William Blair

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Industry Report

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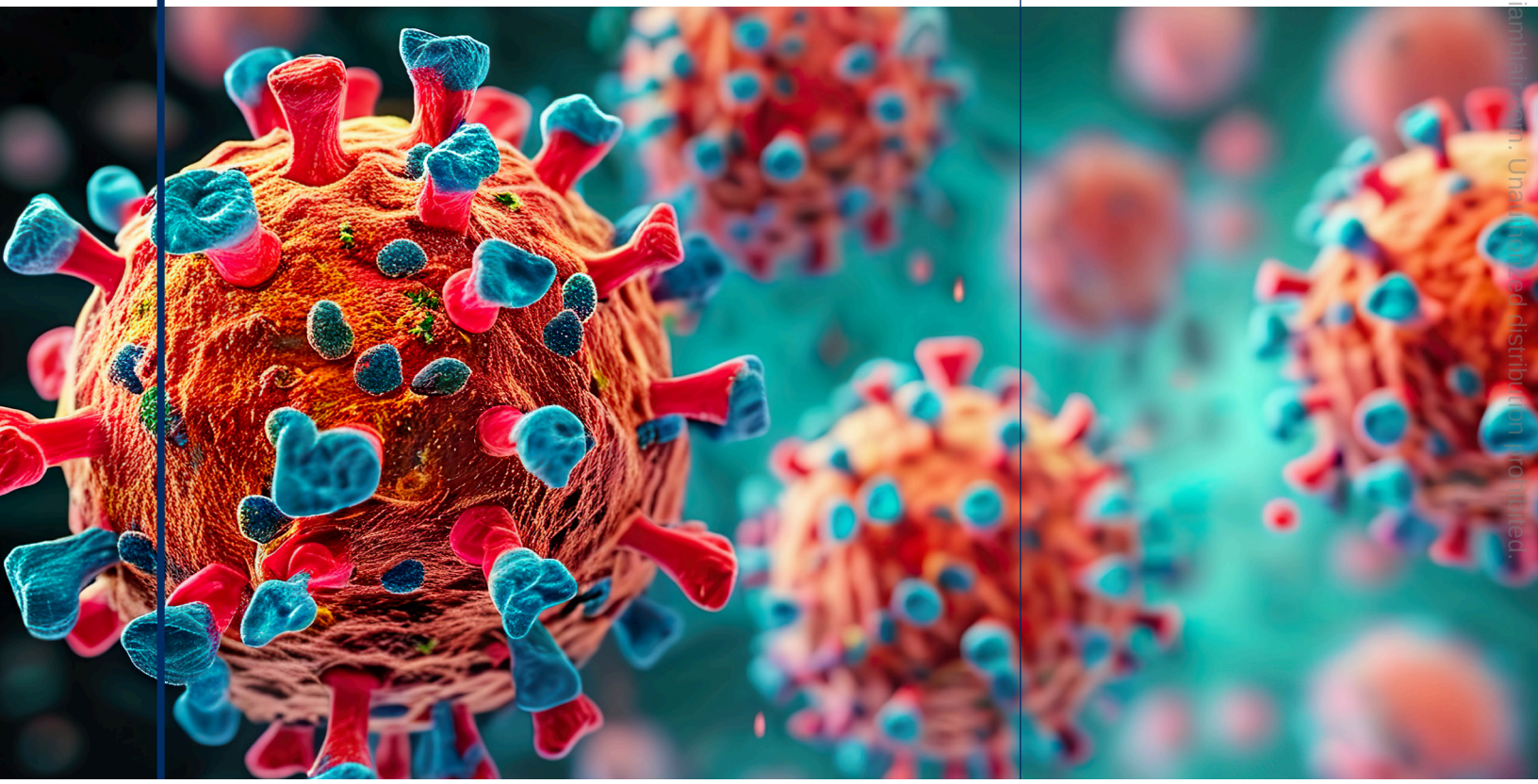
CELLect Horizons

Moving the Needle in Hematological Malignancies



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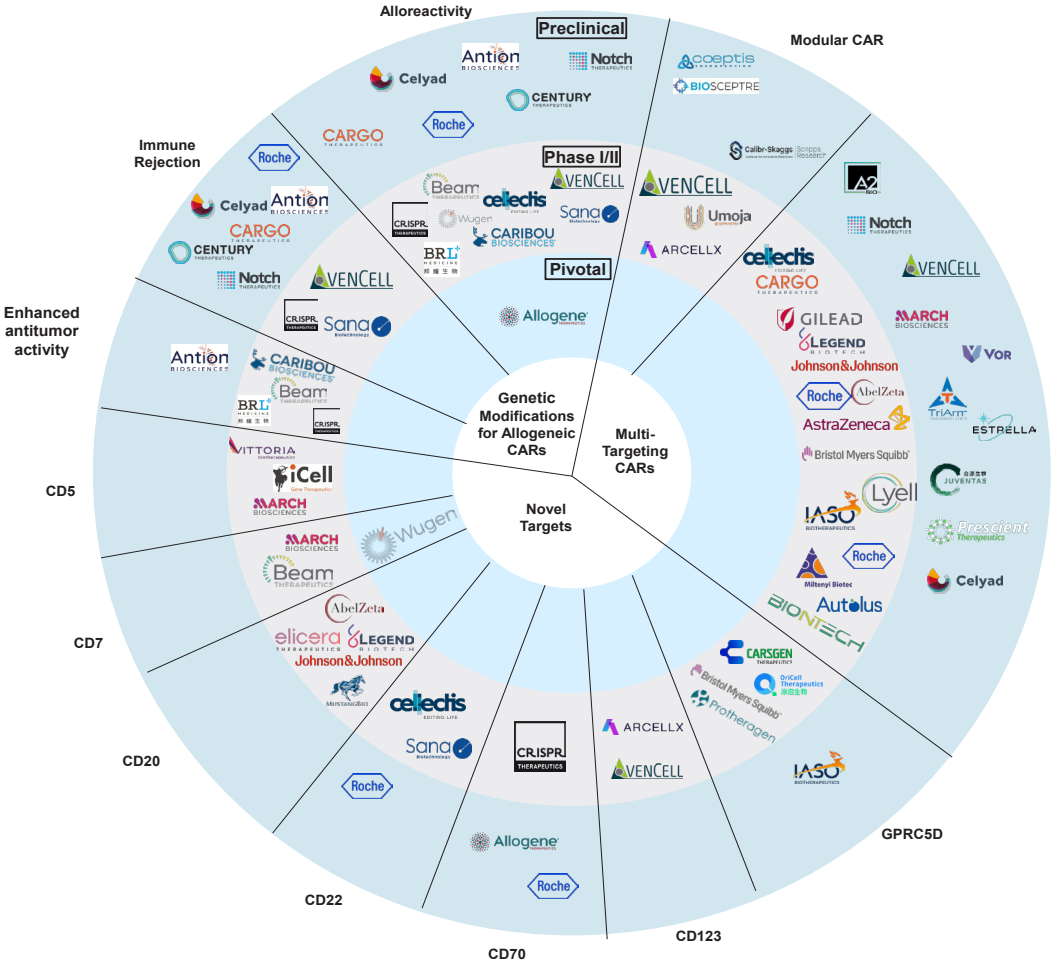
Executive Summary

Approved CAR-Ts have been paradigm-shifting agents in the treatment of certain liquid tumors and generated $4.3 billion in aggregate global sales in 2024. However, all seven approved CAR-T therapies target either CD19 or BCMA, which are not appropriate targets for several hematological malignancies, leaving many patients with no approved CAR-T options. In addition, about 50% and 15%-60% of patients who receive CD19 and BCMA CAR-Ts relapse within 12 months of treatment, respectively, presenting a growing need for efficacious therapies in the post-CD19/BCMA CAR-T setting. Last, all approved CAR-Ts are autologous, which makes them difficult to scale, subject to batch failures, and logistically more challenging to distribute, further limiting patient accessibility. While allogeneic CAR-Ts hold great potential, as they could dramatically decrease the cost of therapy while increasing accessibility, their efficacy has been limited by host-mediated rejection.

In our opinion, there is room for continued innovation in the space to unlock the significant untapped commercial potential of CAR-Ts in hematological malignancies. Specifically, we believe that CAR-Ts designed to address indications that have no approved CAR-T therapy or to rescue patients who have relapsed following treatment with first-gen CAR-Ts have the potential to transform the treatment landscape. In addition, the successful development of allogeneic therapies that exhibit comparable or superior efficacy to autologous therapies would be highly disruptive to the commercial landscape. In this edition of *CELLect Horizons*, we discuss 1) compelling CAR-T antigen targets for hematological malignancies beyond CD19 and BCMA; 2) CAR-Ts capable of targeting more than one antigen; and 3) genetic edits that could improve the efficacy and persistence of allogeneic CAR-Ts. While there are several companies focused on these facets, this report focuses on candidates/platforms that have generated clinical data and select preclinical assets (exhibit 1).

Exhibit 1
CELLect Horizons
Landscape of Next-Generation CAR-T Cell Therapies for Hematological Malignancies

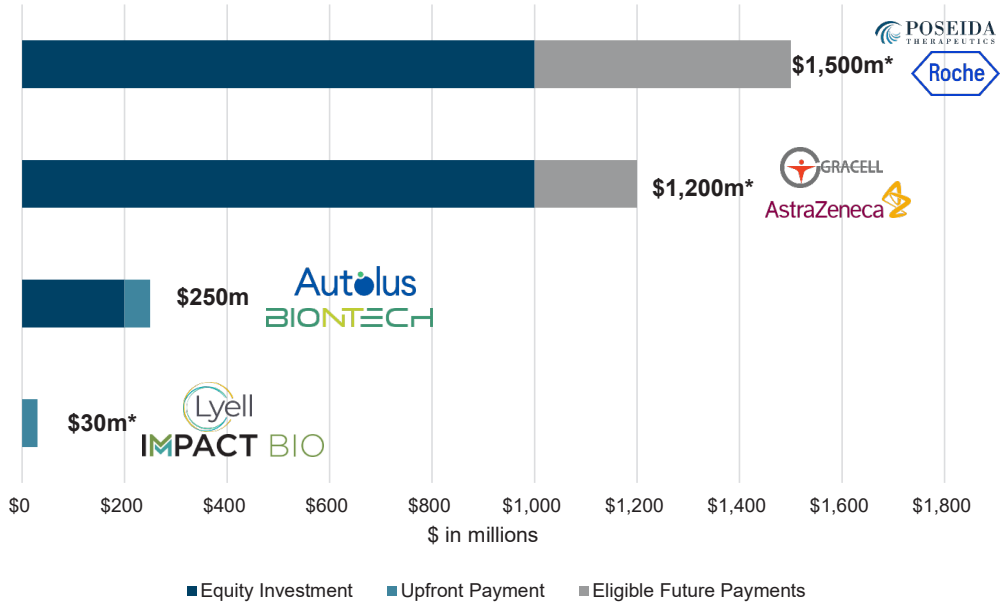


Source: William Blair Equity Research

Based on clinical data generated to date, we believe GPCR5D and CD7 are the most compelling antigen targets for expanding the potential of CAR-T in hematological malignancies. Specifically, **Bristol Myers Squibb's** GPRC5D CAR-T and **Wugen's** CD7 CAR-T have generated compelling clinical responses in specific populations of patients who have failed or are ineligible for commercial CAR-Ts, in our opinion.

Early responses with multi-targeting CAR-T therapies have been extremely encouraging and have led to an increase in business development deals for companies that have developed these assets (exhibit 2). Specifically, we highlight **Poseida Therapeutics** and **Gracell Biotechnologies,** which were each acquired in transactions valued at over $1 billion. We also note that **AbelZeta** and **Johnson & Johnson** amended their collaboration agreement in 2023 to include a dual-targeting CAR-T; however, the economics of the amended collaboration were not disclosed. We believe multi-targeting CARs will be transformational for the hematological malignancies space and, while outside the scope of this report, could also be valuable tools in treating autoimmune diseases. We also believe these modalities will remain a target for business development, which could be a tailwind for other companies in the space, such as **Cargo Therapeutics and Legend Biotech**, which have tri-cistronic CAR-T cell candidates in development.

Exhibit 2
CELLect Horizons
Select Collaborations and Transactions in the Dual CAR-T Cell Space (2023-2024)



*Acquisitions

Sources: Company reports; William Blair Equity Research

We believe that modular CAR-T cell therapies represent a unique and promising approach to conventional CAR-Ts as they provide increased control over the time and extent of CAR-T expansion and associated toxicities. Notably, modular CAR-Ts have significant potential in heterogenous diseases such as acute myeloid leukemia (AML) because adaptor moieties targeting different antigens could be used simultaneously or in succession to redirect the CAR-T cells and prevent relapse due to antigen loss. We highlight private company **AvenCell's** Universal Switchable CAR platform, which has demonstrated clinical proof of concept for modular CAR-Ts and has shown CAR-T expansion and associated toxicities are dependent on the presence of its targeting module. We also highlight that **Arcellx's** ARC-SparX platform, which builds on the company's d-domain technology, is currently being advanced through the clinic, and Kite Pharma has exercised an option for one of Arcellx's ARC-SparX candidates.

A key facet underlying limited allogeneic CAR-T persistence, and therefore reduced durability, is host-mediated graft rejection. While a variety of genetic edits are being evaluated, we believe that **AvenCell** has presented an intriguing case study demonstrating allogeneic CAR-T persistence in peripheral blood out to day 132, supporting its TruAllo platform. In addition, we view **Cargo Therapeutics'** Allo Vector and **Century Therapeutics'** Allo-Evasion 5.0 technology as featuring novel mechanisms to circumvent host immune rejection. However, these platforms are both still in preclinical development, so we look forward to their validation in the clinic in the future. Last, **CRISPR Therapeutics'** recently shared clinical data showed that its second-gen allogeneic CAR-T confers sevenfold peak cell expansion compared with its first-generation candidate, and a case study suggests that the cells could be persisting and enacting antitumor activity out to a year after CAR-T infusion, supporting the additional genetic edits in its second-gen CAR-T platform.

Introduction

Seven CAR-T therapies are currently approved in the U.S., the most recent being Autolus's Aucatzyl, which was approved in November 2024 (exhibit 3). Approved CAR-Ts have been paradigm-shifting agents in the treatment of certain hematological malignancies, and those approved in the second-line treatment setting have demonstrated superior response rates and overall survival than standard-of-care chemotherapy and/or immunotherapies.

