

Sebum Analysis from Dose Escalation and Expansion Phases of the FASN Inhibitor TVB-2640 Phase 1 Trial, A Non-Invasive Biomarker of Target Engagement

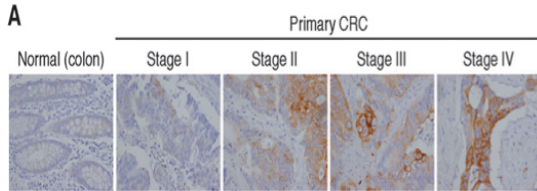


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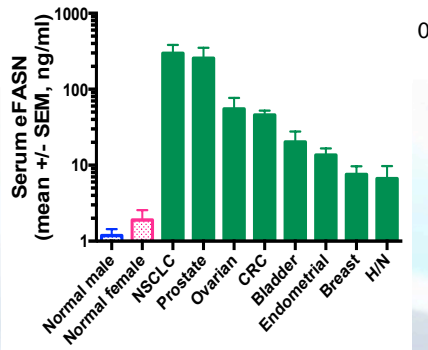
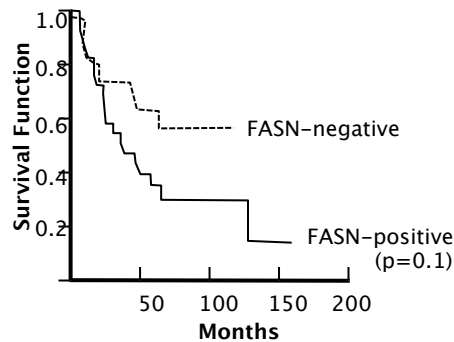
3-V Biosciences Inc., Menlo Park, CA

February 24, 2016

FASN: A Well-Credentialed Target in Oncology



FASN Expression Correlates with Poorer Survival in NSCLC Patients



- Fatty acid synthase (FASN) levels increased in tumors, especially in later stage disease
- High FASN levels predict mortality in several cancers including NSCLC
- High blood FASN levels found in broad array of cancer types
- Normal cell survival not generally dependent on de-novo palmitate synthesis
- Tumor cells become addicted to palmitate FASN inhibition causes apoptosis
- Chemical and genetic FASN inhibitors have antitumor effects in multiple xenograft models
- FASN-derived palmitate integrates into critical oncogenic signaling pathways

Zaytseva et al. *CR*. 2012

Visca, et al, *Anticancer Res*, 2004

Weiss, et al, *Biol. Chem* 367:905 (1986)

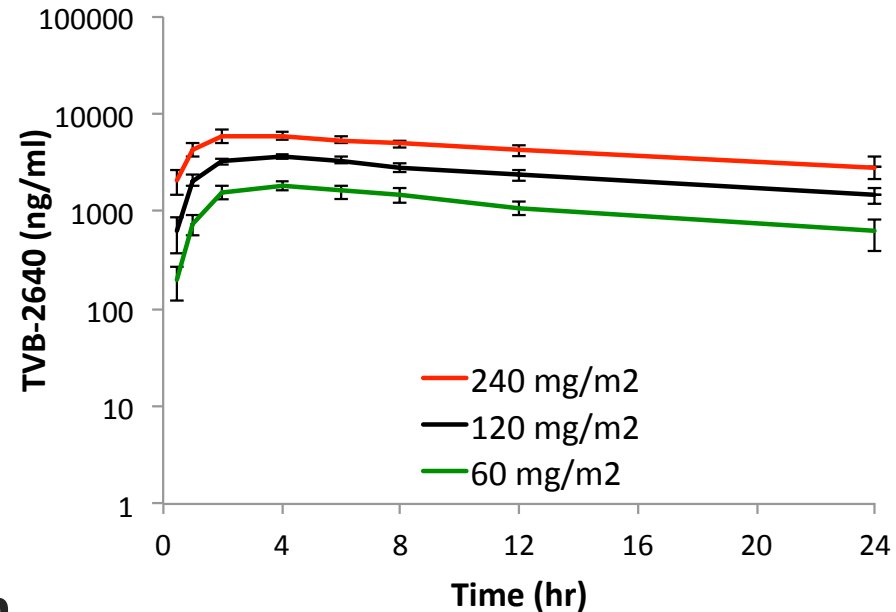
De Schrijver, et al. *Cancer Res* 63:3799 (2003)

Mendez & Lupu, *Nature Rev Cancer* 7:763 (2007)

