

# A First-In-Human Study of the First-In-Class Fatty Acid Synthase (FASN) Inhibitor TVB-2640

## Results of Dose Escalation in Mono and Combination and Evidence of Preliminary Activity

A. Brenner<sup>1</sup>, J. Infante<sup>2</sup>, M. Patel<sup>3</sup>, HT. Arkenau<sup>4</sup>, G. Mak<sup>4</sup>, E. Borazanci<sup>5</sup>, G. Falchook<sup>6</sup>, L.R. Molife<sup>7</sup>, S. Pant<sup>8</sup>, E. Dean<sup>9</sup>, L. Pelosof<sup>10</sup>, J. Lopez<sup>7</sup>, S. Jones<sup>2</sup>, C. Rubino<sup>11</sup>, W. McCulloch<sup>12</sup>, V. Zhukova-Harrill<sup>13</sup>, G. Kemble<sup>12</sup>, M. O'Farrell<sup>12</sup>, H. Burris<sup>2</sup>

<sup>1</sup>Cancer Therapy & Research Center, Texas, USA, <sup>2</sup>Sarah Cannon Research Institute, Tennessee Oncology, Tennessee, USA, <sup>3</sup>Florida Cancer Specialists/Sarah Cannon Research Institute, Florida, USA, <sup>4</sup>Sarah Cannon Research Institute, London; UK,

<sup>5</sup>HonorHealth Research Institute, Arizona, USA, <sup>6</sup>Sarah Cannon Research Institute at HealthONE, Colorado, USA, <sup>7</sup>The Royal Marsden/Institute of Cancer Research, Sutton, UK, <sup>8</sup>Sarah Cannon Research Institute, Univ. of Oklahoma, USA,

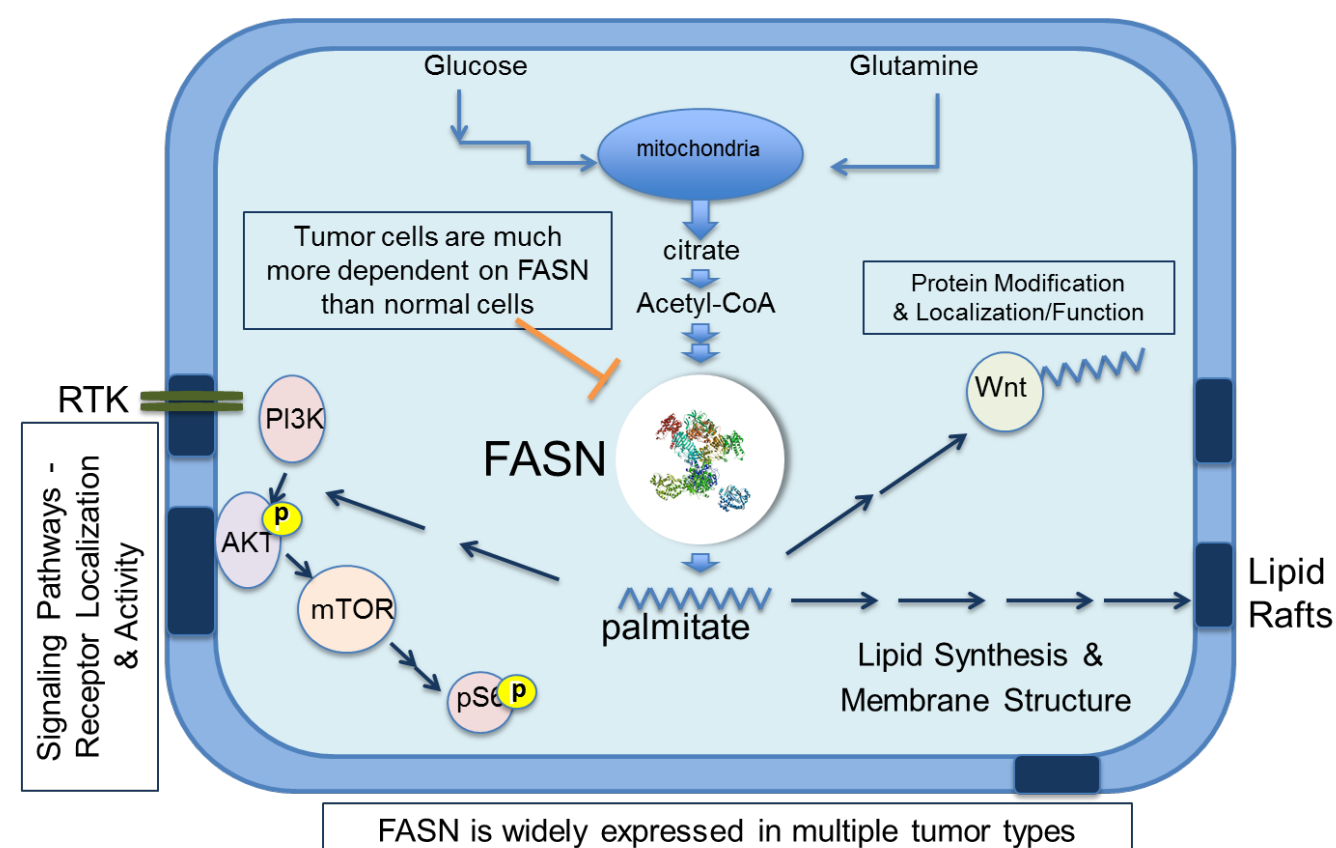
<sup>9</sup>The Christie NHS Foundation Trust / University of Manchester, UK, <sup>10</sup>University of Texas Southwestern, Texas, USA, <sup>11</sup>ICPD, Buffalo, New York, USA, <sup>12</sup>V Biosciences, California, USA, <sup>13</sup>Chiltem Oncology, Medical Affairs, North Carolina, USA