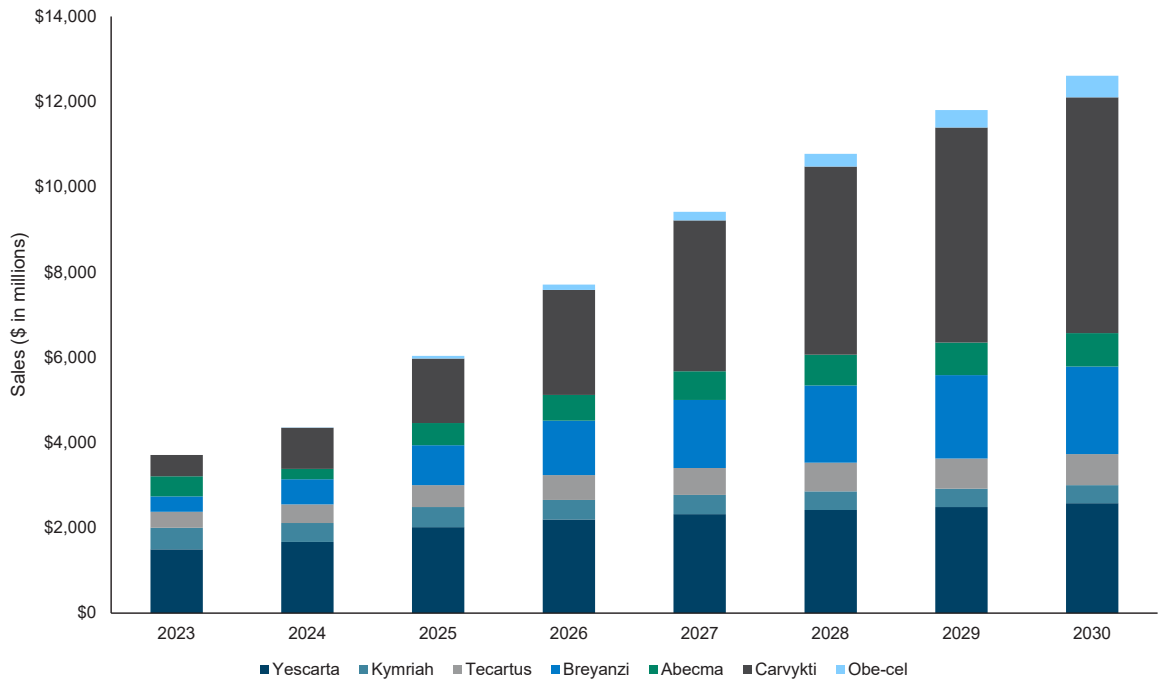
Exhibit 3
CELLect Horizons
FDA-Approved CAR-T Therapies

Sponsor	Product	Product Type	Target	Indication (year of FDA approval)
NOVARTIS	Kymriah	CAR-T	CD19	• r/r B-ALL (2017) • r/r LBCL after ≥2 LOT (2018) • r/r FL after ≥2 LOT (2022)
GILEAD	Yescarta	CAR-T	CD19	• r/r LBCL after ≥2 LOT (2017) • r/r FL after ≥2 LOT (2021) • LBCL refractory to first-line therapy or relapsing <12 months of first-line therapy (2022)
GILEAD	Tecartus	CAR-T	CD19	• r/r MCL (2020) • r/r B-ALL (2021)
Bristol Myers Squibb	Breyanzi	CAR-T	CD19	• r/r LBCL after ≥2 LOT (2021) • LBCL refractory to first-line therapy or relapsing <12 months of first-line therapy and not eligible for HSCT (2022) • r/r CLL and SLL (2024)
Bristol Myers Squibb / 2seventybio	Abecma	CAR-T	BCMA	• r/r MM after ≥4 LOT including a PI, IMiD, and ant-CD38 mAb (2021) • r/r MM after ≥2 LOT including a PI, IMiD, and ant-CD38 mAb (2024)
Johnson&Johnson / LEGEND BIOTECH	Carvykti	CAR-T	BCMA	• r/r MM after ≥4 LOT including a PI, IMiD, and ant-CD38 mAb (2022) • r/r MM after ≥1 LOT including a PI and IMiD, and are refractory to lenalidomide (2024)
Autolus	Aucatzyl	CAR-T	CD19	• r/r B-ALL (2024)

Sources: Company reports; William Blair Equity Research

CAR-T therapies were estimated to have generated $4.3 billion in global revenue in 2024, about 3% of global oncology sales. By 2030, however, these seven therapies could generate at least $12.6 billion and have the potential to account for over 5% of the global oncology market (exhibit 4). This growth is expected to largely be driven by increased Carvykti sales associated with greater penetration in second-line multiple myeloma (MM). However, these estimates do not include the approval of subsequent CAR-T therapies in the next five years (exhibit 5), suggesting that there could be significant upside to these projections.

Exhibit 4
CELLect Horizons
Estimated Sales of Currently Approved CAR-Ts



Sources: Evaluate Pharma; William Blair Equity Research

Exhibit 5
CELLect Horizons
Ongoing Pivotal Trials of CAR-T Cell Therapies That Have Not Previously Been Approved

Company	Product (Target)	Clinical Trial Name	Indication	Trial Start Date (anticipated)	Estimated 2030 Sales (millions)
ARCELLX / GILEAD	Anito-cel (BCMA)	iMMagine-1	3L+ Multiple Myeloma	Q3 2022	$3,195
Allogene Therapeutics	Cema-cel (CD19)	ALPHA3	MRD+ LBCL following R-CHOP	Q3 2024	$740
Wugen	WU-CART-007 (CD7)	NA	r/r T-ALL/LBL	(Q1 2025)	NA

L: lines of therapy
Sources: Consensus Visible Alpha estimates; company reports; William Blair Equity Research

Despite the availability of seven CAR-Ts, all approved CAR-T therapies target either CD19 or BCMA for the treatment of certain hematological malignancies, including various non-Hodgkin lymphoma (NHL) subtypes and MM. In addition, about 50% and 15%-60% of patients will relapse within 12 months of treatment with CD19 and BCMA CAR-Ts, respectively (exhibit 6).

Exhibit 6
CELLect Horizons
Response Rates and Durability With Approved CD19 CAR-T Cell Therapies

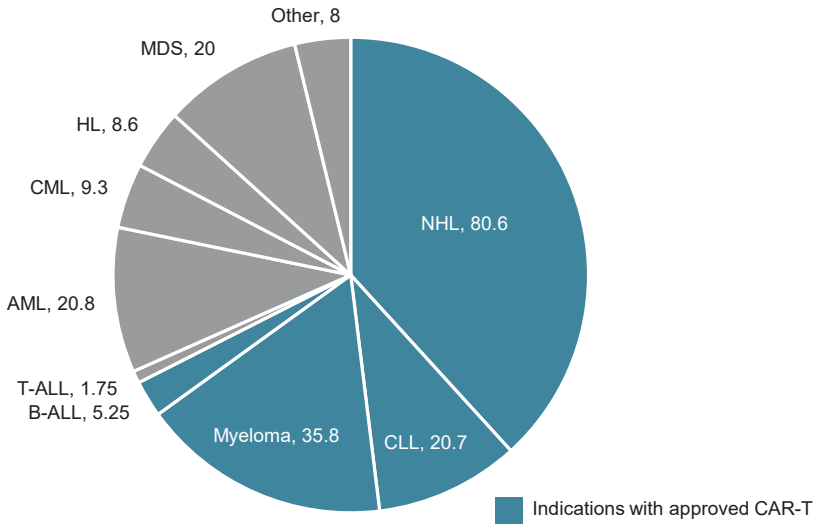
Product	Study/Source	Patient population	Response rate	12-month PFS/EFS	24 month PFS/EFS
Yescarta	ZUMA-7 Locke et al. *NEJM.* 2021	1L+ LBCL	ORR: 83% CRR: 65%	47%	41%
Breyanzi	TRANSFORM Abramson et al. *Blood.* 2023	1L+ LBCL	ORR: 87% CRR: 74%	57%	~52%
Yescarta	ZUMA-1 Jacobson et al. *Blood.* 2021	2L+ LBCL	ORR: 83% CRR: 58%	43%	38%
Kymriah	JULIET Schuster et al. *Lancet.* 2021	2L+ LBCL	ORR: 52% CRR: 40%	~38%	~35%
Breyanzi	TRANSCEND Abramson et al *Lancet.* 2020	2L+ LBCL	ORR: 73% CRR: 53%	44%	41%
Carvykti	CARTITUDE-4 San-Miguel *NEJM* 2023	1L+ MM	ORR: 99% CRR: 86%	85%	N/A
Abecma	KarMMa-3 Rodriguez-Otero et al. *NEJM* 2023	2L+ MM	ORR: 71% CRR: 39%	55%	29%
Carvykti	CARTITUDE-1 ASCO 2023	4L+ MM	ORR: 98% CRR: 83%	76%	61%
Abecma	KarMMa-1 Munshi et a. *NEJM* 2021	4L+ MM	ORR:73% CRR:33%	40%	~18%*
Aucatzyl	FELIX Claire Roddie et al. NEJM. 2024	3L+ B-ALL	ORR: 77% CRR: 55%	50%	N/A

*PFS at target dose (≥150e6 cells)

Source: See source column; William Blair Equity Research

Antigen escape, which occurs when malignant cells lose target antigen expression, has been identified as the mechanism of disease relapse after CAR-T cell therapy in 20%-28% of patients with B-cell lymphoma, in 16%-68% with B-cell acute lymphoblastic leukemia (B-ALL), and at lower incidences in those with MM. Antigen loss in more heterogeneous hematological malignancies, such as AML, has also made it challenging to develop efficacious cell therapies for these indications (exhibit 7).

Exhibit 7
CELLect Horizons
U.S. Annual Incidence of Various Hematological Malignancies ('000s)



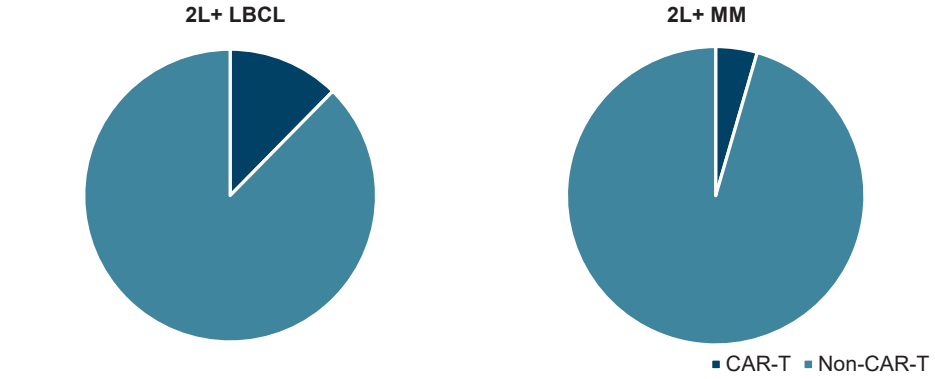
AML, Acute Myeloid Leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CLL, Chronic Lymphocytic Leukemia; CML, Chronic Myeloid Leukemia; HL, Hodgkin lymphoma; MDS, Myelodysplastic Syndrome; NHL, Non-Hodgkin Lymphoma; T-ALL, T-cell acute lymphoblastic leukemia

Sources: American Cancer Society; William Blair Equity Research

Therefore, we believe that CAR-Ts targeting additional antigens, or targeting multiple antigens, could combat or prevent relapse due to antigen loss and be powerful therapeutics for patients who have no approved cell therapy option or have relapsed following treatment with an approved CAR-T. In addition, the successful development of modular CAR-Ts, wherein an antigen-targeting moiety is administered separately from the engineered T cells and can be readily interchanged, could not only address tumor heterogeneity/antigen loss, but also provide greater control of CAR-T cell expansion and resulting toxicities (e.g., CRS and ICANS).

Beyond a lack of targeted antigen diversity, access to approved CAR-Ts remains largely limited because they are autologous and therefore logistically burdensome and expensive to manufacture. As a result of these constraints in manufacturing and distribution, only a small fraction of eligible patients receives CAR-T, leaving significant untapped potential (exhibit 8). Although allogeneic CAR-T therapies could provide more scalable and accessible options, the efficacy and durability of first-generation allogeneic CAR-Ts have largely paled in comparison to their autologous counterparts in the late-line setting. However, we believe the integration of novel genetic edits into next-gen allogeneic CAR-T therapies could lead to increased cell persistence and potency that is comparable to commercial therapies.

Exhibit 8
CELLect Horizons
Percent of U.S. Patients Who Reached 2L+ and Received a CAR-T During Treatment in 2024



Sources: Kite company reports; William Blair Equity Research

Last, while this report focuses on advancements in the design of CAR-T drug products to increase the modality's use in hematological malignancies, other factors could expand the annual number of hematological malignancy patients treated with a CAR-T. Specifically, manufacturing optimizations to increase the scale and/or speed of CAR-T manufacturing and expanded use of CAR-Ts in earlier lines of therapy or unique patient populations could increase CAR-Ts' market opportunity. Exhibit 9 highlights select CAR-T clinical trials targeting unique subsets of patients in the early-line treatment setting.

Exhibit 9
CELLect Horizons
Select Clinical Trials Evaluating CAR-T Cell Therapies in the Early-Line Settings

Company	Product (Target)	Clinical Trial	Key Patient Population	Key Clinical Trial Characteristics	Benefits of Trial Design
LEGEND BIOTECH Johnson&Johnson	Carvykti (BCMA)	CARTITUDE-5	Newly diagnosed multiple myeloma	-Prior exposure to VRd; ASCT **is not** planned as initial therapy -SOC arm: Rd	-SOC arm is representative of current treatment landscape in the 1L setting -Both trials are representative of the two major patient patient populations in the newly diagnosed setting -MRD negativity could be used as a surrogate endpoint for approval
		CARTITUDE-6	Newly diagnosed multiple myeloma	-Received initial therapy with DVRd and ASCT -SOC arm: DVRd followed by ASCT	
ARCELLX GILEAD	Anito-cel (BCMA)	iMMagine-3	1-3 LOT	-Patients exposed to both an immunomodulatory drug and an anti-CD38 monoclonal antibody -SOC arm: KDd, PVd, DPd, Kd	-SOC arm is representative of current treatment landscape in the 2L setting -Eligibility criteria is reflective of evolving treatment paradigm and captures a wide range of patients treated in the 2L -MRD negativity could be used as a surrogate endpoint for approval
Allogene THERAPEUTICS	Cema-cel (CD19)	ALPHA3	MRD-positive following R-CHOP	-Patients who respond to R-CHOP but remain MRD positive -SOC arm: "Wait and watch"	-Uses novel liquid biopsy ctDNA assay to detect MRD positivity - SOC arm is representative of current treatment paradigm -SOC arm does not proclude patients from receiving other CAR-Ts in the future

ASCT, autologous stem cell transplant; LOT, lines of therapy; SOC, standard of care; KDd, carfilzomib, daratumumab, and dexamethasone; Rd, lenalidomide and dexamethasone; PVd, pomalidomide, bortezomib, and dexamethasone; DPd, daratumumab, pomalidomide, dexamethasone; Kd, carfilzomib; VRd, bortezomib, lenalidomide, and dexamethasone
Sources: Company reports; William Blair Equity Research

Expanding the Scope of Targetable Antigens Beyond CD19 and BCMA

Therapies targeting novel antigens aim to: 1) replace available CAR-T therapies by demonstrating a better efficacy/safety profile; 2) provide an efficacious therapeutic option for patients who have relapsed following treatment with a commercial CAR-T; and/or 3) provide a therapeutic option for an indication for which there are no approved CAR-T therapies. In exhibit 10, we highlight the most common CAR-T (not including gamma delta T cells) single-antigen targets in preclinical or clinical development. Despite there being five approved CAR-T cell therapies targeting CD19 and two targeting BCMA, these targets remain heavily investigated in clinical studies, suggesting there is room for improvement for these therapies in the indications they address. However, many of the novel antigens described in exhibit 10 (e.g., CD20, CD22, GPRC5D) are being investigated in dual-targeting CAR-T therapies rather than conventional single-antigen-targeting CAR-Ts since early clinical data from several academic studies has demonstrated that dual-targeting CARs can yield improved responses compared to single-targeting CARs. We also recognize that T-cell malignancies represent an untapped market for CAR-T, with several well-characterized antigens currently being investigated. However, these indications represent a smaller addressable market and require CAR-T cells that avoid cytotoxicity against normal T cells.

