# Biomarker and PK/PD analyses of first-in-class FASN inhibitor TVB-2640 in a first-in-human phase 1 study in solid tumor patients

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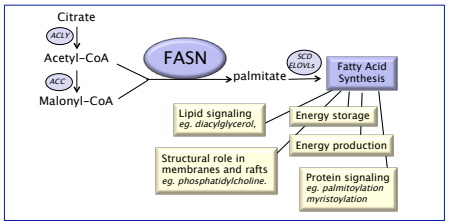
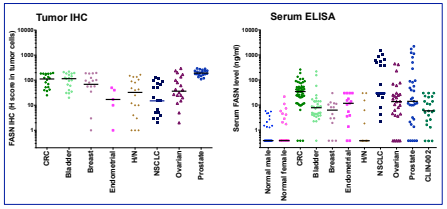
## Fatty Acid Synthase (FASN)

- Central mediator of neoplastic lipogenesis
- Generates palmitate, the building block of long chain fatty acids, providing a mechanism to convert glucose and other carbon sources into lipids to support cancer cell signaling
- Upregulated in tumor vs normal tissue, and correlates with poor prognosis in certain tumor types




## FASN expression survey

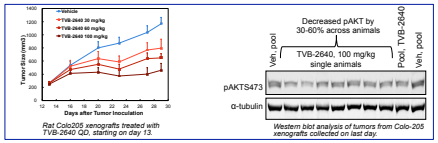



- >300 tumor samples and cancer patient serum tested for FASN expression (unmatched)
- FASN levels markedly higher in both tumor tissue and serum from cancer patients compared to normal donors. NSCLC, CRC and prostate among the highest expression. Of 27 normal tissues tested, only spleen, tonsil and thymus had an IHC signal
- FASN expression in tumor and serum is being tested in ongoing Phase 1 study 3V2640-CLIN-002

*FFPE sections stained with FASN CST rabbit Ab C20G5) using a validated method. H-score in tumor tissue was quantitated by standard pathology review including staining intensity graded 0-3+ and % cells positive. ELISA for FASN was performed on human sera using a commercially available ELISA kit (Immtech). Banked tumors and cancer patient sera were purchased from commercial sources. CLIN-002 samples are from ongoing Phase 1 study, several ongoing re-assay as exceed ULQ. Line indicates median. N of 5 to 20 per tumor type for IHC, and 14 to 55 for ELISA.*

## TVB-2640, FASN inhibitor

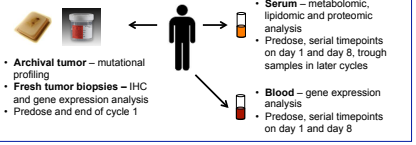
- Oral, first-in-class, small-molecule reversible inhibitor of FASN.
- $IC_{50}$ < 0.05 µM.
- *In vitro* and *in vivo* anti-tumor effects previously shown.




*Rat Colo205 xenografts treated with TVB-2640 QD, starting on day 13.*

*Western blot analysis of tumors from Colo-205 xenografts collected on last day.*

## Biomarker Sampling in FIH Phase I Solid Tumor Study 3V2640-CLIN-002

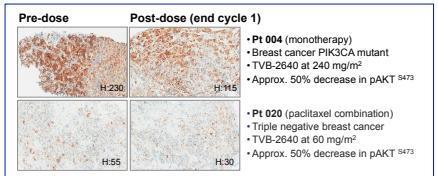


- **Archival tumor** – mutational profiling
- **Fresh tumor biopsies –** IHC and gene expression analysis
- Predose and end of cycle 1

- **Serum** – metabolomic, lipidomic and proteomic analysis
- Predose, serial timepoints on day 1 and day 8, trough samples in later cycles
- **Blood** – gene expression analysis
- Predose, serial timepoints on day 1 and day 8

- Multicenter, open label, ongoing phase 1 study
- Oral, once daily with 21/28 day continuous cycles
- To date, 23 patients enrolled in monotherapy dose escalation at dose levels of 60, 80, 120, 240 mg/m$^2$ or 200 mg flat dose. 7 patients enrolled in combination with paclitaxel.

