Evaluate Vantage

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# Ash 2017 – Transcend fails to prevent Juno's second collapse

Jacob Plieth

Juno had hoped that the Ash meeting would mark its return as a competitive force in CAR-T. Instead, a keenly awaited update of its now pivotal lymphoma trial, Transcend, disappointed, and yesterday's 14% share price collapse marked the second year in a row that Ash left the company nursing heavy losses.

Not that there was anything disastrous in Transcend; rather, with Gilead's Yescarta already approved for lymphoma, and Novartis's Kymriah about to be, the problem is the absence of a knockout result (see table below). Various analysts at an investor event last night told *EP Vantage* that this was a case of Juno failing to meet "whisper numbers".

Whisper numbers typically represent the buyside's view of upcoming data based on hints dropped by a company rather than any formally declared guidance. In Transcend, they ranged as high as a 70% remission rate in lymphoma patients given Juno's JCAR017 at the six-month time point, according to one sellsider speaking anonymously.

In the event even the most optimistic cut of what is by now an extremely complex dataset showed six-month overall remission of only 50% – a sharp drop from the 74% Juno is reporting at three months. With separate Ash updates showing broadly comparable six-month rates for Yescarta and Kymriah, Juno's potential advantage took a hit.

**Complexity**

Another problem is the growing complexity of Transcend, and the way Juno is parsing the study data to get to the analysis that best represents its target market.

In June the company was still treating Transcend as a phase I dose-finding trial, aiming to begin a separate pivotal study. Now – presumably in the interest of speed – it has carved out a pivotal cohort within the same trial, comprising the most aggressive lymphomas and the higher of two doses, 100 million cells.

At a cut taken in October the total dataset comprised 91 subjects, Juno's head of R&D, Sunil Agarwal, told *EP Vantage*; the core disease dataset within that numbered 65 patients, 27 of whom had received the pivotal dose of cells and were evaluable at one month.

Juno's problem therefore seems to be that an initially strong remission rate falls off, rather like what was seen in Yescarta's Zuma-1 trial; at an Ash update of Kymriah's pivotal lymphoma trial, Juliet, Novartis revealed six-month data showing remission rates holding up well from an initially lower base.

| Comparing pivotal CAR-T studies in lymphoma | | | |
|---|---|---|---|
| **Company** | Gilead | Novartis | Juno |
| **Product** | Yescarta | Kymriah | JCAR017 |
| **Generic name** | Axicabtagene ciloleucel | Tisagenlecleucel-T | Lisocabtagene maraleucel |
| **Study** | Zuma-1 | Juliet | Transcend pivotal cohort |
| | | | |
| **Best ORR** | 82% (101) | 53% (81) | 81% (27) |
| **Best CR** | 54% (101) | 40% (81) | 63% (27) |
| | | | |
| **3mth ORR** | 44% (62) | 38% (81) | 74% (19) |
| **3mth CR** | 39% (62) | 32% (81) | 68% (19) |
| | | | |
| **6mth ORR** | 41% (101) | 37% (46) | 50% (14) |
| **6mth CR** | 36% (101) | 30% (46) | 50% (14) |
| *Source: Ash 2017 presentations. Numbers in brackets refer to total subjects in each given cohort.* | | | |

For the record, across Juno's entire Transcend dataset of disease subtypes and doses best overall remission is 74%, falling to 53% at three months and 35% at six. While the numbers are still small, it seems fair to consider the pivotal cohort as the relevant efficacy comparator from now on.

What will the US FDA want for approval? Approximately 75 patients with six-month data at the pivotal dose, reckons Mr Agrawal, implying that another 50 subjects still have to be dosed. "We are enrolling, and will be filing in the second half of next year. We could be approved as early as the end of 2018."

Yescarta was approved in the US for diffuse large B-cell lymphoma on October 18, and Novartis filed Kymriah on the strength of Juliet data less than two weeks later.

Meanwhile, across the whole Transcend study, "we almost have 100 patients of safety data", Mr Agarwal said. "When you look at what it takes for drugs that have been approved, that's about what you need." And at the investor meeting he rejected an earlier suggestion that Transcend had enrolled a less sick population than Zuma-1.

JCAR017 represents Juno's second shot at a CAR-T approval, after JCAR015 was ditched in the wake of cerebral oedema deaths – the cause of Juno's collapse around the time of Ash 2016. Mr Agarwal said there were no diffuse cerebral oedema cases in JCAR017 trials, and one new non-disease related death was deemed not due to JCAR017.

A key question for the pivotal cohort was whether safety would hold up despite higher dosing, and it did, in fact being slightly better numerically. Juno puts this down to JCAR017 being a defined-composition product of CD4+/CD8+ cells, making it more controllable than CARs generated from bulk T cells.

That said, manufacturing will remain a key focus, especially after Novartis's first Juliet data revealed that a worrying number of subjects were unable to get the product (*ICML – Novartis's non-infusion mystery centres on Juliet's design, June 14, 2017*).

In Transcend JCAR017 was successfully manufactured in 126 of 128 subjects, with the falloff to the 91 actually dosed comprising deaths, withdrawals of consent, disease progressions and patients still awaiting dosing.

**Outpatients**

Another idea Juno is proposing is the treatment of CAR-T subjects in an outpatient setting, intending to keep them safe from nosocomial infection risks, for instance, while still providing medical care on demand. The idea is presumably also geared at cutting the overall cost of CAR-T therapy. An outpatient cohort is running in Transcend.

However, Juno's Ash thunder was stolen by Novartis, when the University of Pennsylvania's Dr Stephen

Schuster revealed that a quarter of the Kymriah subjects in Juliet had actually already been treated as outpatients. The setting is realistic only in lymphoma and not in childhood leukaemia, he stressed.

While Juno also used its investor meeting to signal a surprising new push into engineered T-cell receptor therapeutics, its main focus now must be to get JCAR017 over the regulatory finish line while avoiding further surprises from Novartis or Gilead.

Those bemoaning yesterday's stock collapse can content themselves with the 30% run-up Juno had enjoyed since the start of November, though the CAR-T space is unlikely to learn the dangers of overpromising and underdelivering any time soon.

*To contact the writer of this story email Jacob Plieth in Atlanta at jacobp@epvantage.com or follow @JacobPlieth on Twitter*