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

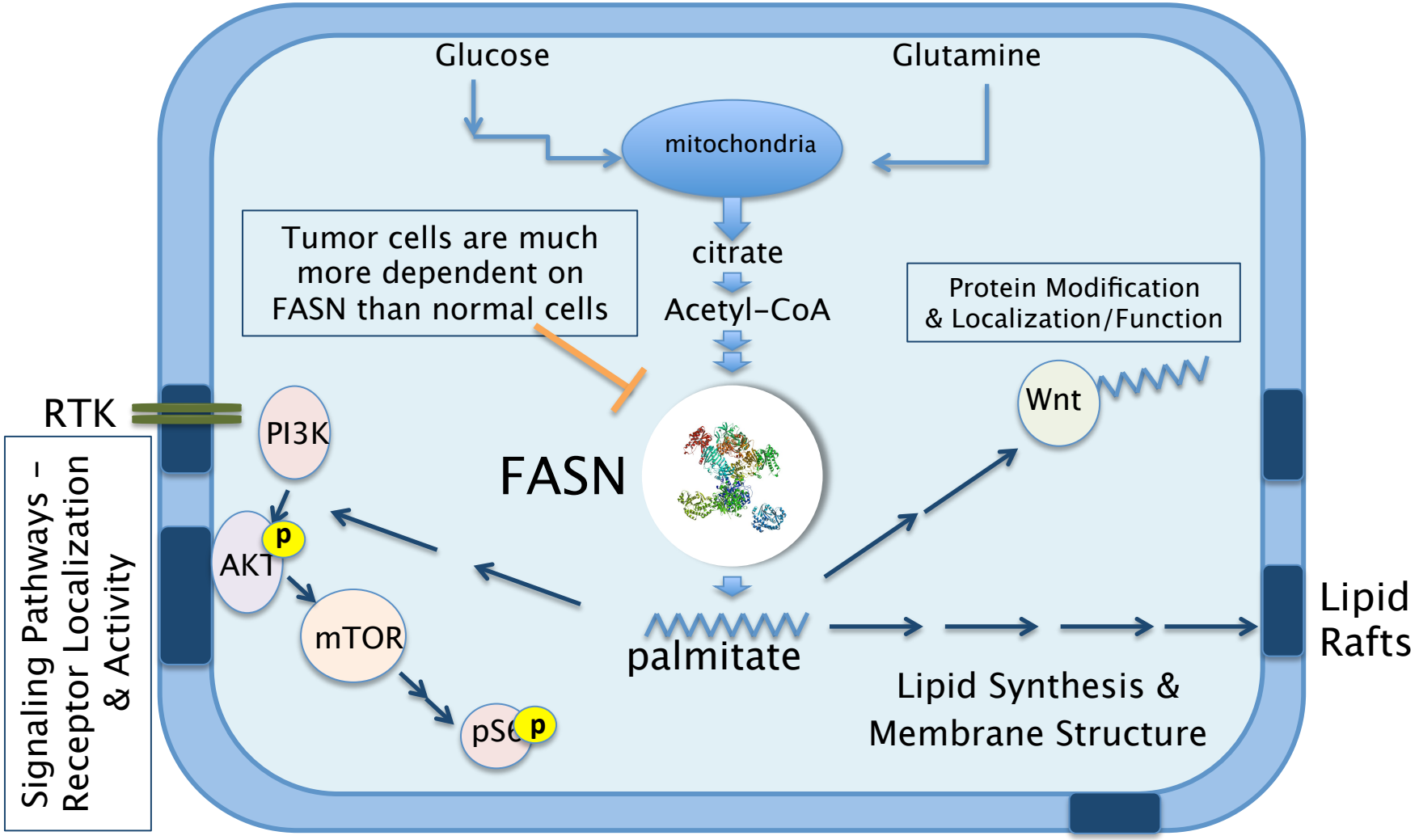
J. Infante[1], M. Patel[2], D. Von Hoff[3], S. Jones[1], H. Burris[1], A. Brenner[4], C. Rubino[5], W. McCulloch[6], V. Zhukova-Harrill[7], M. Parsey[6]

[1]*Sarah Cannon Research Institute, Tennessee Oncology, Tennessee, USA*
[2]*Sarah Cannon Research Institute, Florida Cancer Specialists, Sarasota, USA*
[3]*Scottsdale Healthcare Research Institute, Oncology, Scottsdale, USA*
[4]*Cancer Therapy & Research Center, Oncology, San Antonio, USA*
[5]*Institute for Clinical Pharmacodynamics, Buffalo, USA*
[6]*3-V Biosciences, Clinical Development, Menlo Park, USA*
[7]*Chiltern Oncology, Medical Affairs, North Carolina, USA*

