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

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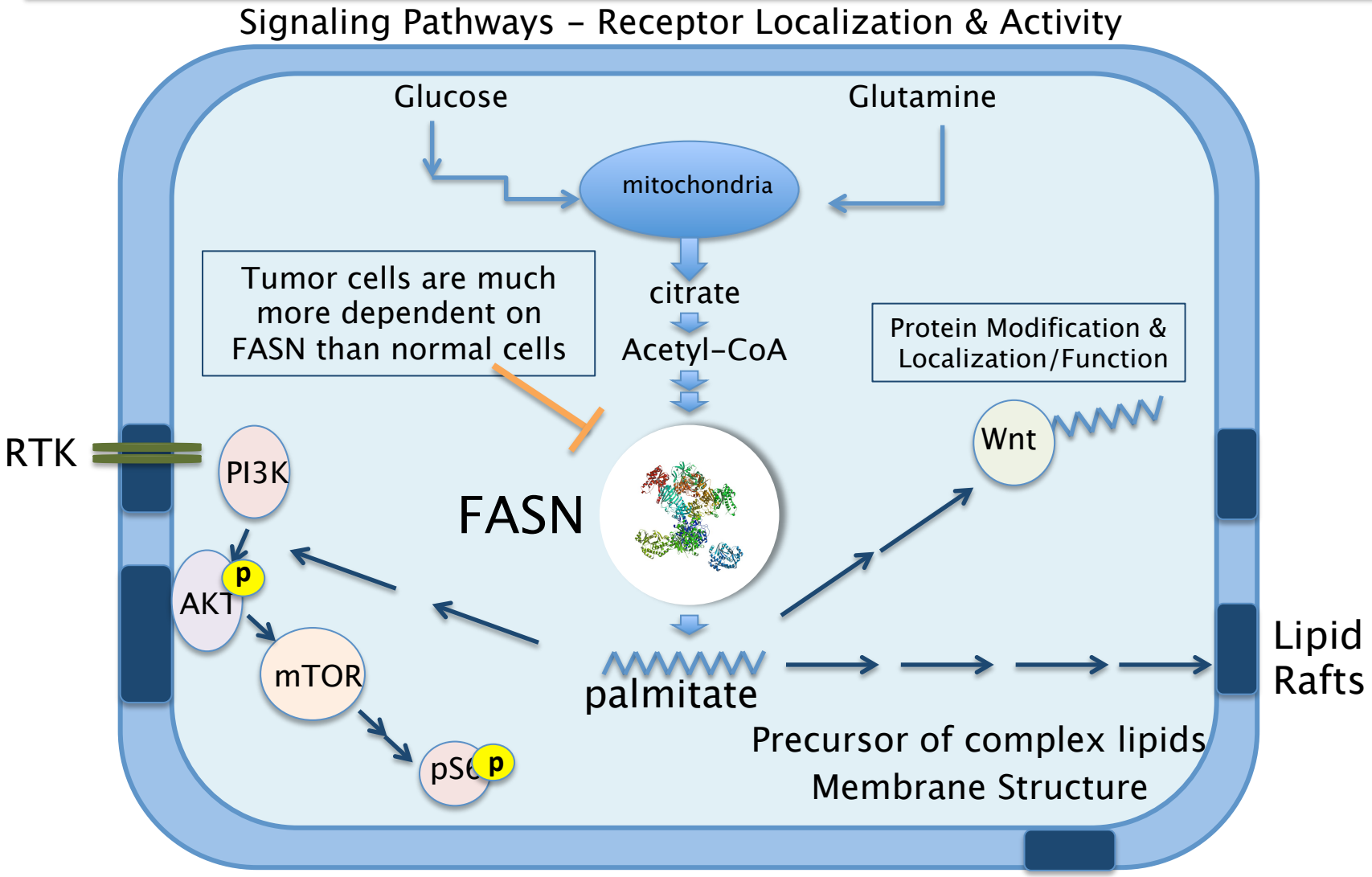
Disclosure Slide

- Presenter: M. Patel
  - Disclosures: None

FASN – Integrated Target in Tumor Cell Biology

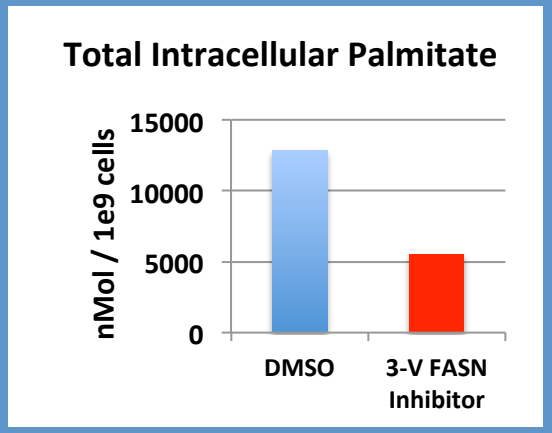


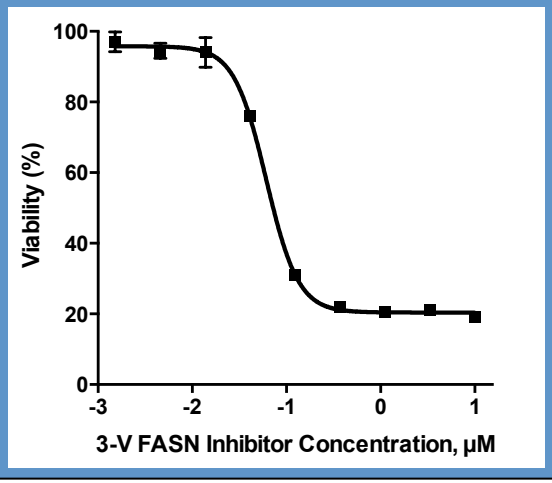
FASN is widely expressed in multiple tumor types