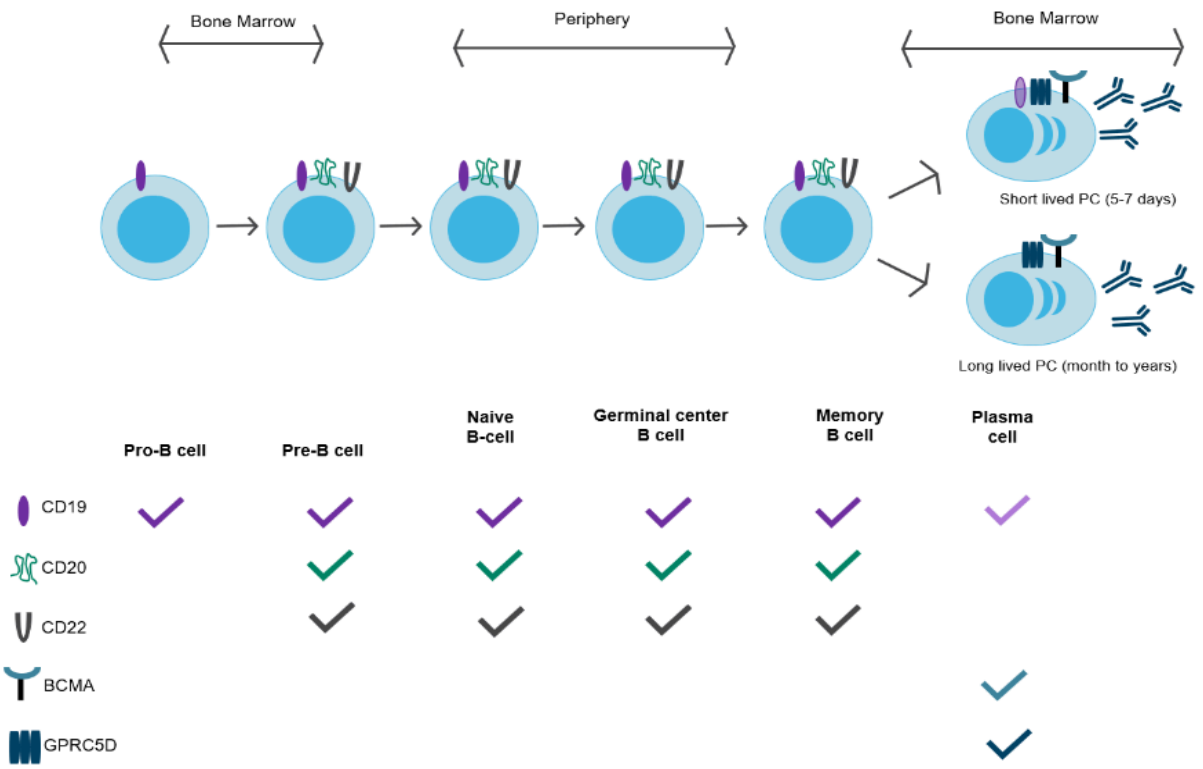
Exhibit 10
CELLect Horizons
Common CAR-T Antigen Targets Being Evaluated for Hematological Malignancies

N=72 (of the publicly disclosed single-antigen CAR-T cell programs)

Sources: BioCentury Inc. and Alpha Sense; company reports; William Blair Equity Research

Development of next-generation CAR-T cell therapies for hematologic malignancies targets unique tumor antigens on B cells in hopes of achieving an improved risk/benefit profile compared with commercial CAR-Ts. Notably, relative expression of canonical B-cell markers (e.g., CD19, CD22, CD20) changes depending on the differentiation state of the cell (Oh et al. *Immune Network.* 2022; exhibit 11).

Exhibit 11
CELLect Horizons
B-Cell Marker Expression During Development and Differentiation



Source: Adapted from Etienne Crickx et al. *Kidney International*. 2020.

Other novel tumor antigens being targeted by CAR-T cell therapies either are nonexclusive to specific immune populations or target normal T-cell populations, thus leading to increased fratricidal risk. Thus, approaches targeting these antigens with CAR-T cell therapies must avoid fratricidal activity toward therapeutic CAR-T cells, while preserving normal lymphoid organs and immune responses. Given the risk of fratricidal activity with these antigens, several studies are investigating approaches to block on-target, off-target CAR-T targeting with antibody-based therapies directed at these antigens. Despite the challenge for targeting these antigens, CAR-T cell therapies present as a unique therapeutic option given that T cells can be genetically modified to be more selective for malignant cells.

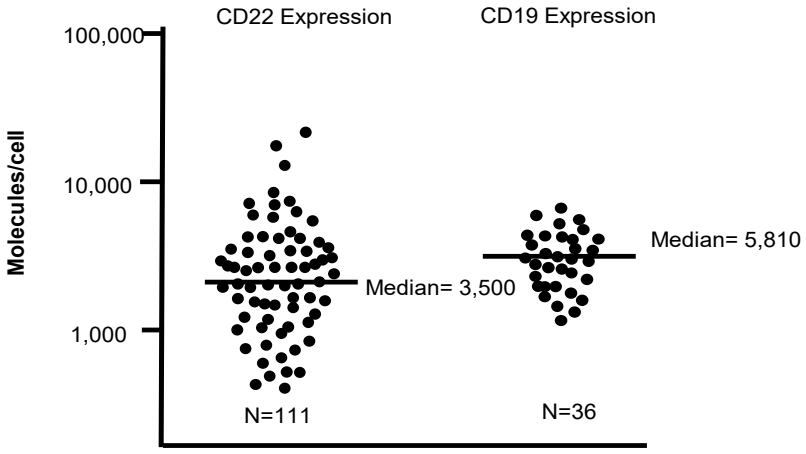
CD22

CD22 is a large glycoprotein (130 kDa to 150 kDa) expressed in B cells across all stages of development until differentiation into plasma cells (exhibit 11, above). Two CD22-targeting therapies have been approved by the FDA for treatment of B-cell malignancies, both of which are used as antibody-drug conjugates (ADCs). Pfizer's inotuzumab ozogamicin (Besponsa) is approved for adult and

pediatric B-ALL and has demonstrated encouraging responses; however, improvement in OS remains limited. In contrast, AstraZeneca withdrew its CD22 ADC from the market due to the low clinical uptake and complexity of the drug use. Notably, CD22 expression is independent of CD19 expression in malignant B cells and thus resistant to downregulation or loss in CD19-negative patients (Jia Xu et. al. *Experimental Hematology & Oncology*. 2023). Therefore, CD22 CAR-Ts could be a compelling therapy for patients who have relapsed following CD19 CAR-T due to antigen down-regulation.

A considerable limitation with targeting CD22 is that cell surface density can be modest in patients. In studies conducted by Stanford University, median CD22 expression levels across 111 patients with B-cell acute lymphoblastic leukemia (BC-ALL) were 3,500 sites per cell, considerably lower than CD19 (exhibit 12; Waleed Haso et al. *Blood*. 2013; Jay Spiegel et al. *American Society for Transplantation and Cellular Therapy*. 2024). Therefore, while CD22 CAR-Ts are being developed to go head-to-head against CD19 CAR-Ts in both NHL and B-ALL, the biological rationale as to why they might generate superior efficacy is unclear, in our view.

Exhibit 12
CELLect Horizons
CD22 and CD19 Expression Levels Pre-CAR-T Cell Treatment



Source: Adapted from Waleed Haso et al. *Blood* . 2013 and Jay Spiegel et al. *Transplantation and Cellular Therapy* . 2024; William Blair Equity Research

In exhibit 13, we highlight initial clinical data generated from two CD22 CAR-T cell therapies. Both assets show encouraging response rates, particularly given the large portions of patients in each trial who are CD19 CAR-T refractory.

Exhibit 13
CELLect Horizons
Clinical Data From CD22 CAR-T Cell Therapies in B-cell Malignancies

	CARGO THERAPEUTICS			cellectis EDITING LIFE
Drug	Firi-cel			UCART22
Product Characteristics	Autologous			Allogeneic
Indication	LBCL	LBCL	B-ALL	B-ALL
Phase	Phase II	Phase I	Phase I	Phase I
Patients numbers	N=51	n=38	n=58	n=3
Baseline Characteristics	N/A	Median age: 65 Median prior LOT: 4 Refractory to all prior therapies: 29% Prior CD19 CAR-T: 97% Stage III/IV disease: 68% Patients receiving bridging therapy: 37%	Median age: 17.5 Prior CD19 CAR-T: 62% Prior HSCT: 67%	Prior CD19 CAR-T: 67%
Dose	DL1: 1.0e6 cells/kg	DL1: 1.0e6 cells/kg DL2: 3.0e6 cells/kg	DL1: 3.0e5 cells/kg DL2: 1.0e6 cells/kg DL3: 3.0e6 cells/kg DL1 TCS: 3.0e5 cells/kg DL2 TCS: 1.0e6 cells/kg	DL2: 1.0e6 cells/kg
Median Follow-up (mo)	ud	31.4	~6	ud
Response Rates **CR** **<CR**	ORR: 77% 43% 34%	ORR: 68% 53% 15%	ORR: 72% 70%	ORR: 67% 33% 34%
CRS All Grade (Grade ≥3)	ud (18%*)	95% (3%)	86% (10%)	67% (0%)
Neurotoxicity All Grade (Grade ≥3)	ud	11% (0%)	32% (2%)	0% (0)%
Long-term endpoints	3 mo CR rate: 18%	mPFS: 3 mo mOS: 14.1 mo	mEFS: 3.2 mo mOS: 13.4 mo	ud
Next Expected Update	Program discontinued			Present clinical data in 2025
Reference	Company reports	*EHA 2024*	Nirali N. Shah et al. *Journal of Clinical Oncology*. 2020.	*ASH 2023*

*Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS); FL, follicular lymphoma; LOT, lines of therapy; N/A, not available ;NHL, Non-Hodgkin's lymphoma; TCS, T cell selected process; ud, undisclosed; WM, Waldenstrom macroglobulinemia

Sources: See reference line

Cargo Therapeutics was developing firi-cel (CRG-022), an autologous anti-CD22 CAR-T cell therapy for the treatment of relapsed refractory (r/r) large B-cell lymphoma (LBCL) patients who have advanced following treatment with a CD19 CAR-T therapy. Notably, firi-cel's CAR is structurally differentiated from other CAR-T cell therapies through the expression of a shorter peptide linker between the scFv regions, which has been shown to increase dimerization and improve expansion. Additional details on Cargo and firi-cel can be found in our initiation report: Pushing the Envelope on How Far CARs Can Go; Initiating With Outperform Rating).

On January 29, 2025, Cargo reported data from an ad hoc analysis of the Phase II FIRCE-1 that was conducted in response to the emergence of severe safety events. Of the 51% people evaluable for efficacy at 1 month, 77% and 43% of patients achieved a response and complete response, respectively, in line with responses observed in the Phase I Stanford trial (ORR: 68%; CR: 53%). However, the durability of complete responses (CRs) at three months was 18%, considerably lower than the Phase I study, wherein the median PFS and OS had not been reached in the 20 patients who achieved a CR (Matthew J Frank et al. *Lancet*. 2024).

In addition, 18% of patients developed immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) that was grade 3 or higher, including three grade 5 events. This is a known toxicity associated with CAR-T and had been observed in previous studies of firicel (two patients treated at the higher dose and one patient treated with a higher dose in the Phase I Stanford study developed <grade 3 and grade 4 IEC-HS, respectively, and 2 patients experienced IEC-HS <grade 3 at the low dose).

Given the limited durability and increased safety concerns, the company decided to discontinue development of firi-cel. Although the underlying cause of firi-cel's minimal durability in the Phase II trial remains unclear, we note that CD22 CAR-T cell activity may be highly dependent on CD22 expression. However, the minimal level of CD22 expression required for a durable long-term response with a CD22 CAR-T is unknown. In addition, it is possible this patient population, which had previously been treated with CD19 CAR-Ts, had a high portion of effector T cells in their starting product, which also could have led to diminished durability. At this time, we believe it is likely firi-cel's novel binder, which showed robust expansion kinetics in Phase I studies, drove the high-grade IEC-HS safety events and could be a concern for similar therapies going forward. We note that **Sana Biotechnology** is evaluating an allogeneic CD22 CAR-T cell therapy that uses the same binder as Cargo and is in Phase I studies.

CD20

CD20, which is expressed on mature B cells but not early B-cell progenitors or short-lived plasma cells, has been extensively studied as a target for B-cell malignancies and is the target of the mAb, rituximab, which is widely used in the frontline management of NHL. Given CD20's expression across B-cell lineages, CAR-T therapies targeting CD20 are being developed as an alternative to CD19 CAR-Ts or for patients who have relapsed following CD19 CAR-T treatment. However, since CD20 is already targeted early on in treatment, CD20 CAR-Ts carry the theoretical risk of reduced efficacy due to rituximab-driven CD20 antigen loss.

In exhibit 14, we summarize the clinical data produced by select CD20 CAR-T cell programs. Generally, these candidates have yielded response rates that are competitive with or superior to CD19 CAR-T therapies with more tolerable toxicity profiles as demonstrated by lower levels of high-grade CRS. However, the durability of responses, with the exception of AbelZeta/Johnson & Johnson's candidate, has been limited. Notably, there are meaningful differences in other facets of the candidates (e.g., allogeneic vs. autologous) and trials (e.g., target indication, patient baseline characteristics), which could have impacted response rates and durability of responses. While this makes it increasingly challenging to conduct cross-trial comparisons between CD20 CAR-Ts and commercially available CD19 CAR-Ts, we believe that the preliminary clinical data suggests CD20 is a viable development target for CAR-T therapies.

Exhibit 14
CELLect Horizons
Results From Clinical Trials of CD20 CAR-T Cell Therapies in B-cell Malignancies

	Acepodia	AbelZeta / Johnson&Johnson	MUSTANGBIO		Adicet Bio
Drug	ACE1831	C-CAR066	MB-106		ADI-001
Product Characteristics	Allogeneic (gamma delta T cell)	Autologous	Autologous		Allogeneic (gamma delta T cell)
Indication	NHL	NHL	NHL	WM	MCL
Phase	Phase I	Phase I	Phase I/II	Phase I/II	Phase I
Patient Numbers	n=5	n=14	n=9	n=10	n=10
Baseline Characteristics	ud	Median Age: 54.5 years ECOG 0/1: 35%/64% IPI 3-4: 57% median prior LOT: 5 Prior ASCT: 14% Prior CD19 CAR-T: 85% Patients receiving bridging therapy: 50%	Median age: 56 Median prior LOT: 4 Prior ASCT: 11% Prior CAR-T: 22%	median prior LOT: 9	median prior LOT: 3 Prior CD19 CAR-T: 30%
Dose	ud	2.0e6 cells/kg 3.0e6 cells/kg	DL1: 3.3e6 cells/kg DL2: 1.0e7 cells/kg	N/A	ud
Median Follow-up (mo)	ud	27.7	ud	ud	ud
Response Rates **CR** **<CR**	ORR: 20% 20%	ORR: 93% 57% 36%	ORR: 100% 63% 37%	ORR: 90% 30% 60%	ORR: 80% 60% 20%
CRS (Grade ≥3)	ud	86% (7%)	56% (0%)	100% (0%)	ud
Neurotoxicity (Grade ≥3)	ud	0%	0%	10% (0%)	ud
Long-Term Endpoints	ud	mPFS: 9.4 mo mOS: 34.8 mo	ud	ud	ud
Next Expected Update	ud	ud	Further development dependent on raising a significant amount of additional funding and/or consummating a strategic partnership		Program discontinued
Reference	Company reports	Ping Li. et al. *Am J Hema*. 2024	*ASH 2023*	*EHA 2024*	Company reports

FL, follicular lymphoma; LOT, lines of therapy; MCL, mantle cell lymphoma; N/A, not available ;NHL, Non-Hodgkin's lymphoma; ud, undisclosed; WM, Waldenstrom macroglobulinemia

Sources: See reference line; William Blair Equity Research

Specifically, we see **AbelZeta** and **Johnson & Johnson's** C-CAR066 as having generated the most compelling clinical data of the CD20 CAR-T assets given the durability of responses in a highly refractory patient population. However, the initial clinical data is from a China-based trial, so a U.S.-based clinical trial has been initiated to replicate the results. According to company reports from January 2024, AbelZeta anticipated sharing clinical data from the U.S.-based Phase Ib study of C-CAR066 in LBCL patients with at least three prior lines of therapy in the second half of 2024; however, no updated data has been disclosed as of the publication of this report. Still, the companies envision that C-CAR066 could be used across all lines of therapy, including first-line (R-CHOP naïve), second-line (R-CHOP failure), and third-line-plus (CD19 CAR-T–naïve or –experienced patients).

