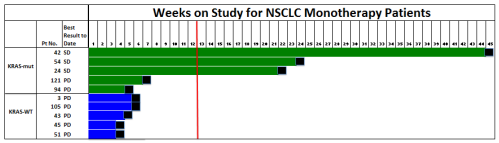
Combotherapy AE Verbatim	Events	Grade 1	Grade 2	Grade 3	N=54
Any Gr 1/Gr 2 Related Adverse Event					47 (87%)
Any 4 Gr 3 Related Adverse Event					10 (26%)
Skin and subcutaneous tissue	40	15	18	7	74%
Gastrointestinal	31	24	5	2	57%
General disorders and administration site	24	12	11	1	44%
Eye	19	12	7	-	35%
Metabolism and nutrition	13	7	5	1	24%
Respiratory, thoracic and mediastinal	12	7	3	2	22%
Blood and lymphatic system	8	-	6	2	15%
Investigations	8	5	2	1	15%
Nervous system	8	3	5	-	15%
Infections	7	2	4	1	13%
Musculoskeletal and connective tissue	6	6	-	-	11%
Ear and labyrinth	1	1	-	-	2%
Renal and urinary	1	-	1	-	2%

SAE Update:

- SAEs were unrelated except a possibly related Gr. 3 Fatigue.
- Four unrelated deaths due to disease progression.

NSCLC Patients Duration on Study

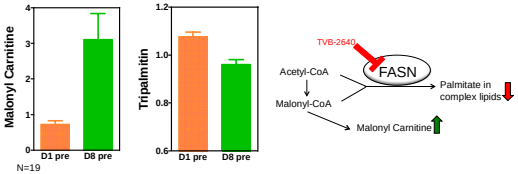
KRAS-MUT have longer duration on study than KRAS-WT



- 10 NSCLC patients enrolled on monotherapy
  - 60% KRAS-MUT on study > 12 weeks
  - 0% KRAS-WT on study > 12 weeks
- Similar plasma TVB-2640 exposure across MUT and WT patients

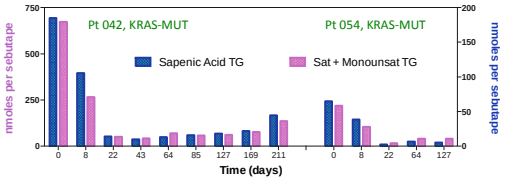
Pharmacodynamics

TVB-2640 inhibits FASN and de novo lipogenesis



N=19
Mean+/-SEM

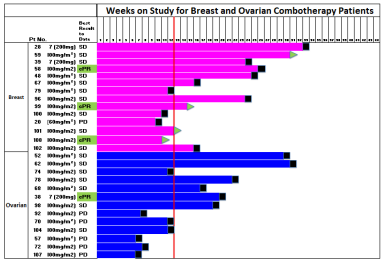
- Increased serum malonyl carnitine, and decreased serum tripalmitin were observed in 90% of patients tested, including both KRAS-MUT and KRAS-WT



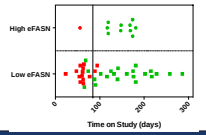
Sebum was collected using Sebutape® patches on the forehead for 30 minutes, and profiled by GC-MS and MS-flame ionization detection for lipid content at Metabolon. Normal donors were not administered TVB-2640. Similar inhibition of de novo lipogenesis observed across all patients tested (n=19).

- 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.

Breast and Ovarian Patients Duration on Study



Baseline serum FASN levels for combination



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

Green = SD
Red = PD

NSCLC Preliminary Anti-Tumor Activity

Tumor Type	Response	Previous Taxane Treatment*	Notes
TVB-2640 monotherapy			
NSCLC KRAS-MUT	SD > 12 weeks **3 of 5**	N/A	1 KRAS-Mut SD = 42 weeks
NSCLC KRAS-WT	SD > 12 weeks **0 of 5**	N/A	
TVB-2640 + paclitaxel			
NSCLC KRAS-MUT	1 Confirmed PR	None	Confirmed PR at 12 weeks; patient now at 36+ weeks
NSCLC KRAS-MUT	SD > 12 weeks **3 of 5**	**1 of 5**	
NSCLC KRAS-MUT	SD > 12 weeks **4 of 6**	**3 of 6**	1 KRAS-WT SD=16 weeks
NSCLC KRAS-WT			

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

Conclusions

- 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:
  - Breast: 3 confirmed PRs and 8 SDs ≥ 12 weeks.
  - Ovarian/Peritoneal: 1 confirmed PR and 58-98% decreases in tumor marker CA-125 in n=6 patients.
  - High baseline serum FASN associated with longest duration on study, a potential patient selection marker.

For more information, please contact: Emma.Dean@christie.nhs.uk

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