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

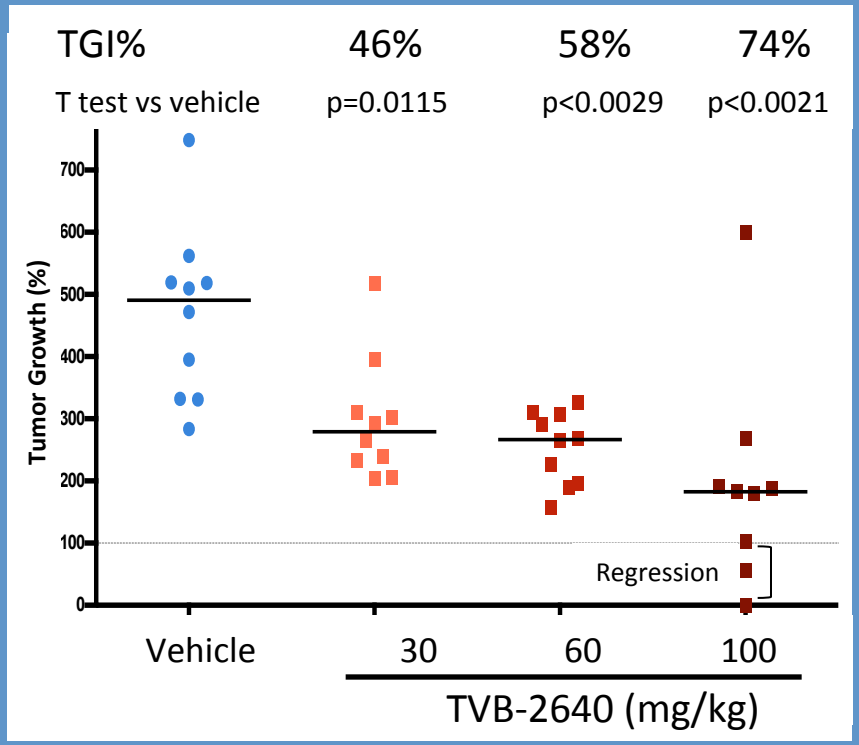
Potent, reversible, specific (IC_{50} <0.05 µM), small molecule inhibitor (<440 M_W)

Inhibition of FASN kills Tumor Cells





TVB-2640 Reduces Growth of COLO-205 Tumors *in vivo* (rat)



Study Design and Objective

- **Phase 1 Study**
  - Oral, once daily; 21 days in monotherapy or 28 days with chemo; continuous cycles
  - Adult patients (ECOG 0-1), with pathologically confirmed metastatic or advanced-stage solid tumors, met accepted ph-1 In/Exclusion criteria
  - Clinically significant ophthalmologic finding, including history of dry eye excluded
- **Primary Objective**
  - Safety, MTD, recommended Phase-2 dose (monotherapy and in combination with chemo)

Patient Baseline Characteristics

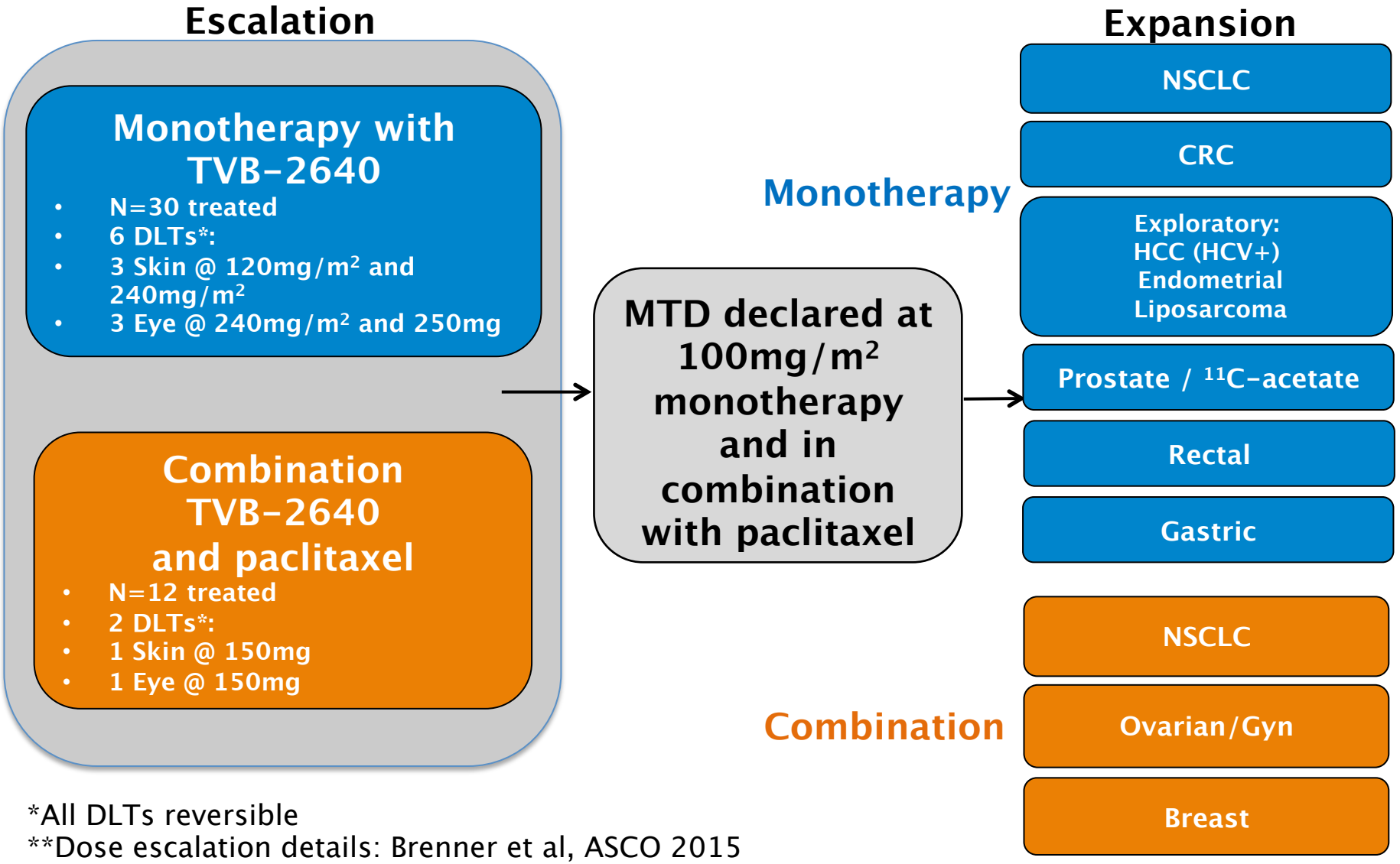
Monotherapy N=53 Patients		
Age (years)	Median	64
Gender	M/F	21:32
ECOG	0	(18) 34%
	1	(35) 66%
*** # of Previous Regimens**	0–2	(10) 19%
	3–4	(21) 40%
	5+	(21) 40%

