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Ash – Relapses spell more CAR-T uncertainty for Juno

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After seeing multiple patient deaths Juno is facing the likely discontinuation of its lead CAR-T asset, JCAR015. Today fresh troubles emerged with JCAR018, its highly promising anti-CD22 construct designed to treat patients who relapse after a CD19-directed CAR.

At Ash this morning the NCI's Dr Terry Fry said a study of JCAR018 in ALL patients showed for the first time that the CD22 antigen can be lost, causing CAR-T patients to relapse for a second time; there has also been a death from sepsis. And Dr Fry cast doubt on JCAR018's potential as a salvage treatment, proposing instead its use as an initial line of CAR therapy.

Of course, this does not mean that this is Juno's policy, since Dr Fry is running his trial at the NCI at arm's length. Juno had independently bought rights to JCAR018 from the private company Opus Bio for around $84m, and paid the sellers a $15m milestone after Dr Fry unveiled data in an initial seven patients at Ash 2015.

He provided a further update at this year's AACR meeting, highlighting four complete remissions in nine patients given JCAR018, and a promising lack of neurotoxicity (*The next CAR-T target generates promise and caution, April 25, 2016*). That had put Juno in pole position as the most advanced developer of a CD22-directed CAR.

Complete remissions

Today at Ash those data were updated, with 16 patients now treated, and nine being put into complete remission, including eight of the 10 on the two highest cell doses.

However, only three of the ALL responders are still in remission, at between three months and over a year. Five relapses were seen at two to six months' follow-up, and there was no update on one lymphoma patient who had responded.

Four of the relapsed patients had loss of the CD22 antigen, either completely or via what Dr Fry termed a "decrease in site density". This is the first documented evidence in patients that CD22 antigen loss can occur – just as it does with CD19, though in the latter case the mechanism is different.

Meanwhile, there is still no neurotoxicity or cytokine release above grade 2 in the trial, but grade 4 hypoxia caused a lowering of cell dose for the three final patients. And one patient died from sepsis after their cytokine release syndrome resolved.

The death need not necessarily be serious for JCAR018, as Dr Fry said sepsis had been seen in CAR-T trials before, and was a known complication of ALL therapy, especially in these types of heavily pretreated patients. But with neurotoxicity likely spelling the end of JCAR015, and Juno separately revealing a death in a trial of JCAR014, this is an extremely pertinent issue.

Anti-CD22 CARs in the clinic		
Group	**Project**	**Trial ID**
Juno/Opus/NCI	JCAR018	NCT02315612
Penn/Novartis	CART22 cells	NCT02588456, NCT02650414
Xinqiao Hospital of Chongqing	MendCART	NCT02721407*
Southwest Hospital, China	Anti-CD22-CAR-transduced T cells	NCT02935153
iCarTAB BioMed	CD22 CAR-T	NCT02794961
Xuzhou Medical University	CD19 CAR + CD22 CAR	NCT02903810
*Note: Cellectis/MD Anderson have UCART22, an allogeneic anti-CD22 project, in preclinical trials; *not recruiting yet.*		

The questions Dr Fry raised over where JCAR018 might fit into therapy also came as a surprise. Strangely, his view that JCAR018 "might not be best used as salvage therapy" does not seem to have been driven by lack of efficacy in CD19-relapsed patients.

Indeed, of the nine patients responding to JCAR018 at the highest doses, five were at least partially CD19-negative at baseline, and one was “completely refractory to CD19 CAR therapy and Blincyto”, Dr Niral Shah, who will present the full data on Monday, told *EP Vantage*.

But Dr Fry suggested that targeting CD22 should be attempted in anti-CD19 CAR-T-naive patients, either as two CARs given together, as two CARs expressed on the same cell, or as a single bispecific construct. At least the first approach would clearly push up the already high cost of this type of therapy.

An anti-CD19/CD22 bispecific CAR has been designed at the NCI, and should enter clinical trials in mid-2017, said Dr Fry. That said, however, where to position JCAR018 is not Juno’s greatest concern; right now the group has far bigger things to worry about.

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