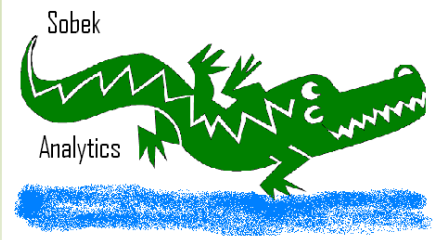


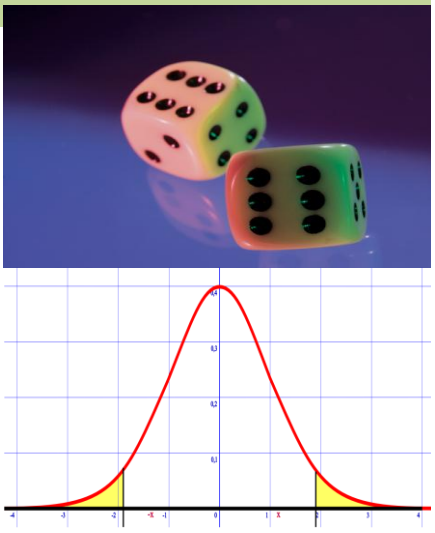
Threshold Pharmaceuticals (THLD): Is the Pancreatic Cancer Data a Good Bet?

The Upcoming Data

Threshold has let investors know that the middle to end of February, they will be releasing data from their current trial of TH-302 in pancreatic cancer. Investor are excited given that the bar seems to be low for pancreatic cancer and the data that the company highlighted at a investor conference in December 2011 seemed quite positive. So the question is what are the odds that the trial will produce statistically significant results in progression free survival (PFS) and/or overall survival(OS)?

In general, my analysis shows that it is likely that the pancreatic cancer trial will show a statistically significant PFS effect and quite possible an OS effect as well. This analysis, however, is contingent on the trial producing a control group PFS and OS similar to the historic averages. Given that the trial is lasting longer than expected, it could be the case that the control group is doing better than its historic controls, so anyone investing for positive trial results is assuming that this is not the case. That being said, it is unlikely that the extend timeline is being completely driven by the control group in which case a PFS effect is still likely but OS would be more of a toss-up.

Contents

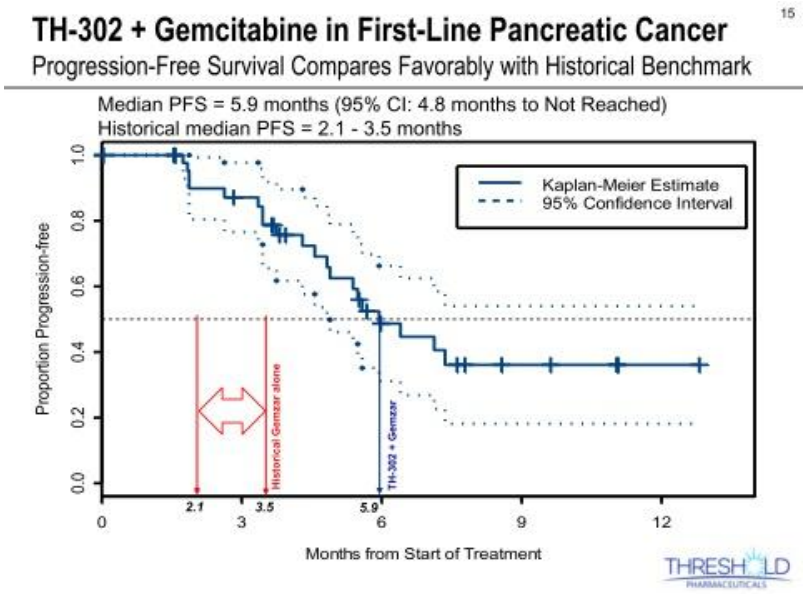


What Produces Statistically Significant Results?