Combination Therapy N=47 Patients		
Age (years)	Median	63
Gender	M/F	9:38
ECOG	0	(19) 40%
	1	(28) 60%
*** # of Previous Regimens**	0–2	(11) 25%
	3–4	(17) 39%
	5+	(16) 37%

Note: Tables include all dose escalation patients and expansion patients enrolled through 12Jan. 2015

* Data for 1–3 patients pending

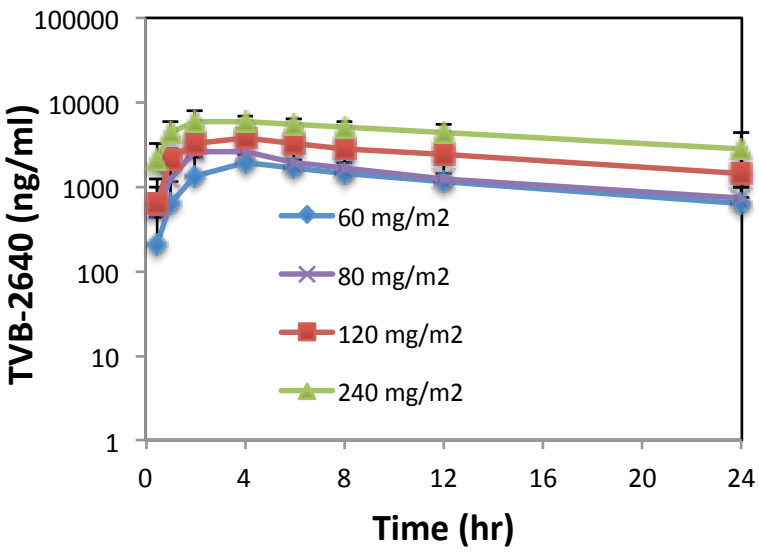
Expansion Cohorts Currently Enrolled



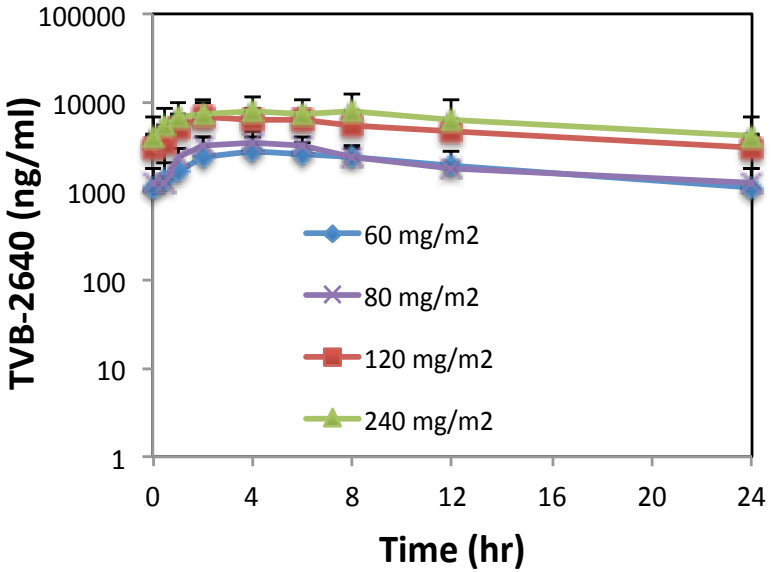
*All DLTs reversible
**Dose escalation details: Brenner et al, ASCO 2015

TVB-2640 Patient Plasma Levels

Day 1



Day 8



Plasma levels of TVB-2640 measured using a validated method. On day 8/15 the predose value is plotted as the 24 hour timepoint. Mean +/- SD for n of 3 to 7 patients per monotherapy cohort.

- Combination patients show similar TVB-2640 exposure to monotherapy patients (not shown)
- No impact of TVB-2640 on paclitaxel exposure, and *vice versa*

