Translational Studies of a First-in-class FASN Inhibitor, TVB-2640, Linking Preclinical Studies to Clinical Laboratory Observations in Solid Tumor Patients

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Introduction

• FASN inhibition is a novel approach to cancer treatment involving the selective disruption of palmitate biosynthesis that, in tumor cells, causes changes in cell signaling, induces apoptosis, and enhances sensitivity to other chemotherapeutic agents, in addition to other effects.
• TVB-2640 is an oral, first-in-class, small-molecule reversible inhibitor of FASN that demonstrates in vitro and in vivo anti-tumor effects with an acceptable non-clinical safety profile.
• This is an update on a dose-escalation study in patients with metastatic or advanced-stage malignant disease refractory to standard therapy and for whom no therapy exists that would be curative or might provide significant benefit.

FASN-Integrated Target in Tumor Biology

Oral, First-in-Class, Potent FASN Inhibitor

TVB-2640

Inhibits Tumor Growth and AKT Phosphorylation in Rat Xenograft

Objectives

Primary: Safety, MTD, recommended phase 2 dose
Secondary: Pharmacokinetics, preliminary anti-tumor activity (monotherapy and in combination with paclitaxel)
Exploratory: Biomarkers of response

Study Design & Key Eligibility Criteria

• Multicenter, open label, phase 1 study
• Oral, once daily with 21 day monotherapy continuous cycles (or 28 days in combination with paclitaxel)
• Single patient, accelerated titration followed by “3+3” design after 2 Grade 2 toxicity

Inclusion

• Adult patients with adequate bone marrow, hepatic and renal function and metastatic or advanced-stage solid malignant tumor
• Up to 4 prior chemo regimens
• ECOG 0-1

Exclusion

• History of clinically significant dry eye
• Clinically significant ophthalmologic findings
• History of risk factors for torsade de pointes (e.g., heart failure, hypokalemia)
• Conditions that might interfere with oral absorption

Pharmacodynamics

TVB-2640 Elicits Significant Changes in Mechanism Related Gene Expression Specifically in Tumor Tissue

TVB-2640 demonstrates a favorable tolerability profile with no significant GI, hematologic, serum chemistry adverse events. Early data in combination with weekly paclitaxel show expected pharmacokinetics and are above those associated with efficacy in clinical models. Skin and ophthalmological toxicity are on-target and reversible. Tumor gene expression, tumor AKT phosphorylation and plasma biomarker profiles demonstrate FASN inhibition in patients. Early data in combination with weekly paclitaxel show expected PK results and no newly emergent toxicities. The combination has been well tolerated to date. Three patients with NSCLC (one monotherapy and 2 in combination) have evidence of stable disease after >12 weeks of treatment. Thank You to the Patients and Their Families.

Conclusions

• TVB-2640 is an oral, selective, potent, reversible FASN inhibitor and is the first FASN inhibitor in clinical trials
• TVB-2640 demonstrates a favorable tolerability profile with no significant GI, hematologic, serum chemistry adverse events
• Exposures of 60 mg/m² and above demonstrate target modulation and are above those associated with efficacy in clinical models
• Skin and ophthalmological toxicity are on-target and reversible
• Tumor gene expression, tumor AKT phosphorylation and plasma biomarker profiles demonstrate FASN inhibition in patients
• Early data in combination with weekly paclitaxel show expected PK results and no newly emergent toxicities. The combination has been well tolerated to date
• Three patients with NSCLC (one monotherapy and 2 in combination) have evidence of stable disease after >12 weeks of treatment

Demographics

TVB-2640 + Monotherapy = 200 mg flat
TVB-2640 + Combination = 120 mg/m² flat

Time on Study

Study Days vs Treatment Cycle #

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This poster is available at: [link to poster at meeting]