TVB-2640: A Novel FASN Inhibitor with Excellent Human Exposure

➤ TVB-2640 FASN inhibitor

- First in class
- Potent
- Highly selective
- Reversible



➤ Pharmacokinetics in human

- Plasma levels increase with dose
- Mean half-life approximately 15 hours
- Steady state reached by day 8
- Exceeds threshold for preclinical efficacy at all doses

CLIN-002: A Phase 1 Study of TVB-2640 in Human Subjects with Advanced-Stage Solid Tumors

➤ Design

- Oral, once daily; DLT period 21 days (monotherapy) or 28 days (with paclitaxel); continuous cycles
- Adult patients (ECOG 0-1), with pathologically confirmed metastatic or advanced-stage solid tumors, who 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 paclitaxel)

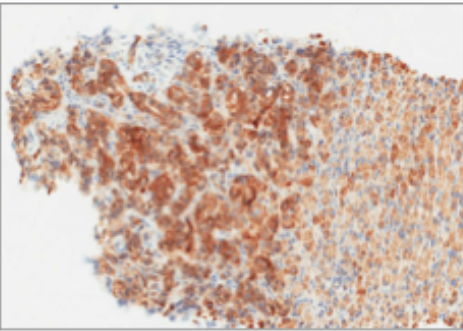
➤ MTD identified, currently in expansion cohorts

- All comers solid tumors dose escalation cohorts completed
- MTD declared at 100mg/m² for monotherapy and in combination with paclitaxel

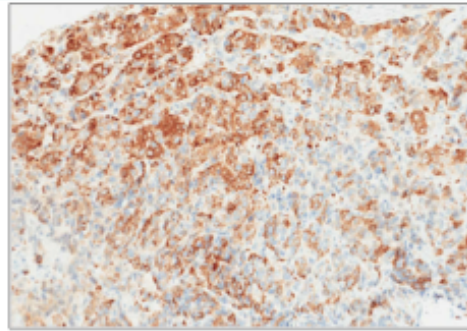
TVB-2640 PD Activity in Patient Tumor and Serum Previously Demonstrated

Tumor

Gene expression (RNA Seq analysis) shows more changes in tumor than normal tissue