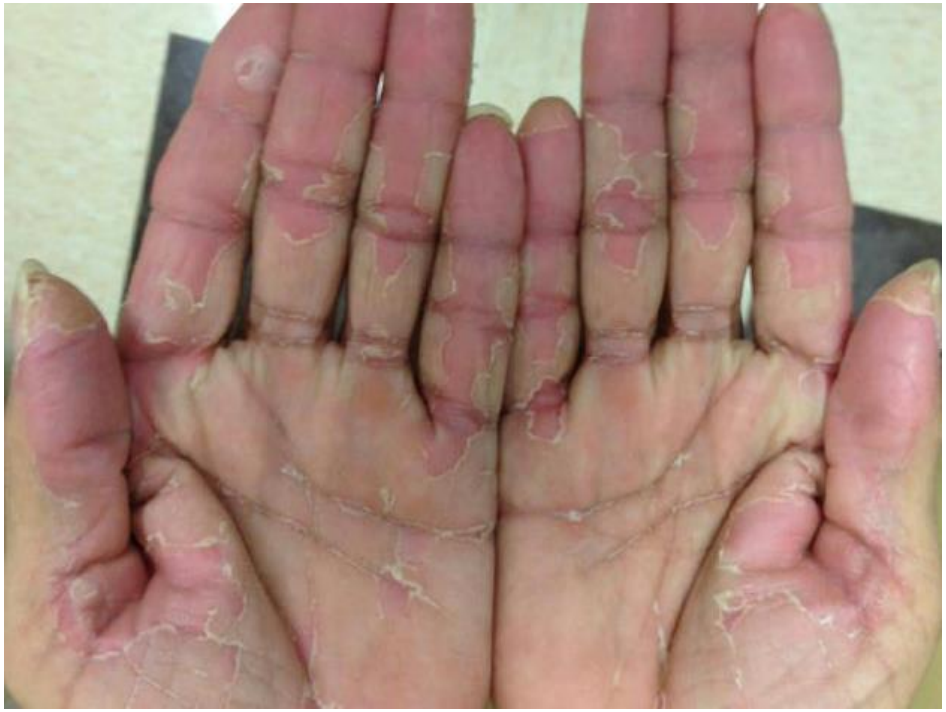
Monotherapy Gr 1/Gr 2/Gr 3 Related AEs

Monotherapy AE Verbatim	Events	Grade 1	Grade 2	Grade 3	N=53
Any Gr 1/Gr 2 Related Adverse Event					48 (91%)
Any ≥ Gr 3 Related Adverse Event					12 (22%)
Skin and subcutaneous tissue	41	20	17	4	77%
Gastrointestinal	26	21	5	-	49%
Eye	26	15	8	3	49%
General disorders and administration site conditions	22	10	10	2	42%
Nervous system	11	9	2	-	21%
Metabolism and nutrition	10	5	3	2	19%
Respiratory, thoracic and mediastinal	5	4	1	-	9%
Infections	3	1	2	-	6%
Investigations	3	2	1	-	6%
Blood and lymphatic system	2	1	-	1	4%
Congenital, familial and genetic	1	1	-	-	2%

Combotherapy Gr 1/Gr 2/Gr 3 Related AEs

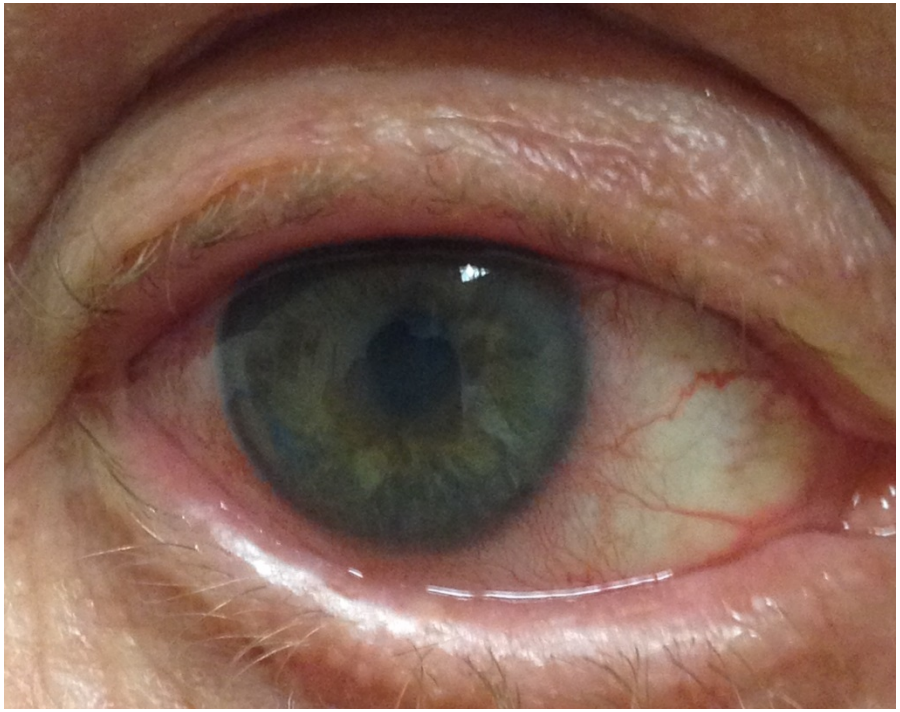
Combotherapy AE Verbatim	Events	Grade 1	Grade 2	Grade 3	N=47
Any Gr 1/Gr 2 Related Adverse Event					41 (87%)
Any ≥ Gr 3 Related Adverse Event					11 (23%)
Skin and subcutaneous tissue	32	14	13	5	68%
Gastrointestinal	29	22	5	2	62%
General disorders and administration site conditions	21	12	9	-	45%
Eye	15	9	6	-	32%
Metabolism and nutrition	11	7	3	1	23%
Respiratory, thoracic and mediastinal	7	5	2	-	15%
Blood and lymphatic system	7	1	4	2	14%
Musculoskeletal and connective tissue	6	6	-	-	13%
Investigations	6	4	1	1	13%
Nervous System	5	3	2	-	11%
Infections	5	0	4	1	10%

