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Allogene Advances Off-The-Shelf Mission With Pivotal Trial Progress, Solid Tumor Data

Early Renal Cell Carcinoma Results Offer Proof-Of-Concept

by Mandy Jackson

R&D head Zachary Roberts spoke with *Scrip* about Allogene's Phase II pivotal trial for ALLO-501A and the firm's hopes for overcoming challenges with allogeneic CAR-T therapies in solid tumors.

Allogene Therapeutics Inc. achieved a big first for allogeneic chimeric antigen receptor T-cell (CAR-T) therapies last year when it initiated the Phase II ALPHA2 clinical trial of its CD19-targeting ALLO-501A in third-line or later treatment of diffuse large B-cell lymphoma (DLBCL). This year, the company achieved another big milestone when it reported initial results from the ongoing Phase I TRAVERSE trial of ALLO-316, a CD70-targeting candidate, in advanced or metastatic renal cell carcinoma (RCC), providing proof-of-concept data for its allogeneic CAR-T approach in solid tumors.

Executive vice president of research and development, and chief medical officer, Zachary Roberts described in an interview with *Scrip* how achievement of these and several other upcoming milestones will help Allogene advance its mission of delivering off-the-shelf CAR-T therapies to cancer patients who currently may not be able to access these treatments due to the complex, time-consuming, individualized manufacturing of autologous CAR-T therapies.

The company aims to deliver allogeneic products with similar efficacy as their autologous counterparts, but with off-the-shelf convenience, which is a goal that no allogeneic CAR-T therapy has

KEY TAKEAWAYS

achieved to date. Allogene has the most advanced allogeneic CAR-T candidate in the clinic with ALLO-501A – the first allogeneic CAR-T therapy to move into a pivotal trial. (Also see "*Trials In Focus: Allogene Off-The-Shelf Study Mirrors Earlier CAR-T Trials*" - Scrip, 7 Oct, 2022.)

"We have shared lots of clinical data on this program in the context of an open-label Phase I, but in Q4 last year we started the pivotal Phase II trial," Roberts said. "The vast majority of centers that were involved in the Phase I have carried on into Phase II, so that allowed us to open many centers a little bit faster than if we'd started from scratch."

Allogene plans to complete enrollment in ALPHA2, in third-line or later DLBCL, during the first half of 2024 and report results by the end of next year. The company initiated the Phase II EXPAND trial earlier this year to test its lymphodepletion agent ALLO-647, an anti-CD52 monoclonal antibody, in combination with fludarabine and cyclophosphamide (known as FCA90) versus fludarabine and cyclophosphamide alone, both administered prior to treatment with ALLO-501A. It also expects results from that study around the end of 2024.

- Allogene is at the forefront of developing allogeneic, or off-the-shelf, CAR-T products, and has started the ALPHA2 pivotal trial for ALLO-501A in DLBCL and released Phase I data for ALLO-316 in renal cell carcinoma, offering proof-of-concept for use in solid tumors.
- Enrollment is paused for trials of the firm's BCMA-targeting CAR-Ts in development for multiple myeloma while the company reviews manufacturing to make sure outcomes will be similar or improved relative to competing products.
- Current autologous products are frequently hindered commercially by access and manufacturing issues. Allogene says it can produce 100 doses from a manufacturing run, which would produce only a single dose for an autologous CAR-T.
- The company is funded through Q2 2025, which will get it to pivotal data from ALPHA2, but is looking for partners to further improve its cash position and help it advance programs more rapidly.

Updated Phase I data for ALLO-501A were presented at the American Society of Clinical Oncology meeting (ASCO) on 3 June, showing seven of 12 patients (58%) who received FCA90 followed by ALLO-501A achieved a complete response as of the data cut off of 20 April. Five patients (42%) maintained a complete response through month six. There were no dose-limiting toxicities and no grade 3 or higher cases of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) or graft-versus-host disease (GvHD). (Also see "*Allogene May Have Cracked The Off-The-Shelf CAR-T Problem*" - Scrip, 5 Jun, 2023.)

“We believe Allogene could provide an updated progression-free survival curve at ASCO, which we expect to compare favorably to autologous CD19 CAR-Ts, including Yescarta and Kymriah,” Canaccord Genuity analyst John Newman wrote in a 26 May note. “This would significantly raise physician sentiment, in our view, boosting pivotal study enrollment and patient quality, with positive pivotal data expected YE24. Investors have consistently doubted pivotal ALPHA2 data, due to concerns that doctors would enroll only sub-par patients that are not eligible for customized, autologous CAR-Ts.”

Solid Tumor Data Open Another Allogeneic Door

Data from the Phase I TRAVERSE trial of ALLO-316 in RCC patients previously treated with standard therapies, such as immune checkpoint inhibitors and tyrosine kinase inhibitors, were presented at the American Association for Cancer Research (AACR) in April. The AACR presentation covered 18 patients, including 10 with CD70-positive RCC. The overall response rate was 17% overall and 30% in the CD70-positive population, while the disease control rate was 89% and 100%, respectively.

In terms of safety, there were no cases of GvHD – a potential concern for cell therapies developed with donor cells – and rates of grade 3 or higher CRS and neurotoxicity were low at 5% and 11%, respectively. CRS and neurotoxicity rates of any grade were 58% and 68%. There were no cases of ICANS.

“This CAR is unique in many ways, not just the target that it engages,” Roberts said, explaining that CD70 is an “exciting target” for CAR-T therapy because it is expressed on multiple solid tumors and on some non-Hodgkins lymphomas, including large B-cell lymphoma.

ZACHARY ROBERTS *Source: Allogene*

ALLO-316 also incorporates Allogene’s Dagger technology, which is meant to prevent rejection of allogeneic CAR-T cells by host T-cells expressing the same antigen, allowing enough time for CAR-T cells to expand and kill tumor cells.