### Introduction

- FASN inhibition is a novel approach to cancer treatment.
- Selective disruption of palmitate biosynthesis leads to apoptosis in many tumor cells.
- TVB-2640 is the only selective FASN inhibitor in clinical trials.
- Broadly active, oral, once-daily treatment.
  - Monotherapy activity in multiple solid tumors, including NSCLC.
  - Well tolerated with grade 1-2 adverse events at the MTD; even when combined with paclitaxel.
- Safety profile and schedule enable combination regimens.
  - Synergistic activity in combination with paclitaxel pre-clinically.
- No discernible PK interference of either drug.

### FASN-Integrated Target in Tumor Biology



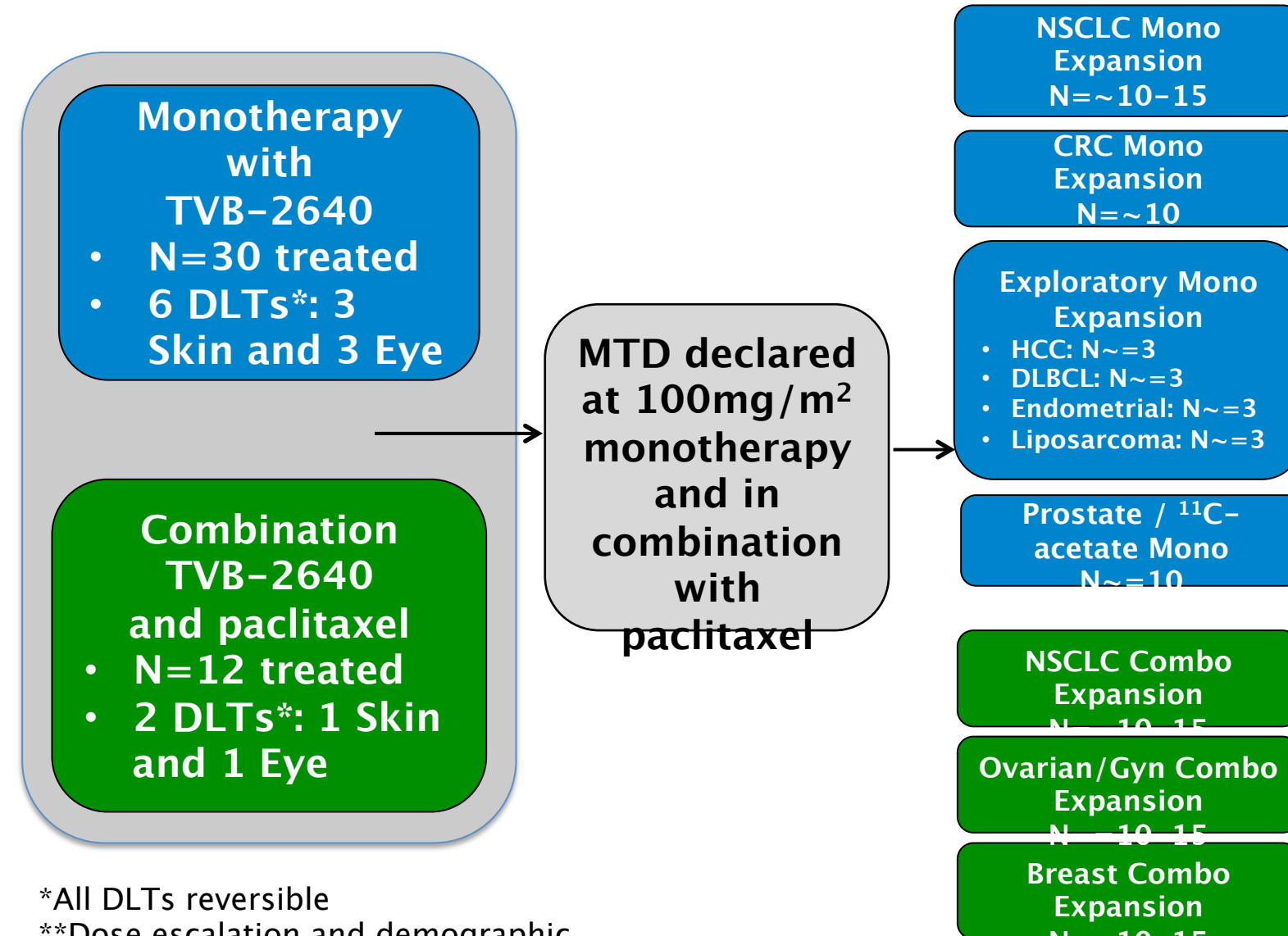
### Objectives

- 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

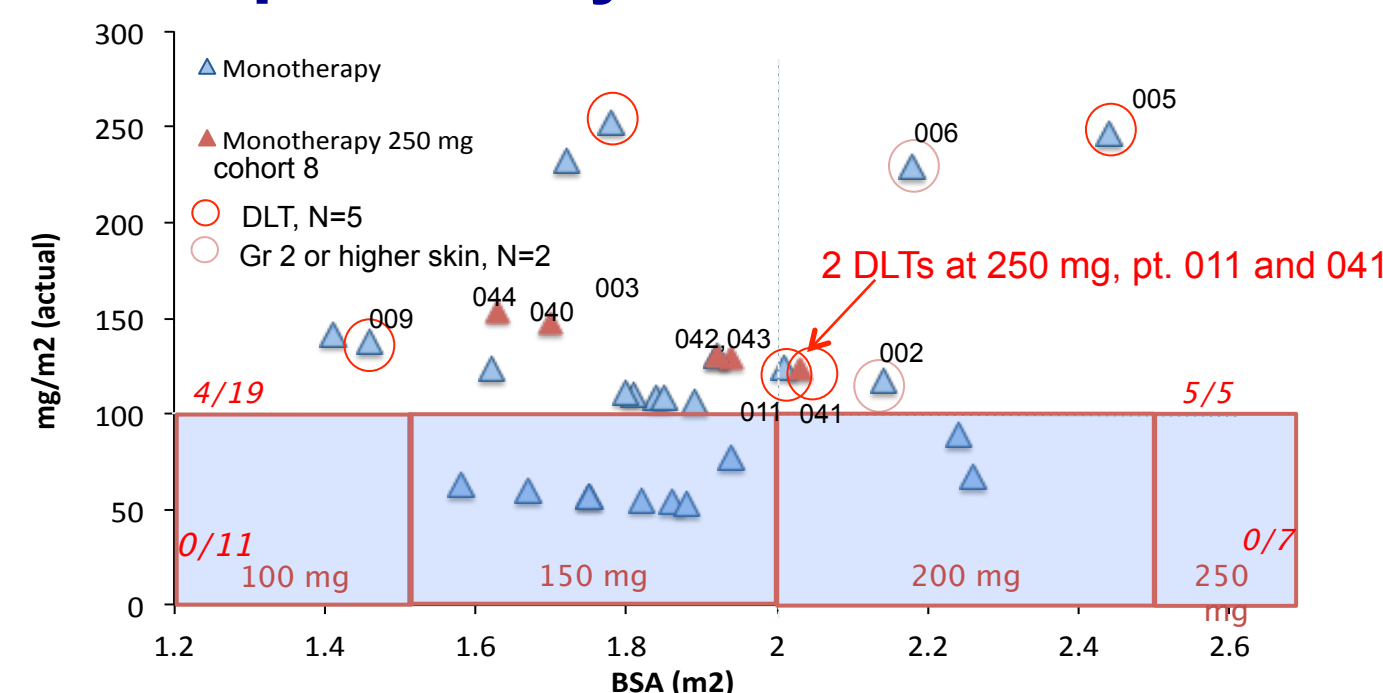
- Oral, once daily; DLT period 21 days or 28 days with chemo; continuous cycles
- Adult patients (ECOG 0-1), with pathologically confirmed metastatic or advanced-stage solid tumors, met standard accepted ph-1 In/Exclusion criteria
- Clinically significant ophthalmologic finding, including history of dry eye excluded