Disclosure Slide

- Presenter: J. Infante
  - Disclosures: None

FASN – Integrated Target in Tumor Cell Biology

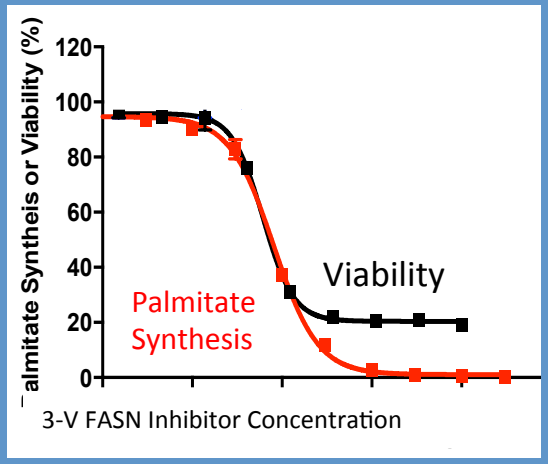


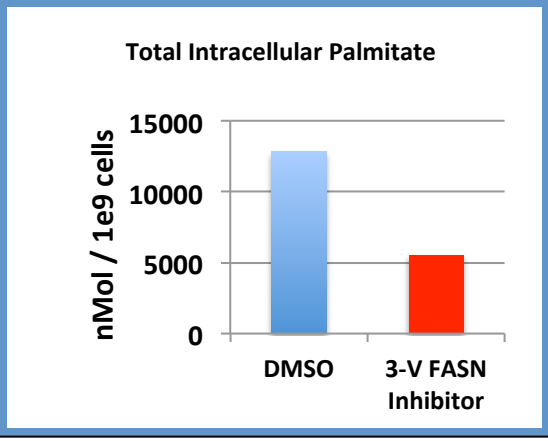
FASN is widely expressed in multiple tumor types

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

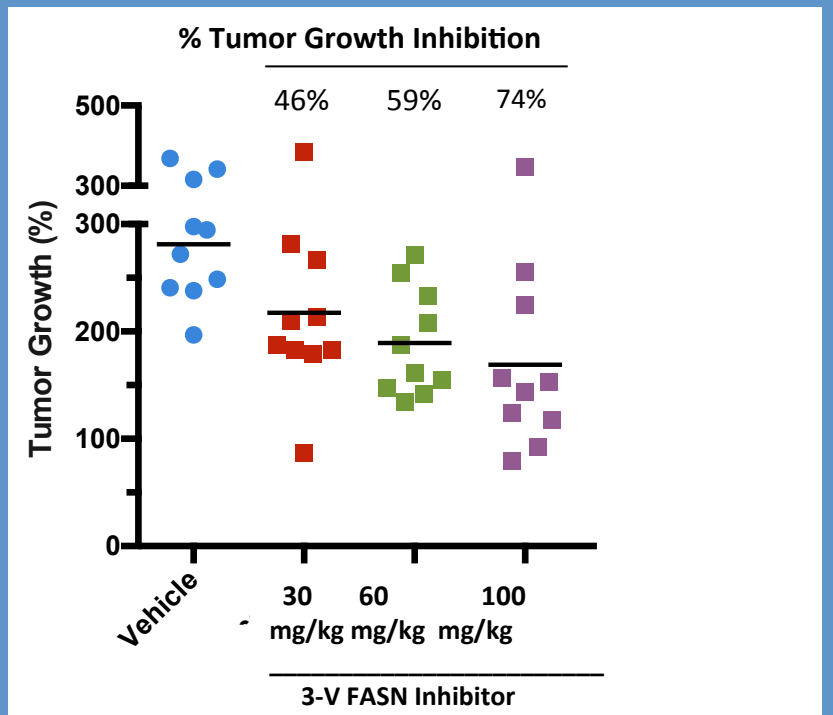
- Potent, reversible, and specific (IC_{50} < 0.05 μM), small molecule inhibitor (<440 M_W)

Inhibition of FASN kills Tumor Cells





3-V FASN Inhibitor Reduces Growth of OVCAR8 Tumors *in vivo*



Objectives

- Primary
  - Safety, MTD, recommended Phase II dose (monotherapy and in combination with chemo)
- Secondary
  - Pharmacokinetics, preliminary anti-tumor activity
- Exploratory
  - Biomarkers of response, assess any variability in TVB-2640 PK

Study Design

- Multicenter, open label, phase 1 study
- Oral, once daily with 21 day continuous cycles
- Single patient, accelerated titration followed by “3+3” design after ≥ Grade 2 toxicity

