# Heavily Pre-Treated Breast Cancer Patients show Promising Responses in the First in Human Study of the First-In-Class Fatty Acid Synthase (FASN) Inhibitor, TVB-2640 in Combination with Paclitaxel

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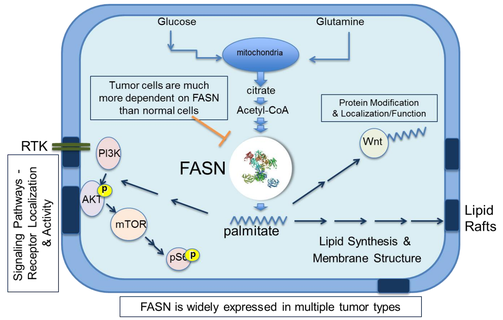
3–V BIOSCIENCES

## Introduction

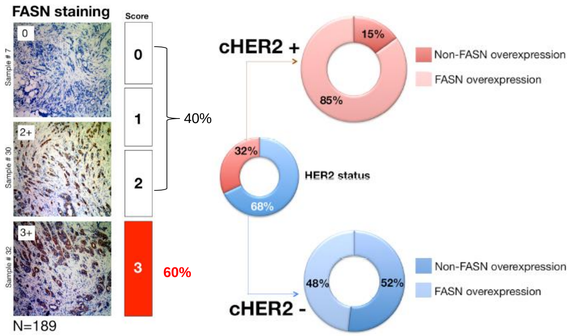
- FASN inhibition is a novel approach to cancer treatment.
- Selective disruption of palmitate biosynthesis leads to apoptosis in many tumor cells.
- FASN is highly expressed in breast tumors and correlates with poor prognosis (Visca et al., 2004).
- TVB-2640 is the only selective FASN inhibitor in clinical trials.
- Preliminary data show:
  - -3 confirmed RECIST partial responses (cPR)
  - -Multiple cases of prolonged stable disease (SD) (≥16 wks) with 1 continued SD at week 65+
  - -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 Breast

Immunophenotypic classification of FASN over-expression in HER2- and HER2+ invasive breast carcinoma. (Menendez et al., 2006).




N=189

HER2: 0-2+: Non- FASN overexpression

HER2: 3+ : FASN overexpression

## 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. 15 hr and was unaffected by paclitaxel.

**More information regarding study design:**

## Safety

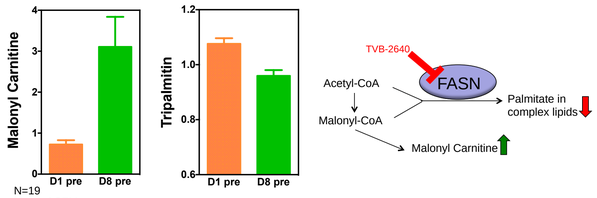
| Adverse Event (related) | Monotherapy N=74 all enrolled N=54 ≤ the MTD | | | | Combination w Paclitaxel N=55 all enrolled N= 48 ≤ the MTD | | | |
|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3+ | N (%) | G1 | G2 | G3+ | N (%) |
| Any G1/G2 related AE | | | | 51 (68.9) | | | | 49 (89.1) |
| Any G3 or > related AE | | | | 19 (25.7) | | | | 17 (30.9) |
| Skin and subcutaneous ≤ the MTD | 24 (44.4) | 16 (29.6) | 6 (11.2) | 45 (83.3) | 14 (27.4) | 14 (32.5) | 7 (16.2) | 35 (72.9) |
| Eye Disorders ≤ the MTD | 16 (29.6) | 10 (18.5) | - | 24 (44.4) | 12 (20) | 5 (11.6) | - | 17 (35.4) |
| Gastrointestinal ≤ the MTD | 20 (37.0) | 6 (11.1) | - | 26 (48.0) | 21 (43.7) | 3 (6.9) | 2 (4.6) | 27 (56.2) |
| **SAE*** | **G1** | **G2** | **G3+** | **N (%)** | **G1** | **G2** | **G3+** | **N (%)** |
| Fatigue | - | - | 1 (1.4) | 1 (1.4) | - | - | - | - |
| 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$^2$

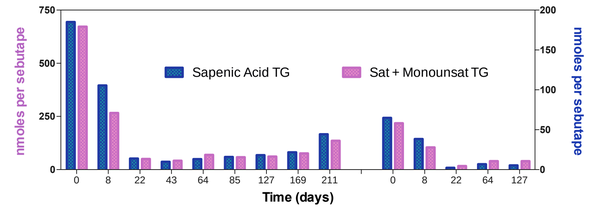
**1 grade 5

## Pharmacodynamics

### TVB-2640 inhibits FASN and de novo lipogenesis



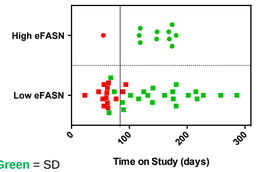

Increased serum malonyl carnitine, and decreased serum tripalmitin were observed in 90% of patients tested.




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.

*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).*

### Baseline serum FASN levels for all combination patients

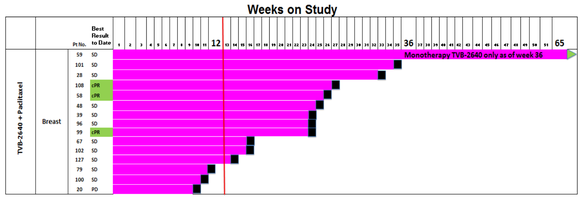



Green = SD

Red = PD

- 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

## Duration on Study




## Breast Preliminary Anti-Tumor Activity

| Tumor Type | Hormone/Her2 Status | Response | Notes |
|---|---|---|---|
| **RECIST Confirmed Partial Responders (cPR): 3 of 15** | | | |
| **Breast (#058)** | ER+, PR+, Her2+ | cPR | -Time on study =25 weeks<br>-Previous docetaxel best result = CR |
| **Breast (#099)** | ER-, PR-, Her2+ | cPR | -Time on study =23 weeks<br>-Previous docetaxel best result = SD |
| **Breast (#108)** | ER+, PR+, Her2- | cPR | -Time on study =26 weeks<br>-Previous docetaxel best result = UNK (adjuvant setting) |
| **Stable Disease: 11 of 15 for 10+ weeks** | | | |
| **Breast (#059)** | ER+, PR+ , Her2- | SD | -Time on study =69+ weeks paclitaxel DC'ed at week 36 and monotherapy TVB-2640 treatment continues<br>-Previous paclitaxel best result = SD |

- Patients are heavily pretreated and all but 2 of 15 are considered taxane resistant
- Average number of prior regimens (including taxanes) = 7

## Conclusions

- TVB-2640 combined with weekly paclitaxel resulted in multiple RECIST cPRs and prolonged SD in 93% of patients treated.
- 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. Though not observed in monotherapy, symptomatic pneumonitis has been observed in 5 pts treated in combination with paclitaxel.
- Biomarker analysis demonstrates target engagement (FASN inhibition), and inhibition of lipogenesis in patients.
- Further exploration of biological activity is underway including Investigator Sponsored Trials of TVB-2640 in monotherapy and in combination treatment.

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Thank You to the Patients and Their Families