## Tumor IHC in Phase 1



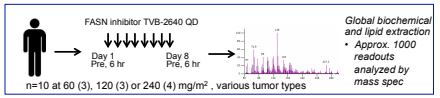

- **Pt 004** (monotherapy)
- Breast cancer PIK3CA mutant
- TVB-2640 at 240 mg/m$^2$
- Approx. 50% decrease in pAKT $^{S473}$

- **Pt 020** (paclitaxel combination)
- Triple negative breast cancer
- TVB-2640 at 60 mg/m$^2$
- Approx. 50% decrease in pAKT $^{S473}$

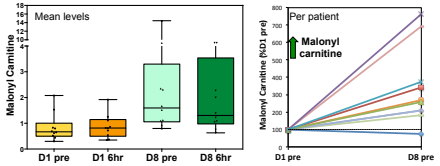
*FFPE sections stained with pAKT $^{S473}$ (Dako, rabbit clone 14-5 )(CST rabbit Ab C20G5) using a validated IHC method. H-score in tumor quantitated by standard pathology review (staining intensity graded 0-3+ and % cells positive). 20x.*

- 2/2 evaluable biopsy pairs show inhibition of pAKT$^{S473}$
- pAKT$^{S473}$ inhibition also observed in preclinical rat xenograft
- 1 additional pair did not show pAKT inhibition but predose was several weeks prior to first dose, and disparate tumor locations

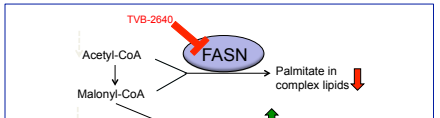
## Malonyl Carnitine Response to FASN Inhibition

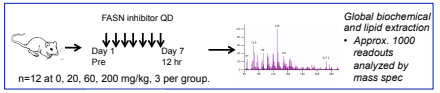



n=10 at 60 (3), 120 (3) or 240 (4) mg/m$^2$ , various tumor types

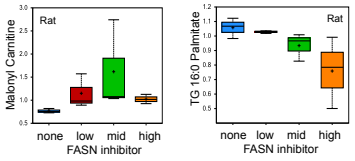



- 9/10 patients showed increased malonyl carnitine on day 8 relative to day 1, up to 7-fold with mean of 3.4-fold
- p<0.05 for D8 pre versus D1 pre for 120 and 240 mg/m$^2$ dose levels
- Clear evidence of FASN pathway inhibition in serum
- Similar effect in rats treated with FASN inhibitor as below

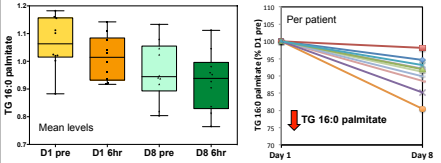



n=12 at 0, 20, 60, 200 mg/kg, 3 per group.

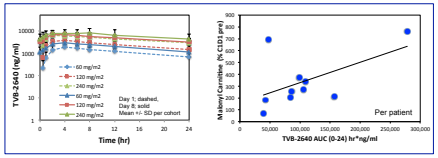



## Serum Palmitate Response to FASN Inhibition




- 9/10 patients tested show decreased TG16:0 palmitate on day 8
- p<0.05 for D8 pre versus D1 pre overall, and for 120 and 240 mg/m$^2$ dose levels
- Other palmitate derivatives also decreased (not shown)
- Preliminary analysis shows good correlation with TVB2640 exposure for malonyl carnitine and TG 16:0 palmitate

## PK/PD




## Summary

- TVB-2640 is a first-in-class FASN inhibitor currently in a Phase 1 oncology clinical study 3V2640-CLIN-002
- Excellent QD oral PK profile
- Pharmacodynamic biomarkers identified in patient sera and target engagement observed in ongoing Phase 1 study
  - Increased malonyl carnitine
  - Decreased TG16:0 palmitate
  - Good correlation with TVB-2640 plasma exposure
  - Similar pharmacodynamic activity in rat model
- Pharmacodynamic activity shown in patient tumors
  - Decreased pAKT S473 in 2/2 patients, also in xenografts
- Comprehensive biomarker analysis is underway with analysis in additional patients in ongoing 3V2640 CLIN-002 Phase 1 study
- Poised to understand the clinical impact of FASN inhibition

*C7203. Patel et al. First-In-Human Study of the First-In-Class Fatty Acid Synthase (FASN) Inhibitor, TVB-2640. Monday April 20, 8:00 AM - 12:00 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*

**Thank you to the patients and their families**

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