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A late Christmas present for Allogene

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US clinical hold over Allogene's entire pipeline has just been lifted.

Three months is all it has taken for the FDA to lift its hold on Allogene's clinical pipeline. The news, revealed today just as the JP Morgan conference is getting under way, will be welcomed by investors who had seen 45% of the company's market cap erased since October 8.

This will also come as a relief to other biotechs developing allogeneic Car-T therapies, a field that has moved slowly, and over which Allogene's clinical hold had hung. It was especially worrying that chromosomal abnormalities were involved, but Allogene today revealed that these were unrelated to its gene editing process or manufacturing, and "had no clinical significance".

The company was able to make this assessment, and to convince the FDA of it, thanks to "complex analytical assays that allowed us to interrogate samples, map and sequence inversion site, and facilitate a deep analysis related to various aspects of gene editing and product quality", it told *Evaluate Vantage*.

Allogene reckons such a process could have taken a year to develop, but it managed to do so in less than three months. Interestingly, the company now sees the fact that it has such assays in place as a competitive advantage, and this has made it increasingly confident of its position.

That said, it will clearly take some time for the company's studies to restart. The hold concerned five trials of five different Car-T projects, and all Allogene will say for now is that these will resume as quickly as possible.

Additionally, a sixth study, a pivotal phase 2 test of ALLO-501A in relapsed/refractory large B-cell lymphoma, is to begin in mid-2022, pending final FDA discussions.

Allogene's clinical pipeline

Project	Trial	Indication	Status
ALLO-501A (anti-CD19 without Rituxan switch)	Pivotal ph2	R/r non-Hodgkin lymphoma	Starting mid-2022
	Alpha-2	R/r non-Hodgkin lymphoma	Resuming as soon as possible
ALLO-501 (anti-CD19 with Rituxan switch)	Alpha	R/r non-Hodgkin lymphoma	Resuming as soon as possible
ALLO-715 (anti-BCMA)	Universal	R/r multiple myeloma	Resuming as soon as possible
ALLO-316 (anti-CD70)	Traverse	Renal cell carcinoma	Resuming as soon as possible
ALLO-605 (anti-BCMA with chimaeric cytokine receptor)	Ignite	R/r multiple myeloma	Resuming as soon as possible

Source: company website & clinicaltrials.gov.

The hold resulted when “chromosomal abnormality of unclear clinical significance” was detected in ALLO-501A cells in a lymphoma patient in the Alpha-2 trial after this subject underwent bone marrow biopsy to investigate progressive pancytopenia.

It was curious that only some ALLO-501A cells in the patient were affected, and Allogene has now revealed that the abnormality had occurred after the cell product was administered. It was not detected in any of its manufactured allogeneic Car-T products or in any other patient treated with the same lot of ALLO-501A.

Of particular concern was that the abnormality occurred on chromosome 14, which contains the Trac locus that Allogene’s Talen nucleases knock out to prevent expression of endogenous T-cell receptors. Thus there was a major worry that Talen gene editing had brought about the chromosomal change.

However, Allogene says the exact site of the inversion, identified by sequencing analysis, was not the Trac locus, or indeed “any other potential Talen gene-editing site”, thus apparently clearing the group’s manufacturing process of possible involvement. The abnormality can now be said to have involved regions of the T-cell receptor and immunoglobulin genes that naturally undergo rearrangement as part of T cell or B cell maturation.

There will undoubtedly be lessons here for all developers of car-T therapies. Allogene says the data from its investigation into this issue will be published at a future scientific forum.