In May 2023, Johnson & Johnson and AbelZeta entered a worldwide collaboration and license agreement to develop, manufacture, and commercialize next-generation CD20 CAR-T cell therapies. Under the terms of the agreement, J&J made an upfront payment of $245 million, with the opportunity for additional future payments based on the achievement of certain development, regulatory, and sales milestones and tiered royalty payments on worldwide net trade sales, excluding Greater China. The collaboration agreement was subsequently amended in December 2023 to include an option for commercialization of products in China.

GPRC5D

G protein–coupled receptor class C group 5 member D (GPRC5D) is a novel therapeutic target being evaluated for the treatment of MM. Currently, the target ligand for GPRC5D is unknown, with a majority of its signaling mechanisms and function in normal tissue and MM also not well understood (Paula Rodriguez-Otero et al. *Blood Cancer Journal.* 2024). In the immune cell compartment, the GPRC5D protein is predominantly expressed in cells with a plasma cell phenotype, with little to no expression on normal B cells, T cells, NK cells, monocytes, granulocytes, or bone marrow progenitors. Importantly, similar mRNA expression levels of GPRC5D have been detected in the epithelium (hair follicles, eccrine glands, and skin) and at the base of filiform papillae on the tongue (Paula Rodriguez-Otero et al. *Blood Cancer Journal.* 2024), suggesting there could be on-target, off-tumor toxicity with a GPRC5D-targeted therapy. Notably, GPRC5D expression is not essential for long-term survival of myeloma cells, so questions remain on how durable GPRC5D-targeted therapies are in MM patients.

Talquetamab (Talvey), a humanized monoclonal bispecific antibody, is the first and only FDA-approved therapeutic targeting GPRC5D for the treatment of r/r MM. Talquetamab was approved based on the Phase II MonumenTAL-1 study, which demonstrated a 74% ORR in 187 patients who were not exposed to prior T-cell redirection therapy. At a median follow-up of 14 months, 35% of patients achieved a CR or better. Most skin-, nail-, and taste-related AEs were low grade, rarely required dose modifications, and were manageable. Some of the more common safety events were related to CRS and neurotoxicity, which were typical of bispecific therapies and manageable. Since Talvey's approval in August 2023, Johnson & Johnson has not disclosed its sales; however, sell-side estimates project Talvey generating $490 million in sales by 2028. In contrast, BCMA bispecifics and CAR-T cell products are estimated to generate over $5 billion in sales in 2028. Overall, we believe this suggests there is room in the market for novel MM therapies, particularly those targeting GPRC5D; however, their market opportunity may be limited given the robust efficacy generated by BCMA therapies.

In exhibit 15, we summarize clinical data generated by GPRC5D CAR-T cell programs currently in development. GPRC5D CAR-T assets have demonstrated high response rates in early clinical studies, with Bristol Myers Squibb's Arlocabtagene autoleucel (arlo-cel; BMS-986393) achieving responses in the early- and late-line setting and encouraging PFS and OS survival at extended follow-up.

Exhibit 15
CELLect Horizons
Results From Clinical Trials of GPRC5D CAR-T Cell Therapies in Multiple Myeloma

	Bristol Myers Squibb™		CARSGEN THERAPEUTICS	OriCell Therapeutics 原启生物
Drug	Arlo-cel		CT071	OriCAR-017
Product Characteristics	Autologous		Autologous	Autologous
Indication	MM		MM	MM
Phase	Phase I Cohort A (≥ 3+ prior regimens)	Phase I Cohort B; cohort C (1-3 prior regimens)	Phase I	Phase I
Patients numbers	n=84	n=31	n=17	n=10
Baseline Characteristics	Median age: 63 Median prior LOT: 5 EMD patients: 46% Prior BCMA targeted therapy: 49%	Median age: 62 Median prior LOT: 2 EMD patients: 29% Prior ASCT: 52%	Median age: 63 Median prior LOT: 5 Stage III disease: 24% EMD patients: 24% Prior CAR-T: 23% Prior ASCT: 53%	Median age: 64 Median prior LOT: 5 Stage III disease: 30% EMD patients: 40% Prior BCMA targeted therapy: 50%
Dose	25-450e6 cells	150e6 cells	0.1e6 cells 0.3e6 cells	1e6 cells/kg 3e6 cells/kg 6e6 cells/kg
Median Follow-up (mo)	16.1	8.8	6.2	~24
Response Rates **CR** **<CR**	ORR: 87% 53% 34%	ORR: 96% 46% 50%	ORR: 94% 53% 41%	ORR: 100% 80% 20%
CRS (Grade ≥3)	82% (4%)	84% (0%)	65% (0%)	100% (0%)
Neurotoxicity (Grade ≥3)	21% (10%)	10% (0%)	0%	0%
Long-term endpoints	mPFS: 18.3 21-mo OS rate: 84%	pts with ongoing response: 74%	6-mo CR rate: 67%	mPFS: 11.4 mo
Next Expected Update	Additional Phase I data and initial Phase II data in 2026		ud	ud
Reference	ASH 2024	ASH 2024	ASH 2024	ASCO 2024

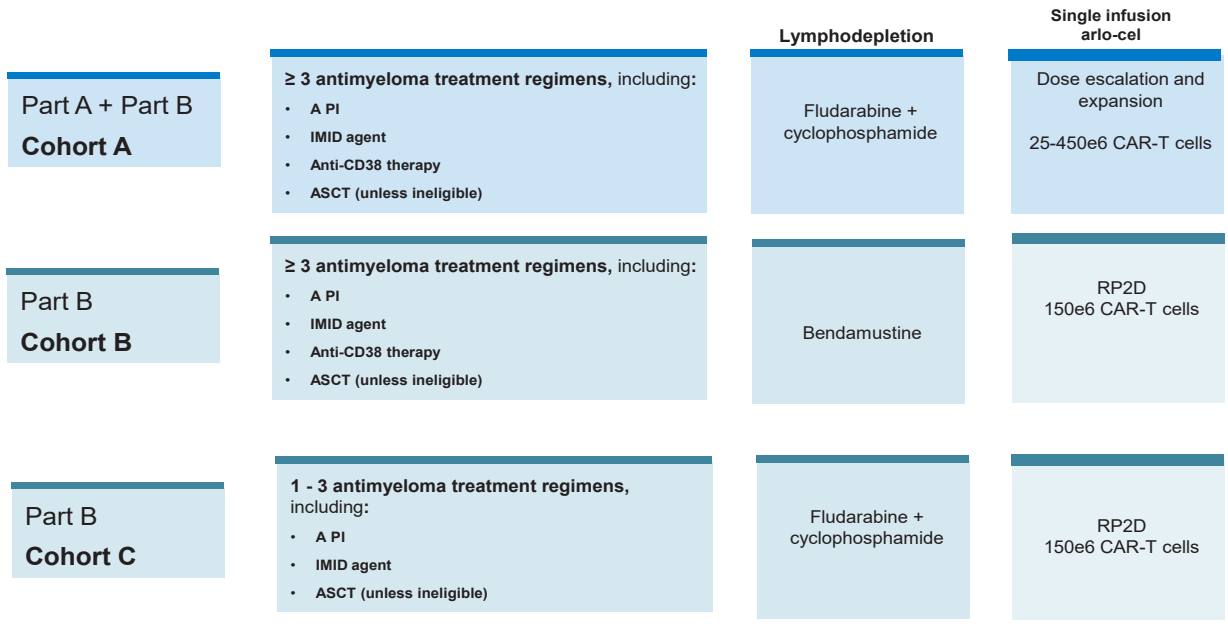
EMD, extramedullary plasmacytomas; LOT, lines of therapy; N/A, not available; MM, multiple myeloma; ud, undisclosed;

Sources: See reference line

Given the breadth of data collected thus far, we believe **Bristol Myers's** arlo-cel has demonstrated the most compelling data among the GPRC5D candidates being evaluated. In addition, we highlight that Bristol Myers's clinical trials are being conducted in the U.S., which we believe compares favorably to competitor studies being conducted in China. Last, we believe ongoing studies evaluating arlo-cel with novel lymphodepletion regimens (e.g., bendamustine) could provide additional upside for arlo-cel's therapeutic profile in MM patients.

Arlo-cel is an autologous GPRC5D CAR-T cell therapy for the treatment of r/r MM. The Phase I study (NCT04674813) is evaluating a single infusion of arlo-cel in three different patient cohorts (exhibit 16), including both late-line (>3 lines of treatment [LOT]) and early-line (1-3 LOT) patients and those previously treated with a BCMA-directed therapy. At the ASH 2024 conference, Bristol Myers presented updated data from patients treated in the study (see: ASH Recap: Evolving Multiple Myeloma Therapeutic Landscape, Bispecific Combinations, and Next-Gen SCD Therapies Making Waves), which is summarized below.

Exhibit 16
CELLect Horizons
Design of Bristol Myers's Phase I Trial of Arlo-cel in Multiple Myeloma



Sources: Company reports; William Blair Equity Research

- ***Cohort A (part A and B):*** Cohort A focused on evaluating heavily pretreated patients who received at least three prior lines of therapy. In the 79 patients who received arlo-cel, 87% achieved a response, with 53% achieving a CR. Notably, responses were improved in patients treated at the RP2D ($150x10^6$ cells), with 91% of patients achieving a response, 48% of which were CRs. The median PFS was 18.3 months. The median OS was not reached, but the 21-month OS rate was 84%.

  In regard to safety, CRS was primarily grade 1 or 2. Grade 3/4 CRS occurred in 4% of patients, and one patient experienced a grade 5 CRS event at the highest dose. In addition, 4% of patients experienced grade 3/4 macrophage activation syndrome/hemophagocytic lymphohistiocytosis. Most cases of on-target, off-tumor toxicity, including skin, nail, and oral events, did not require intervention. Grade 3/4 ICANS occurred in 2% of all patients, and grade 3 other

select neurotoxicity events (dizziness, ataxia, neurotoxicity, dysarthria, and/or nystagmus) occurred in 7% of patients (none were grade 4 or 5). No cases of parkinsonism, Guillain-Barre syndrome, or cranial nerve palsy were observed.

- ***Part B (cohort C):*** In part B cohort C of the study, enrolled patients had previously received one to three prior lines of therapy and were treated with arlo-cel at the RP2D dose following lymphodepletion (cohort B: bendamustine; cohort C: Flu/Cy). As of the August 23, 2024, data cutoff, 31 patients in part B cohort C have been treated. Across 24 patients with evaluable efficacy, a 96% ORR and 46% CR rate were reported. In addition, the median time to response was 1 month (range: 0.9 to 2.9), and responses deepened over time in 13 patients. As of the data cutoff, 74% of responses were ongoing (17/23) and there were no patient deaths. Select AEs of interest included CRS (84%; all grade 1 or 2), infections and infestations (48%; all grade 1 or 2), ICANS (10%; all grade 1 or 2), and neurotoxicity (one grade 2 ataxia), which occurred 142 days after infusion. On-target, off-tumor adverse events included oral (39%), nail (35%), and skin (26%) toxicities, which were all grade 1 or 2.

In the near term, Bristol is planning to initiate a registrational Phase III study (QUINTESSENTIAL-2, NCT06615479) comparing arlo-cel to standard regimens in the second- to fourth-line MM setting (projected readout in 2028). An additional Phase I study (NCT06121843) evaluating arlo-cel combinations (alnuctamab, mezigdomide, and iberdomide combos) in patients with RRMM with one to three prior lines of therapy is ongoing, as is a Phase II study (QUINTESSENTIAL) evaluating arlo-cel monotherapy in fourth-line plus MM (data expected in 2026).

CD123

CD123 is the alpha chain of the interleukin 3 receptor (IL-3Rα), which is responsible for growth, proliferation, survival, and differentiation of hematopoietic cells (HSCs), along with immunity and inflammatory response. Under normal conditions, CD123 is restricted to HSCs; however, certain hematologic malignancies, such as blastic plasmacytoid dendritic cell neoplasm (BPDCN), AML, acute lymphoblastic leukemia/lymphoma (ALL), hairy cell leukemia (HCL), and systemic mastocytosis (SM), upregulate CD123 (Hanadi El Achi et al. *Cancers*. 2020). Notably, CD123 expression ranges considerably between indications. Currently, Menarini Group's tagraxofusp (Elzonris), a recombinant IL-3 fused to a cytotoxin, is the only FDA-approved treatment targeting CD123 tumors. The FDA approved tagraxofusp for the treatment of BPDCN in adults and pediatric patients 2 years and older based on a 67% ORR and a median OS of 8.5 months (Pemmaraju N et al. *NEJM*. 2019). It is important to note that tagraxofusp has a black-box warning for capillary leak syndrome (CLS), which was reported in 19% of patients and was associated with two deaths in the pivotal study. Therefore, treatment with tagraxofusp requires stringent monitoring of serum albumin, weight, and blood pressure.

CD123 has been a target of interest for CAR-T therapies being developed in AML. In exhibit 17, we summarize clinical data produced by CD123 CAR-T cell programs in development by AvenCell and Cellectis. In contrast to other hematological malignancies, we note that AML is a very heterogeneous and aggressive disease, with disease control and bridging to transplant still being the primary objective of treatment. With that context, we believe that early data from CD123 CAR-Ts have demonstrated efficacy but may possess a greater risk for high-grade CRS compared to CAR-Ts for other hematological malignancies.