AE: Skin



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

AE: Ocular

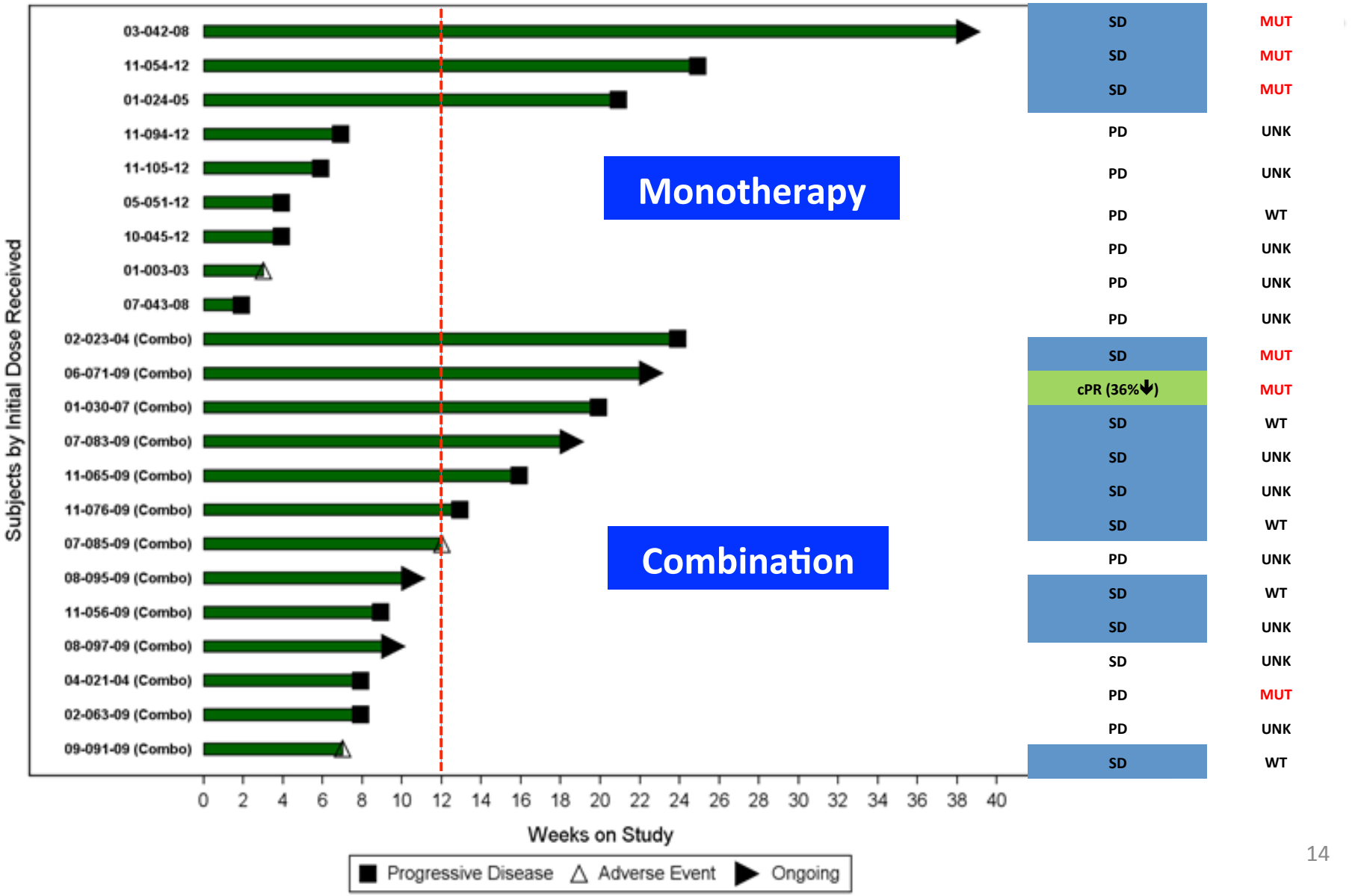


- 240 mg/m^2
- DLT of Gr. 3 Corneal Edema
- Onset on Cycle 2, Day 1
- Resolution 5 days later

