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EASL Preview – Hep C combination therapies to take centre stage

Jonathan Gardner

The excitement over Merck & Co's boceprevir and Vertex Pharmaceuticals' telaprevir has peaked, and attention in the hepatitis C world is turning to successors that, for example, may allow physicians to pull interferon from treatment plans altogether. The upcoming scientific meeting of the European Association for the Study of the Liver (EASL) may shine a new spotlight on combination therapies from established players that could improve on the progress expected from the first protease inhibitors for the liver disease.

EASL's International Liver Congress is also expected to be a coming-out party of sorts for Pharmasset's antiviral combination, which if successful would remove interferon and ribavirin from standard therapy. Shares in the New Jersey firm surged to a record high of $69.63 last week following release of EASL abstracts, demonstrating that investor confidence has been building (*Pharmasset staging a remarkable recovery on hepatitis C franchise, November 5, 2010*). Away from hepatitis C, some specialists will also be interested in phase I/II data from a novel treatment for liver cancer.

Differentiators

For many in the field boceprevir, now called Victrelis, and telaprevir are considered done and dusted. Both have published phase III results showing improvements over the accepted standard of care, a combination of antiviral ribavirin and immunomodulator peginterferon alfa and both are filed for approval.

Telaprevir is expected to be the biggest launch of 2011, with more than $4bn in sales forecast in 2016 for Vertex and ex-US partner Johnson & Johnson, while boceprevir will earn a useful $789m, according to *EvaluatePharma's* consensus forecast (*Which of 2011's launches will be future blockbusters?,February 3, 2011*).

At this point, the name of the game for both drugs is getting a labelling edge, as the data scheduled for release at EASL for both drugs makes plain – presentations will include data on race and ethnicity; geography; fibrosis, cirrhosis, anaemia and IL28b genotype status; and those who fail to respond to respond to previous treatments.

Analysts from UBS described the data on the two protease inhibitors as "largely incremental," with Vertex's data showing significantly better response than standard of care in patients with the IL28b genotype - a subgroup of particularly good responders – being a positive to relieve any reimbursement worries.

The only surprises for these two drugs at this point would be negative ones - a negative FDA advisory committee review as both face a panel of experts in late April, a complete response letter or an unexpected safety signal. But both have continued to meet most expectations so far.

Combinations

Expectations have been brewing for combination therapies in the hopes that hep C patients could be weaned from one or both of the standard of care drugs – interferon has flu-like and neuropsychiatric side effects, while ribavirin can cause anaemia. Thus it was disappointing when, because of viral breakthrough, Vertex cancelled phase II work on its combination of VX-222 and telaprevir alone in a trial that also included arms with the interferon-ribavirin pairing.

However, Pharmasset's combination of polymerase inhibitors PSI-938 and PSI-7977 has yielded impressive results in reducing viral load in a 14-day phase I study of 16 patients sans the standard of care. Analysts from Leerink Swann said the data has the potential to position the company as a "front runner" in the quest for an interferon free treatment strategy.

As it is early-stage research, it is a long way from confirmation, but it certainly could heighten interest in these unpartnered assets or in Pharmasset as a takeout target (*Sanofi-Genzyme deal leaves few biotech targets standing, February 16, 2011*).

Similarly, Gilead Sciences, which has developed experience in combination therapies involving protease

inhibitors in HIV, is working on an interferon-free combination of GS 9256 and GS 9190. So far it has sufficient data to measure rapid and early viral response – all 13 patients in the interferon-free arm registered viral response at 12 weeks - but data on sustained viral response is not expected until later this year.

Bristol-Myers Squibb's combination of protease inhibitor BMS-790052 and an NS5A inhibitor with standard of care has also scored impressive sustained viral response in patients who have failed to respond to other treatments – 10 of 10 patients in that arm achieved SVR at 12 weeks. However, diarrhoea, elevated liver enzymes and neutropaenia were also reported, suggesting that safety may hold back this combination, the UBS analysts said.

Some non-viral data

Signalling that interest in oncolytic viruses continues to grow, data for Jennerex's JX-594, which targets hepatocellular carcinoma and liver metastases through the epidermal growth factor receptor pathway, showed early positive results (*Therapeutic focus – Oncolytic viruses enter pivotal year, January 26, 2011*). Twenty-three of 35 evaluable patients showed target tumour necroses and decreased density.

However, hepatitis C will dominate proceedings, at least as far as pharmaceutical interventions are concerned. The data suggest that the much-lauded first generation of protease inhibitors will eventually have a great deal to worry about as researchers seek better treatment strategies.