Exhibit 17
CELLect Horizons
Results From Clinical Trials of CD123 CAR-T Cell Therapies in AML

	AVENCELL	cellectis EDITING LIFE
Drug	AVC-101	UCART123v1.2
Product Characteristics	Autologous	Allogeneic
Indication	AML	AML
Phase	Phase I	Phase I
Patient Numbers	n=22	n=18
Baseline Characteristics	ud	Median age: 57 Median prior treatments: 4 Median baseline bone marrow blasts: 37% Prior HSCT: 50%
Dose	DL1: 1.0e6 cells DL2: 2.5e6 cells DL3: 5.0e6 cells	DL1: 2.5e5 cells/kg DL2: 6.25e5 cells/kg DL2i: 1.5e6 cells/kg DL3: 3.30e6 cells/kg
Median Follow-up (mo)	ud	ud
Response Rates **CR** **<CR**	ORR: 68% 36% 32%	ORR: 12% 12%
CRS (Grade ≥3)	ud	29% (24%)
Neurotoxicity (Grade ≥3)	ud	6% (6%)
Long-Term Endpoints	N/A	N/A
Next Expected Update	Phase I expansion/ Phase II study in early 2Q2024	Present clinical data in 2025; Program discontinued
Reference	Company reports	ASGCT 2023

N/A, not available; ud, undisclosed

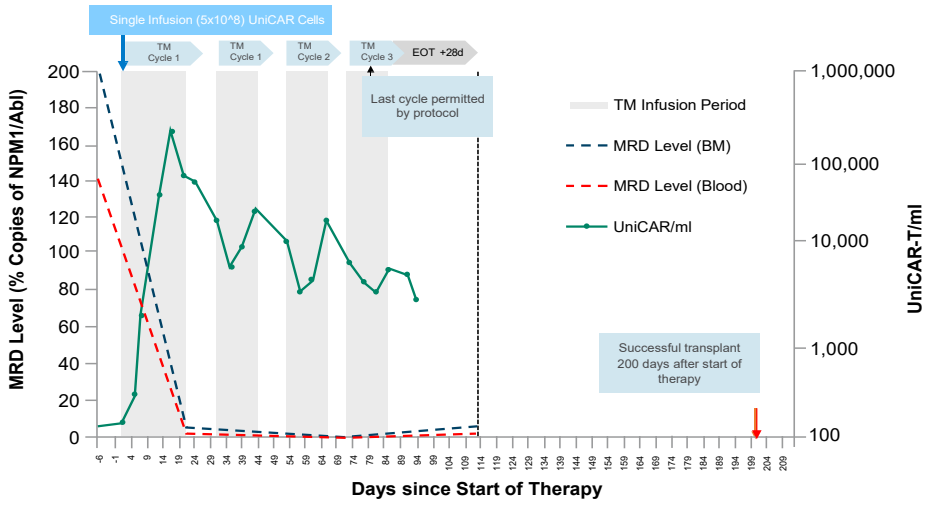
Sources: See reference line

Specifically, we highlight **AvenCell's** AVC-101, an autologous CD123 CAR-T cell therapy for the treatment of AML. AvenCell's CAR-T platform features a proprietary Universal Switchable CAR construct that is designed to only activate T-cell signaling in the presence of soluble adaptors called "targeting modules." We discuss AvenCell's universal CAR in more detail in the "Modular CAR-Ts" section below.

In March 2020, AvenCell dosed the first patient in the first-in-human Phase I study of AVC-101 in CD123-positive patients with r/r acute leukemias (NCT04230265). The multicenter, open-label study is being conducted at university centers in Germany and the Netherlands and treating patients with a single infusion of AVC-101 at one of three dose levels (DL1: 100 million CAR-T cells, DL2: 200 million CAR-T cells, DL3: 500 million CAR-T cells). Different concentrations of targeting modules were also evaluated ranging from 2 mg to 4 mg per day. Targeting modules were administered over 21 days as continuous infusion via a mobile pump beginning on day 1, the same day of AVC-101 infusion. All patients received standard lymphodepletion with fludarabine/cyclophosphamide before cell infusion.

As of December 2024, AvenCell had dosed 22 patients in the Phase I study. To date, responses to AVC-101 have been observed in 15 of 22 patients (68%), with 8 patients (36%) achieving a CR. Notably, one patient who achieved a CR with prior therapies but was still MRD positive with "high-risk" disease achieved MRD negativity within 30 days post AVC-101 infusion (exhibit 18).

Exhibit 18
CELLect Horizons
MRD Response and T-cell Expansion Following Treatment With AvenCell's AVC-101



Source: Company reports; William Blair Equity Research

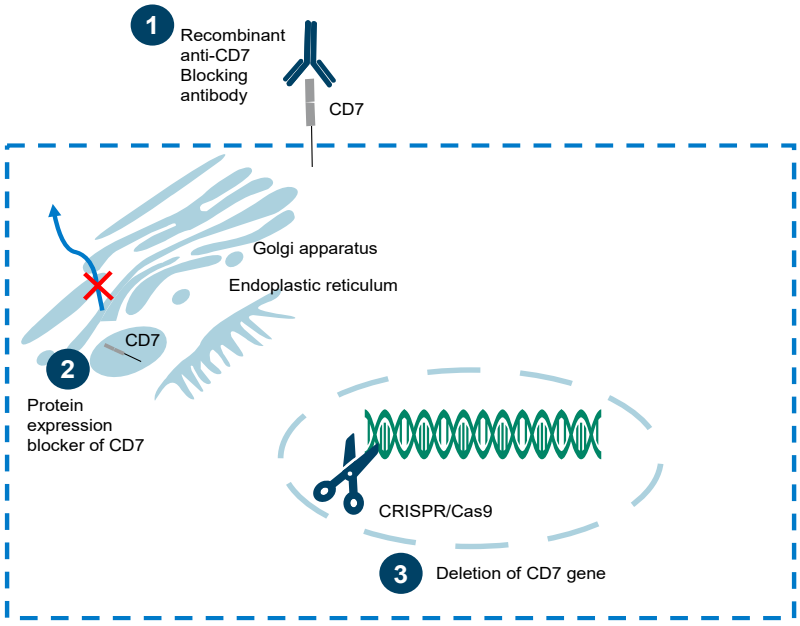
Although the company has not disclosed the safety results, in a previous data cut presented at ASH 2023 conference, CRS was observed in 13 patients, 3 of which were grade 3 or higher. All three severe CRS cases resolved following termination of targeting module administration. Importantly, cell activity and associated toxicities can be successfully modulated with administration/elimination of the targeting module. Similarly, one patient experienced a grade 2 CAR T-cell-related encephalopathy syndrome (CRES) identified by a disorientation and loss of writing capability. However, upon withholding targeting module administration, the writing capability reverted within hours. No additional updates regarding updates for this program have been disclosed.

AvenCell is also developing an allogeneic CD123 cell therapy, AVC-201, for the treatment of AML. In February 2024, the company dosed the first patient in the Phase Ia study (NCT05949125), which will include up to 37 patients. The study is being conducted at multiple sites in Germany and the Netherlands. AVC-201 comprises several genetic edits, which are discussed in more detail later in this report.

CD7

CD7 is a cell membrane glycoprotein that is highly expressed in T-cell acute lymphoblastic leukemia (T-ALL), T-lymphoma, and a minority of AML tumors (30%). Despite the robust expression in hematologic malignancies, early studies targeting CD7 have shown limited efficacy in patients (Frankel AE et al. *Leuk Lymphoma*. 1997). Importantly, CD7 surface expression is also found on normal T lymphocytes and NK cells, as well as progenitors of thymocytes, lymphocytes, and myeloid cells. Therefore, to prevent fratricide during manufacturing, CAR-Ts targeting CD7 must be blocked with antibodies, genetically edited to knock out CD7, or manufactured from a subset of naturally occurring CD7-negative T cells (exhibit 19).

Exhibit 19
CELLect Horizons
Schematic of Approaches Used to Suppress CD7 in Normal Immune Cells

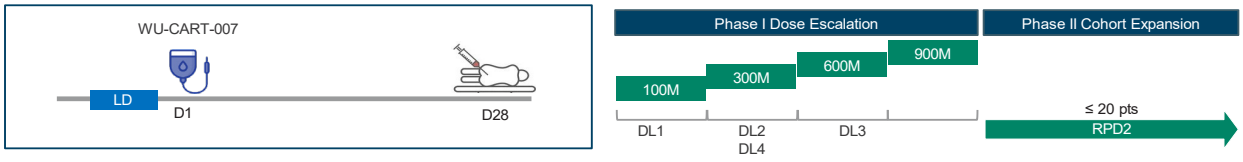


Source: Adapted from Jile Liu et al. *Frontiers Immunolog* y. 2023; William Blair Equity Research

Private company **Wugen** is developing WU-CART-007, an allogeneic CD7-targeted CAR-T cell therapy for the treatment of r/r T-ALL. In addition to a CD7-targeted CAR, WU-CART-007 contains genetic knockouts of CD7 (to prevent fratricide) and T-cell receptor alpha constant (TRAC) to prevent graft-versus-host disease (GvHD). Notably, Wugen's allogeneic approach is favorable to autologous approaches, given that autologous products could contain malignant T cells collected during apheresis.

At the 2024 ASH conference, Wugen presented updated clinical data from patients treated in the global Phase I/II study of WU-CART-007 (NCT04984356). Patients enrolled in the study were eligible to receive a single infusion of WU-CART-007 at DL1: 100 million, DL2: 300 million, DL3: 600 million, or DL4: 900 million cells following lymphodepletion with standard regimens of Flu/Cy (flu 30 mg/m^2/day x 3; cy 500 mg/m^2/day x 3; exhibit 20). In the Phase II expansion cohort, patients received an enhanced lymphodepletion regimen (eLD; flu 30 mg/m^2/day x 4; cy 1,000 mg/m^2/day x 3) and the recommended Phase II dose (DL4, 900e6 cells).

Exhibit 20
CELLect Horizons
Design of the Phase I/II Trial of WU-CART-007



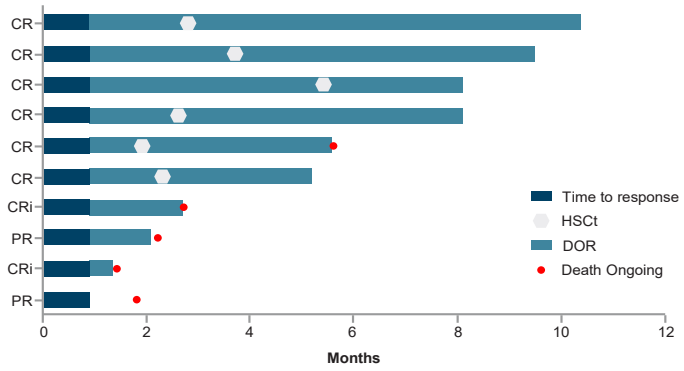
Lymphodepletion Conditioning Chemotherapy (sLD) Phase 1 Dose Escalation:
- Fludarabine 30 mg/m²/day ×3 (Days -5, -4, and -3)
- Cyclophosphamide 500 mg/m²/day ×3 (Days -5, -4, and -3)

Enhanced Lymphodepletion Conditioning Chemotherapy (eLD) Phase 2 Cohort Expansion:
- Fludarabine 30 mg/m²/day ×4 (Days -6, -5, -4, and -3)
- Cyclophosphamide 1000 mg/m²/day ×3 (Days -5, -4, and -3)

Sources: Company reports; William Blair Equity Research

As of August 8, 2024, 10 of the 11 patients evaluable for efficacy achieved a response (ORR: 91%), with 73% (8/11) achieving a composite complete response (CRc; exhibit 21). In addition, MRD negativity was achieved in four of the six (67%) CRc responders. WU-CART-007 also demonstrated efficacy in patients with EMD at baseline, with 80% (4/5) of EMD patients achieving responses (2 CRs; 2 partial responses [PRs]). Six of the 10 responders went on to receive consolidating allogeneic hematopoietic stem-cell transplantation (HSCT). In a subgroup analysis of the adolescent patients treated at the RP2D (ages 12-17), WU-CART-007 demonstrated an ORR of 100%, with three of four patients achieving a CR followed by a transition to HSCT. Most patients experienced low-grade CRS (69%, 9/13), and four experienced a grade 3 or greater CRS (31%). In addition, two patients experienced grade 5 adverse events, one of which was due to multi-organ failure in the setting of rapid disease progression, and the other was attributed to unrelated fungal sepsis. One case of ICANS was reported.

Exhibit 21
CELLect Horizons
Clinical Responses in T-ALL Patients Treated With Wugen's WU-CART-007



Source: ASH 2024; William Blair Equity Research

In July 2022, the FDA granted WU-CART-007 orphan drug, fast track, rare pediatric disease, and regenerative medicine advanced therapy (RMAT) designations for the treatment of r/r T-ALL and T-LBL. In addition, the EU granted WU-CART-007 PRIME (Priority Medicines) in similar indications. Wugen plans to initiate a global, pivotal, single-arm study of WU-CART-007 (NCT06514794) in patients with r/r T-ALL or T-LBL in the first quarter of 2025. The trial will also evaluate an exploratory MRD-positive cohort.

At ASH 2024, **Beam Therapeutics** presented clinical data on four T-ALL patients treated with BEAM-201, its allogeneic, CD7-targeted CAR-T. Of the three patients evaluable for efficacy, one achieved a CR and two achieved CRi, with two patients successfully bridging to HSCT. Despite the encouraging early efficacy, Beam is deprioritizing the development of BEAM-201.

CD70

CD70 has recently emerged as an immunotherapeutic target, given its ability to promote tumor B-cell proliferation and facilitate immune evasion through the tumor microenvironment (TME) (Tal Flieswasser et al. *Cancers* [Basel]. 2019). Interestingly, CD70 is aberrantly expressed on hematological malignancies, including AML, B-ALL, B-cell chronic lymphocytic leukemia (B-CLL), chronic myeloid leukemia (CML), non-Hodgkin lymphoma (NHL), and several T-cell lymphomas. CD70 expression is also observed in several solid tumor types, but that is beyond the scope of this report. However, activated T and B cells can transiently express CD70, and thus caution must be taken when evaluating anti-CD70 approaches given that off-target effects remain a challenge (Tal Flieswasser et al. *Journal of Experimental & Clinical Cancer Research*. 2022).

CRISPR Therapeutics is developing CD70 CAR-T therapies for the treatment of T-cell lymphoma (TCL). Its first-generation, allogeneic CD70 CAR-T candidate, CTX130, was engineered to knock out B2M and CD70 and insert the CD70 CAR construct into the TRAC locus. The company presented initial data from the Phase I COBALT-LYM study of CTX130 at the EHA 2022 Congress, which included 18 CD70+ r/r TCL patients. Of the 18 patients evaluable for efficacy, 10 had transformed cutaneous TCL (CTCL) and 8 had peripheral TCL (PTCL). Patients were treated across four dose levels, ranging from 3e7 (DL1) to 9e8 cells (DL4), with 28% of patients (5/18) receiving a second dose of cells after experiencing a partial response, stable disease, or disease progression with clinical benefit. Across all dose levels and patient subsets, overall response rate (ORR) was 50% (9/18) with a 22% (4/18) CR rate. At DL3 or higher (DL≥3; n=10), the ORR was 70% with a complete response rate of 30%. In the subsets of TCL, CTX130 achieved an 80% ORR (4/5) and 40% CR rate (2/5) in PTCL and a 60% ORR (3/5) and 20% CR rate (1/5) in CTCL at DL≥3. Safety was also favorable with no AEs of special interest (GvHD, tumor lysis syndrome, hemophagocytic lymphohistiocytosis, or infusion reactions), dose-limiting toxicities, CRS, or ICANS. The most common grade 3 or higher AE was infection, occurring in 22% of patients. It is important to note that no new safety signals were observed in patients receiving a second infusion of CTX130. One patient death related to a lung infection (7%) deemed unrelated to treatment was reported.