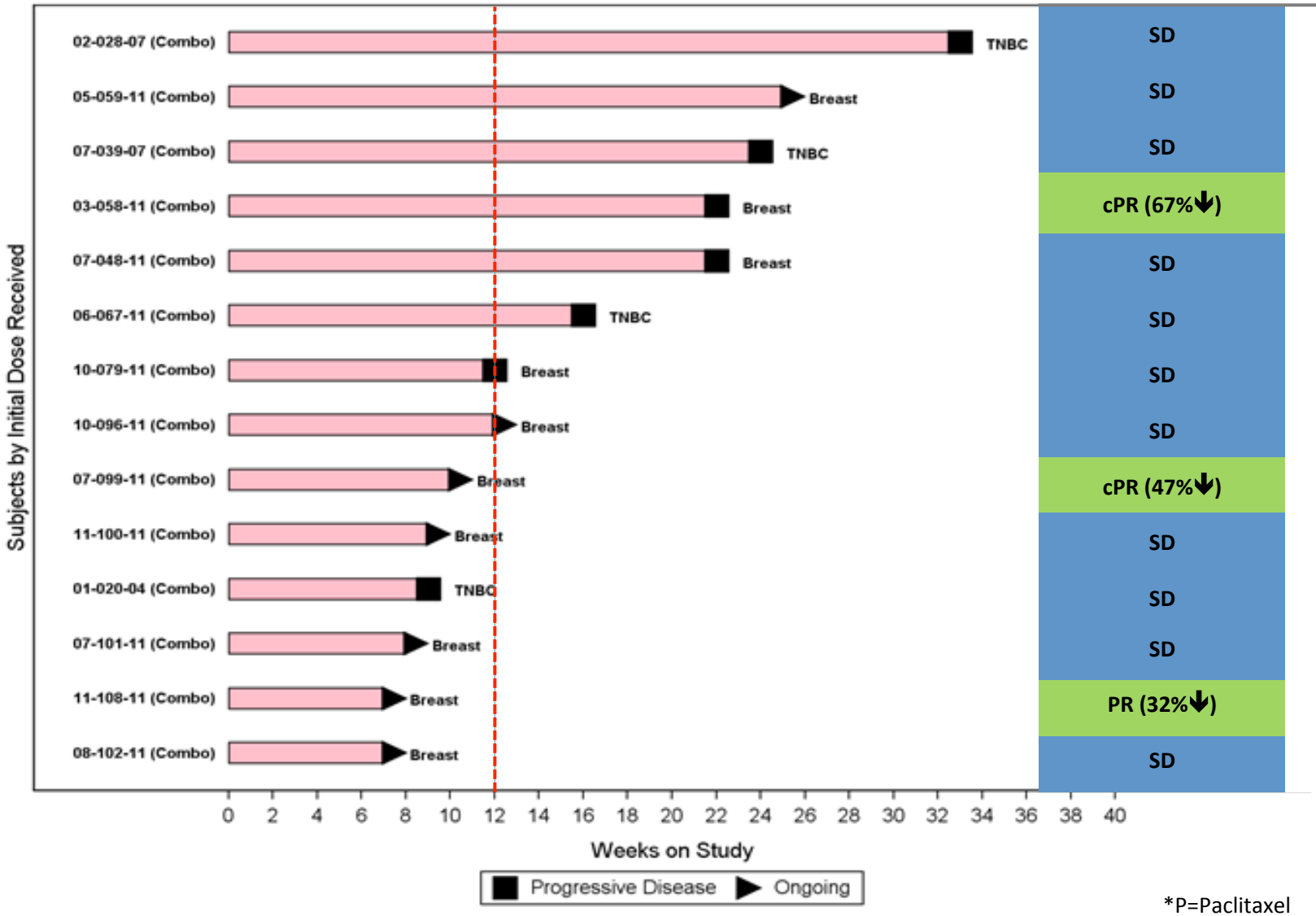
Safety Summary

- DLTs (Eye tox, HFS) were reversible
- At the MTD of 100mg/m^2: On target expected adverse events
  - Eye toxicity: 100% AE's were ≤ Grade 2
  - Skin toxicity: 85% AE's were ≤ Grade 2
- No added toxicities with TVB-2640 + Paclitaxel
- No QTc prolongation has been seen
- Mild GI toxicity

