Threshold Pharmaceuticals is about to go up against the Feuerstein-Ratain rule with its hypoxia-activated alkylating agent evofosfamide, not just once but twice over the next few weeks. Unfortunately, this rule of thumb does not predict success for evofosfamide's pivotal trials in soft tissue sarcoma and pancreatic cancer.

Named after the TheStreet.com's biotech commentator Adam Feuerstein and University of Chicago oncologist Mark Ratain, the F-R rule forecasts the outcome of cancer drug phase III readouts using biotech companies' market capitalisation six months before that key date. It predicts failure for those companies falling short of $300m. Threshold, whose market cap at the appointed time was, and still is, $260m, does not make the cut.

Breaking the rules

Threshold will be hoping to be the first to break the F-R rule. However, strictly speaking it might not apply – the rule was only ever applied to unpartnered assets and the company has a development partner for evofosfamide in the form of Merck KGaA.

Whether this will make any difference to the underlying tenet of the formula is unclear: turned around, the F-R rule suggests the stock market is very good at identifying late-stage oncology programmes that are unlikely to succeed by ascribing low valuations to those companies.

Threshold is conducting the 406 phase III trial of evofosfamide in soft tissue sarcoma, while Merck is handling a similar study, named Maestro, in pancreatic cancer. Both studies are fully enrolled and have or are shortly expected to reach the required number of deaths for analysis, so that top-line data are expected around the year end.

The soft tissue sarcoma trial is examining evofosfamide in combination with doxorubicin versus doxorubicin alone in patients with locally advanced unresectable and metastatic disease. The study completed enrolment of 640 patients in December 2013 and requires 434 events for its final analysis.

The trial aims to show a 33% reduction in risk of death with evofosfamide, with a hazard ratio of 0.75, assuming longer survival in the control arm. This HR would equate to a four-month OS benefit, but this now seems low, and is perhaps one of the main reasons for long-running investor scepticism.

Another could be the fact that, in spite of already increasing the number of patients from the original enrolment target, the 406 study might still be underpowered to show an effect – suggested by longer-than-expected 17-month survival in a doxorubicin-only control arm in an unrelated study of Ziopharm’s palifosfamide.

In spite of these concerns, Threshold believes an overall survival improvement of only 21% would still be sufficient for approval.

Pancreatic cancer

Meanwhile, the Merck-run study in the famously challenging indication of pancreatic cancer tests evofosfamide in combination with gemcitabine versus gemcitabine alone. The study recruited 694 patients and requires 508 events for the final analysis.

Here, the main issue for investors is that since the study started, the standard of care for first line pancreatic cancer has moved to gemcitabine/Abraxane. A phase I study of evofosfamide plus gemcitabine/Abraxane has been conducted to show that the drugs can be safely combined, but even with a positive result in Maestro, doctors would have to speculate on the clinical benefit of this triple-pronged strategy.

Whether or not the F-R rule applies to Threshold, the company is clearly approaching a critical phase in its development that could reward investors if the studies are a success.
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Indication</th>
<th>Design</th>
<th>n</th>
<th>ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>406</td>
<td>Soft tissue sarcoma</td>
<td>doxorubicin +/- evofosamide</td>
<td>640</td>
<td>NCT01440088</td>
</tr>
<tr>
<td>Maestro</td>
<td>pancreatic cancer</td>
<td>gemcitabine +/- evofosamide</td>
<td>694</td>
<td>NCT01746979</td>
</tr>
</tbody>
</table>

To contact the writer of this story email Robin Davison in London at news@epvantage.com or follow @RobinDavison2 on Twitter

© Copyright 2019 Evaluate Ltd.