Following the promising results observed in the COBALT-LYM study, CRISPR developed a next-generation, allogeneic, CD70 CAR-T, CTX131, which includes two additional knockouts aimed at increasing cell potency: Regnase-1 and TGFBR2 (we discuss CRISPR's allogeneic genetic edits in more detail in the section below). In the second quarter of 2024, CRISPR announced that it has initiated a Phase I/II study of CTX131 in hematologic malignancies, including T-cell lymphomas (TCLs). No additional updates on timing for initial data from this program have been disclosed.

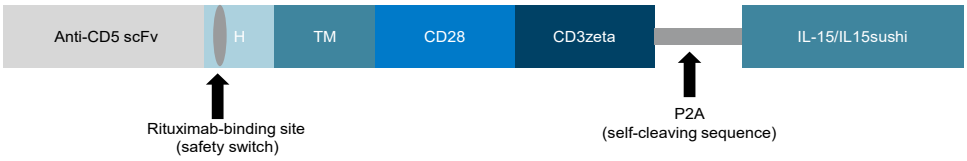
CD5

CD5 is a target commonly associated with T-cell malignancies, specifically T-ALL and peripheral T-cell lymphoma (PTCL). Despite its expression on malignant cells, CD5 is also expressed on normal T cells. Therefore, treatment with anti-CD5 CAR-T cells may be associated with potential T-cell depletion. Although B-cell depletion with CD19 CAR-T cell therapies can be managed with intravenous immunoglobulin (IVIG) supplementation, no such therapies for replacement of T-cell deficiencies are available. However, despite the risk of long-term T-cell immunodeficiency with CAR-T in patients with T-cell malignancies, irreversible B-cell aplasia is not commonly observed in clinical trials of CD19 CAR-T trials. In addition, preclinical studies with CD5 CAR-T cells demonstrated that CAR-T cells preferentially target malignant T cells while sparing the normal T-cell population

(Maksim Mamonkin et al. *Blood*. 2015). Additional preclinical studies suggested that CD5 expression on anti-CD5 CAR-T cells is downregulated over time, thus reducing self-targeting and destruction (Maksim Mamonkin et al. *Blood*. 2015; Masauki *Wada et al. Stem Cell Rev Rep*. 2020.).

Private company **iCell Gene Therapeutics** is evaluating a CD5 CAR-T therapy for the treatment of T-cell lymphoblastic lymphoma/leukemia (T-LBL). Unique to iCell, the company's CD5 CAR secretes an IL-15 protein, a cytokine that is important for innate and adaptive immune cell homeostasis. Notably, IL-15 is posited to affect CAR-T by increasing T-cell numbers through altered metabolic activity and survival, enhancing effector function, and promoting the early trafficking of effector and memory T cells to desired locations for therapeutic effect (Jia Feng et al. *Stem Cell Reviews and Reports*. 2021). Given the short half-life of IL-15 (2.5 hours), iCell fused the IL-15 gene construct with a subdomain of the IL15 receptor, which binds to soluble IL-15 with high affinity and significantly increases its half-life (exhibit 22). Importantly, IL-15 can also activate survival and proliferation of endogenous T and B cells, including malignant immune cells (Paola Sindaco et al. *Frontiers*. 2023). Therefore, IL-15 treatment can have a pathogenic role in the development and progression of B- and T-cell neoplasms.

Exhibit 22
CELLect Horizons
Schematic Representation of iCell Gene CD5-CAR



H, hinge region; TM, transmembrane region
Source: Adapted from Jia Feng et al. *Stem Cell Reviews and Reports.* 2021; William Blair Equity Research

In 2021, iCell published results from a single-patient study evaluating its CD5 CAR-T in a 22-year-old patient with relapsed T-LBL with CNS involvement (Jia Feng et al. *Stem Cell Reviews and Reports*. 2021). Before CAR-T infusion, the patient received standard lymphodepletion with Flu/Cy. The CAR-T cells were generated from HLA-matched donor allogeneic hematopoietic stem cells (the patient's sister) and dosed at 2e6 cells/kg, which was split across two days.

Before treatment, the patient's left eye showed significant exophthalmos, redness, and swelling, which substantially improved one week following CAR-T infusion. At three weeks post-infusion, all signs of orbital involvement had completely recovered. In addition, CAR-T cell therapy reduced CSF lymphoblastic levels from 80% to undetectable levels four weeks post-infusion. The patient experienced a CRS event that was considered grade 1. No additional details on iCell's CD5 CAR-T program have been disclosed.

March Biosciences is developing an autologous CD5 CAR-T, MB-105, for the treatment of several hematologic malignancies, including TCL, T-ALL, CLL, and MCL. MB-105 CAR-T cells are unedited for endogenous CD5 in the CAR-T cells; however, in preclinical studies, March's pan-CD5 CAR demonstrated limited and transient fratricide activity in mice (LaQuisa C. Hill et al. *Blood*. 2024). In March 2024, March shared first-in-human Phase I studies evaluating MB-105 in a cohort of r/r mature TCL patients. In nine patients evaluated for efficacy, four (44%) achieved a response with two (22%) achieving a CR. At 200 days of follow-up, three of five (60%) patients were alive and undergoing a CR, with one patient maintaining a CR out to three years. No grade 3 or higher CRS or neurologic events occurred. Two patients died during the immediate toxicity evaluation period due to rapidly progressive disease. No additional details on March's MB-105 program have been disclosed.

Going Beyond Single-Antigen Targeting: Multi-Targeting and Modular CAR-Ts

As the CAR-T cell market continues to expand, alternative therapies will be required to address these resistance mechanisms, including downregulation and/or loss of tumor antigen. CAR-T cells targeting two or more different tumor antigens are poised to address this common mechanism of resistance and potentially improve on responses in patients. Two modalities poised to target more than one antigen are T cells equipped with multiple CARs or modular CARs.

Dual- and Trispecific CARs

We believe multi-targeting CARs will be transformational for the hematological malignancies space and, while outside the scope of this report, could also be valuable tools in treating autoimmune diseases. In exhibits 23 and 24, we summarize dual- and trispecific CAR-T cell programs that have generated clinical data and are in early development for liquid tumors, respectively. The most extensively studied antigen combinations include CD19, CD20, or CD22, which are also some of the most common single-antigen targets in development.

Exhibit 23
CELLect Horizons
Results From Clinical Trials of Multi-targeting CAR-T Cell Therapies

	AbelZeta Johnson&Johnson	Lyell	AstraZeneca		Autolus BIONTECH	cellectis EDITING LIFE	Miltenyi Biotec
Drug	C-CAR039	IMPT-314	GC012F/ AZD0120	GC502	AUTO1/22	UCART20x22	Zamto-cel
Product Characteristics	Autologous	Autologous	Autologous	Autologous	Autologous	Allogeneic	Autologous
Target	CD19xCD20	CD19xCD20	BCMAxCD19	CD19xCD7	CD19xCD22	CD20xCD22	CD19xCD20
Indication	NHL	NHL	Multiple Myeloma	B-ALL	B-ALL	NHL	DLBCL
Phase	Phase I	Phase I	Phase I	Phase I	Phase I/II	Phase I	Phase II
Patients numbers	N=48	N=23	N=29	N=4	N=12	N=3	N=69
Baseline Characteristics	Median age: 55 Median prior LOT: 3 Stage III/IV: 75% Received bridging therapy: 25% Prior CD20 targeted therapy: 100%	Median age: 65 Median prior LOT: 3 Received bridging therapy: 53% ≥ stage III: 57%	Median age: 57 Median prior LOT: 5 EMD plasmacytomas: 28% High-risk profile: 90% Prior ASCT: 38%	Median age: 28 Median prior LOT: 5 High-risk: 50% EMD lesions: 25% Prior allo-HSCT: 25%	EM disease: 58% Prior SCT: 50% Prior CAR-T cell therapy: 33%	Median age: 65 Prior CD19 CART: 67% Median prior LOT: 4	N/A
Dose	1.0-5.0e6 cells/kg	DL1: 100e6 cells DL2: 300e6	DL1: 1e6 cells/kg DL2: 2e5 cells/kg DL3: 3e5 cells/kg	DL1: 1.0e7 cells/kg DL2: 1.5e7 cells/kg DL3: 2.0e7 cells/kg	10e6 cells/kg	DL1: 50e6 cells	2.5e6 cells/kg
Median Follow-up (mo)	30	6.3	30.7	N/A	8.7	ud	min 3 mo
Response Rates **CR** <CR	ORR: 92% 85% 7%	ORR: 94% 71% 23%	ORR: 93% 83% 10%	ORR: 100% 100%	ORR: 83% 83%	ORR: 100%* 67% 33%	ORR: 73% 51% 22%
CRS (Grade ≥3)	94% (2%)	70% (0%)	86% (38%)	100% (50%)	92% (0%)	100% (0%)	46% (0%)
Neurotoxicity (Grade ≥3)	6% (0%)	26% (13%)	0%	0%	50% (8%)	0%	13%(4%)
Long-term endpoints	24-mo PFS rate: 63% 24-mo OS rate: 77%	6-mo CR rate: 75%	36-mo PFS rate: 51% mPFS: 38 mo	N/A	6-mo CR rate: 100% 12-mo CR rate: 75%	N/A	6 mo PFS rate: 55%
Next Expected Update	ud	ud	ud	ud	ud	Update on late-stage development strategy in 2025	ud
Reference	ASH 2023	ASH 2024	ASCO 2023	EHA 2022	Sara Ghorashian et al. *Blood* . 2024	ASH 2023	ASH 2024

*Complete metabolic responses. EMD, extramedullary plasmacytomas; LOT, lines of therapy; N/A, not available; ud, undisclosed;

Sources: See reference line

Exhibit 24
CELLect Horizons
Other Multi-Targeting CAR-T Cell Therapies in Development

	Bristol Myers Squibb	GILEAD		Roche	LEGEND BIOTECH		IASO BIOTHERAPEUTICS	CARGO THERAPEUTICS	A2 BIO	AVENCELL	
Drug	N/A	KITE-363	KITE-753	P-CD19CD20-ALLO1	ud	ud	CT120	CRG-023	A2B356	AVC-203	AVC-202
Product Characteristics	Autologous	Autologous	Autologous	Allogeneic	Autologous	Autologous	Autologous	Autologous	Autologous	Allogeneic	Allogeneic
Target	BCMAxGPRC5D	CD19/CD20	CD19/CD20	CD19xCD20	CD19xCD20xCD22	CD19xGPRC5D	CD19xCD20	CD19xCD20xCD22	CD33xCLL1	CD19xCD20	BCMAxCD38
Indication	Multiple Myeloma	B-cell malignancies	B-cell malignancies	B-cell malignancies	B-cell malignancies	Multiple Myeloma	B-NHL/ ALL	B-cell malignancies	AML	DLBCL	Multiple Myeloma
Phase	Phase I	Phase I	Phase I	Phase I	Phase I	Phase I	ITT	IND cleared	Preclinical	Preclinical	Preclinical
Next Expected Update	ud	ud	ud	ud	ud	ud	ud	Patient enrollment expected in mid-2025	ud	CTA submission 1H25	CTA submission 1H25

Sources: See reference line

Specifically, we highlight **AbelZeta** and **Johnson & Johnson's** bispecific CAR-T, C-CAR039, given that it has produced the most robust dataset of all the multi-targeted CAR-Ts, and **Cargo Therapeutics'** CRG-023 because it is the most compelling tri-targeted CAR-T candidate, in our view. In addition, **Lyell Immunopharma** has generated encouraging clinical data from its dual CD19/CD20 CAR-T asset, IMPT-314, which was acquired from its acquisition of ImmPACT Bio in 2024.

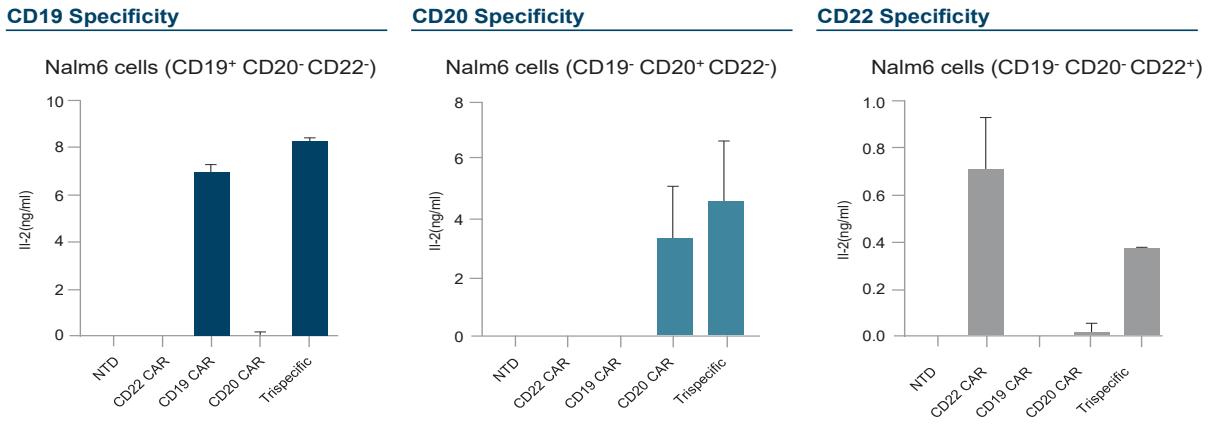
AbelZeta and Johnson & Johnson are co-developing C-CAR039, an autologous CAR-T cell therapy targeting CD19/CD20, for the treatment of NHL. At the 2023 ASH conference, the companies provided a clinical update on the ITT of C-CAR039, which is being conducted in China. In the study, 48 patients received C-CAR039 at a dose between 1e6 and 5e6 cells/kg following standard lymphodepletion. Ninety-two percent of patients achieved a response, with 85% of patients achieving a CR. As of September 25, 2023 (median follow-up of 30 months), 49% of patients (23/47) remain in CR, with 10 sustained past 36 months. The median PFS and OS was not reached at most recent follow-up, but the estimated 24-month PFS and OS rates were 62.6% and 76.5% across all patients, respectively. CRS was observed in 93.8% of patients, with one patient experiencing a grade 3 CRS that resolved with tocilizumab and corticosteroids treatment, and three patients experienced ICANS.

In October 2024, Lyell Immunopharma announced the acquisition of ImmPACT Bio, which included the company's autologous bispecific CD19/20 CAR-T, IMPT-314, for the treatment of B-cell malignancies and autoimmune disease. Lyell's CAR-T cells are enriched for CD62L, a marker expressed on T central memory cells, which improves cell persistence, reduces cell exhaustion, and lowers off-target toxicity. At ASH 2024, the company presented initial clinical data from the Phase I/II clinical trial. Patients treated in the study received a single infusion of IMPT-314 at 100e6 or 300e6 CAR-T cells shortly following standard lymphodepletion with Flu/Cy. As of October 22, 2024, 23 patients had been treated with IMPT-314 and had a median follow-up of 6.3 months. The ORR in the 17 patients evaluable for efficacy was 94% (16/17), with 71% (12/17) of patients achieving a CR. Of the seven patients with at least six months of follow-up, the ORR was 100%, with a complete response rate of 85%. Grade 1 and 2 CRS were reported in 70% of patients. Six patients (26%) experienced an ICANS event, with three events characterized as grade 3. Lyell plans to initiate a pivotal trial for IMPT-314 in 2025 for the treatment of CAR-T–naive patients with large B-cell lymphoma in the third-line-plus setting.

