Evaluate Vantage

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EASL 2020 – Assembly finds a partner as hepatitis B inches forward

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As fresh data confirm the promise of RNAi technology in hepatitis B, Assembly brings on Arbutus for its combo strategy.

Arbutus might seem a strange choice of partner for Assembly Biosciences, a company that is already struggling to keep up with bigger players in the hepatitis B space. A recent update on AB-729, the former's RNAi-based hep B candidate, was poorly received; perhaps Assembly had little choice, with other RNAi projects already tied up in existing deals with big pharma.

The agreement between the two companies, announced yesterday, will see Assembly's lead core inhibitor, ABI-H0731, tested in combination with AB-729 and a nucleotide reverse transcriptase inhibitor (NRTI); the latter are the standard of care in this disease. The news was timed to coincide with the EASL medical conference, where several updates from other RNAi contenders are due; these will show the standards for which Arbutus and Assembly need to strive.

Data emerging from Vir Biotechnology is of particular interest. VIR-2218 is an siRNA currently not earmarked for triple combination studies; with J&J working with Arrowhead, and Roche and Dicerna paired up, there was some speculation that Vir and Assembly could have struck a deal.

VIR-2218 appears to be efficiently knocking out HBsAg; also known as surface antigen, it is believed that this closely-watched biomarker needs to be suppressed for a functional cure to be achieved. An ongoing phase II trial of 24 patients found that those in a 50mg dose group achieved maximal reductions in HBsAg at week 12, with a mean reduction of 1.5 log10 from baseline.

A mean reduction of 1 log10 was maintained through Week 28 in this cohort, EASL will hear; this seems to be an encouraging update from a four-week cut of the data, released in April (*Vir bids to enter the hepatitis B race, April 16, 2020)*.

EASL will also get a look at Johnson & Johnson's RNAi contender, licensed from Arrowhead, from a trial conducted in combination with NRTI therapy. Across three doses of JNJ-3989, 22 of 40 patients had sustained HBsAg reductions of more than 1 log10 approximately nine months after the last dose, suggesting impressive durability.

Data from a triple combination study, which adds in a core inhibitor, are eagerly awaited in the wake of data in 12 patients presented at AASLD last year. The longer and larger Reef 1 trial was started last year.

Safety a focus

Elsewhere, early data from a novel antisense project also show what Arbutus and Assembly are up against. A Glaxosmithkline-Ionis presentation of GSK3228836 updates previous AASLD results with a few more patients – across 24 patients, six had HBsAg reductions of more than 3 log10.

Still, one patient in this trial suffered a liver enzyme elevation that was classified as a serious adverse event, although this self resolved. Safety will be closely scrutinised as the full details of all these projects emerge – liver enzyme elevations were seen from Arbutus in March, and this will remain a focus as the Assembly partnership progresses.

Glaxo is confident enough to push on: the company said today that a phase IIb programme will get under way before the end of the year, and it will be interesting to see what combinations it pushes forward.

Assembly and Arbutus, meanwhile, said a phase III triple combination trial will start next year in around 60 virologically suppressed patients. The need for speed in this competitive space is understandable but Assembly is still fighting concerns that its own core inhibitor is underwhelming. An AASLD presentation showed that very few subjects treated with ABI-H0731 managed to achieve a greater than 0.5 log decrease in HBsAg, and an EASL update does not promise to show much more.

Assembly has tried to argue that HBsAg is a less important measure for core inhibitors, and it is true that the project has managed to impressively quash other markers of infection, such as viral DNA and RNA. Mizuho analysts, who recommend buying Assembly shares, point out that making direct comparisons with other agents is not entirely fair due to different doses and combinations used, which is certainly true; at the four week mark ABI-H0731's HBsAg log reduction is in the same ballpark as seen with other projects over a similar timeframe, they argue.

Data due next year from Assembly, looking at what happens to patient's viral load after treatment is reduced, remains a critical milestone for the company (*AASLD 2019 – Assembly asks investors to keep the faith, November 13, 2019*).

But with both Assembly and Arbutus arguably trailing much bigger rivals in the highly competitive hepatitis B space, it remains to be seen whether this nascent partnership will improve either company's chances.