Evaluate Vantage

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Upcoming events – crucial cancer data for Tocagen and Syndax

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Tocagen could soar or sink on interim brain cancer data, while judgement day approaches for Syndax.

Welcome to your weekly digest of approaching regulatory and clinical readouts. At first glance it appears that Tocagen has two clinical-stage assets, but in fact Toca 511 & Toca FC is a single product – a combination administered in stepwise fashion. The forthcoming readout of a pivotal trial in brain cancer will be a critical catalyst for the company's stock.

It is perhaps the difficulty of treating brain cancers that has led to Tocagen developing a project with such an involved mechanism of action. After resection of the tumour Toca 511, a retroviral replicating vector encoding the enzyme cytosine deaminase, is injected into the surgical site. The vector is preferentially taken up by the rapidly dividing cancer cells, Tocagen says, which then produce the enzyme.

The patient then takes repeated oral doses of Toca FC, an extended release form of 5-fluorocytosine, which is converted by cytosine deaminase into the chemotherapy fluorouracil, in theory killing the tumours.

The Toca 5 trial is pitting Toca 511 & Toca FC against the standard of care – the investigator's choice of either Avastin or chemo – in 400 patients with either glioblastoma multiforme or anaplastic astrocytoma. The statistical plan assumes a median overall survival of 9.8 months for control versus 14.3 months for the Toca 511 & Toca FC cohort. 257 events (deaths) will provide the study with 85% power to detect a hazard ratio of 0.685, Tocagen says.

At the first interim cut last August, when half the deaths had occurred, it was decided that the trial would continue unchanged. A second look, due in the next couple of months, will take place after 75% of the events, and if survival is good enough at this point the trial could be stopped early and the project filed for approval.

If this comes to pass Tocagen's stock will soar, with Leerink analysts suggesting that it might reach $70 – the shares currently change hands for $9.13. But the same analysts only give the study an 11% chance of success, citing the dismal history of phase III trials in glioblastoma. Safety with lack of efficacy would see Toca 5 continue to final analysis later this year.

Jonathan Miller at Evercore ISI is more bullish, stating that the interim data have "a good shot at hitting". Tocagen must hope that this analysis is right; if Toca 5 fails the company's next most advanced trials, also of Toca 511 & Toca FC in brain cancer, are phase I.

Toca 511 & Toca FC annual sales ($m)			
2018	**2020e**	**2022e**	**2024e**
-	4	99	275
Source: EvaluatePharma.			

Syndax landmark

Meanwhile, entinostat already has two strikes against it in immune checkpoint combination studies, and Syndax has focused all near-term efforts on a third, NCI-sponsored trial. This test, coded E2112 and combining the HDAC inhibitor with Aromasin, enrolled 608 second-line, HR-positive, Her2-negative breast cancer subjects, and interim data are due in the current quarter.

E2112 has overall and progression-free survival as co-primary endpoints, and a positive hit will lead to regulatory filing. This "would be a landmark result that will be transformative", Syndax said last month. "It will require our focus and resources."

Still, while the group insists that HR-positive, Her2-negative breast cancer has blockbuster potential, the setting actually has relatively good prognosis. Aromasin is a hormone therapy approved in the adjuvant and first and second-line settings, the last in combination with Novartis's Afinitor.

In E2112 the entinostat combo will be trying to beat Aromasin alone, and Syndax has especially played up chances of an OS hit. This is clearly because in phase II the combo prolonged median OS, an exploratory endpoint, from 19.8 to 28.1 months, yielding a nominal p value of 0.036, while a numerical PFS benefit did not hit significance at 0.05.

The company accepts that anti-CDK4/6 therapies like Pfizer's Ibrance are being used increasingly first line in this setting, but says there is a clear need in patient who relapse. It says 30-40% of the E2112 subjects will have progressed on an anti-CDK4/6 agent.

The focus on E2112 came after the failures of studies combining entinostat with Bavencio and Tecentriq, and even a surprise success in combination with Keytruda did not prompt a change of tack (*AACR 2019 – Entinostat turns Syndax's frown upside down, April 1, 2019*). Syndax raised money before the E2112 readout, however, and this might not be a particularly positive sign.

This is an updated version of an earlier article.