The gold standard in controlled drug trials is statistically significant effects. In general, this means that there is only a 5% (or lower) possibility that the favorable results are produced by chance. In other words, there is a low probability that the results are spurious implying a high probability that the drug is producing a positive effect. The problem when moving from non-controlled to controlled trials is that there is no prior data available to handicap the odds that a statistically significant effect will be seen. In this case, THLD has shown impressive effects in a single arm study but without a control group there is no way to know if those results are real or lucky.

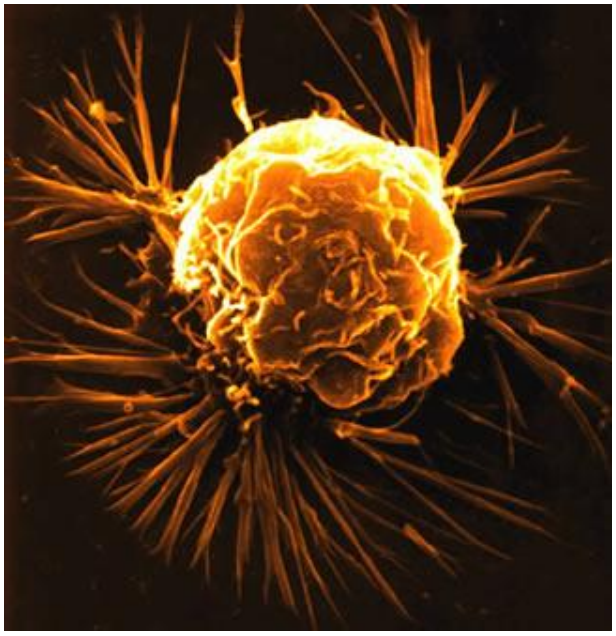
Often when a company provides data from a single-armed study, they include an historical control group. This historical control is based on past trials and is difficult to interpret for a number of reasons. First, the population that the historic control is based on is not the same as the trial. Second, the historic control is often based off of early uses of the control drugs. This is important as doctors get more experience with a drug, they likely get better able to deal with side effects and increase the benefit of its use. As such, historic controls can actually understate what would be seen in a controlled trial setting (see AVEO for this problem).

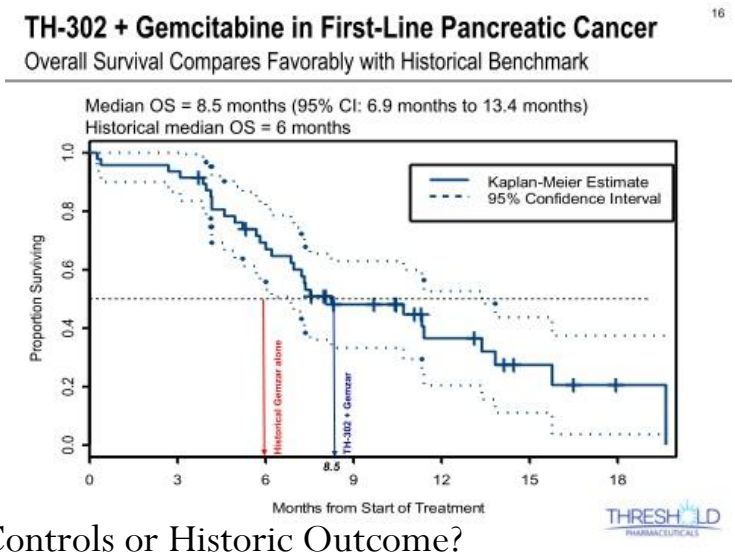
Given that there is only a 5% chance that the median PFS would be 4.8 or below, then the 4.16 likely needed to reach statistical significance seems like a good bet.



Can TH-302 Hit a PFS Endpoint?