Data as of 31 October 2014

Key Eligibility Criteria

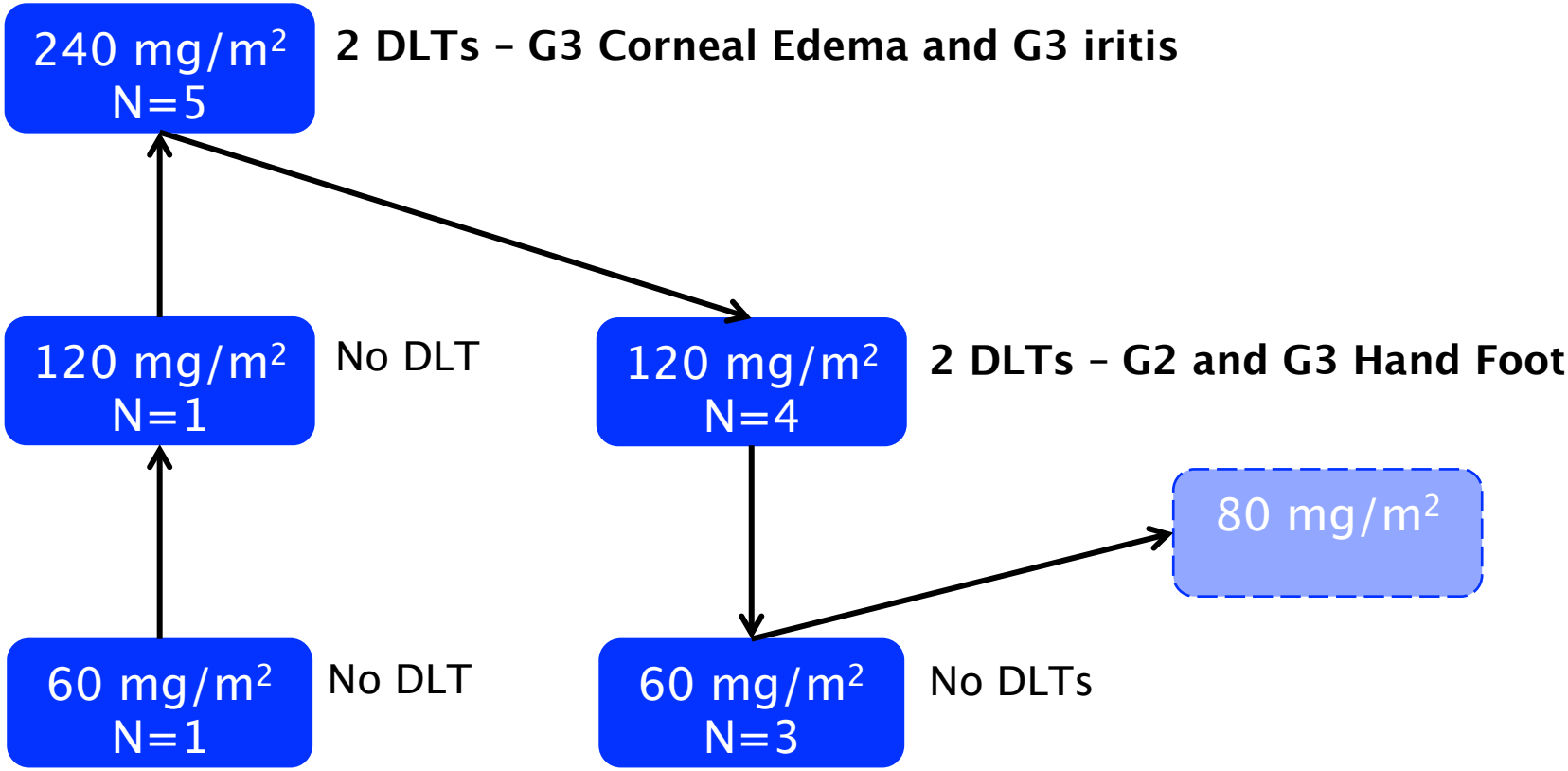
- Inclusion
  - Adult patients with pathologically confirmed metastatic or advanced-stage solid malignant tumor
  - Patient may have received up to 4 prior regimens
  - ECOG 0-1
- Exclusion
  - History of dry eye
  - Clinically significant ophthalmologic finding
  - History of risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome)

Baseline Characteristics

N=14 Patients		
Age (years)	Median	64
	Range	50–78
Gender	Male	8
	Female	6
Race	Caucasian	13
	Asian	1
ECOG Performance Status	0	7
	1	7
Number of Previous Regimens	0–2	6
	3–4	6
	5+	2

