Evaluate Vantage

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Crispr's reminder about allogeneic Car-T redosing

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Crispr follows Allogene with backing for off-the-shelf Car-T therapy – and adds big concerns over lack of durability.

Given the clinical hold that hit Allogene last Thursday, yesterday's update from Crispr Therapeutics' rival allogeneic Car-T therapy CTX110 was notable for a lack of similar concerns. This in itself was positive, as was an impressive rate of initial remissions in an enlarged cohort of lymphoma patients.

But this is where the good news ends; the data, from the first-in-human Carbon study, showed CTX110 to be short-lived, with the vast majority of initially responding patients relapsing within six months. Crispr argues that relapsed patients can be rescued by redosing Car-T cells, but this seems impractical in the real world.

No allogeneic Car-T therapy is on the market, but autologous therapies have set a baseline price, and if off-the-shelf Car-T treatment becomes something that relies on multiple infusions that will clearly require an entirely new pricing paradigm whose viability investors, companies and payers have yet to consider.

No durability

For now it is abundantly clear that off-the-shelf Car-T therapy lacks durability. Allogene showed as much earlier this year with ALLO-501, in a trial where 50% of initially responding patients relapsed within six months, and yesterday Crispr reminded investors how serious this problem is.

The Carbon study's first iteration last year showed CTX110's viability in a handful of patients, though this was overshadowed by a treatment-related death. Yesterday the evaluable dataset had grown to 26 lymphoma patients, and on the plus side there had been no further treatment-related deaths.

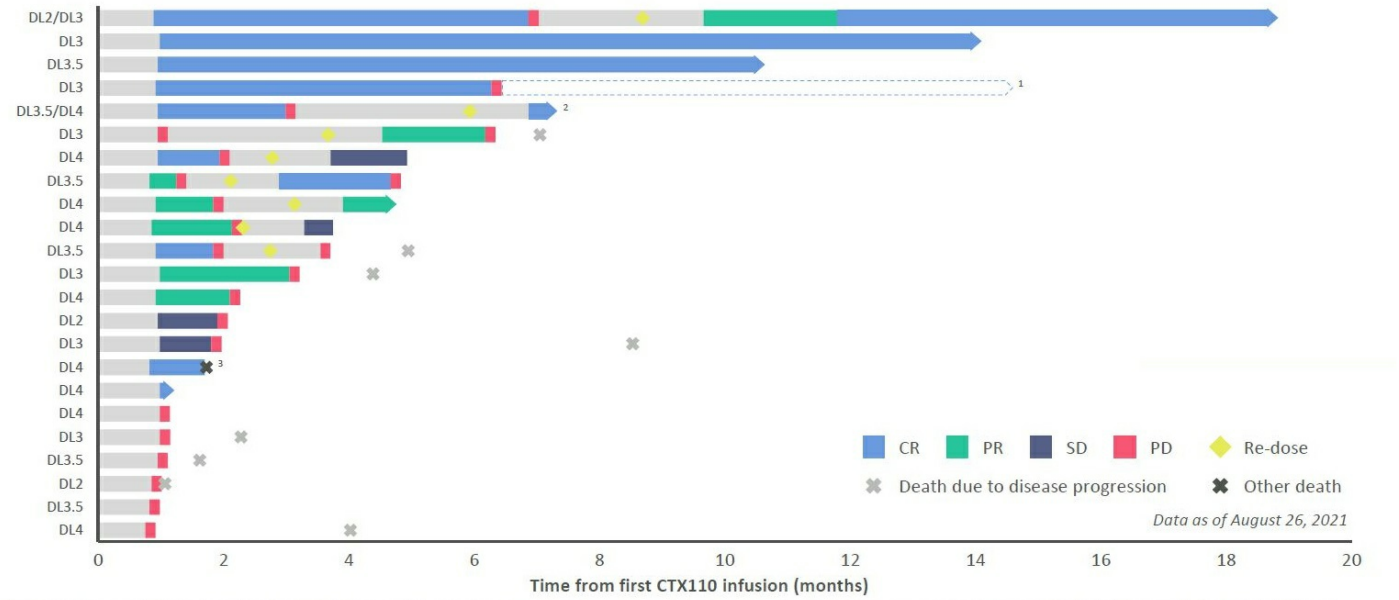
Crispr trumpeted a 58% ORR among the 24 subjects given 100 million cells or more as being in line with approved autologous Car-T. But one fact stood out like a sore thumb: by around six months all but three initial responders had relapsed (including the earlier disclosed death), and one of these was just one month out from treatment.

CTX110 comprises multiple Crispr-based gene edits. The Car transgene is knocked into the Trac locus to disrupt the endogenous T-cell receptor and avoid GvHD, and the β2M locus is knocked out to prevent major histocompatibility complex (MHC1) expression and stop a patient's T cells from rejecting the graft.

However, cells lacking MHC1 can still be recognised as foreign by a patient's NK cells. Stifel analysts say NK

cells rejuvenate quickly after lymphodepletion, and reckon CTX110 kinetics suggest that it is NK cells that are rejecting CTX110 and causing remissions to be of such short duration.

Not so durable? CTX110 in r/r non-Hodgkin lymphoma



Dose level of re-dose indicated if different from initial dose level; Imaging per protocol occurs at M1, M3, and M6; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease
(1) Patient had a localized tumor recurrence that was excised and is clinically well having received no additional anticancer therapy; (2) Unaudited data as of Oct. 7 after the data cut; (3) As disclosed in Oct. 2020

Source: Crispr Therapeutics.

So can relapsing patients be rescued by a second Car-T cell dose? This is much easier to do with a therapy available quickly off the shelf than with an autologous treatment, and Crispr redosed seven subjects who had relapsed, plus an eighth who had not responded.

On the plus side this yielded five new remissions; but three subjects did not respond at all, and two of the five responders again relapsed in short order. In Allogene's case five patients were redosed, all then went into remission, but two again relapsed.

Assuming that redosing is scientifically sound it raises other problems since a second dose of marketed therapy might conceivably have to be paid for a second time. Moreover, every time a patient is retreated they need to undergo lymphodepletion to wipe out a their immune system – something patients and doctors might be loath to do more than once.

And these might all be dismissed as teething problems were Crispr Therapeutics not worth over $7bn, even considering this morning's 8% slide and the stock's 50% collapse year to date. After all, if lack of durability makes CTX110 a non-starter the same applies to the rest of the company's Car-T pipeline, which also relies on β2M knockout.

Allogene's blowup last week suggested that deleterious gene edits could cause serious problems for some allogeneic Car-T therapies, but Crispr has reminded investors that the space might have even more fundamental issues.