Evaluate Vantage

July 11, 2017

The CTL019 adcom mists begin to clear

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Briefing documents to guide the review of Novartis's US filing for CTL019 seem to have made at least one thing clear: the focus of the panel tomorrow will be on safety and manufacturing, and not on efficacy. The basic level of information provided suggests that Novartis might expect an easy ride.

Safety questions centre on some long-standing problems of gene therapies, as well as toxicities that have plagued CAR-T in particular, but the advice accepts that efficacy is beyond doubt. The good news for Novartis is that this is also in line with a physicians' survey carried out by *EvaluatePharma*.

This found that the US doctors – mainly paediatric oncologists – thought the main concern for the panel would be CTL019's lengthy, complex and relatively unreliable manufacturing process, with toxicity in second place.

Meanwhile, the view was that efficacy would drive uptake, though reimbursement and availability of safer treatments would be the biggest constraints. The adcom will discuss the CTL019 construct, production and safety in the morning, before considering risk-mitigation and follow-up trials, and finally voting on CTL019's benefit-risk profile.

Readers are invited to register to follow a live blog, a collaboration between *Stat* and *EP Vantage*, taking place all day tomorrow.

Unpredictable

Manufacturing issues are spelled out in the briefing documents, which state that the starting composition of T cells from apheresis is highly variable and not predictable. Given this lack of control "inter-patient variability in the manufacturing process" might have to be addressed, the documents suggest.

On a press call on Friday Novartis said it was continuing to optimise manufacturing, especially to minimise production failures and to ensure scalability. 30-35 hospitals will initially be used for cell apheresis and reinfusion, and production will take place solely at Morris Plains.

The Eliana trial that serves as the basis for CTL019's filing in ALL used Morris Plains as well as a German contract manufacturer, the Fraunhofer Institute. Eliana "in general" used the commercial production process, Novartis said; while Morris Plains can meet global supply, Fraunhofer will be included in a later EU filing.

Management also played up the use of frozen apheresis product, which they insisted enabled cells to be held to give patients and doctors scheduling flexibility. However, the need for this also arises because current production is lengthy, necessitating bridging chemotherapy in 85% of Eliana patients (*Seven questions CTL019 adcom should consider (and two it won't), July 6, 2017*).

A separate consideration proposed in the briefing documents concerns post-marketing risk-mitigation, not only for the short-term risk of cytokine release but also for longer-term safety concerns over insertional mutagenesis.

Insertional mutagenesis concerns the theoretical activation of oncogenes, triggering malignancies, as a result of the material coding for the CAR being integrated near growth-promoting genes. It has been seen with some gene therapies, but not with CAR-T, possibly because the mature T cells here are less susceptible to malignant transformation than pluripotent stem cells.

Another theoretical issue raised is the risk that the lentivirus – inactivated HIV – used as the vector for the CAR construct might be capable of replication. However, Oxford Biomedica, Novartis's lentivirus manufacturer, specifically tests to rule this out.

Cytokine release

The briefing documents state that cytokine release syndrome (CRS) is the major CTL019 adverse event, seen in 63% of Eliana patients, and seek reassurance that treatment algorithms exist to minimise this.

Curiously, they opine that CRS does not correlate with remission. Meanwhile, the specific number of Eliana

deaths not due to disease progression is put at four (*Spotlight – Putting a number on CAR-T deaths, June 26, 2017*).

CTL019 study deaths not due to disease progression					
Indication	**Study**	**Trial ID**	**Description of grade 5 event**	**Deemed due to CTL019?**	**Source**
Lymphoma	Penn study (Stephen Schuster)	NCT02030834	Encephalitis	Yes	ASH 2015
Adult ALL & lymphoma	Penn studies (Noelle Frey)	NCT02030847 & NCT01029366	CRS, influenza B	Yes	ASCO 2016
Adult ALL & lymphoma	Penn studies (Noelle Frey)	NCT02030847 & NCT01029366	CRS, Pseudomonas infection	Yes	ASCO 2016
Adult ALL & lymphoma	Penn studies (Noelle Frey)	NCT02030847 & NCT01029366	CRS, Strenotrophomonas infection	Yes	ASCO 2016
Paediatric ALL	Eliana	NCT02435849	Cerebral haemorrhage	Yes	ASH 2016
Paediatric ALL	Eliana	NCT02435849	Encephalitis	Possibly	EHA 2017
Paediatric ALL	Eliana	NCT02435849	Systemic mycosis	Possibly	EHA 2017
Paediatric ALL	Eliana	NCT02435849	Bacterial respiratory tract infection	Possibly	Adcom briefing docs
Note: only the Eliana number is confirmed; remaining deaths reflect numbers given periodically at scientific conferences.					

Given the very sick state of the patients this mortality rate is unlikely to trouble the adcom, and neither is CTL019 efficacy. Eliana efficacy data make up a small part of the briefing documents, which do not even cite a true intent-to-treat remission rate number, and say the primary endpoint was overall remission at three months; Eliana's Clinicaltrials.gov entry states six months.

Of course, the FDA in considering approval is entitled to carry out its own analysis. Easy ride or not, the day's session promises to be fascinating.

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Jacob Plieth and the Stat journalists Adam Feuerstein and Damian Garde will take part in a live blog of the CTL019 adcom on July 12.