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

Monotherapy Dose Escalation



All DLTs reversible

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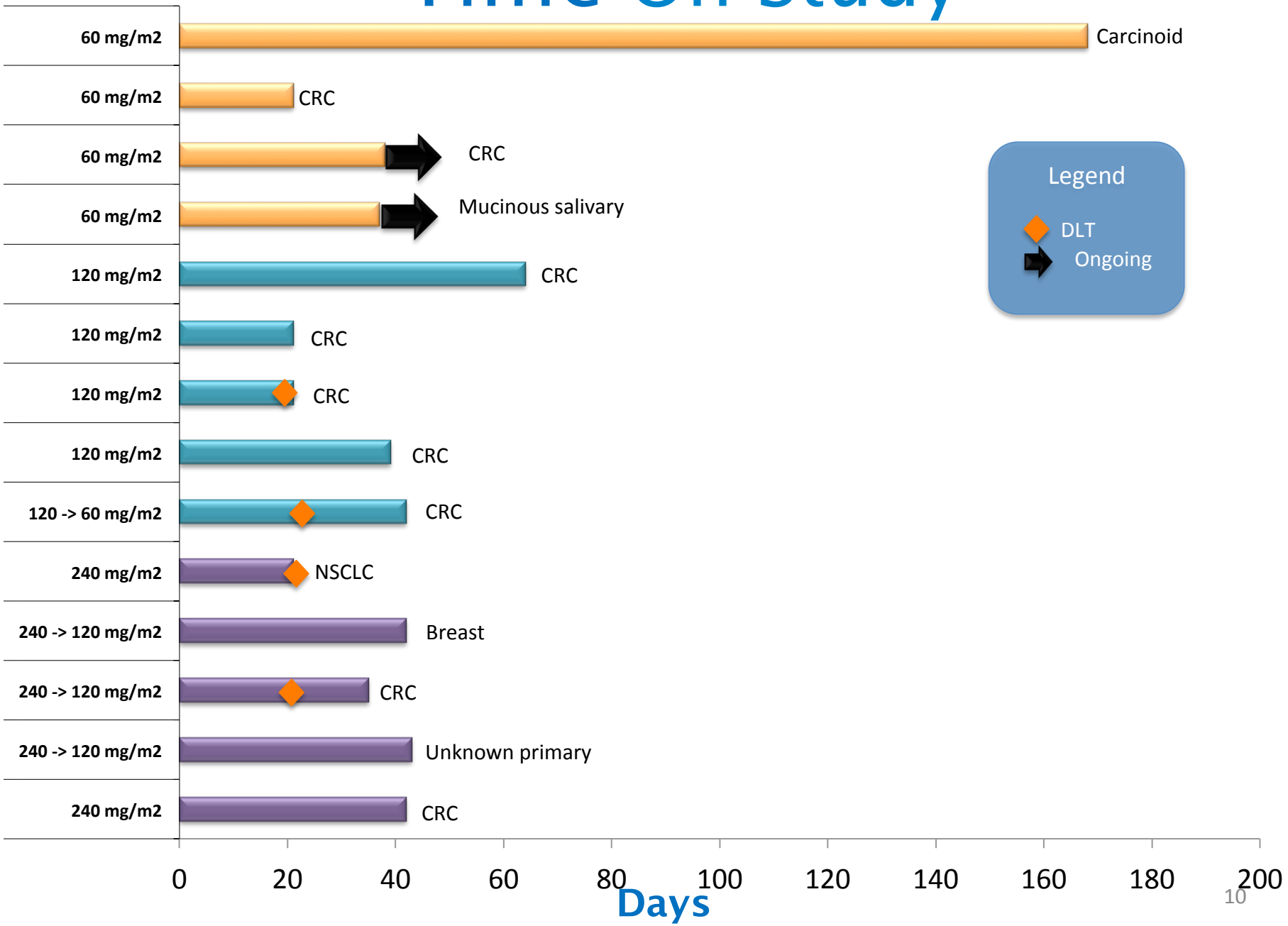
Time On Study