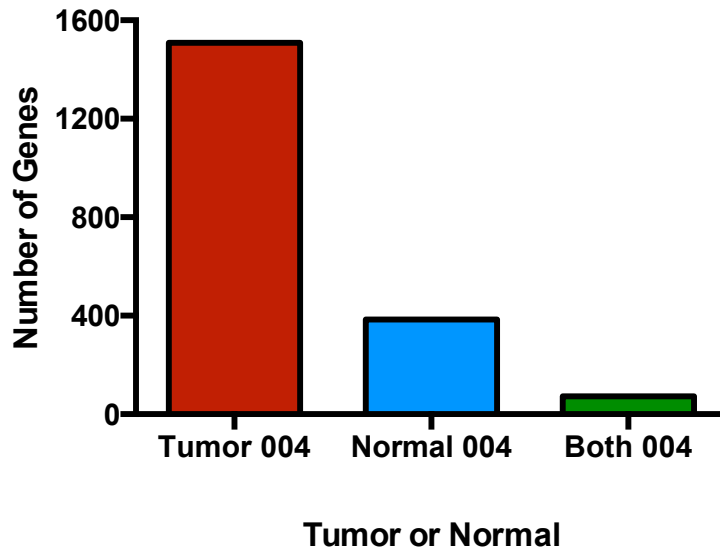


Breast, PIK3CA mut. Monotherapy pAKT S473 staining



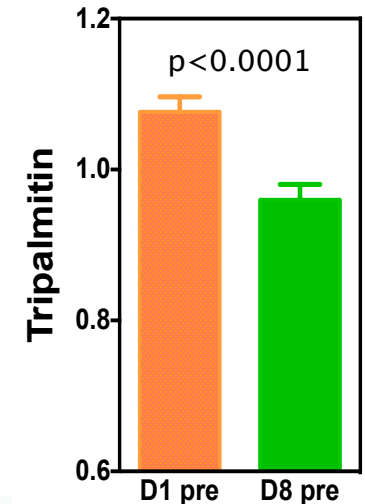
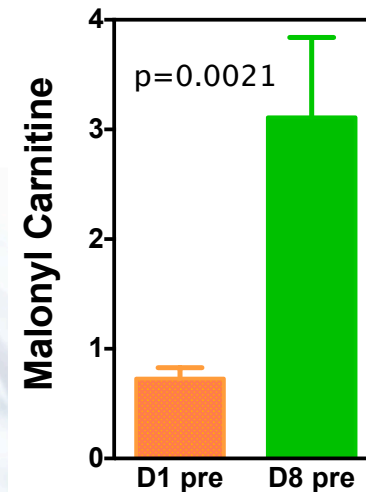
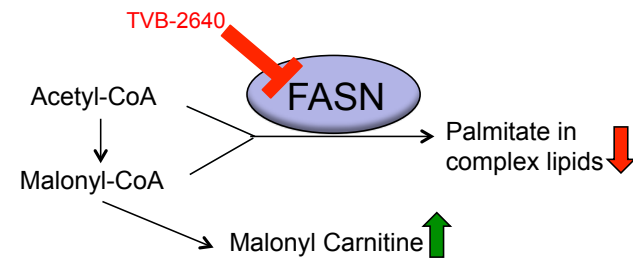
50% pAKT S473 inhibition with TVB-2640 treatment

≥5-Fold Gene Expression Change Post TVB-2640



Serum

Metabolomic analysis shows increased malonyl carnitine from substrate buildup and decreased palmitate containing lipids



N=19 Mean+/-SEM

Sampling Forehead Sebum with Sebutape®

Why study sebum?

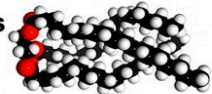



- Lipid composition suggests high FASN activity
- Easily accessed, high patient compliance
- Completely non-invasive sampling
- Potential for a rapid quantitative assay of TVB-2640 activity in human subjects

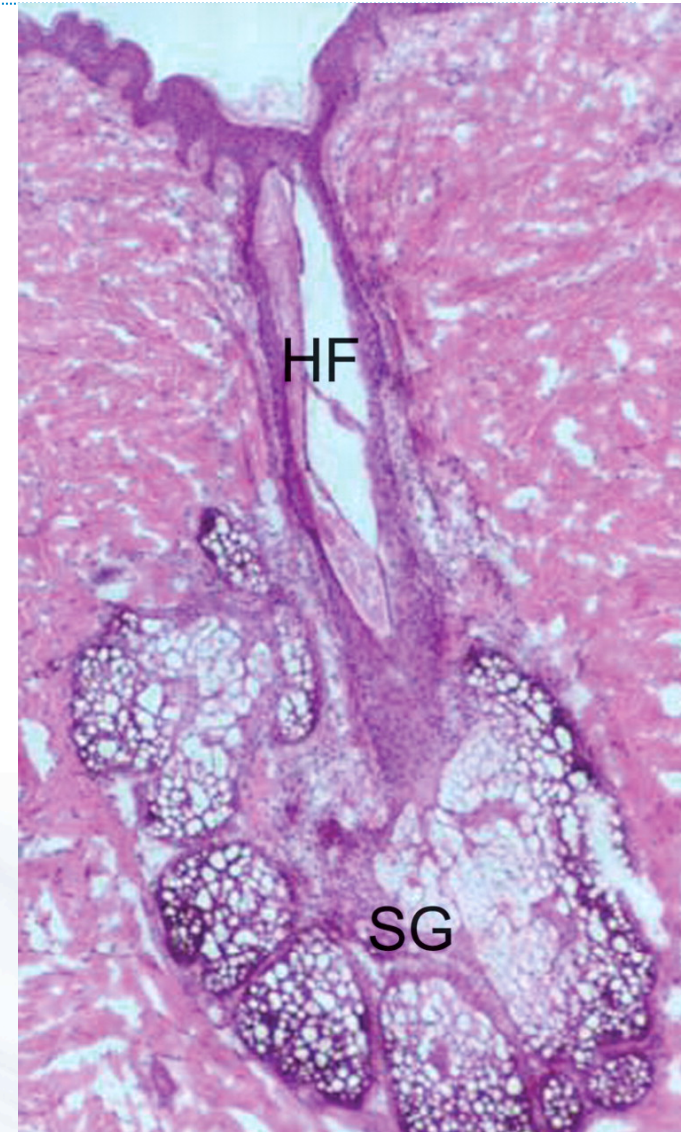


Sebaceous Gland Secretion

- Sebum secretion by holocrine production – release of entire cellular contents by lysis of the sebocyte
- Transit time for holocrine secretion in man ~1 week
- Both dietary fatty acids and newly synthesized lipids are incorporated into sebum

