FASN inhibition is a novel approach to cancer treatment. Selective disruption of palmitate biosynthesis leads to apoptosis in many tumor cells. FASN is highly expressed in breast tumors and correlates with poor prognosis (Visca et al., 2004). TVB-2640 is the only selective FASN inhibitor in clinical trials. Preliminary data show: -3 confirmed RECIST partial responses (cPR) -Multiple cases of prolonged stable disease (SD) (>16 wks) with 1 continued SD at week 65 -Well tolerated with majority grade 1-2 adverse events at the MTD; even when combined with paclitaxel.

**FASN: An Integrated Target in Tumor Biology**

**Introduction**
- FASN inhibition is a novel approach to cancer treatment.
- Selective disruption of palmitate biosynthesis leads to apoptosis in many tumor cells.
- FASN is highly expressed in breast tumors and correlates with poor prognosis (Visca et al., 2004).

**Objectives**
- Safety, MTD, PK, recommended Phase-2 dose (monotherapy and in combination with chemos) and preliminary activity.
- Biomarkers of response and pharmacodynamic biomarkers.

**Study Design & Key Eligibility Criteria**
- 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-1 In-Exclusion criteria.
- Clinically significant ophthalmologic finding, including history of dry eye, excluded.
- The RP2D has been defined as 100mg/m² 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. 15 hr and was unaffected by paclitaxel.

**More information regarding study design:**

**Safety**

**Pharmacodynamics**

TVB-2640 inhibits FASN and de novo lipogenesis

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Hormone/Her2 Status</th>
<th>Response</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>ER+, PR+, Her2+</td>
<td>cPR</td>
<td>Time on study =&lt; 23 weeks -Pretreatment/dose/best result = CR</td>
</tr>
<tr>
<td>Breast</td>
<td>ER+, PR-, Her2+</td>
<td>cPR</td>
<td>Time on study =&lt; 23 weeks -Pretreatment/dose/best result = SD</td>
</tr>
<tr>
<td>Breast</td>
<td>ER-, PR+, Her2+</td>
<td>cPR</td>
<td>Time on study =&lt; 23 weeks -Pretreatment/dose/best result = LM (adjacent setting)</td>
</tr>
</tbody>
</table>

**Stable Disease:** 11 of 15 for 10+ weeks

**Conclusions**
- TVB-2640 combined with weekly paclitaxel resulted in multiple RECIST cPRs and prolonged SD in 93% of patients treated.
- TVB-2640 demonstrates a favorable tolerability profile with no significant GI, hematologic or serum chemistry adverse events; no evidence of QTc prolongation by Holter monitoring. Though not observed in monotherapy, symptomatic pneumonitis has been observed in 5 pts treated in combination with paclitaxel.
- Biomarker analysis demonstrates target engagement (FASN inhibition), and inhibition of lipogenesis in patients.
- Further exploration of biological activity is underway including Investigator Sponsored Trials of TVB-2640 in monotherapy and in combination treatment.

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Thank You to the Patients and Their Families