NSCLC weeks on study

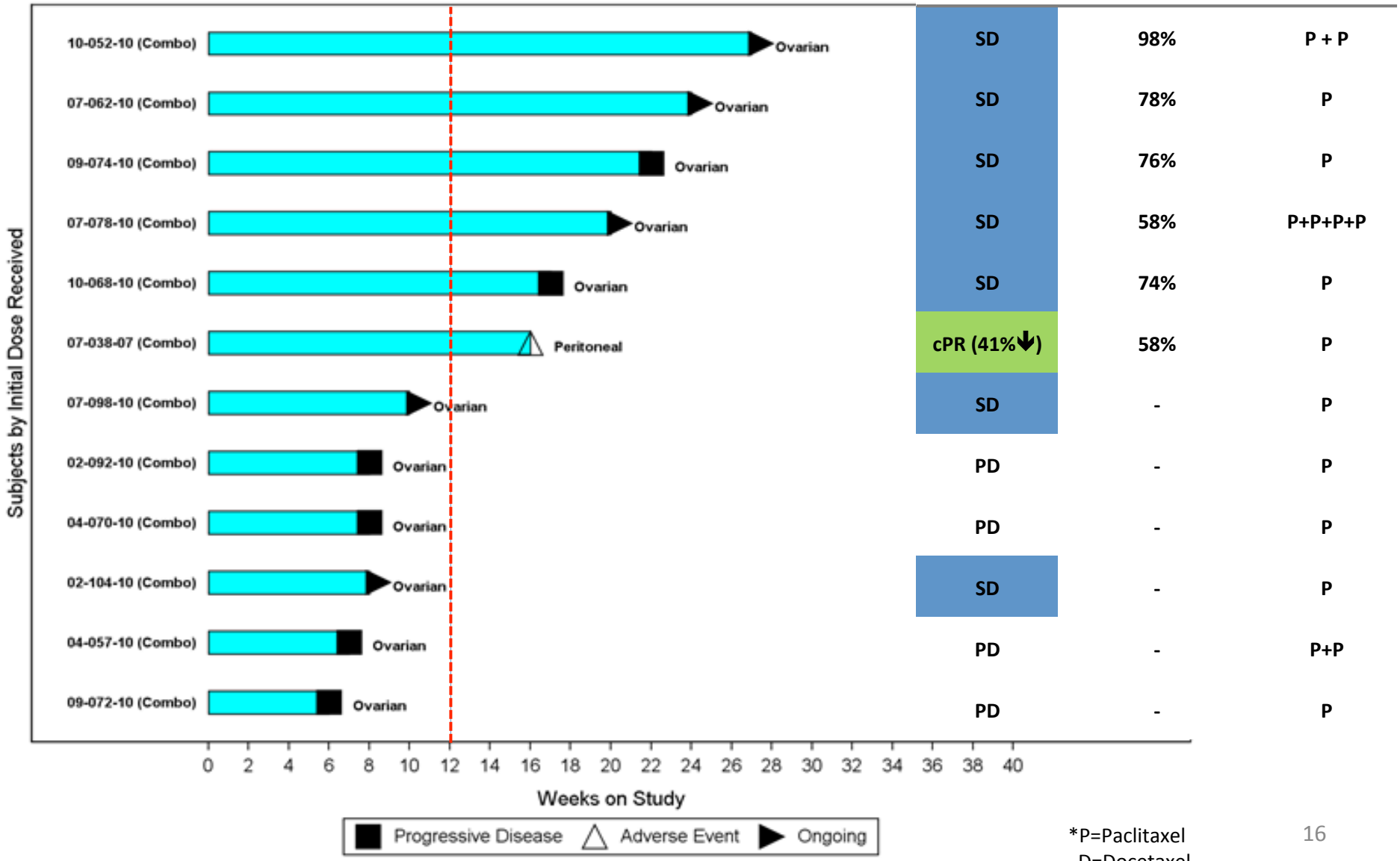


Breast Weeks on Study



*P=Paclitaxel
D=Docetaxel

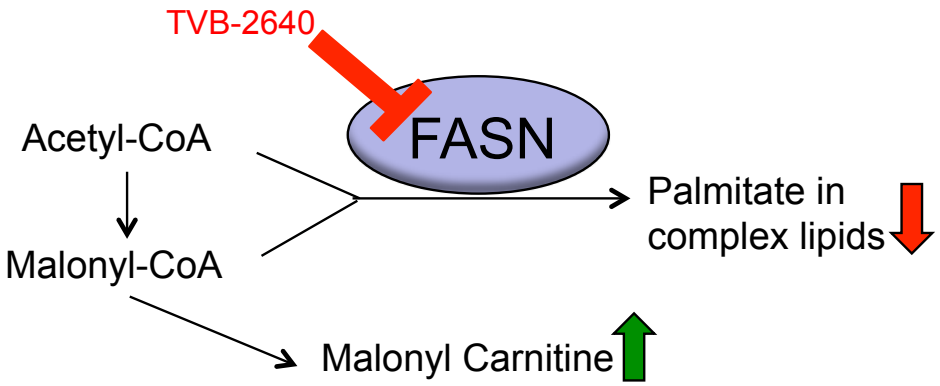
Ovarian Weeks on Study



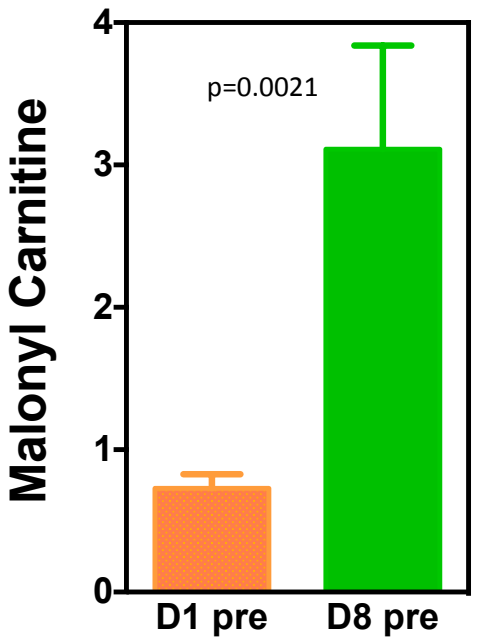
	Best Response	CA-125 Drop	Taxane *
10-052-10 (Combo)	SD	98%	P + P
07-062-10 (Combo)	SD	78%	P
09-074-10 (Combo)	SD	76%	P
07-078-10 (Combo)	SD	58%	P+P+P+P
10-068-10 (Combo)	SD	74%	P
07-038-07 (Combo)	cPR (41%↓)	58%	P
07-098-10 (Combo)	SD	-	P
02-092-10 (Combo)	PD	-	P
04-070-10 (Combo)	PD	-	P
02-104-10 (Combo)	SD	-	P
04-057-10 (Combo)	PD	-	P+P
09-072-10 (Combo)	PD	-	P

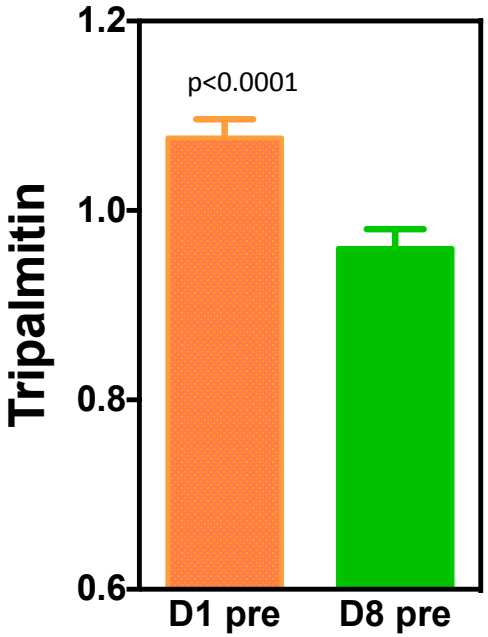
*P=Paclitaxel
D=Docetaxel

TVB-2640 Inhibits FASN in Patients



- Mechanism related metabolites in serum change in line with preclinical data
- Evidence of FASN engagement



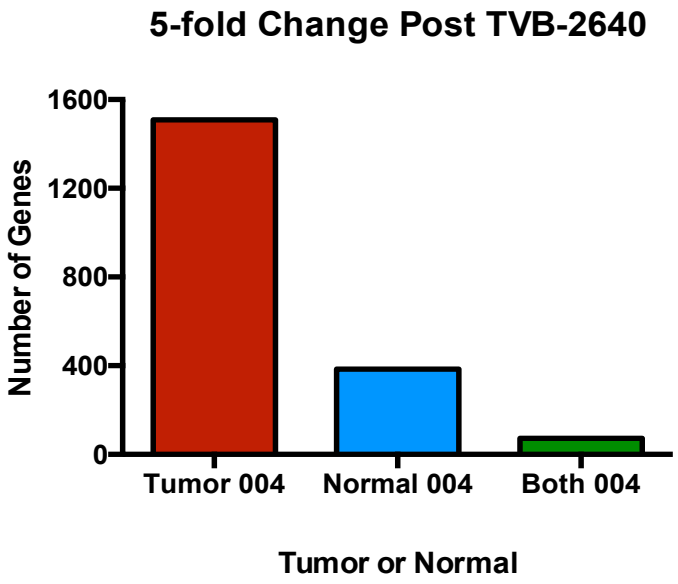


N=19
Mean+/-SEM

Activity in Patient Tumor Biopsies Demonstrated

Tumor – exploratory biomarkers

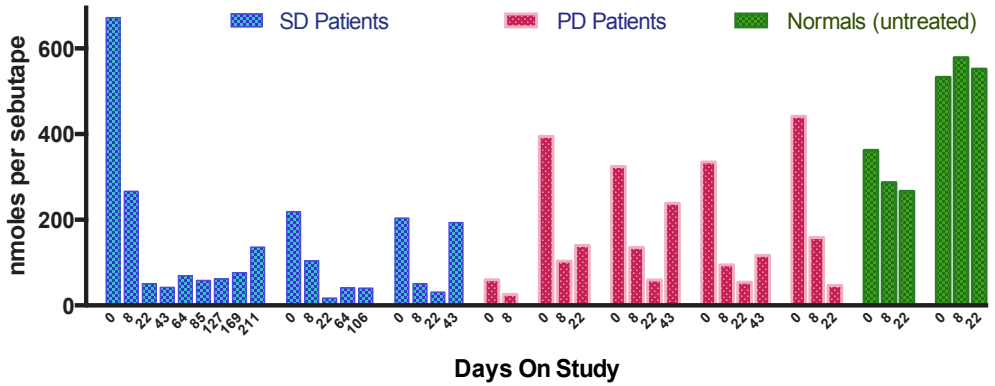
- Gene expression in macro-dissected tumor by RNA-Seq
- Significantly more genes altered in tumor than normal tissue