Sebum Composition

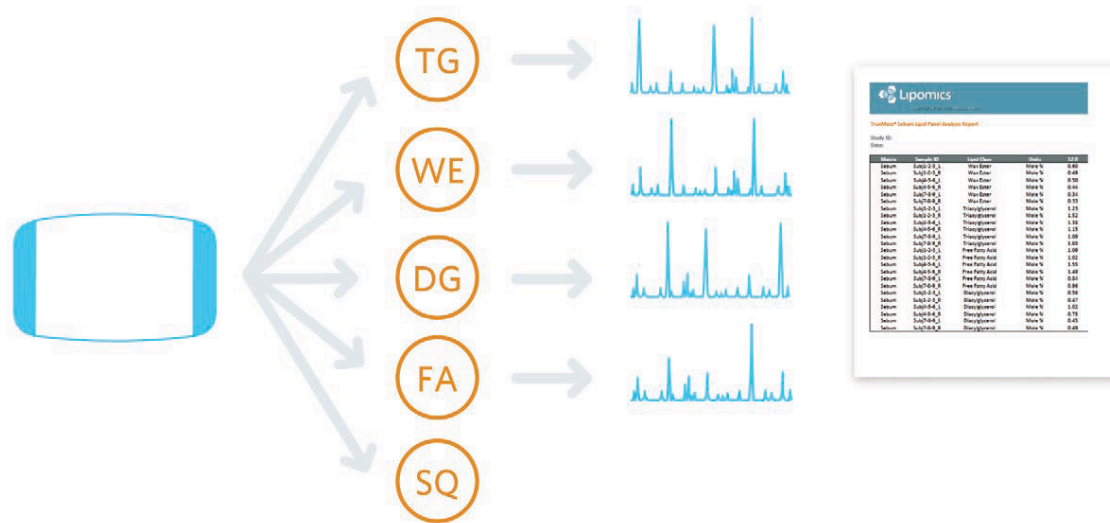
	Sebum %
Glycerides 	30–50
Free Fatty Acids 	15–30
Wax Esters 	26–30
Squalenes 	12–20
Cholesterol Esters	3.0–6.0
Cholesterols	1.5–2.5



