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ASH 2020: Novel CAR-T Approaches Chase BCMA-Targeting Frontrunners

New Poseida Manufacturing Boosts Efficacy; Allogene Has First Allogeneic

by **Mandy Jackson**

BMS/bluebird and Janssen/Legend have the leading BCMA-targeting CAR-T therapies for multiple myeloma but Poseida, Allogene, CARsgen, Gracell and CBMG are emerging with novel approaches.

Several companies presented results for next-generation B-cell maturation antigen (BCMA)-targeting chimeric antigen receptor T-cell (CAR-T) therapies in relapsed or refractory multiple myeloma during the recent American Society of Hematology (ASH) meeting with early data that could give frontrunners [*Bristol Myers Squibb Company/bluebird bio*](#) and [*Janssen Pharmaceutical Cos./Legend Biotech Corp.*](#) a run for their money.

[*Allogene Therapeutics Inc.*](#) presented the first-ever clinical trial results at ASH for an off-the-shelf allogeneic BCMA-targeting CAR-T therapy – made from donor T-cells rather than from each patient's own cells, like the autologous candidates from BMS/bluebird and Janssen/Legend. Also, [*Poseida Therapeutics, Inc.*](#), [*Cellular Biomedicine Group, Inc.*](#) (CBMG), [*Gracell Biotechnologies Co. Ltd.*](#), [*CARsgen Therapeutics*](#) and [*Arcellx, Inc.*](#) each presented data from their novel takes on autologous treatments with impressive early results.

BMS and bluebird are likely to win the first approval for a CAR-T therapy targeting BCMA on myeloma cells, since the biologic license application (BLA) for their candidate idecabtagene vicleucel (ide-cel; bb2121) has a US Food and Drug Administration action date of 27 March. (Also see "[*Approval Of BMS/Bluebird's Ide-Cel May Come Just In Time*](#)" - Scrip, 22 Sep, 2020.) However, longer-term data for ciltacabtagene autoleucel (cilta-cel; JNJ-4528) from [*Johnson & Johnson*](#) subsidiary Janssen and partner Legend showed that response rates continue to outpace results seen with ide-cel.

Analysts see the 97% overall response rate (ORR) and 67% complete response (CR) rate among 97 patients treated with cilta-cel in the Phase Ib/II CARTITUDE-1 clinical trial as a high bar for other BCMA-targeting therapies to meet. Janssen plans to submit a BLA for cilta-cel to the US FDA by the end of 2020, so it may quickly follow ide-cel onto the market.

Updated Phase I results from BMS and bluebird at ASH showed a 76% ORR and 39% CR rate among 62 patients in the CRB-401 study, but with a lower rate of cytokine release syndrome (CRS) and a lower incidence of severe neurotoxicity than seen with cilta-cel. CRS and neurotoxicity are early-onset and sometimes severe adverse events often associated with CAR-T products.

Next-generation BCMA-targeting CAR-T therapies aim to improve upon the convenience, response rates, safety and durability of their predecessors through various means. For instance, Allogene's allogeneic therapy ALLO-715 was administered to 90% of the initial patients in its ongoing Phase I UNIVERSAL trial while it typically takes a few weeks for autologous CAR-T therapy makers weeks to receive, reengineer and return boosted T-cells to patients enrolled in their trials.

The UNIVERSAL trial also is testing ALLO-647, Allogene's anti-CD52 monoclonal antibody, as part of the fludarabine and cytarabine pre-conditioning chemotherapy regimen typically given to patients before infusion of CAR-T cells. ALLO-647 so far appears to be working as it is designed, which is to help the chemo regimen more effectively clear out the patients' own immune cells so that the native T-cells do not block the effects of the ALLO-715 CAR-T cells. Patients who received a higher dose of ALLO-647 had higher response rates than those who received a lower dose.

Poseida presented early results for its candidate P-BCMA-101 that showed a new nanoplasmid-based manufacturing process resulted in better responses than those seen in the first few patients treated with the CAR-T product manufactured with the company's first-generation plasmid. P-BCMA-101 was developed with Poseida's piggyBac platform, which uses a non-viral vector – a transposon – to deliver CAR-T cells to targeted cancer cells.

The nanoplasmid encapsulates the transposon and is less toxic, since it is smaller than the prior

ASH 2020: J&J/Legend's Cilta-Cel Shines, But BMS/Bluebird's Ide-Cel Is In First Place

By **Mandy Jackson**

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Cilta-cel maintained high response rates in longer-term multiple myeloma data, but ide-cel causes less cytokine release syndrome and severe neurotoxicity – and it has a March decision date at the US FDA.

[Read the full article here](#)

plasmid. Its small size makes it easier to work with in manufacturing and leads to a higher CAR-T cell yield and produces healthier cells with greater capacity to proliferate in the patient. In addition, P-BCMA-101's original differentiating characteristics, such as its ability to generate a high percentage of stem cell memory cells, were maintained. (Also see "[Poseida, Legend/Janssen Look To Snag Celgene/Bluebird's BCMA Crown](#)" - Scrip, 4 Dec, 2018.) Poseida is using the nanoplasmid technology, which it licensed from [Nature Technology Corp.](#), to manufacture all of its CAR-T therapies going forward.