### Escalation and Expansions



\*All DLTs reversible  
\*\*Dose escalation and demographic details: Brenner et al, ASCO 2015

### Exposure by Dose and DLT's



### Treatment Related Adverse Events

Monotherapy (N=30)	Events	Grade 1/2	Grade 3	Grade 4	N=44
<b>Any Treatment Related Adverse Event</b> 37 (84%)					
Skin and subcutaneous	30	28	2	-	68%
Gastrointestinal	21	21	-	-	50%
Eye	20	16	3	1	46%
General disorders and administration site conditions	17	16	2	-	39%
Nervous System	10	10	-	-	23%
Metabolism and nutrition	8	8	2	-	19%
Respiratory, thoracic and mediastinal	3	3	-	-	7%
Infections	2	2	-	-	5%
Investigations	1	1	-	-	2%
Constitutional, familial and genetic	1	1	-	-	2%
Blood and lymphatic system	1	1	-	-	2%

**SAE Update:** SAEs: All unrelated except one possibly related Gr. 3 Fatigue. Four unrelated deaths due to disease progression.

#### More Information

Quick reference code:

Brenner et al, AACR-NCI-EORTC 2015

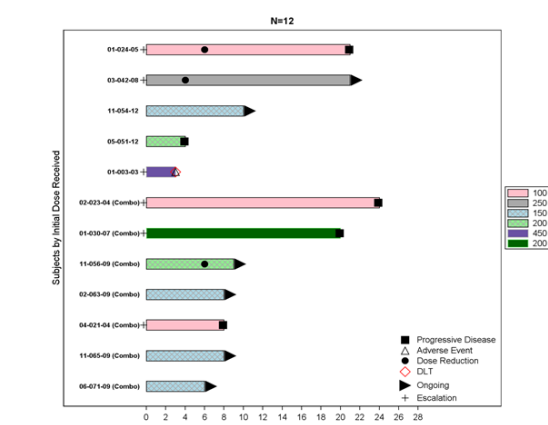


### Preliminary Anti-Tumor Activity with TVB-2640

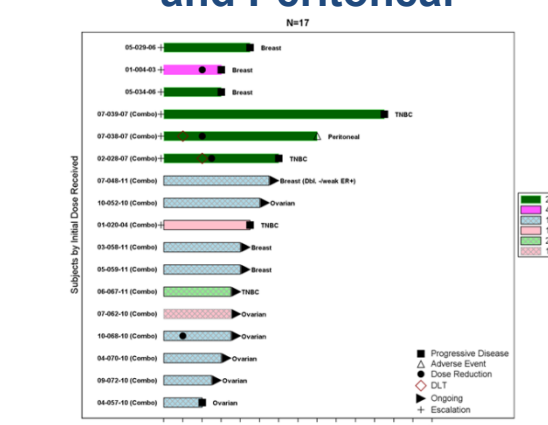
Tumor Type	Response	Tumor Markers	Previous Taxane Treatment *	Notes
<b>Partial Responders (All treated in combination with paclitaxel)</b>				
Primary Peritoneal	Confirmed PR	CA-125 58% at C2	Yes	Confirmed PR at 16 weeks
Breast (ER+/PR+/HER2+)	uPR	CA-15-3 No significant changes detected	Yes	Confirmation scan pending
NSCLC (KRAS mut.)	uPR	N/A	No	Confirmation scan pending
<b>Stable Disease (&gt;12 weeks)</b>				
<b>TVB-2640 monotherapy</b>				
NSCLC	SD: 2 of 3	N/A	1 of 3	1 KRAS Mut. SD=21 weeks 1 KRAS UNK SD=21 weeks
Liposarcoma	SD: 1 of 1	N/A	N/A	SD=13 weeks
<b>TVB-2640 + paclitaxel</b>				
NSCLC	SD: 2 of 3	N/A	3 of 3	1 KRAS WT SD=16 weeks 1 KRAS Mut. SD=24 weeks
Breast	SD: 2 of 3	CA-15-3 No significant changes detected	3 of 3	2 TNBC subjects both at SD=24 weeks
Ovarian	Too early	CA-125 1=79% at C1 1=98% at C2 1=70% at C2	7 of 8 1 of 8 unknown	8 patients enrolled 3 of 3 w/ decreased C-125, data for 5 additional pending