Related AEs = Gr 1/2

N = 14; N in Table = 14

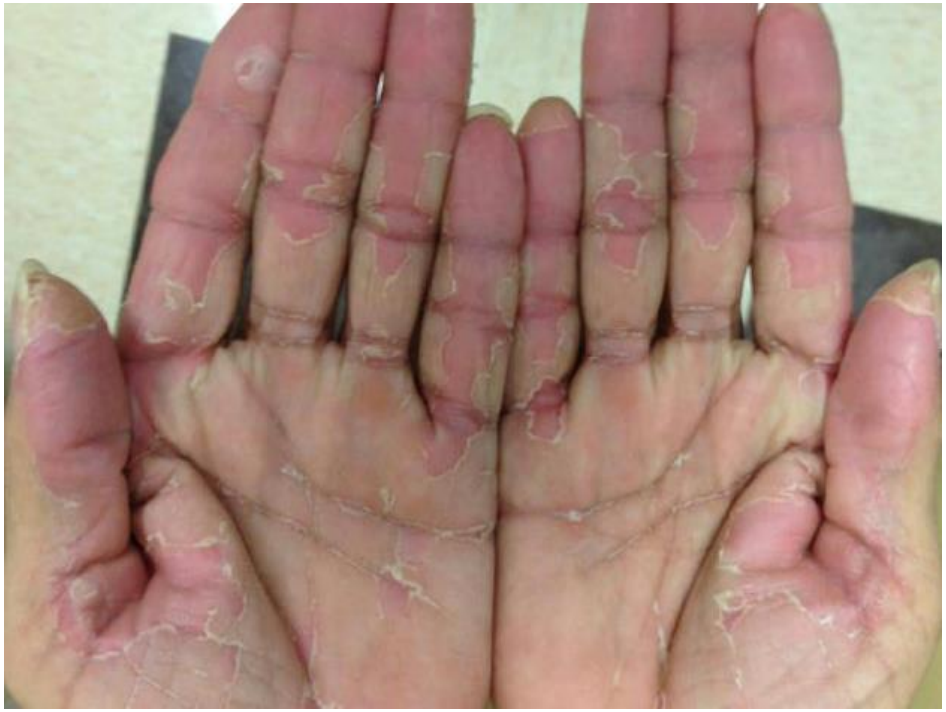
AE Verbatim	N	Grade 1	Grade 2	%
Hand/Foot Skin Reaction	12	5	7	**86%**
Alopecia	10	6	4	**71%**
Fatigue/Weakness	8	3	5	**57%**
Iritis/Corneal Edema/Conjunctivitis	5	4	1	**36%**
Diarrhea	4	3	1	**29%**
Anorexia/Appetite Loss	4	4	–	**29%**
Oral Mucositis/Mouth Tenderness	4	4	–	**29%**
Eye Pain	3	3	–	**21%**
Neuropathy (fingers)	3	2	1	**21%**
Blurry Vision	3	2	1	**21%**
Drainage/Watery Eye	3	3	–	**21%**
Vomiting	2	1	1	**14%**
Nausea	2	2	–	**14%**
Dry Eye	2	2	–	**14%**
Light Sensitivity	2	1	1	**14%**
Facial Erythemia	2	2	–	**14%**
Change in Taste	2	2	–	**14%**
Fever	2	–	2	**14%**
Trichiasis	1	1	–	**7%**

AE: Skin

Skin	Grade 1	Grade 2	Grade 3	N=14
Any Skin Toxicity				10 (71%)
Alopecia	4	4	–	8 (57%)
Hand/Foot Skin Reaction	–	4*	1*	5 (35%)
Erythema	2	–	–	2 (14%)
Skin Exfoliation	2	–	–	2 (14%)
Dermatitis	1	–	–	1 (7%)
Nail Disorder	1	–	–	1 (7%)
Photosensitivity Reaction	1	–	–	1 (7%)
Pruritus	1	–	–	1 (7%)
Rash	1	–	–	1 (7%)

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

AE: Skin



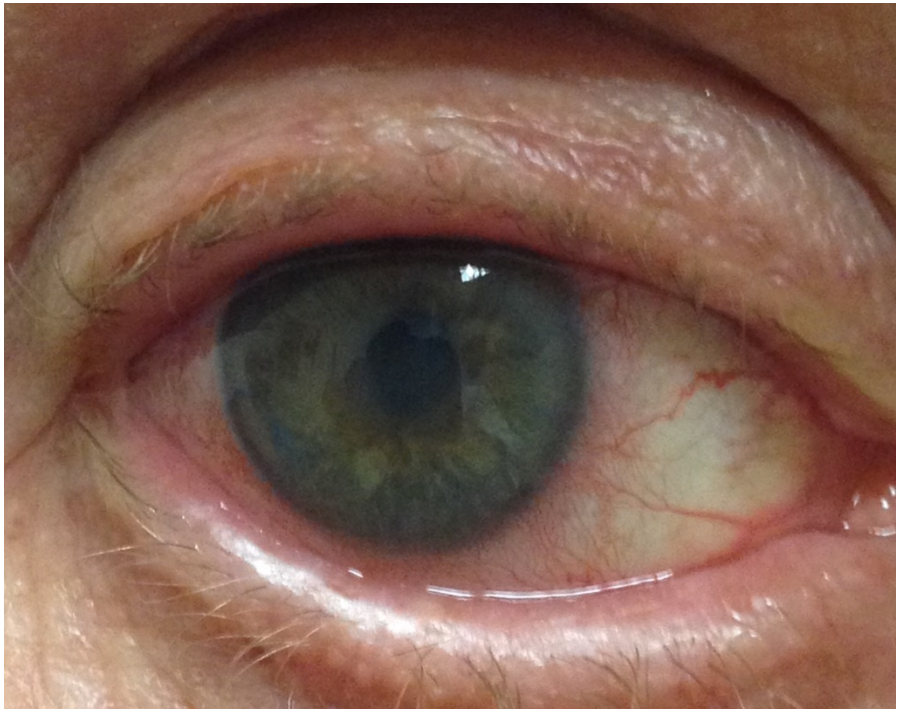
- 120 mg/m^2
- Gr. 2 Hand/Foot Skin Reaction
- Onset on Cycle 3, Day 8
- Resolution 35 days later

