Evaluate Vantage

June 14, 2017

ICML – Novartis's non-infusion mystery centres on Juliet's design

Jacob Plieth

Since hotly awaited data from the Juliet study of Novartis's CTL019 were toplined last week investors have been troubled by one key question: why had so many of the enrolled subjects – 40%, no less – ultimately not received the CTL019 CAR-T cells?

At today's presentation of the data at the International Conference on Malignant Lymphoma the University of Pennsylvania's Dr Stephen Schuster stressed that 28 of the 43 non-infused patients had had disease progressions. However, he also accepted that the trial's design had delayed infusion after apheresis; this might have opened up a window in which patients progressed (see tables below).

This at least explains the anomaly that such a high rate of disease progressions pre-infusion had not been seen in the Zuma-1 study of Novartis's rival Kite Pharma's CAR-T project. The Zuma-1 design had not included any bridging chemotherapy, and Kite boasts of a "vein-to-vein" time of 17 days; in Juliet there was bridging chemo, as well as disease restaging, before lymphodepletion and CTL019 infusion.

Novartis had earlier tried to head off the doubts. Shortly after the Juliet abstract went live in the ICML programme, it put out its own statement discussing the data, and saying 43 of the 121 discontinued before infusion, the majority owing to "rapid progression of their disease or deterioration in their clinical status".

The market, however, had already started to fear the worst, sending Kite's stock up 18% over the past five days. The Juliet data are important for Kite, since they concern aggressive lymphoma – the lead indication for Kite's KTE-C19, in which it has already been filed in the US.

The US FDA has set November 29 as its action date for the KTE-C19 filing, while Novartis's CTL019 is due to be submitted for lymphoma in the second half of this year. CTL019 was the first CAR-T project to be filed, for paediatric ALL, a smaller use for which an advisory panel will be convened on July 12, with an FDA action date around September 29.

Manufacturing success

Beyond the remission data – which are essentially comparable across the Juliet and Zuma-1 studies, as well as with that of a third CAR-T player, Juno's JCAR017 in the non-pivotal Transcend trial – manufacturing questions continue to persist.

The issue first came to prominence at the 2015 Ash meeting, where an academic study of CTL019 in lymphoma revealed a striking 14% rate of failure to generate the CAR-T cells. This is typically down to patients presenting with insufficient T cells to expand, or inconsistencies in the production process used.

However, companies have stressed that academic manufacturing bears little resemblance to a commercial process, where production aims to be more uniform, and patients not meeting certain thresholds would not even be considered for treatment. This has largely been borne out in subsequent trials, which is why the revelation in Juliet caused eyebrows to be raised.

At ICML Dr Schuster drilled down into the 43 Juliet subjects who, of the initial 141 enrolled, had not received CTL019: there were nine manufacturing failures, 28 disease progressions (including 16 deaths), two adverse events, two investigator decisions not to infuse, one patient withdrawal and one protocol deviation. An additional 13 subjects are still awaiting infusion.

Infusion success in selected recent CAR-T studies					
	Zuma-1	**Transcend**	**Juliet**	**CTL019 academic***	**Eliana****
Subjects enrolled	111	88	141	43	81
…pending infusion	*0*	*7*	*13*	*0*	*5*
SAE/reassessment/withdrew consent etc	9***	2	34#	7##	9###
Manufacturing failure (% excludes those pending)	1 (1%)	8 (10%)	9 (7%)	6 (14%)	5 (7%)
Subjects who got CAR-T cells	101	71	85	30	62
*Note: *lymphoma study carried out by Penn, presented at Ash 2015; **CTL019 trial in paediatric ALL; ***2 disease progressions, 7 SAEs; #28 disease progressions, 2 SAEs, 2 investigator decisions, 1 withdrawal, 1 protocol violation; ##4 disease progressions, 3 withdrawals of consent; ###6 disease progressions, 3 SAEs.*					

In terms of efficacy, the remission rates presented at ICML today tallied with that unveiled in the abstract earlier, and were broadly in line with that reported by Kite in Zuma-1, and by Juno in Transcend (*Asco – Juno throws down another lymphoma marker for Novartis, June 5, 2017*).

Grade 3 or higher adverse events included cytokine release syndrome and neurotoxicity, seen in 26% and 13% of Juliet subjects. This compares against 13% and 28% respectively at the six-month data cut from Zuma-1, and 2% and 16% in Transcend, as reported at Asco.

Thus it will now come down to teasing out fine differences between the subjects' baseline characteristics. For instance, 51% and 49% of subjects in Juliet and Transcend respectively were post-transplant – suggestive of a lower disease burden – versus just 20% of those in Zuma-1. Juno said 61% of Transcend patients had received bridging chemo.

This, along with trial design, will no doubt be a key focus of the US FDA's deliberations as the agency this year considers the first CAR-T approvals.

Across-trial comparison of Kite, Novartis and Juno lymphoma studies									
	Zuma-1 (KTE-C19)			**Juliet (CTL019)**			**Transcend (JCAR017)**		
	Total patients	**ORR**	**CR**	**Total patients**	**ORR**	**CR**	**Total patients**	**ORR**	**CR**
Best response	101	82%	54%	51	59%	43%	54	76%	52%
3 months	62	44%	39%	51	45%	37%	41	51%	39%
6 months	101	41%	36%	NA	NA	NA	NA	NA	NA
Patient population	Refractory			Relapsed or refractory			Relapsed or refractory		
Prior transplant	20%			51%			49%		
Treatment-related deaths	Hemophagocytic lymphohistiocytosis			None			Diffuse alveolar damage		
	Anoxic brain injury								
	Cerebral oedema (safety expansion phase)								

This story was updated to add information about bridging chemo in Transcend.

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