“The CD70 that's expressed on tumors is also widely expressed on normal blood cells, including activated T-cells,” Roberts explained. “And so, when the cells are infused into the patient, because these are fully HLA unmatched cells, there's going to be always a tissue mismatch. So, the hosts T-cells, or the recipient T-cells, will recognize the incoming HLA unmatched CAR-T cells as foreign and often will mount an allogeneic rejection response. This is a universal phenomenon in off-the-shelf CAR-T therapy.”

However, in addition to the safety and efficacy results that Allogene presented for ALLO-316 at AACR, the data showed “marked expansion and remarkable persistence” of the CAR-T cells “even at the lowest cell doses that were tested, 40 million and 80 million cells,” according to Roberts. The data also showed the Dagger technology worked to suppress CD70-expressing host

T-cells.

“We are continuing with the dose exploration in that program,” Roberts said. “We've got a couple more doses to go still and then we're hoping to get to where we intend to get to dose expansion by the end of this year. We're also looking at potentially increasing eligibility criteria to include additional cancer types, according to CD70 expression.”

BCMA-Targeting Program In Myeloma Remains Paused

Allogene is also developing two allogeneic BCMA-targeting CAR-T therapies for multiple myeloma, ALLO-715 and ALLO-605, that it hopes will have similar efficacy to the autologous BCMA-targeting CAR-T therapies Abecma (idecabtagene vicleucel) from *Bristol Myers Squibb Company* and *2seventy Bio, Inc.* and Carvykti (ciltacabtagene autoleucel) from *Johnson & Johnson* and *Legend Biotech Corp.*, as well as J&J’s recently approved anti-BMCA bispecific antibody Tecvayli (teclistamab). (Also see "*J&J Adds Second Anti-BCMA Myeloma Therapy In US With Tecvayli Approval*" - Scrip, 26 Oct, 2022.)

“We recently published those Phase I results [for ALLO-715] in *Nature Medicine*, showing that the Allogene approach to cell manufacturing and lymphodepletion with this sort of three-part lymphodepletion regimen is able to generate good engraftment, cell persistence and clinically meaningful, durable remissions in patients with multiple myeloma,” Roberts said.

However, enrollment in clinical trials of both of Allogene’s BCMA-targeting CAR-T therapies has been paused while the company reviews its manufacturing for both assets to make sure outcomes for patients treated with the allogeneic therapies will be similar or improved relative to competing products.

“We are looking at our data stacked up against the other two CAR-T products, Abecma and Carvykti, as well as the bispecific antibody Tecvayli,” Roberts said. “We decided to take an opportunity to spend the next several months carefully examining the manufacturing process that we use for that product to ensure that we are extracting every cell activity from the manufacturing process. We've actually paused enrollment in both of our BCMA programs and anticipate potentially resuming dosing early next year.”

He noted that there is a lot of room for improvement in both the market for BCMA-targeting CAR-T therapies for multiple myeloma and CD19-targeting CAR-T therapies for DLBCL. The two markets have six approved autologous products, but many patients are unable to receive treatment. Therapy may be limited by access to leukapheresis, in which T-cells are taken from patients to be reengineered by the autologous cell therapies’ makers. In other cases, some patients don’t have time to wait for autologous products to be manufactured or the therapies are unable to be manufactured properly.

“We estimate between 10% and 20% of patients who qualify, based on the labels for those products, are actually receiving them and that has to do with patient access, it has to do with manufacturability,” Roberts said. “A significant fraction of these commercial products fail to manufacture or are out of spec. And many patients actually can't wait the one to two months that it takes to manufacture.”

Rather than producing one CAR-T dose for each patient, Allogene can manufacture 100 or more patient doses from a single manufacturing run and its existing facility can generate 20,000 patient doses per year, so the company believes that it can go a long way to meeting patient demand with its off-the-shelf treatments.

“Patients will have lower disease burden because they haven't had two months waiting for therapy,” Roberts said. “So, it’s not just having those products available, but we believe it will likely have beneficial effects on outcomes as well, at least that's our hope.”

Balance Sheet Enables Upcoming Milestones

Allogene has about two years’ worth of capital on its balance sheet – $514m as of 31 March, the end of the first quarter of 2023. The company expects that money to last into the second quarter of 2025, which should fund its operations beyond the pivotal readout for ALLO-501A in DLBCL.

“We're focused right now. We are absolutely in execution mode here,” Roberts said. “Our primary focus is on ALLO-501A and getting those two studies enrolled and getting to the dose expansion of CD70.”

At the same time, Allogene is also looking for potential partners that may be able to enhance its cash position and advance some of the company’s clinical-stage programs more rapidly.

“We've got three products with positive clinical data, three different malignancies,” Roberts said. “That's giving us a huge amount of confidence that we're on the right track here and we just frankly don't have the bodies or the dollars to do all of these things at the same time at full speed. So, we're looking very much for partners where we can see synergies, potentially help our balance sheet, but really advance our therapies and get them to patients faster.”

J.P. Morgan analyst Brian Cheng said in a 4 May note that upcoming data readouts and achievement of clinical trial milestones should boost interest in Allogene for potential partners and investors.

“Broadly, we continue to view its allogeneic cell therapy platform positively based on the clinical evidence collected across its portfolio,” Cheng said. “We believe the near-term catalysts, notably TRAVERSE [second half of 2023] updates in RCC, could re-attract market appreciation.”

[Editor's Note: This article was updated on 20 June 2023 to update the number of patients for which data were reported at AACR in April, and to clarify rates of neurotoxicity and ICANS observed in that study of ALLO-316. The article also was updated to clarify the response rates reported for ALLO-501A at ASCO in June.]