CEO Eric Ostertag said in an interview with *Scrip* that the company continues to evaluate dosing of P-BCMA-101 in its Phase I trial using the nanoplasmid manufacturing process and is fine-tuning its lymphodepletion regimen, but it has ruled out at least one dosing strategy already. Cyclic dosing – administering the CAR-T cells in two or three separate infusions – did not impact efficacy and it will not be used going forward. The company still is testing lymphodepletion regimens that include Rituxan (rituximab) or Revlimid (lenalidomide) but hasn't ruled out either agent.

"We have still a little bit more work to do to decide about whether or not to proceed with the Rituxan or the Revlimid, and that decision should be made in the first quarter of next year," Ostertag said. "Once we have the pre-conditioning homed in, and once we have the dose homed in, then all patients at that point are full speed ahead in the Phase II portion of the trial."

The company also plans to file an investigational new drug (IND) application with the US FDA in 2021 for its first allogeneic CAR-T therapy, which also will target BCMA for the treatment of multiple myeloma.

Among the other autologous BCMA-targeting CAR-T therapies presented at ASH:

- BMS and bluebird updated the Phase I results for bb21217, which uses the same CAR-T construct as ide-cel but it is cultured with a PI3K inhibitor to increase the durability of responses.
- CBMG's C-CAR088 is designed to increase efficacy by increasing specificity and reducing immunogenicity through the use of an scFv antibody domain to target epitope cluster E3 in the BCMA extra-cellular domain with high affinity.
- Gracell's GC012F is produced with the company's FastTCAR technology that enables next-day manufacturing of the CAR-T therapy and it targets both BCMA and CD19 to increase myeloma cell-killing activity.
- Like CBMG's C-CAR088, CARsgen's CT053 uses a fully human anti-BCMA scFv domain with the goal of reducing immunogenicity and improving safety.

- Arcellx developed CART-ddBCMA with its two-part ARC-sparX platform, which uses sparX proteins that bind to antigens on diseased cells and flags them for destruction by ARC-T cells. The engineered T-cells bind to the sparX proteins and kill the flagged cells.

The table below lists the response rates and incidence of CRS and neurotoxicity for these novel BCMA-targeting CAR-T therapies.

Next-Generation BCMA-Targeting CAR-T Therapy Results To Date		
	Response Rates	CRS And Neurotoxicity
ALLO-715 (Allogene)	At a 30 October cutoff, 35 patients were enrolled in the Phase I study, 31 were evaluable for safety and 29 were evaluable for efficacy across four doses. At the third highest dose of 320 million cells six out of 10 patients responded for an ORR of 60% and four achieved very good partial response (VGPR) or better; VGPR-plus was defined as VGPR, CR or stringent CR (sCR).	There were 14 cases of CRS (45%) but all were grade 1 (n=5; 16%) or grade 2 (n=9; 29%). No immune effector cell-associated neurotoxicity syndrome (ICANS) was observed.
P-BCMA-101 (Poseida)	Among six people treated with a 750,000 cell/kg dose of P-BCMA-101 manufactured with the nanoplasmid process, four patients responded (ORR=67%) and three patients (50%) achieved a VGPR or CR. The ORR was 50% among four patients treated at this dose manufactured with the prior process.	Poseida reported safety for 53 patients treated with P-BCMA-101 across doses and both manufacturing processes in its ongoing Phase I dose-escalation study. Nine patients developed CRS (17%) with no grade 3 or higher cases. Two patients (3.8%) experienced neurotoxicity; both were grade 3 adverse events.
bb21217 (BMS/bluebird)	Data from 69 patients treated in the ongoing Phase I trial show a 68% ORR with 17 patients (29%) achieving CR or sCR and 15 VGPRs (25%).	CRS occurred in 48 patients (70%), including one grade 3 (1%) and two grade five (3%) events. Eleven patients (16) had neurotoxicity, including two grade 3 (3%) and one grade 4 (1%) event.
C-CAR088 (CBMG)	Data from four patients treated at four sites in China show a 95.7% ORR (n=22)	CRS was observed in 21 patients (91.3%), but only one