AE: Ocular

Eye	Grade 1	Grade 2	Grade 3	N=14
Any Eye Toxicity				8 (57%)
Conjunctivitis	1	1	–	2 (14%)
Iritis	–	1	1*	2 (14%)
Lacrimation Increased	2	–	–	2 (14%)
Photophobia	1	1	–	2 (14%)
Eye Pain	1	1	–	2 (14%)
Corneal Edema	–	–	1*	1 (7%)
Corneal Scar	1	–	–	1 (7%)
Dry Eye	1	–	–	1 (7%)
Pruritus	1	–	–	1 (7%)
Ocular Hyperaemia	1	–	–	1 (7%)
Trichiasis	1	–	–	1 (7%)
Blurred Vision	–	1	–	1 (7%)
Reduced Visual Acuity	1	–	–	1 (7%)

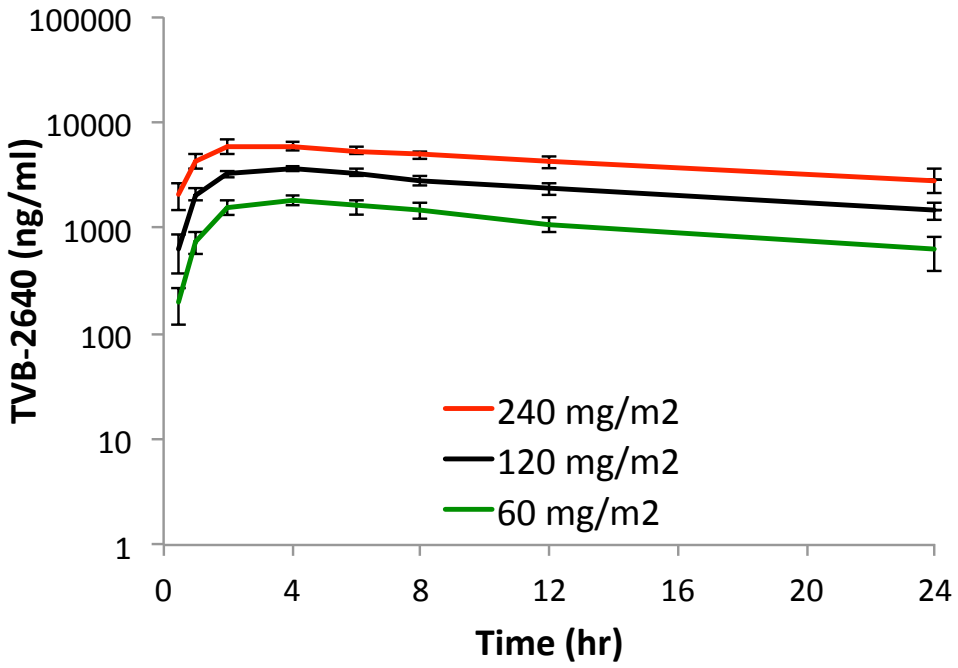
* Dose Limiting Toxicities: one grade 3 Iritis and one grade 3 Corneal Edema

AE: Ocular



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

TVB-2640 Plasma Levels Day 1



- Plasma levels increase with dose
- Steady state reached by day 8
- Mean half-life approximately 18 hours
- Exceeds threshold for preclinical efficacy

N of 14 patients, (mean +/- SEM of 3 or 4 per cohort)

Conclusions

- TVB-2640 is a potent, specific oral FASN inhibitor
- Skin and eye toxicity are on-target and reversible
  - No significant GI or hematologic adverse events
  - No QTc prolongation
- Exposures at 60 mg/m^2 exceed those found to be efficacious in preclinical models
  - 80 mg/m^2 is being explored to further define the MTD
- Comprehensive biomarker analysis is underway
- Chemotherapy combinations are planned and alternate dosing schedules are being considered

Preclinical Abstract 591 Poster 163, Heuer et al.

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

Thank You to the Patients and Their Families

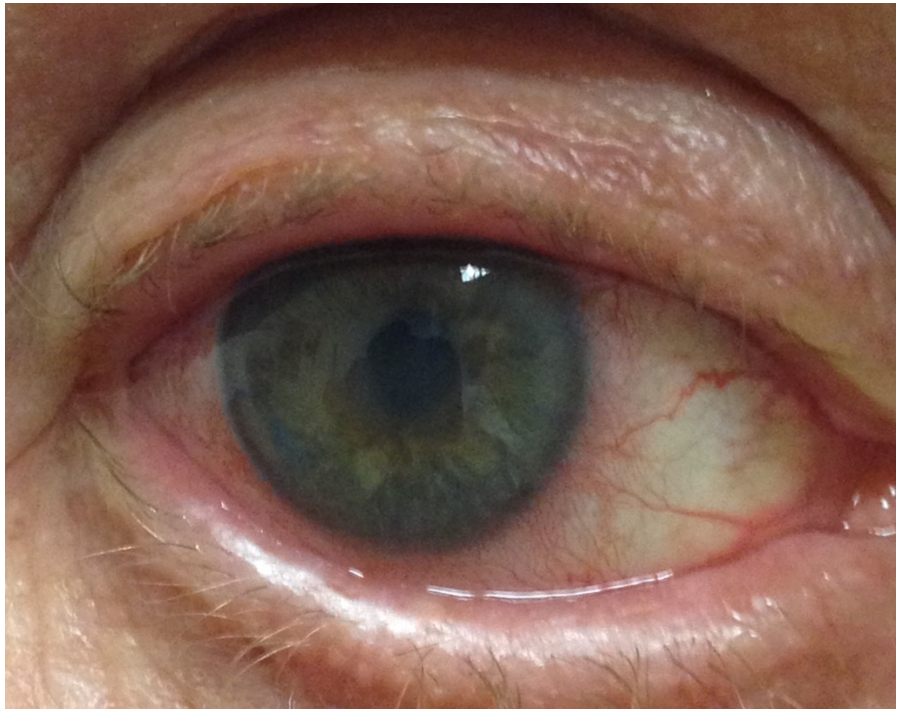
Jeffrey R. Infante MD
Sarah Cannon Research Institute
Nashville TN
jinfante@tnonc.com

