Introduction

• 3-V Biosciences’ first-in-class, oral FASN inhibitor is in Phase I clinical trials for the treatment of solid tumors
• Fatty acid synthesis (FASN) catalyzes the synthesis of palmitate from acetyl-CoA, malonyl-CoA, and NADPH
• Palmitate and palmitate-derived lipid function in vital cellular processes such as energy metabolism and cellular membrane biosynthesis
• Palmitate is conjugated directly to specific proteins as a mechanism to affect protein localization and activation
• FASN tumor expression has been found to be increased in a stage-dependent manner with high expression associated with diminished patient survival
• FASN activity promotes the tumorigenic capacity of cells by multiple mechanisms including enhanced macromolecular biosynthesis and glucose metabolism, cell growth and survival signal transduction, cellular stress response, and resistance to chemotherapeutics
• In vitro and in vivo studies in preclinical tumor models demonstrate that FASN inhibition reduces tumor cell proliferation and induces apoptosis
• Preclinical studies have discovered biomarker candidates and provided insight into the mechanisms of action that result in tumor growth inhibition and apoptosis

TVB-2640 Inhibition of COLO-205 and HCT-116 Rat Xenograft Tumor Growth Aligns with In Vitro Sensitivity Data

TVB-2640 Induces a Metabolic Signature of FASN Inhibition in COLO-205 Xenograft Tumors

• Elevated malonyl carnitine, decreased palmitic acid, and altered beta-oxidation among most significant changes observed by metabolic profiling

TVB-2640 Indicates Gene Expression Changes in Metabolic, Growth, Proliferation, and Survival Pathways in COLO-205 Xenograft Tumors, Less Significantly in HCT-116 Tumors

Inhibition of AKT and Beta-Catenin Pathways by TVB-2640 Associates with Efficacy in COLO-205 Xenograft Tumors

Results

In Vitro Sensitivity of Selected Tumor Cell Lines to FASN Inhibition

• Tumor growth inhibition by TVB-2640 is associated with inhibition of Lipogenic

Conclusions and Status

• TVB-2640, a first-in-class oral FASN inhibitor, is in Phase I clinical development for the treatment of solid tumors
• Expression of total beta-catenin and S657 phosphorylated beta-catenin associate with sensitivity in FASN inhibition for many tumor cell lines
• TVB-2640 demonstrates dose-dependent single agent tumor growth inhibition in the COLO-205 and HCT-116 rat xenograft tumor models with relative sensitivities that align with in vivo data
• Tumor growth inhibition by TVB-2640 is associated with inhibition of p-c-Jun, c-Myc and AKT and modulation of tumor gene expression
• Tumor cell line stratification according to published biological, classical epithelial or mesenchymal candidates
• Additional preclinical studies are ongoing to expand the discovery and assessment of biomarkers using tumor cell line and patient-derived tumor data

References


Gene Expression Signatures Classify Sensitivity of Tumor Cell Lines to FASN Inhibition