	with 10 patients achieving CR or sCR (44%), 11 with VGPR (48%) and one partial response (PR; 4%).	patient had grade 3 or higher CRS (4.3%). One patient experienced neurotoxicity (4.3%) but it was mild and resolved in one day.
GC012F (Gracell)	Sixteen patients were enrolled in a Phase I investigator-initiated clinical trials as of 17 July across three dose levels. The ORR was 93.7% and all six patients at the highest dose achieved a minimal residual disease (MRD)-negative sCR; four of these patients retained their response at six months.	Grade 1 or 2 CRS was experienced by 87.5% of patients and two additional patients had grade 3 CRS (12.5%). No ICANS was observed.
CT053 (CARsgen)	Results from 58 patients across three studies were presented. In two years of follow-up from 24 patients in China, the ORR was 87.5% and the CR/sCR rate was 79.2%. Among 20 patients treated in the Phase Ib LUMMICAR STUDY 2 in the US, the ORR was 94% for the first 18 patients with eight weeks of follow-up. The ORR was 100% for 14 patients in the Phase I LUMMICAR STUDY 1 in China.	In all three datasets, there was no grade 3 or higher CRS, but 15 patients (62.5%) had grade 1 or 2 CRS in the first dataset and 15 out of 19 patients (79%) had grade 1 or 2 CRS in LUMMICAR 2. There was no CRS-related neurotoxicity in LUMMICAR 1, but one patient (4.2%) had grade 3 neurotoxicity in the initial dataset in China and three patients (15.8%) had ICANS in LUMMICAR 2, including one grade 3 ICANS event (5.3%).
CART-ddBCMA (Arcellx)	All six patients treated at the first dose level of 100 million cells in Arcellx's Phase I study responded to treatment and four (67%) achieved sCR and there were two PRs (33%).	All six patients had grade 1 or two CRS and one had grade 1 or 2 neurotoxicity.
<i>Sources: Company reports, ASH presentations, William Blair, Bernstein</i>		

The relapsed or refractory multiple myeloma patients in these studies had four to eight median prior lines of therapy across these studies, so they were heavily pre-treated with standard-of-care regimens. Most were triple-refractory, meaning their disease progressed after treatment with an immunomodulatory drug (IMiD), proteasome inhibitor (PI) and a CD38 inhibitor. Many

patients were penta-refractory, having progressed after five different myeloma therapies.

“In general, response data have been skewed toward VGPRs, and given that Johnson & Johnson showed data from the CARTITUDE-1 study showing more rapid progression among these patients compared to those achieving an sCR, it seems likely that given a choice, physicians would choose a therapy with the greater chance of achieving a sCR or CR,” William Blair analysts Raju Prasad and Matt Phipps said in a 7 December report on ASH presentations for BCMA-targeting therapies.

The William Blair report noted that with lower response rates than ide-cel, BMS/bluebird’s bb21217 does not appear to perform as well as its predecessor, despite what may be more durable responses.

“Allogeneic dosing has its advantages, but efficacy falls short of that shown by autologous CAR-Ts, and possibly bispecifics, thus far. We’ll need to see more to get excited,” Bernstein analysts Vincent Chen and Ronny Gal said in a 6 December note. They weren’t convinced that the 480 million cell dose of ALLO-715 that has only recently been implemented in Allogene’s Phase I trial will be significantly more effective than the 320 million cell dose highlighted at ASH.

Allogene CEO David Chang told *Scrip* that the company is pleased with the efficacy data to date because it indicates that ALLO-715 is an active BCMA-targeting therapy in these difficult-to-treat patients, but he acknowledged that the company still has work to do in terms of testing higher doses that may generate higher response rates as well as to determine the best dose and lymphodepletion regimen for a Phase II clinical trial.

“Of course, this is Phase I, but all the indications are very positive,” Chang said. “In terms of the overall safety that we are seeing – and this is, ranging from graft-versus-host disease, cytokine release syndrome, neurotoxicity and infection – all of these look quite manageable and, if anything, some are favorable compared to what other cell therapies have shown.”

The company has two additional strategies to improve on the allogeneic BCMA-targeting CAR-T data it has presented to date. First, it will begin enrolling patients in UNIVERSAL in 2021 that will be treated with ALLO-715 and SpringWorks Therapeutics Inc.’s gamma secretase inhibitor nirogacestat, which should increase the expression of BCMA on myeloma cells and that should prompt greater expansion of ALLO-715 cells.

Allogene also plans to submit an investigational new drug (IND) application to the US FDA during the first half of 2021 to test ALLO-605, an allogeneic BCMA-targeting CAR-T therapy developed with the company’s TurboCAR technology, which harnesses the patients’ cytokines to aid in CAR-T cell expansion, persistence and efficacy.

Initial data for Allogene's ALLO-501 in lymphoma were presented at the end of May. (Also see "[Allogene Takes Step Closer To Off-The-Shelf CAR-Ts](#)" - Scrip, 31 May, 2020.)

As for the earlier-stage autologous BCMA-targeting programs in multiple myeloma presented at ASH, the Bernstein analysts were impressed with CARsgen's 94% ORR for CT053, which they said "is competitive with [Janssen/Legend's cilta-cel] and we imagine that responses will deepen somewhat with more runout, but it may be hard to hit the high bar set by the current leader [cilta-cel]."

Similarly, the Bernstein analysts said the data for the dual BCMA/CD19-targeting CAR-T construct that Gracell used for GC012F "looks quite impressive and similar to [cilta-cel] and if the higher dose keeps doing this well, maybe it's better."

They noted that the results for P-BCMA-101 are impressive for the nanoplasmid-encapsulated cells but said more data from additional doses are needed before Poseida's new manufacturing process can be considered a game-changer for the therapy.

[Editor's Note: This article was updated on to amend the number of VGPRs in the bb21217 data from 12 to 15.]