Sebum - lipogenesis

- Novel non-invasive approach using sebutape on forehead

Lipid Reduction at C1D8 vs. C1D0 Treated vs. Control p<0.0001

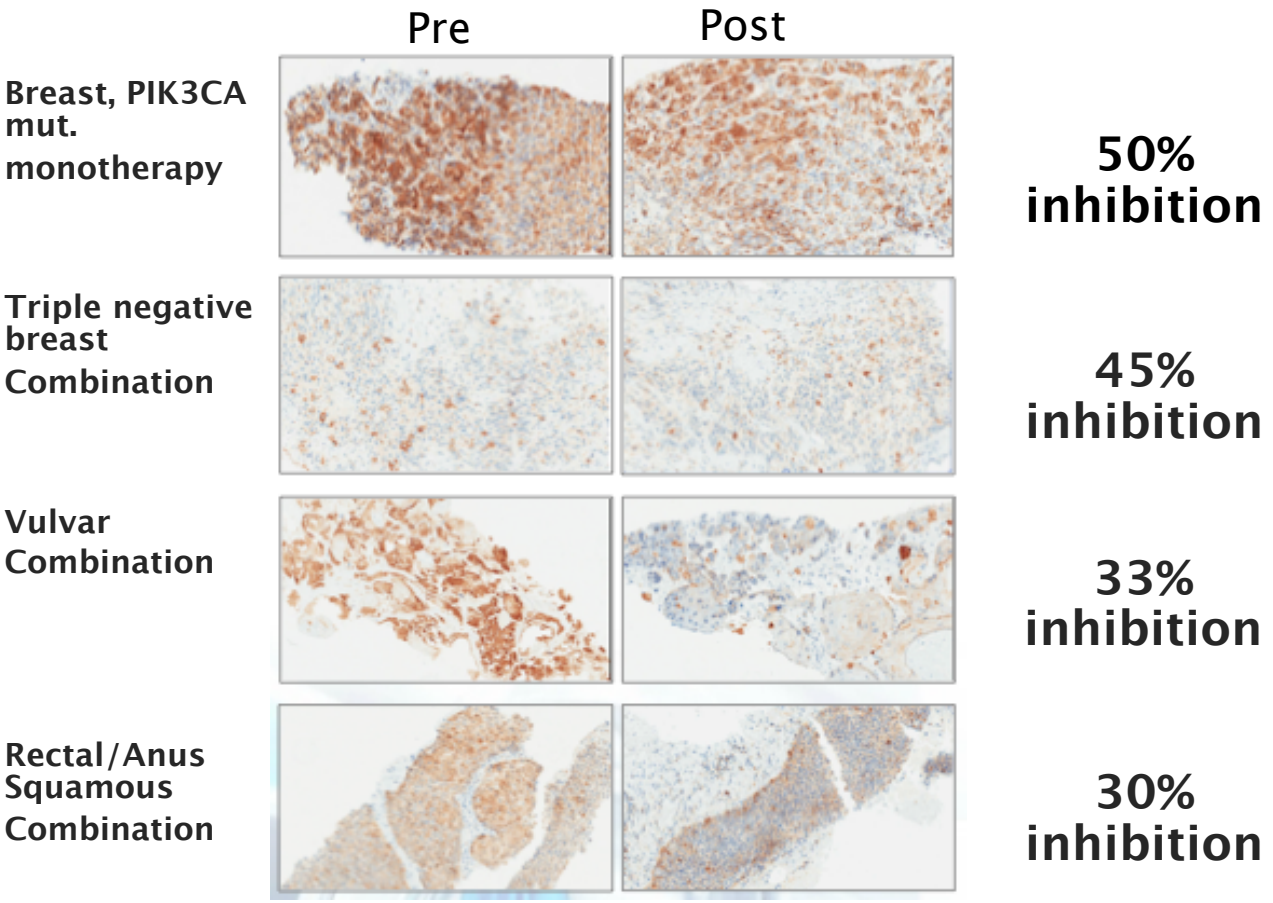


Sebum profiled by GC-MS and MS-flame ionization detection. N=8 patients, plus 2 normal donors not receiving TVB-2640

- All 8 patients show decreased triglycerides
- Inhibition of lipogenesis
- Maintained over time

Activity in Patient Tumor Biopsies Demonstrated

4/9 patients with paired biopsies had decreased pAKT S473 after 1 cycle



20x images. H score in tumor used to calculate % inhibition.

Conclusions

- Promising early signs of clinical activity have been seen in heavily pre-treated patients:
  - Four confirmed partial responses when combined with weekly paclitaxel.
  - Prolonged SD in both treatment arms.
  - Responses have been seen across multiple tumor types, including $KRAS^{mut}$ NSCLC, ovarian and breast cancer.
- Toxicity profile manageable: skin and eye toxicity are on-target and reversible, only minor GI symptoms, no QTc prolongation, no additive toxicity with paclitaxel.
- Biomarker analysis demonstrates target engagement and inhibition of lipogenesis.
- Further exploration of activity in specific tumor types is ongoing.

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

Thank You to the Patients and Their Families