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


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Abstract

FASN is the rate limiting enzyme in de novo lipogenesis (DNL). It is a validated therapeutic target in cancer and has been shown to be essential for growth in many tumor types. A first-in-class, selective FASN inhibitor (TVB-2640) was recently developed and has shown to inhibit tumor growth in vitro and in vivo.

Methods: The First-in-Human Phase I study was a multicenter, dose escalation study conducted in patients with advanced solid tumors. The primary objective was to determine MTD. Secondary objectives were to assess antitumor activity and characterize safety.

Results

• Oral, once daily; 21 days in monotherapy or 28 days in combination with paclitaxel.
• 14 NSCLC patients enrolled on monotherapy.
• 75% KRAS-MUT on study > 12 weeks.
• 0% KRAS-WT on study > 12 weeks.
• Similar plasma TVB-2640 exposure across MUT and WT patients.

TVB-2640 is the only selective FASN inhibitor in advanced-stage solid tumors. FASN expression correlates with poor prognosis. Selective disruption of palmitate biosynthesis (which is primarily derived from DNL) leads to apoptosis in many tumor cells.

FASN: An Integrated Target in Tumor Biology

- Broad monotherapy activity in multiple solid tumors, including 75% (6 of 8) NSCLC KRAS-MUT patients with > 12 weeks SD.
- Well tolerated with majority grade 1-2 adverse events at the MTD, even when combined with paclitaxel.

FASN Expression in Human NSCLC

- Markedly higher in NSCLC patients compared to normal donors
- NSCLC serum FASN among the highest expression of >10 patients tested.

Archived FFPE sections stained with FASN CST rabbit Ab (sc-20633) using standard method. Immunohistochemistry analysis was performed on archived fixed tissue using a commercially available ELISA kit (PerkinElmer, MA).

Objectives

- Safety, MTD, PK, recommended Phase-2 dose (monotherapy and in combination with chemo) and preliminary activity.
- Biomarkers of response and pharmacodynamic biomarkers.
- FASN inhibition is a novel approach to cancer treatment.
- Selective disruption of palmitate biosynthesis leads to apoptosis in many tumor cells.
- FASN expression correlates with poor prognosis in certain tumor types including NSCLC (Visca et al. 2004).
- TVB-2640 is the only selective FASN inhibitor in clinical trials.
- Preliminary data show:
  - Markedly higher in NSCLC patients compared to normal donors.
  - NSCLC serum FASN among the highest expression of >10 tumor types tested.

Study Design and Key Eligibility

- Oral, once daily; 21 days in monotherapy or 28 days with a taxane; continuous cycles.
- Adult patients (ECOG 0-1), with pathologically confirmed metastatic or advanced-stage solid tumors, standard accepted Ph-I Inclusion criteria.
- Excluded pts with clinically significant ophthalmologic finding, including history of dry eye.
- The TP2D has been defined as 100mg/mL with DLs of palmar plantar erythrodysesthesia and corneal edema. The trial is currently in dose expansion in multiple tumor types as monotherapy and in combination with taxane regimens:
  - TVB-2640 plasma exposure increases with dose, has a half life of approx. 16 hr and was unaffected by paclitaxel.

Results

- TVB-2640 demonstrates a favorable tolerability profile with no significant GI, hematologic or serum chemistry adverse events; no evidence of 0% prolongation by Heller monitoring.
- Biomarker analysis demonstrates target engagement (FASN inhibition), and inhibition of lipogenesis in patients.
- NSCLC KRAS-MUT patients remain on study longer than NSCLC KRAS-WT patients, when treated with TVB-2640 monotherapy.
- Further exploration of biological activity is underway in heavily pre-treated ovarian and breast cancer patients in combination with paclitaxel and docetaxel:
  - Breast: 3 confirmed PRs and 8 SDs (in combination with paclitaxel).
  - Ovarian/Peritoneal: 1 confirmed PR and 58-98% decreases in tumor marker CA-125 in mii patients (in combination with paclitaxel).
- High baseline serum FASN associated with longer duration of study, a potential patient selection marker.

Conclusion

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Thank you to the Patients and Their Families