Cargo Therapeutics is developing CRG-023, an autologous CAR-T cell therapy with three independent CARs targeting CD19, CD20, and CD22 expressed through a single vector. CRG-023 was designed to address relapse due to tumor antigen loss (e.g., CD19) or low-density antigen expression, loss of costimulation (e.g., CD58), or lack of T-cell persistence. The CD22 CAR expresses 4-1BB, CD19 CAR expresses CD28, and the CD20 CAR expresses CD2 (CD2 signaling promotes CAR-T functionality). In addition, each CAR uses a novel, human single-chain variable fragment (scFv), which reduces immunogenicity.

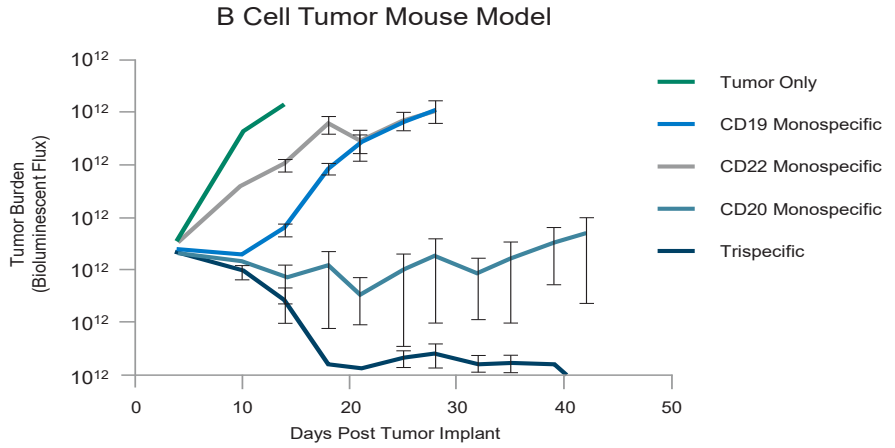
In preclinical models, CRG-023 demonstrated increased secretion of IL-2 in response to individual antigens at levels similar to monospecific CAR-T cells (exhibit 25), and in leukemic xenograft mouse models, CRG-023 drastically reduced tumor burden compared to mice treated with monospecific CAR-T cells (exhibit 26). Importantly, in leukemic xenograft mouse models deficient in expression of one of the three antigens (CD19, CD20, CD22), CRG-023 antitumor activity was maintained. In January 2025, Cargo announced that the FDA cleared its IND application for CRG-023. The Phase I study will evaluate CRG-023 in LBCL patients starting at a dose level of 25 million cells with enrollment expected to begin mid-2025. The company anticipates demonstrating proof of concept in the third-line-plus setting, including in CAR-T–naive patients, before rapidly progressing CRG-023 into earlier lines and additional indications in B-cell malignancies.

Exhibit 25
CELLect Horizons
Antitumor Activity of Cargo's CRG-023 Across Individual Tumor Antigens



Source: Company reports; adapted by William Blair Equity Research

Exhibit 26
CELLect Horizons
Antitumor Activity of Cargo's CRG-023

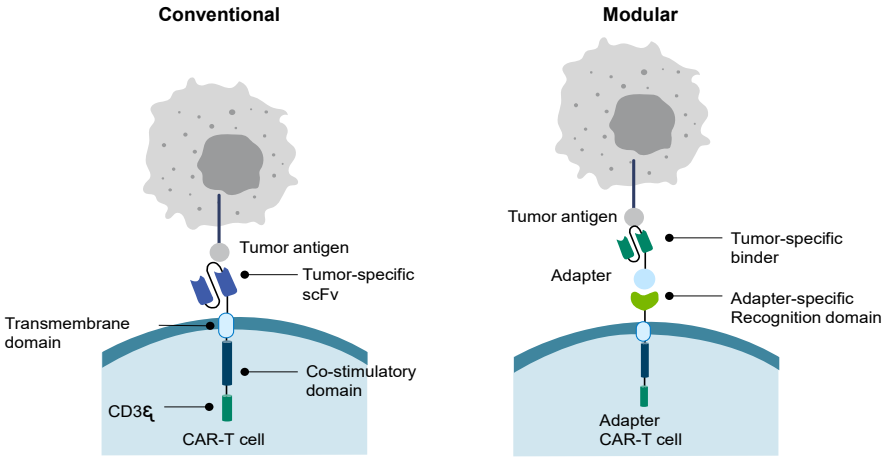


Source: Company reports, adapted by William Blair Equity Research

Modular CAR-Ts

Advances in protein engineering have led to the development of soluble adapter molecules that can direct CAR-T cells to targeted cells, presenting a potential alternative to traditional scFv constructs. Compared to conventional CAR-T constructs wherein antigen targeting is unmodifiable once expressed on the T cell, modular CAR-T cells uncouple the intrinsic signaling domain of the T cell and the tumor antigen targeting domain (exhibit 27).

Exhibit 27
CELLect Horizons
Comparison of Conventional CAR T and Modular CAR T



Source: Adapted from Amelia C McCue et al. *Adv Drug Deliv. Rev*. 2023; William Blair Equity Research.

Modular CAR-T cells offer several advantages over traditional scFvs (exhibit 28), including the ability to overcome antigen loss and resistance by administering adapter molecules targeting different antigens simultaneously to address the inherent tumor heterogeneity or sequentially to redirect the engineered T cells to different tumor targets in the event of tumor relapse due to antigen loss or refractory disease. Modular CAR-Ts could also provide increased control over the time and extent of CAR-T expansion and associated toxicities by modulating the administration of the adapter molecule and reduce CAR-T cell exhaustion by limiting tonic signaling. It is important to note that adapter molecules can be easily interchanged without having to redose the engineered T cells and a universal T cell could aid in manufacturing scalability as the same lentivirus encoding the adapter domain is used regardless of the indication. We believe modular CAR-T approaches will be best suited for heterogeneous indications such as AML.

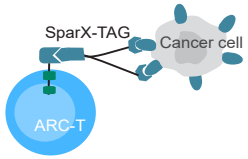
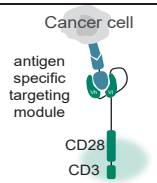
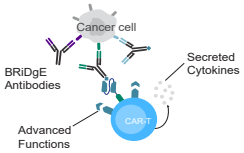
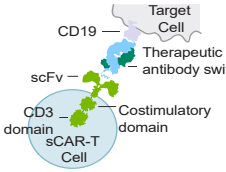
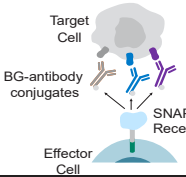
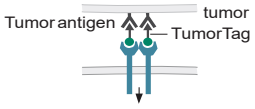
Exhibit 28
CELLect Horizons
Benefits and Challenges of Modular CAR-T Cell Therapies vs. Conventional CAR-T Cells

	Conventional CAR-T	Modular CAR-T
Product Activity	⊖ Less controllability of CAR-T product after infusion.	⊕ Temporal control of T-cell cytotoxicity
CAR targeting	⊖ Single target per CAR construct. Multi-targeting CARs require more extensive manufacturing process.	⊕ Switchable CAR targets (avoid relapse)/Combination of antigen adapters
Safety Attributes	⊖ On-target, off-target toxicity	⊕ Potentially limited on-target, off-target toxicity
Manufacturing	⊖ Less scalable across multiple CARs targeting different antigens	⊕ Standard lentiviral construct between tumor antigens allowing for increased manufacturing scalability

Source: William Blair Equity Research

Various approaches to modular CAR-T cell therapies are being developed (exhibit 29), although we view **Arcellx's** and **AvenCell's** platforms as the most advanced and provide more details on their programs below. In addition, **Umoja's** TumorTag platform could also have applicability in heterogeneous hematological malignancies; however, since it is only in clinical development for solid tumors, it is outside the scope of this report.

Exhibit 29
CELLect Horizons
Modular CAR-T cell Therapies

Company	Technology		Key Characteristics	Lead Program (Target)	Stage of Development
ARCELLX	Arc-SparX		• Cytolytic activity is controlled by treatment with antigen-specific "SparX proteins" that bind to ARC-T cells expressing d-domains. • Arcellx's adapter recognition domain (d-domain) is less than half the size of other extracellular antigen recognition domains, which could aid in relative transduction efficiency and immunological synapse formation.	ACLX-002 (CD123)	Phase I/II
AVENCELL	Universal Switchable CAR		• Switchable on/off CAR: Rapid off-switch that is designed to act in less than 4 hours by the short PK half-life and fast internalization of soluble adaptors. • CARs have reduced susceptibility for immunosuppression by Tregs through use of CD28 versus 4-1BB.	AVC-101 (CD123)	Phase I/II
BIOSCEPTRE	BRiDGECAR System		• A specific mix of targeted antibodies are infused with CAR-T cells for CAR-T directed tumor cell killing.	ud	Preclinical
Calibr-Skaggs Scripps Research	Switchable CAR-T		• Universal design that uses antibody-based switches that can be used to target multiple antigens.	CLBR001+SWI019 (CD19)	Phase I
coeptis THERAPEUTICS	SNAP-CAR		• A monoclonal antibody conjugated (tagged) to a benzyl guanine linker, which is recognized by the custom SNAP-CAR cells. • Potential to generate a variety of SNAP-CAR effector cells (T cells and NK cells) in the autologous or allogeneic settings.	ud	ud
Umoja BIOPHARMA	TumorTag		• Universal fluorescein "tag" antigen targeted tumor and stromal cells for CAR-T cells for targeted cytotoxic activity. • Potential to generate autologous or allogeneic CAR-T cells.	ud	Phase I

ud, undisclosed
Source: Company reports; William Blair Equity Research

Arcellx's Arc-SparX platform comprises a 26 kDa C-terminal fragment of human alpha fetoprotein (TAG) fused to one or more antigen-specific binding domains and T cells expressing d-domains with a binding moiety specific to TAG (ARC-T). Importantly, the d-domain on ARC-T cells is designed to exclusively bind to TAG and is unable to bind to human alpha fetoprotein. SparX protein is administered independently of ARC-T cells, and ARC-T cell activation is dependent on the presence of SparX, which has an estimated half-life in humans of several hours.

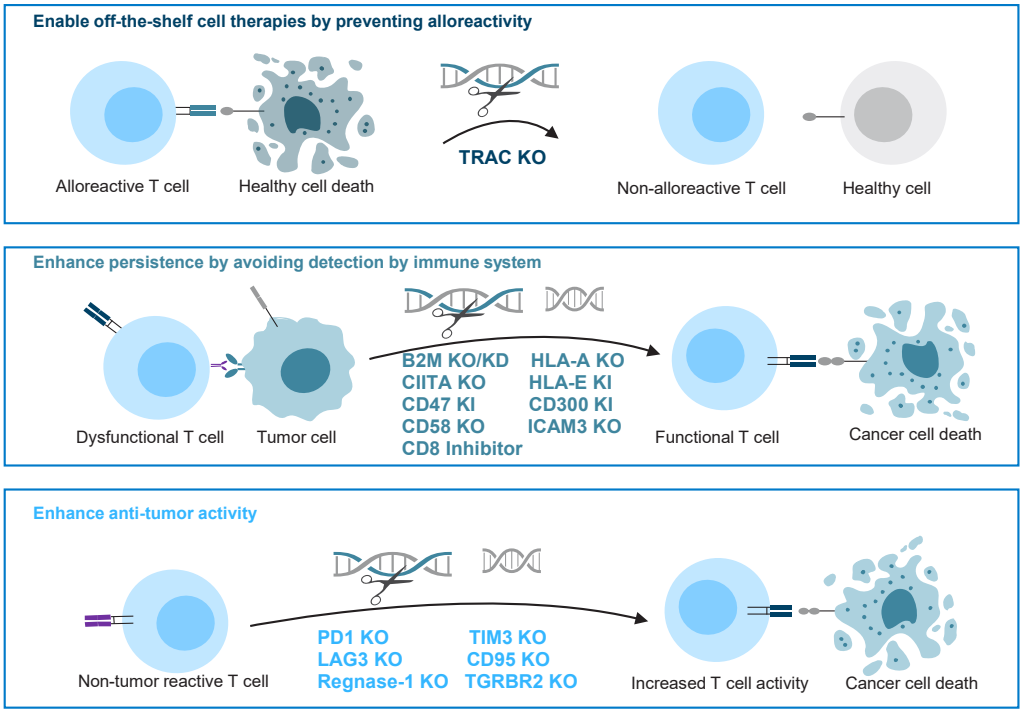
Arcellx's lead ARC-SparX program is ACLX-002, which uses a SparX protein targeting CD123 for the treatment of r/r AML and MDS. In December 2022, the company announced the initiation of the Phase I study for ACLX-002; however, no additional updates on timing for initial data have been disclosed. In November 2023, Gilead exercised its option to negotiate a license for one of Arcellx's other ARC-SparX programs, ACLX-001, which comprises ARC-T cells and SparX proteins that target BCMA. Last, Arcellx is in advanced preclinical development of two additional ARC-SparX programs, ACLX-003 and ACLX-004, which will target undisclosed antigens in AML/MDS.

AvenCell's UniCAR platform features a proprietary Universal Switchable CAR construct that is designed to only activate T-cell signaling in the presence of soluble adaptors called "targeting modules," which bind to a desired tumor antigen. AvenCell's most advanced candidate using the platform, AVC-101, uses a targeting module for CD123 that is linked to a motif that is recognized by the universal CAR for the treatment of AML. Initial clinical results from the program are summarized in the above section on CD123, but the initial data shows that the administration of the targeting module leads to antitumor activity and the withholding of the targeting module reduces CAR-related toxicities, providing clinical proof of concept for the platform. Outside AML, AvenCell is also developing two dual CAR-T cell therapies, AVC-203 and AVC-202, targeting CD19/CD20 and BCMA/CD38, respectively. In the second half of 2025, AvenCell plans to submit CTA for AVC-203 and AVC-202 for the treatment of diffuse large B-cell lymphoma (DLBCL) and MM, respectively.

Genetic Modifications Could Enable Allogeneic CAR-Ts to Reach Their Full Potential

The first wave of off-the-shelf allogeneic CAR-T therapies has shown limited efficacy compared with their autologous counterparts, mainly because of reduced CAR-T persistence due to host rejection of cells. However, we still believe allogeneic therapies will ultimately be necessary to increase accessibility and remove barriers for adoption, including eliminating the need for apheresis, reducing the cost of goods, and reducing the time to treatment. Different genetic modifications are being investigated to improve efficacy that: 1) prevent alloreactivity; 2) enhance persistence by reducing detection and elimination by the host immune system; and 3) enhance antitumor activity by improving gene expression profiles and leveraging physiologic gene regulation elements (exhibit 30). In exhibit 31, we include a table of disclosed allogeneic CAR-T cell therapies in development for hematological malignancies.

