Evaluate Vantage

July 28, 2020

A turn-up for Spectrum’s book

Jacob Plieth

Poziotinib unexpectedly succeeds in a lung cancer niche, but competition from Takeda must be tracked closely.

After the failure of Spectrum’s poziotinib in a potentially pivotal study cohort in December hopes for the trial’s remaining arms were low. But analysis of the second cohort yesterday yielded a positive outcome, sending the company’s stock up 30% this morning.

Spectrum looks set to file on the latest data, pending agreement with the US FDA, though the niche in which poziotinib has succeeded, a subset of a subset of non-small cell lung cancer, is more poorly diagnosed and even smaller than the one in which it failed. Investors also need to remember the threat of Takeda's competing and potentially more efficacious project.

For now, however, Spectrum can bask in some glory. In its multi-cohort Zenith20 trial poziotinib has yielded an independently adjudicated overall remission rate of 28% among 90 second-line or later NSCLC subjects with a Her2 exon 20 insertion.

Zenith20 is designed so almost any one of its arms can be registrational, and Spectrum confirmed that it would request a meeting with the FDA to discuss filing. The benchmark Spectrum had set in cohort 2 of the uncontrolled trial was a lower bound of 17%, and as the 95% confidence interval for the ORR was 18.9-38.2% it deemed this part of the trial a success.

Poziotinib's Zenith20 study in NSCLC (possibly registrational cohorts)			
Cohort	**Setting**	**Subjects**	**Data**
1	Relapsed, EGFR exon 20 insertions	115	Fail: confirmed ORR 14.8%, mDOR 7.4mth
2	Relapsed, Her2 exon 20 insertions	90	Success: confirmed ORR 27.8%, mDOR 5.1mth
3	1st-line EGFR exon 20 insertions	70	Due late 2020
4	1st-line Her2 exon 20 insertions	70	–
6	EGFR Tagrisso failures	30	–
7	Atypical EGFR or Her mutations	30	–
Source: Spectrum. ORR=overall remission rate; mDOR=median duration of response.			

Zenith20's first cohort, relapsed NSCLC driven by EGFR exon 20 insertions, had failed, yielding an ORR of just 15%. On a call today Spectrum confirmed that both analyses had been verified by the same central review committee, but it could offer no explanation for the disparate result, beyond citing "different receptor targets".

This raises fresh questions about why poziotinib, a Her2 inhibitor, was taken forward in this NSCLC niche; Spectrum had initially been looking at breast cancer, but was persuaded otherwise by MD Anderson's Cancer Moon Shots programme, which had preclinically identified poziotinib as a potent agent against exon 20 mutations (*The first test of Spectrum's shift, November 28, 2019*).

Spectrum investors will be aware of a key competitor in the exon 20 insertion niche: Takeda's mobocertinib (TAK-788), which at Asco 2019 yielded a 43% ORR, with 7.3-month median duration of response in EGFR exon 20 insertion-mutant NSCLC.

On a cross-trial basis these data clearly beat Zenith20's cohort 1. Unfortunately Takeda has not yet generated any results in Her2 exon 20 mutants, so a comparison against Spectrum's latest dataset is not possible.

Niche

If Spectrum's poziotinib strategy simply needs refining, then investors should be aware of how small the niche is. Takeda reckons 6% of EGFR-mutated NSCLC tumours have exon 20 insertions; Spectrum says this equates to 2.1% of NSCLC, versus just 1.5% for exon 20 insertions in Her2.

Thus the space Spectrum's latest dataset could open up amounts to 6,500 US and EU patients a year, across all therapy lines. And a separate problem is that Her2 exon 20 mutations are generally not screened for at present, whereas thanks to drugs like Iressa and Tagrisso diagnosis of specific types of driver EGFR mutations is pretty standard.

Spectrum hopes that clinicians will start testing based on the data it has generated, but without a big partner to drive such an effort this is wishful thinking. Spectrum also surely needs some of Zenith20's other cohorts to succeed to show that yesterday's readout was not a fluke.