Sebutape® Analysis Method

TRUEMASS® SEBUM LIPID PANEL

COMPLETE ANALYSIS OF LIPID CLASS CONCENTRATION AND COMPOSITION



EXTRACTION
IS ADDITION

SEPARATION OF
LIPID CLASSES

FATTY ACID ANALYSIS
OF EACH LIPID
CLASS

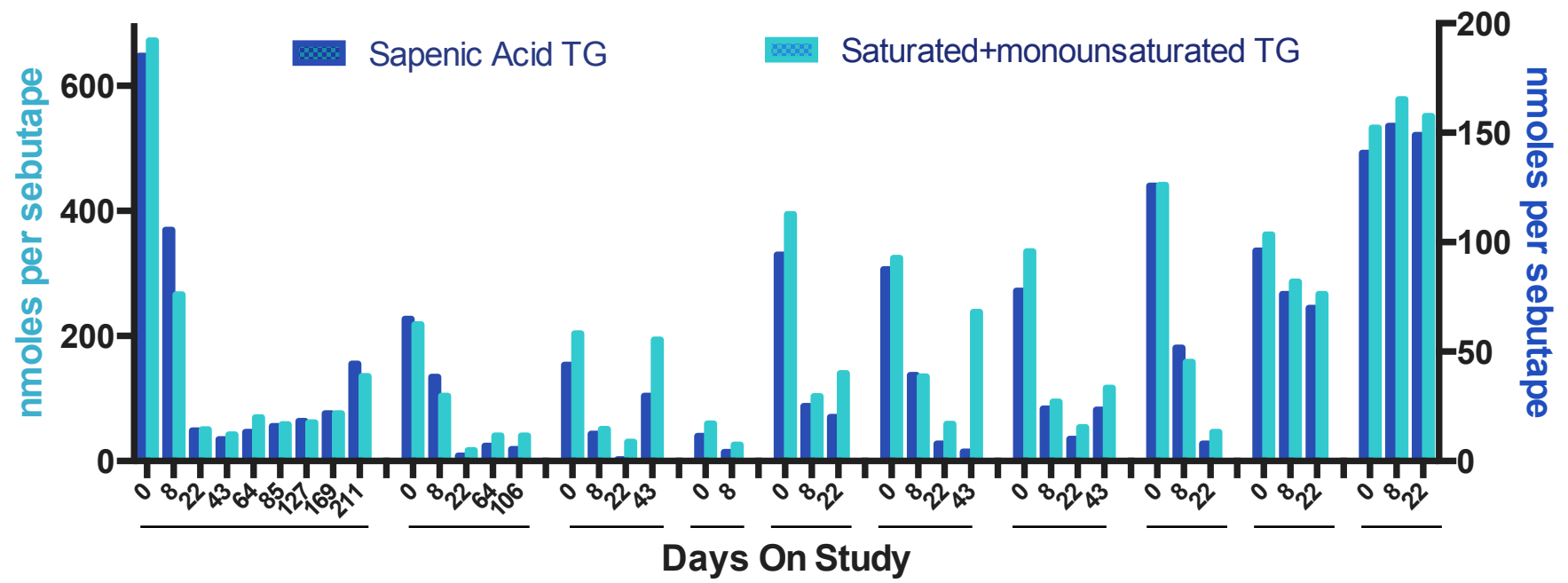
QUANTITATIVE
DATA REPORT

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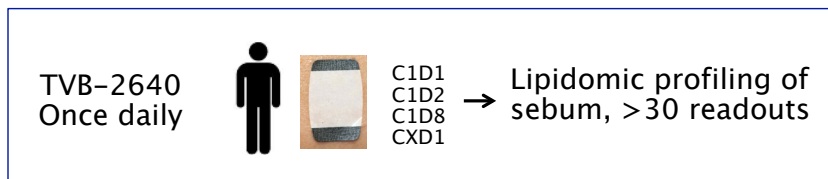
Sebum-specific Lipid Sapenic Acid (16:1, n-10) in TG

Sapenic Acid is an immediate downstream derivative of palmitate (FASN)