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

#### NSCLC

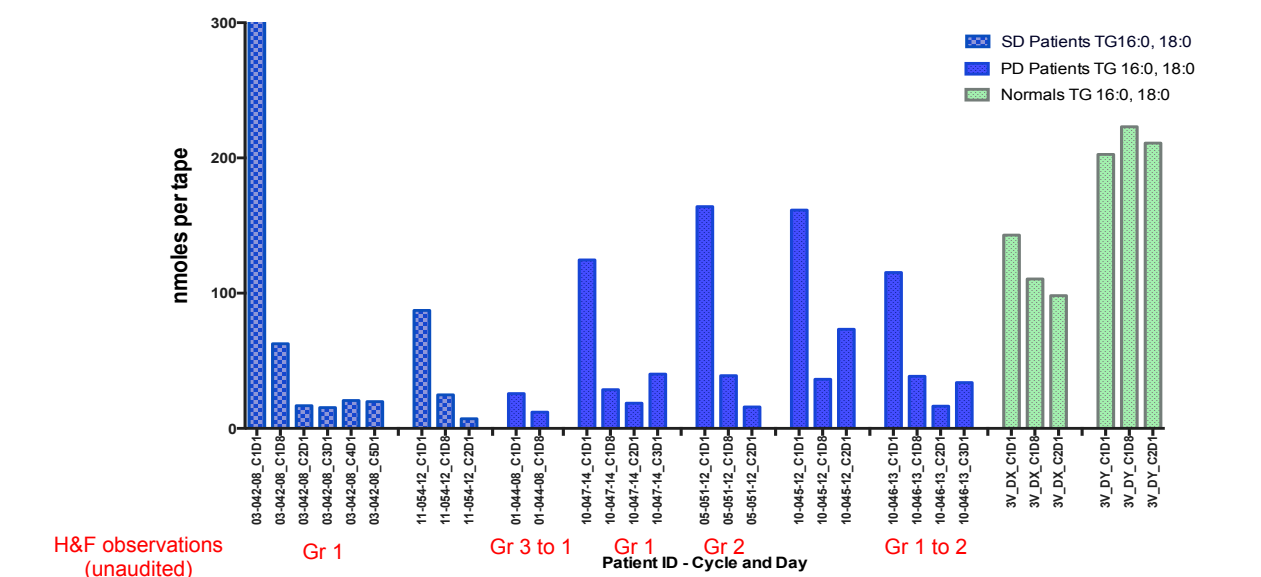


#### Breast, Ovarian and Peritoneal



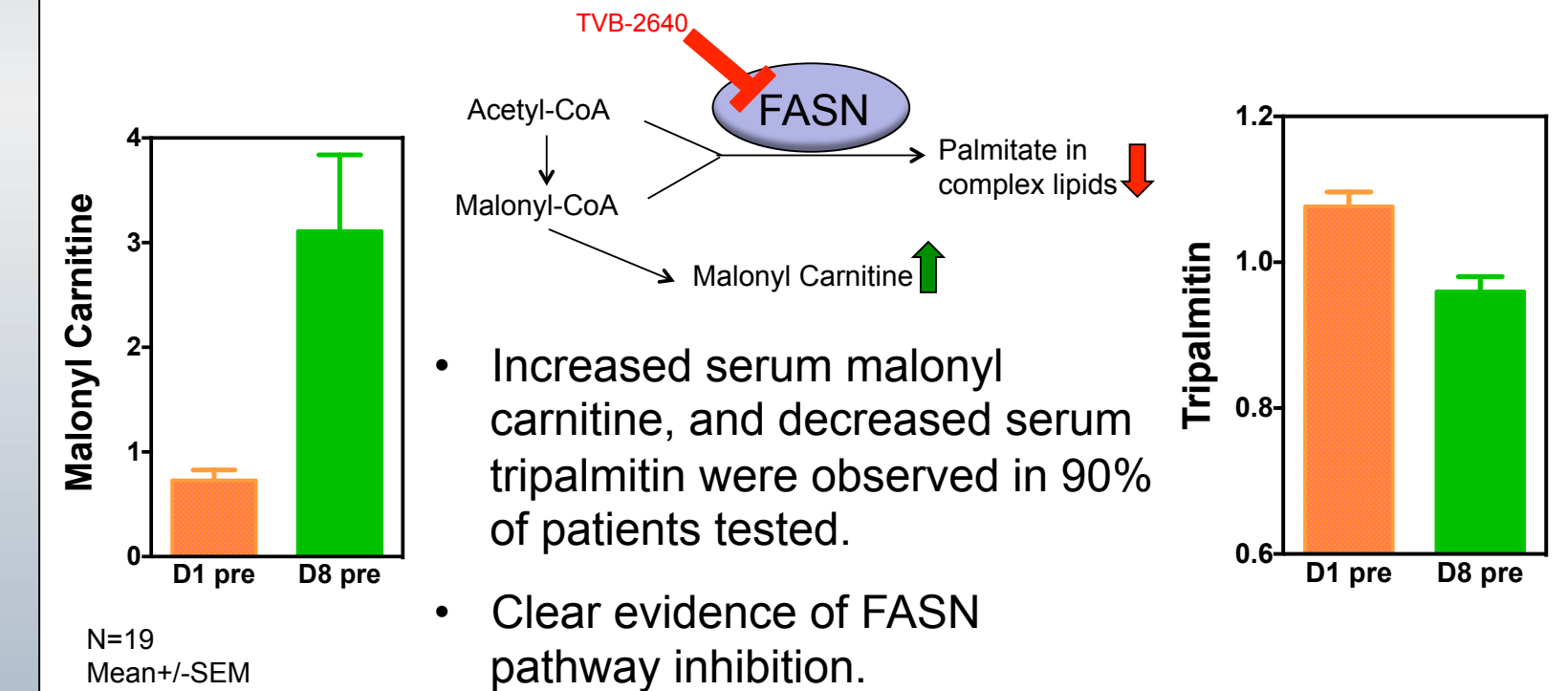
### Pharmacodynamics

#### Changes in Sebum Lipids



- Significant reductions in sebum saturated triglycerides were observed after one week of treatment and generally remained low through subsequent cycles of treatment.

### FASN pathway inhibition



- Increased serum malonyl carnitine, and decreased serum tripalmitin were observed in 90% of patients tested.
- Clear evidence of FASN pathway inhibition.

### Conclusions

- An MTD of 100mg/m<sup>2</sup> TVB-2640 has been defined for both mono and paclitaxel combination therapy.
- 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; no additive toxicity with paclitaxel.
- Biomarker analysis demonstrates target engagement (FASN inhibition), and inhibition of lipogenesis in patients.
- Promising early signs of clinical activity have been seen in heavily pre-treated patients, in monotherapy and in combination with paclitaxel:
  - Three PRs (one confirmed) and several SDs beyond 12 weeks.
  - Significant decreases in tumor marker CA-125.
- Further exploration of biological activity is underway in expansion cohorts.

Thank You to the Patients and Their Families