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Therapy focus – How do you solve a problem like CAR-T relapse?

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Several companies' CAR-T therapies have already produced impressive remission rates in leukaemia patients, but a high rate of relapses continues to cloud their long-term potential, especially considering the likely cost.

Several strategies have emerged to overcome this, one of which is Novartis's design of a CAR construct with a humanised antigen-binding region, the theory being that the commonly used murine CARs are being rejected by the immune system. But if this is the way forward it could leave Novartis's CTL019 – the industry's most-advanced CAR-T asset – and other murine constructs in a bind.

There is little data to go on at present, but one of the most hotly awaited presentations of the recent ASH meeting concerned the first data from a trial of six CTL019-treated patients retreated with Novartis's new humanised, CD19-targeting CAR, CTL119. Three of these went into complete remission, one of which was still ongoing at almost six months.

Dr Shannon Maude, of the Children's Hospital of Philadelphia, said it was particularly impressive that one of the remitting patients had had no response to the murine CTL019. It is early days, but further positive data in a larger patient set would put Novartis in a quandary: should the group even bother filing CTL019, or should it just switch to CTL119?

This might hit sentiment behind Novartis and the entire CAR-T space alike, given that the Swiss firm is the furthest advanced here, and it still hopes to submit CTL019 for approval next year. Switching to CTL119 would naturally imply a later filing.

Little is known about other players' plans to develop humanised CARs; Kite has made a patent filing for one, while Juno refers to a bonus due to its R&D head, Mark Frohlich, on first patient dosing in a pivotal trial with a fully humanized CAR-T cell product.

CD19-positive or antigen escape?

Of course such considerations relate to so-called CD19-positive relapses – where patients' leukaemia continues to express the CD19 antigen, with relapse due to waning CAR-T cells or loss of the CAR construct.

In the latest cut of Novartis's CTL019 data a highly impressive 93% of ALL patients went into complete remission after a month, though less impressively this rate was down to 30% by one year. At ASH the Children's Hospital of Philadelphia's Dr Stephan Grupp said CD19-positive relapse was responsible for a third of recurrences (*ASH – CAR-T struggles to travel beyond leukaemia, December 8, 2015*).

The remaining two thirds relapse because of loss of the CD19 antigen, and clearly require an entirely different retreatment approach. One strategy is to target a separate antigen, and fortunately in B-cell malignancies an alternative one seems to exist: CD22.

The leading project here is JCAR018, an anti-CD22 CAR derived from work at the NIH that Juno bought from Opus Bio last year for about $120m. A first-in-human trial of JCAR018 featured at a separate ASH poster detailing a cohort of seven evaluable ALL patients, six of whom had been treated with an anti-CD19 CAR, and five of whom had had CD19-negative relapse.

Complete remission was seen in two patients. It is early days here, too, and the best that can be said beyond initial efficacy hints is that there was no severe cytokine release syndrome, suggesting relative safety of JCAR018, though most of the patients were given the lowest CAR-T cell dose.

Anti-CD22 projects in development			
Mechanism	**Project**	**Company**	**Status (indication)**
Anti-CD22 MAb-calicheamicin conjugate	Inotuzumab ozogamicin	Pfizer/UCB	Phase III (ALL & NHL)
Anti-CD22 MAb-PE38 conjugate	Moxetumomab pasudotox	AstraZeneca	Phase III (HCL)
Anti-CD19 & CD22 MAb	OXS-1550/DT2219ARL	Oxis/ University of Minnesota	Phase II (NHL)
Anti-CD22 MAb-monomethyl auristatin E conjugate	Pinatuzumab vedotin	Roche/ Seattle Genetics	Phase II (NHL)
Anti-CD22 MAb-yttrium 90 conjugate	IMMU-102 (Y-90 epratuzumab tetraxetan)	Immunomedics	Phase II (NHL)
Anti-CD22 CAR-T therapy	JCAR018/ LG740	Juno/ Opus Bio	Phase I
Anti-CD22 CAR-T therapy	UCART22	Cellectis	Research (ALL)
DT-CD22 fusion protein	CD22-DIDT	Angelica Therapeutics	Research
Anti-CD19 & CD22 CAR-T therapy	CD19/CD22 bispecific CAR	NCI (NIH)	Research
Source: EvaluatePharma.			

Selection of antigens against which CAR-T therapies are being developed has tended to follow development of antibodies, and CD22 is no exception, but it is interesting that anti-CD22 MAbs, including MEDI-553 and IMTOX 22-97, have all failed in oncology, while UCB's epratuzumab failed in lupus.

Several antibody-drug conjugates are in development, as well as UCART22, an allogeneic CAR-T therapy from Cellectis that also has a *dCK* gene knockout to confer fludarabine resistance.

At ASH the NCI's Dr Daniel Lee said he was continuing to enrol CD19-escaped patients into a CD22 CAR-T study, though all the data and IP arising from this will presumably belong not to the NCI's CRADA partner Kite, but rather to Juno.

Dr Lee also cited a planned study of a bivalent CD19-CD22 CAR, a highly unusual single CAR construct that was featured at an ASH poster. The NCI authors concluded that the order of the CD19 and CD22 binding domains, and the length of the linker, affected function, and despite some evidence of activity further optimisation is needed before this enters the clinic.

Persistence problems

When it comes to CD19-positive relapses, developers of CAR-T therapies have to contend with a separate problem, namely the lack of persistence of the CAR construct on the T cells, or its inability to generate a sufficiently sustained response.

Since there are differences in the design of different players' CAR constructs it is hoped that further data will shed light on which of these differences might affect persistence. For instance, Kite employs a gamma-retrovirus to transfect its construct, which uses a CD28 co-stimulatory domain, while Novartis's uses lentiviral transfection and a 4-1BB co-stimulatory element.

Juno has both: JCAR015, a CD28/gamma-retroviral construct from Memorial Sloan Kettering (MSK), and JCAR017, a 4-1BB/lentiviral one from the Fred Hutchinson Cancer Research Center. Again there is a lack of hard evidence, but Dr Grupp of the Philadelphia children's hospital says his construct, which is used by Novartis, enables persistence of around four years, versus around 30 days for the MSK/Kite projects.

During a recent investor call Dr Grupp stated that CD28 co-stimulation tends to give a strong early response but the T cells then "burn out", while gamma-retroviruses are known to risk causing gene silencing.

"Solely based on the data that's published right now, I'd say there's more compelling data that CD28 versus 4-1BB is a bigger part of the [persistence] equation than lentiviral versus gamma-retroviral," he speculated. "But that is just a guess."

If further trials do substantiate this view then Kite especially will be left with some rethinking to do.

Project	Company	Study	Trial ID	ASH abstract
CTL119	Novartis	CTL019 ALL study treating some relapsing pts	NCT02228096	683
JCAR018	Juno	Multi-dose, 57 pts with B-cell malignancies	NCT02315612	1324
CD19/CD22 bispecific CAR	NCI (NIH)	Early work on design of CAR construct	–	4427

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