If you just look at this slide it seems obvious that TH-302 could hit a PFS endpoint. The 95% confidence intervals are clearly higher than the historic control, so what is the issue? To rephrase the question slightly, what are the odds that if the control group in the phase II trial is at the high end of the historical control data that the 95% confidence intervals of TH-302 do not straddle it? For instance, you could have a median PFS of 5 months and a confidence interval of 2 months and then it would hit the 3.5 month historic control indicating a statistically insignificant result. But is that outcome likely? There is no way of know for sure because it depends on the mean effect and the standard errors. With a larger data set the standard errors will be smaller but we will not know how much smaller. With essentially a tripling of the sample size between both a larger trial and its expansion, it is reasonable to expect a 40% decrease in the size of the standard errors. From this figure at .50, confidence interval appears to be about 1.1 months to the left of the median PFS, which with a 40% decrease one could figure that PFS has to be .66 months ahead of the control to be statistically significant. So given the upper edge of the historic control, the median PFS would have to be 4.16 or higher. While it is difficult to know for sure, the above figure shows the 95% confidence interval's lower bounds crossing at about 4.8. Given that there is only a 5% chance that the median PFS would be 4.8 or below, then the 4.16 likely needed to reach statistical significance seems like a good bet. Of course, the story does not end there.





Historic Controls or Historic Outcome?

As the previous section indicated, if the control group has a PFS outcome similar to historic controls (even the upper end), then there is a high probability of a statistically significant PFS. But there are always risks associated with using historic control. In addition, the trial has lasted longer than expected as this is an event driven analysis. While it is easy to get excited that the longer trial is driven by longer treatment effects, the recent AVEO results (which was also an event driven trial that lasted longer than expected) showed that controls can show unprecedented effects. So the question becomes, what happens if the longer trial is driven by a better control group?

The trial is essentially lasting about 2 months longer than expected. So if we assume that is completely driven by the control group and that the company was using the high end control as their expectation, then we could see a control PFS of 5.5 months. In order to get a statistically significant treatment effect with the assumptions above, we would need a median PFS for TH-302 of 6.16. Given the previous results of 5.9 this would be a difficult target to hit. In fact, there is probably only a 40% chance that the median PFS would be 6.16 or higher. The question, however, is how likely is the extended trial time caused by the control group or the treatment group or a little bit of both? There is no clear answer to this and the data that we have do not speak to it. That is a decision that any potential investor needs to make.

Hitting OS: More Difficult

Hitting a statistically significant OS mark would be much more difficult. Even with the previous data, it almost did not reach it. With the OS data, we can estimate the confidence intervals for the low end OS to be lower and at about 1.14 months. Assuming the historic control of 6 months, the median OS in the new trial needs to be 7.14 months. Unlike the PFS analysis this falls within the 95% confidence interval. In addition, if we add the two months of the extended trial to the historic control, it means that the OS now needs to be 9.14.

As such, the results show that hitting an OS effect is possible but less likely than one for PFS. Given that it is a secondary endpoint, it is very likely that the trial is not even close to being powered to find an OS effect.

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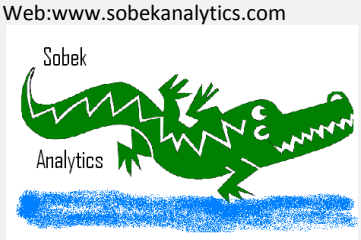

Conclusions

In general, there seems to be a high probability that the pancreatic cancer trial will produce a statistically significant PFS effect. In addition, it is quite possible that there will be an OS effect as well. The key caveat, however, is the control group and the additional time needed to complete the trial. If one assume it is not associated with the control group, then it is almost impossible for the trial not to hit its points. Keep in mind that is an assumption and it is also within the realm of possibility that this is driven by the control group in which case, PFS is possible and OS unlikely.

Disclaimer

I am not a certified financial analyst. All the information provided in this report is my interpretation and may contain errors. Please, do not invest based solely on my opinions as it is critical for all investors to conduct their own due diligence and invest in ways that best fit their own needs. In addition, I own shares of THLD.