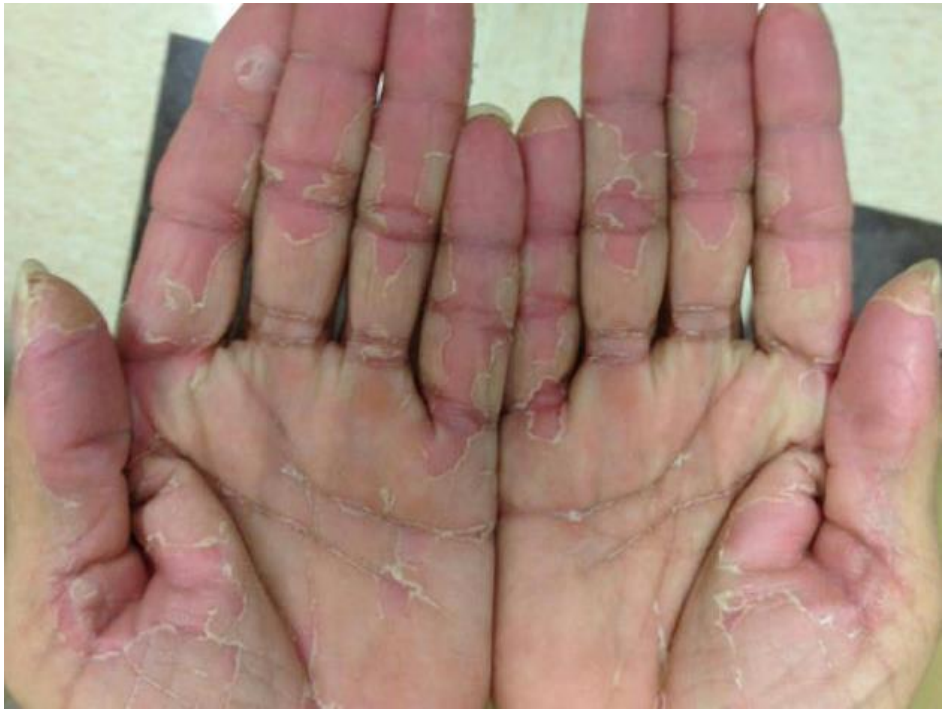
AEs ≥Gr 3 (excluding DLTs)

N = 14; N in Table = 9

AE Verbatim	N	Toxicity Grade	Related?	SAE?
Volume Overload	1	3	Unlikely	Yes
A-fib related to CHF	1	2	Unrelated	Yes
Biliary Obstruction	2	3	Unrelated	Yes (1) / No (1)
Elevated Alk Phos	1	3	Unrelated	No
Elevated Bilirubin	4	3	Unrelated	No
Elevated Lipase	2	4 (1) / 3 (1)	Unrelated	No
Hypertension	1	3	Unrelated	No
Hypokalemia	1	3	Unrelated	No
Ileus	1	2	Unrelated	Yes
Pancreatitis	1	3	Unrelated	Yes
Cardiac Tamponade	1	Not recorded	Unrelated	Yes
Pericardial Effusion	1	4	Unrelated	Yes