TVB-2640 Effects on Sebum-specific Sapenic acid TG

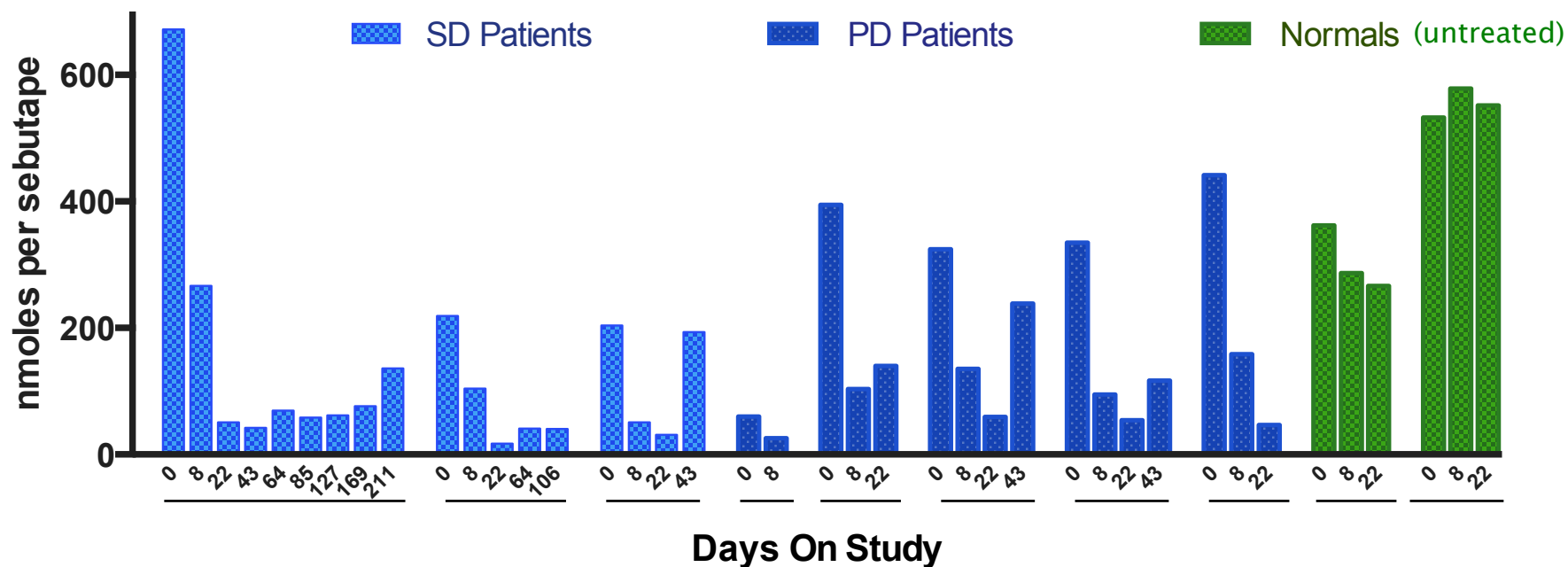


TVB-2640 Monotherapy – Sebum Triglycerides



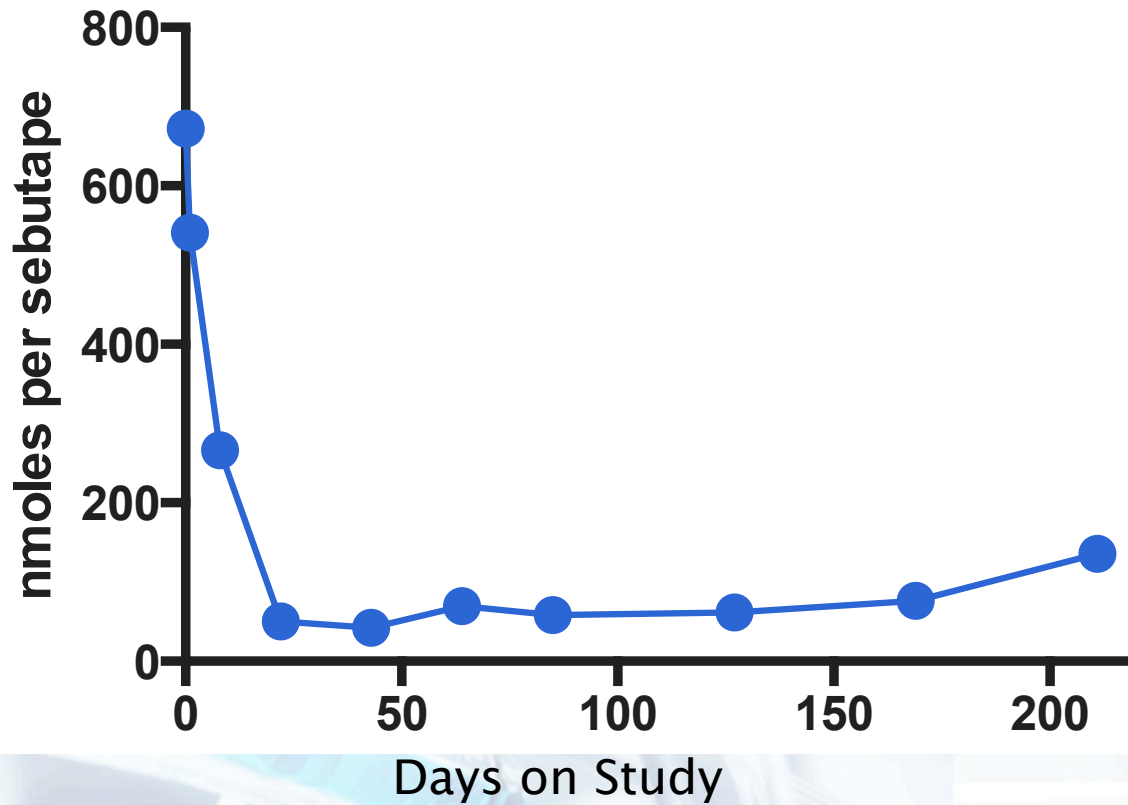
TVB-2640 Effects on Sebum Saturated and Monounsaturated Triglycerides

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



TVB-2640 - Persistent Inhibition of Lipogenesis >30 Weeks in a NSCLC Patient - KRAS^{mut}

Saturated and monounsaturated TG in Sebum



Summary and Conclusions

- **Sebum analysis provides a non-invasive measure of TVB-2640 PD activity in patients**
- **TVB-2640 causes significant inhibition of de novo lipogenesis by sebocytes**
- **Sebum lipid production was significantly reduced after 7 days exposure to TVB-2640**
- **No obvious sebum differences between SD and PD patients.**
- **Dietary lipids do not substitute for de novo synthesized lipids in sebum production**

See Poster #1022

Acknowledgments

The authors gratefully acknowledge the contributions of:

- **The patients, families and investigators who have participated in the CLIN-002 Trial**
- **The Lipidomics Group at Metabolon for performing the sebum lipid analysis**
- **The team at 3V Biosciences**