Threshold Pharmaceuticals Inc. (THLD)

Updated Data Presented at SNO for Threshold's TH-302 in Glioblastoma

Threshold Pharmaceuticals (NasdaqCM: THLD) announced updated data from a Phase I/II investigator-sponsored trial (IST) of TH-302 in combination with Roche’s Avastin (bevacizumab) for glioblastoma. The data were presented on November 14 at the 2014 Society for Neuro-oncology (SNO) meeting, indicating that the combination of TH-302 and Avastin leads to a median progression free survival and overall survival rate exceeding historical control values in patients whose disease progressed after single-agent Avastin treatment. The results support the launch of a planned Phase II IST that will be funded by a grant from the FDA.

- **64% Clinical Benefit for TH-302 plus Avastin in GBM Patients who Progressed on Avastin alone.** Threshold’s TH-302 is being examined in a Phase I/II investigator-sponsored trial (IST) in GBM patients who are refractory to Avastin. TH-302 is a hypoxia-activated prodrug intended to reduce disease progression from GBM, which is associated with hypoxia, in patients who have failed Temodar (temozolomide) and Avastin and need a third-line treatment. Results presented at SNO show that combination therapy of TH-302 and Avastin led to a clinical benefit rate of 64% (14/22).

Out of 22 patients evaluable for response according to the Response Assessment in Neuro-Oncology (RANO) criteria, best responses included 1 complete response (CR), 3 partial responses (PR), and 10 cases of stable disease (SD). Median progression free survival (PFS) was 2.8 months and median overall survival (OS) was 4.6 months. This is promising considering that patients who normally receive a second Avastin-containing regimen experience median PFS of approximately 1 month and those who discontinue the regimen experience a median OS of less than 3 months.¹

- **Fully Funded Phase II Trial Planned.** The lead investigator of the Phase I/II study, Dr. Andrew Brenner of Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center, San Antonio, has received funding for a Phase II study of TH-302 in refractory GBM from the FDA’s Office of Orphan Product Development. The study is designed to enroll up to 33 patients who will be treated with the recommended Phase II dose of 670 mg/m² TH-302 plus Avastin. Threshold and Merck KGaA will provide TH-302.

Expected Upcoming Milestones

- December 2014 – Multiple myeloma data at ASH meeting.
- H2 2015 – Number of events reached (n=434 deaths) for Phase III soft tissue sarcoma trial; top-line data expected thereafter.
- Q1 2016 – Primary analysis of overall survival for Phase III soft tissue sarcoma trial.
- 2016 – Top-line data from Merck KGaA-sponsored MAESTRO Phase III pancreatic cancer study.
**Fast Track Designation for TH-302 in Soft Tissue Sarcoma.** On November 11th, Threshold reported Fast Track Designation from the FDA for TH-302 as a treatment for soft tissue sarcoma (STS) patients with metastatic or locally advanced disease in the first-line setting. Fast Track is granted to drugs in development for conditions with no current therapy or that have potential to exceed the benefits of existing treatments. It allows for more frequent meetings with the FDA and for companies to submit an NDA on a rolling basis. The new designation is a positive development as Threshold moves closer to Phase III data from its ongoing trial with TH-302 in STS, which are expected in Q1 2016.

**Details of SNO Data.** Dr. Brenner led a Phase I/II IST that enrolled 28 patients who had failed Avastin therapy. The first 14 patients were randomized in a 2:1 ratio to a single dose of TH-302 administered at 575 mg/m² pre-surgery, or placebo. Following surgery, 9 patients proceeded to combination therapy of Avastin at 10 mg/kg plus TH-302 at one of three dose levels (240, 340, 480 mg/m²) every two weeks until disease progression. After the first 5 patients were enrolled into the highest dose cohort, the protocol was amended to allow patients to proceed directly to combination therapy without surgery. A total of 14 patients proceeded directly to combination therapy with 480 mg/m² (n=1) or 670 mg/m² (n=13). The median number of prior therapies was 3.

Out of 22 patients evaluable for response, there was 1 CR, 3 PRs, and 10 cases of stable disease, for a clinical benefit rate of 64%. Figure 1 shows the percentage change in tumor volume for each patient and the corresponding dose of TH-302. At the time of poster presentation, three patients remained on TH-302/Avastin treatment and the two evaluable for a response are noted by a “+”. More than 50% of patients receiving 670 mg/m² of TH-302 achieved SD or a tumor response, and this will be the dose used in the upcoming Phase II trial.

*Figure 1. Change in Tumor Size and Best Tumor Response for Each Dose Cohort*

Dr. Brenner also presented median PFS and OS data that were updated since the last presentation at the 2014 American Society of Clinical Oncology meeting. Figure 2 shows the median PFS and OS in months, and the 4 and 6-month survival rates. By way of comparison, although we must be careful when comparing results from different studies, the median PFS and OS values from a retrospective analysis of 54 patients are listed in the table. In the retrospective analysis, patients who failed Avastin and received a second Avastin-containing regimen experienced a median PFS of 37.5 days compared to 2.8 months for the TH-302 plus Avastin study. Similarly, the median OS of patients who discontinued a second Avastin-containing regimen was 82 days compared to 4.6 months for patients receiving TH-302.
and *Avastin*. The data indicate that TH-302 may provide a viable option for patients who are refractory to single-agent *Avastin* and have no effective option to extend survival.

**Figure 2. Progression Free and Overall Survival**

<table>
<thead>
<tr>
<th>Study</th>
<th>Survival</th>
<th>Median, months (95% CI)</th>
<th>4-month Rate (95% CI)</th>
<th>6-month Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TH-302 study</td>
<td>PFS</td>
<td>2.8 months (1.9-3.9 months)</td>
<td>22% (3.2-41%)</td>
<td>11% (0-29%)</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>4.6 months (3.4-6.2 months)</td>
<td>55% (33-77%)</td>
<td>33% (12-55%)</td>
</tr>
<tr>
<td>Retrospective analysis</td>
<td>PFS</td>
<td>38 days</td>
<td>~5%</td>
<td>~3%</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>82 days</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Source: Brenner, A. et al., 2014*

- **Hypoxia Analysis.** A second poster was presented at SNO regarding the identification of hypoxia biomarkers for use in diagnosing and monitoring disease progression in GBM.\(^3\) Patients from the TH-302 study were given an exogenous marker of hypoxia known as pimonidazole (pimo) prior to surgery and tumor samples were analyzed for pimo staining and levels of a natural hypoxia marker, carbonic anhydrase IX (CAIX). Out of 11 resected tumor samples, there was a strong correlation and co-localization between pimo and CAIX (p<0.001). There tended to be more hypoxia in patients with PRs or SDs, and patients treated with a single dose of TH-302 prior to surgery tended to have higher levels of γ-H2A.X, a marker of DNA damage, than those who received placebo prior to surgery. Patients who were treated with TH-302 prior to surgery and who displayed high levels of γ-H2A.X tended to have a better outcome, which is consistent with TH-302 being more active in these patients. The data imply that CAIX could be used as a predictive biomarker, and that γ-H2A.X may be used to monitor TH-302 activity. Finally, analysis of patient tissue and serum samples using mass spectrometry indicate that elevated tumor hypoxia is associated with detection of atypical fatty acids, which may be applicable as non-invasive biomarkers of brain tumor hypoxia.


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