Eye and Skin Toxicity





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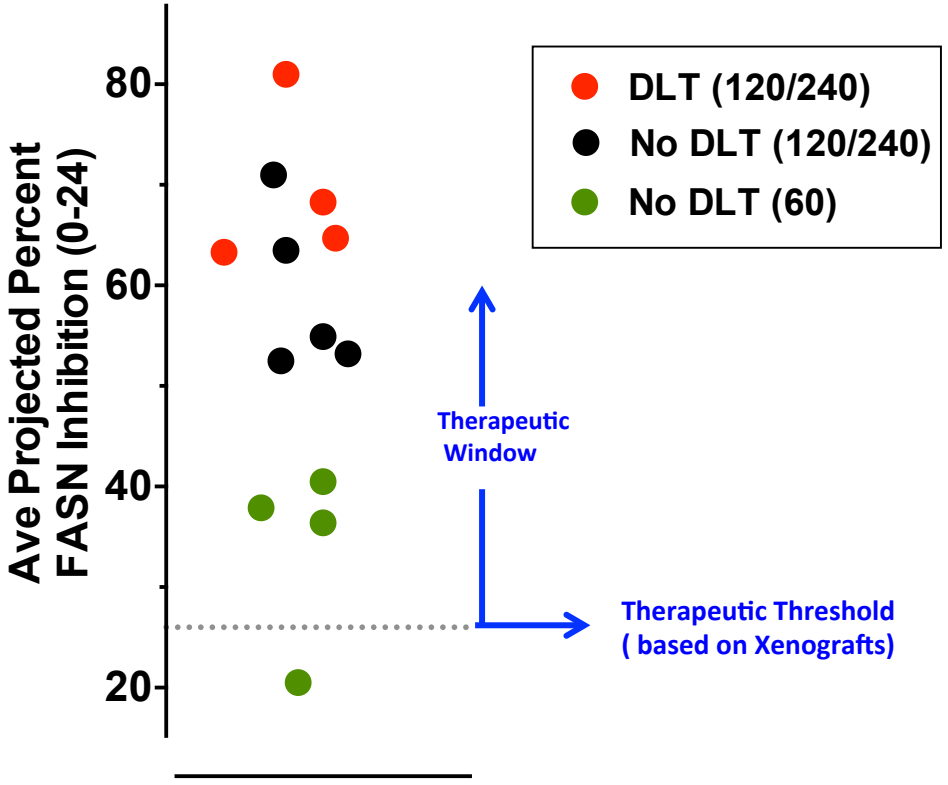
FASN Inhibition Modeling

- Graph of average FASN inhibition during a 24 hour period
- 25% inhibition of FASN inhibits Tumor Growth in murine xenografts
- Most patients exceed that minimum threshold
- DLTs occurred at very high levels of FASN inhibition

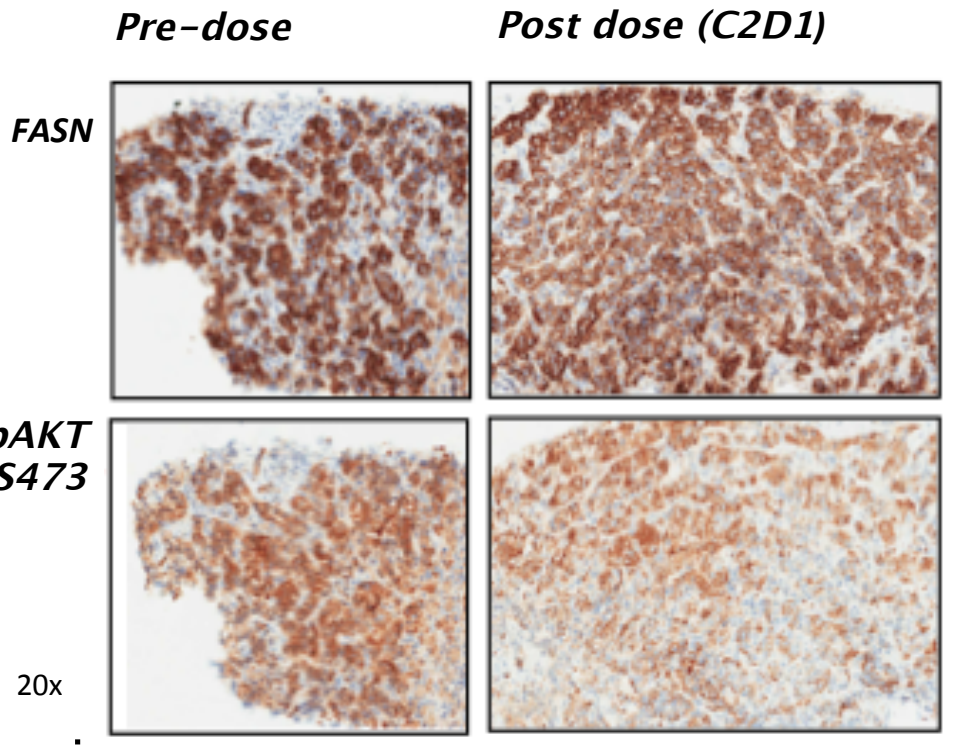


n=13. Pt 008 (no day 8 data).

PD & Biomarker Approaches

Tumor

- IHC of archival biopsies shows FASN expression in all patients to date
- IHC of paired biopsies in 1 patient (PIK3CA mutant breast cancer) at 240 mg/ m^2 shows inhibition of pAKT S473



50% decrease in tumor pAKT H score

Blood cells as surrogate tissue

- Gene expression profiling ongoing

Serum

- Secreted FASN analysis ongoing
- Lipidomic and metabalomic profiling ongoing