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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Introduction

FASN: A Well-Credentialed Target in Oncology

- 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

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 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 IV
  - 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

Methods

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

Sebutape® Analysis Method

TRUEMASS® SEBUM LIPID PANEL
COMPLETE ANALYSIS OF LIPID CLASS CONCENTRATION AND COMPOSITION

Results

Sebum-specific Lipid Saponic Acid in TG

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

TVB-2640 Monotherapy – Sebum Triglycerides

TVB-2640 Effects on Sebum-specific Saponic acid in TG

TVB-2640 - Persistent Inhibition of Lipogenesis

>30 Weeks in a NSCLC Patient - KRASmut

TVB-2640/Paclitaxel Combo – Effects on Sebum Triglycerides

TVB-2640 + Paclitaxel Effects on Saturated+Monounsaturated TG

Conclusions

- Sebum analysis provides a completely non-invasive means of assessing TVB-2640 PD activity in patients
- Daily administration of TVB-2640 as monotherapy or in combination with paclitaxel causes significant inhibition of de novo lipogenesis by sebocytes
- Sebum lipid production was significantly reduced after 7 days exposure to TVB-2640
- Patients with stable disease do not show different sebum lipid responses to TVB-2640 when compared to patients with progressive disease
- Dietary lipids do not substitute for de novo synthesized lipids in sebum production

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Poster #1022
Poster will be available after the meeting at: http://www.3vbio.com