Exhibit 30
CELLect Horizons
Overview of Key Goals of Genetic Modifications in Allo CAR-T Therapies



Source: Adapted from Murty and Mackall *Molecular Therapy* 2021; William Blair Equity Research

Exhibit 31
CELLect Horizons
Overview of Allogeneic CAR-T Cell Therapies With Disclosed Genetic Modifications in Development

Company	Candidate	Antigen/s	Phase	Alloreactivity	Immune Rejection	Anti-Tumor Activity	Others
Allogene	Cema-cel	CD19	Pivotal	TRAC KO	-	-	CD52 KO
Antion Biosciences	miCAR19	CD19	Preclinical	TRAC KO	B2M miRNA	PD1, TIGIT and TIM3 miRNA	CD52 miRNA
AVENCELL	AVC-201 AVC-203 AVC-202	CD123 CD19/CD20 ud	Phase I/II Preclinical Preclinical	TRAC KO	HLA-A and CIITA KOs	-	-
Beam Therapeutics	BEAM-201	CD7	Phase I/II	TRAC KO	-	PD1 KO	CD7 KO; CD52 KO
BRL Medicine 邦耀生物	BRL-201 BRL-301 BRL-305 BRL-202	CD19 CD19 BCMA ud	Phase I/II Phase I/II Preclinical Preclinical	TRAC KO	-	PD1 KO - PD1 KO	-
Caribou Biosciences	CB-010 CB-011 CB-012	CD19 BCMA CLL1	Phase I/II Phase I/II Phase I/II	TRAC KO	- B2M KO and KI of B2M-HLA-E fusion	PD1 KO - PD1 KO	-
Cargo Therapeutics	ND	ND	Preclinical	TRAC KD	MHC class I KD; MHC class II KO	CD8 Inhibitor	-
cellectis	UCART20x22 UCART22	CD20/CD22 CD22	Phase I/II Phase I/II	TRAC KO	-	-	CD52 KO
Celyad	ND ND	NKG2D NKG2D/ND	Preclinical Preclinical	CD3ζ miRNA	B2M miRNA and CIITA miRNA	PD1, LAG3, TIM3, CD95 miRNA	-
Century Therapeutics	CNTY-308	CD19	Preclinical	TRAC KO	B2M KO; CIITA KO; Insertion of CD300 a TASR pan-NK; Insertion of cell-surface enzyme to degrade IgG	-	-
CRISPR Therapeutics	CTX112 CTX131	CD19 CD70	Phase I/II Phase I/II	TRAC KO	B2M KO	Regnase-1 KO; TGRBR2 KO	-
Notch Therapeutics	ND	CD19/CD20	Preclinical	TRAC KO	B2M KO; CIITA KO; HLA-E KI; CD58/ICAM3 KO	-	-
Roche	P-BCMA-ALLO1 P-CD19CD20-ALLO1 P-BCMACD19-ALLO1 P-CD70-ALLO1	BCMA CD19/CD20 CD19/BCMA CD70	Phase I/II Phase I/II Preclinical Preclinical	TRAC KO	Partial B2M KO	-	-
Sana Biotechnology	SC262	CD22	Phase I/II	TRAC KO	B2M KO; CIITA KO; CD47 KI	-	-
Wuger	WU-CART-007	CD7	Phase I/II	TRAC KO	-	-	CD7 KO

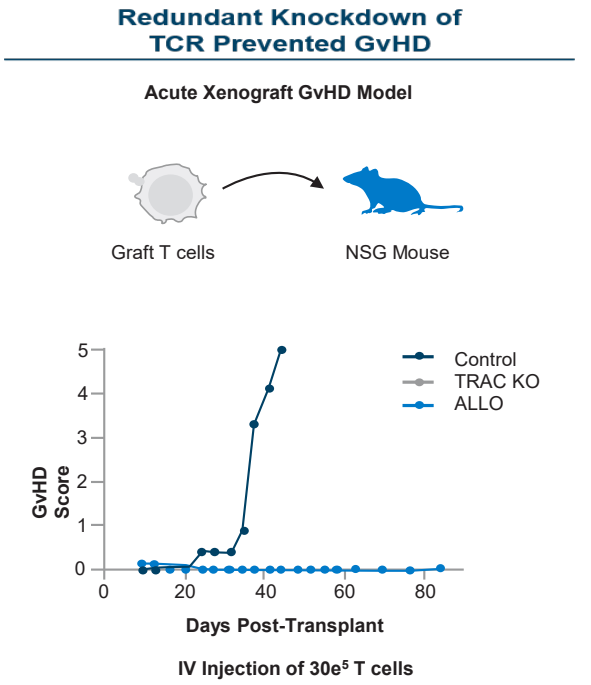
Source: Company reports; William Blair Equity Research ND= non-disclosed

Preventing Alloreactivity

Graft-versus-host disease (GvHD) is a potentially fatal complication of allogeneic cell therapies, wherein an immunologic mismatch between donor and recipient leads to the adoptive, donor T cells attacking the patient's healthy cells. To prevent this serious adverse event, all allogeneic T-cell therapies in clinical development are engineered to knock out the endogenous T-cell receptor (TCR). This is performed by either genetically knocking out the TRAC locus, preventing TCR expression, or inserting a CAR construct directly into the TRAC locus, thereby disrupting TCR expression (see: "Off the Shelf" – The Next Step for Cell Therapy). To our knowledge, all allogeneic CAR-T (derived from αβ T cells) assets in development are modified to disrupt expression of the TCR, and no evidence of CAR-mediated GvHD has been observed with allogeneic CAR-Ts in the clinic.

In contrast to most allogeneic CAR-Ts that use gene editing machinery to prevent expression of the TCR, **Cargo Therapeutics** uses a transgene encoded in its Allo Vector platform to eliminate expression of the TCR. Cargo's Allo Vector also contains a short hairpin RNA (shRNA), which is designed as a redundant measure to downregulate TCR expression post-transcriptionally. Notably, **Celyad Oncology** also uses vectors encoding shRNA to eliminate TCR expression in its allogeneic CAR-T products. Cargo's and Celyad's methods allow for gene silencing without gene editing. In a preclinical mouse model, Cargo's Allo Vector prevented allogeneic rejection in line with traditional TRAC knockout methods (exhibit 32), and Celyad has not reported any cases of GvHD in the clinic with a previous allogeneic CAR-T candidate (CYAD-211).

Exhibit 32
CELLect Horizons
Cargo's Allo Vector Prevents Alloreactivity in Mice Models

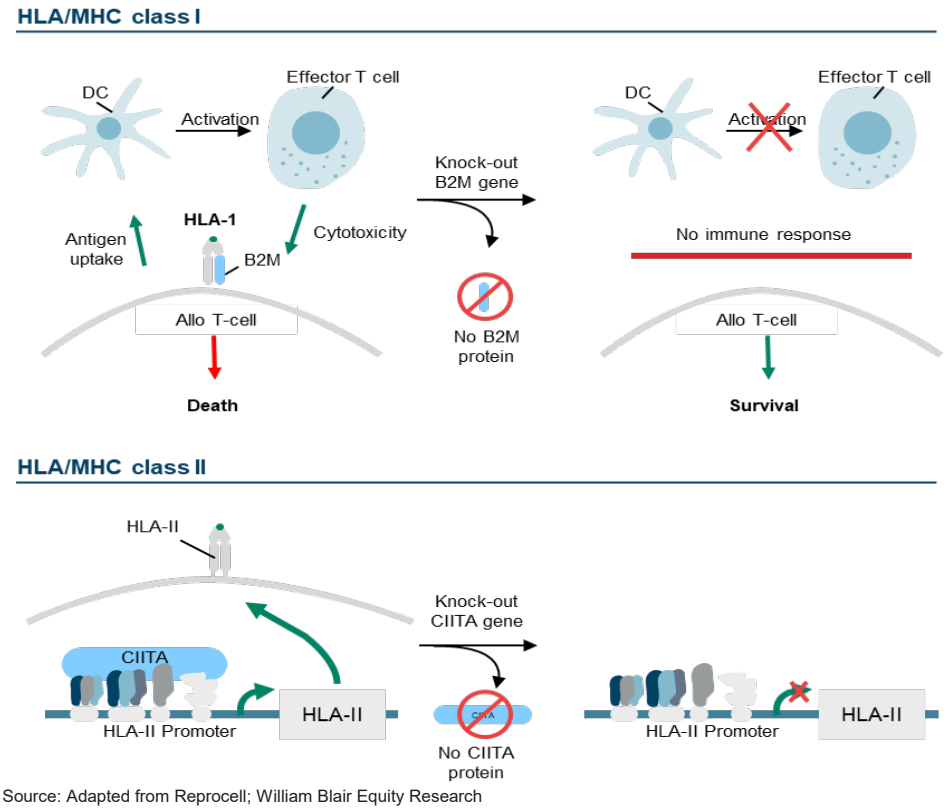


Source: CRGX company reports; William Blair Equity Research

Enhancing Persistence by Reducing Detection and Elimination by the Host Immune System
A key facet underlying limited allogeneic CAR-T persistence, and therefore reduced durability, is host-mediated graft rejection due to host-donor human leukocyte antigen (HLA) allele mismatch. Therefore, reducing or eliminating the expression of HLA (analogous to major histocompatibility complex (MHC) molecules in animals) is being evaluated as a strategy for reducing adoptive cell rejection by host T cells.

HLAs are heterodimer proteins comprising alpha chains and a stabilizing scaffold protein called β macroglobulin. In HLA class I molecules (e.g., HLA-A, HLA-B, HLA-C), alpha chains associate with β2 macroglobulin, which is encoded by the B2M gene. Genetically altering the B2M gene ubiquitously knocks out all HLA class I molecules, so it has been a popular genetic modification for clinical allogeneic CAR-Ts. Genetic disruption of the class II major histocompatibility complex transactivator (CIITA) gene, which is a transcriptional coactivator essential for all HLA class II expression (exhibit 33), is also becoming increasingly used in allogeneic CAR-T therapies. **Century Therapeutics, Sana Biotech,** and **Notch Therapeutics** are knocking out both B2M and CIITA in their allogeneic assets for hematological malignancies, which could completely mitigate host T-cell–driven CAR-T clearance.

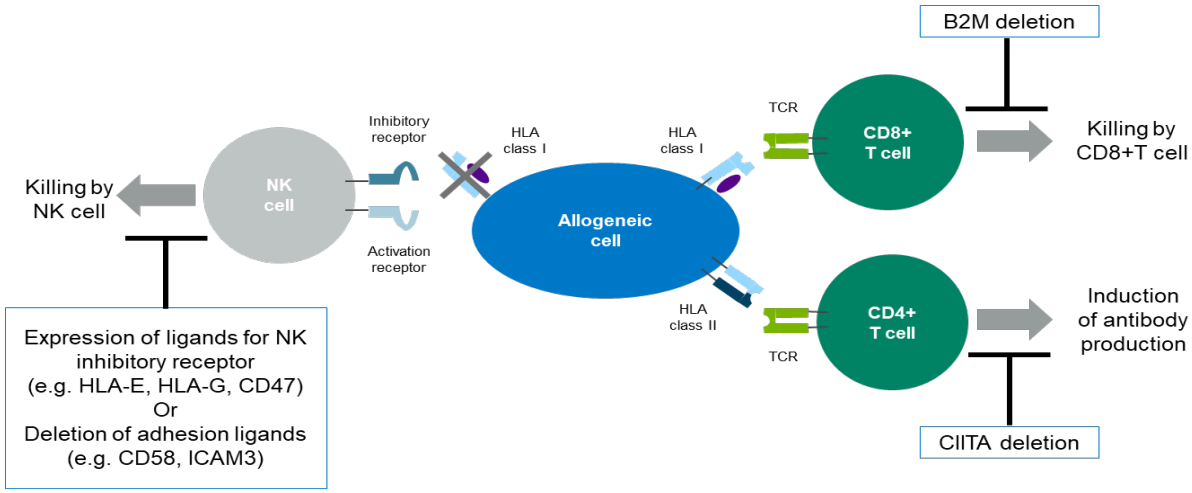
Exhibit 33
CELLect Horizons
B2M and CIITA Genetic Modifications to Disrupt HLA Class I and II Expression



Source: Adapted from Reprocell; William Blair Equity Research

However, loss of HLA class I molecules, which function as ligands for natural killer (NK) cell inhibitory receptors, can lead to host NK-cell–mediated CAR-T rejection. Thus, some companies are exploring partial HLA matching or additional genetic modifications to prevent NK-cell–mediated graft rejection, including overexpression of certain NK inhibitory ligands (e.g., HLA-E, HLA-G, or CD47) or eliminating adhesion ligands (e.g., CD58 and ICAM3; exhibit 34).

Exhibit 34
CELLect Horizons
Mechanisms of Genetic Modifications in CAR-T Cells to Evade Immune Rejection

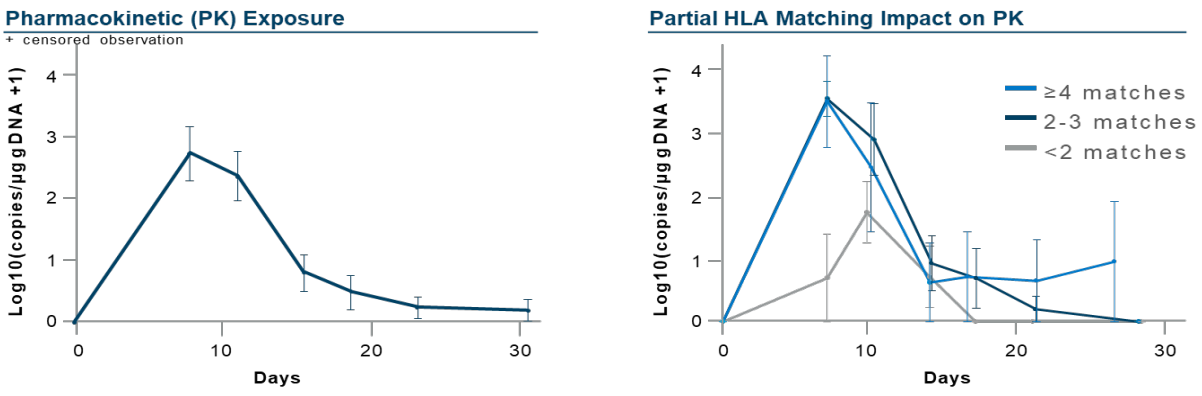


Source: Adapted from Koga et al. *Inflammation and Regeneration* 2020; William Blair Equity Research

For example, **Caribou Bioscience's** lead asset, CB-010 (CD19), does not contain any HLA-related edits. Therefore, the company implemented a partial HLA matching strategy for one cohort in the Phase I ANTLER trial of CB-010, in which patients received CB-010 product manufactured from a donor with ≥4 matching HLA alleles (both HLA class I and II). Although the data is limited, the partial HLA matching strategy appears to be associated with longer CAR-T cell persistence and more durable responses compared with patients with fewer HLA matches (exhibit 35). The company expects to share data further confirming its HLA matching strategy for CB-010 in the first half of 2025, with plans to initiate the pivotal Phase III trial in the second half of 2025.

Exhibit 35
CELLect Horizons
Caribou's CB-010 Efficacy Assessment With and Without Partial HLA Matching

Endpoints (N, %)	All patients ≤3 HLA matches (N=33)	All patients ≥4 HLA matches (N=13)	LBCL ≥4 HLA matches (N=11)
Overall response rate (ORR)	23 (69%)	12 (92%)	10 (91%)
Duration of response (DoR), median months (range)	2.0 (1-23+)	13.5 (1-23+)	NR (1-15+)
Complete response (CR) rate	15 (45%)	6 (46%)	4 (36%)
Duration of CR, median months (range)	5.0 (1-23+)	NR (5-23+)	NR (5-15+)
6-month PFS	25%	62%	53%
PFS, median months (range)	2.8 (1-24+)	14.4 (2-24+)	NR (2-16+)

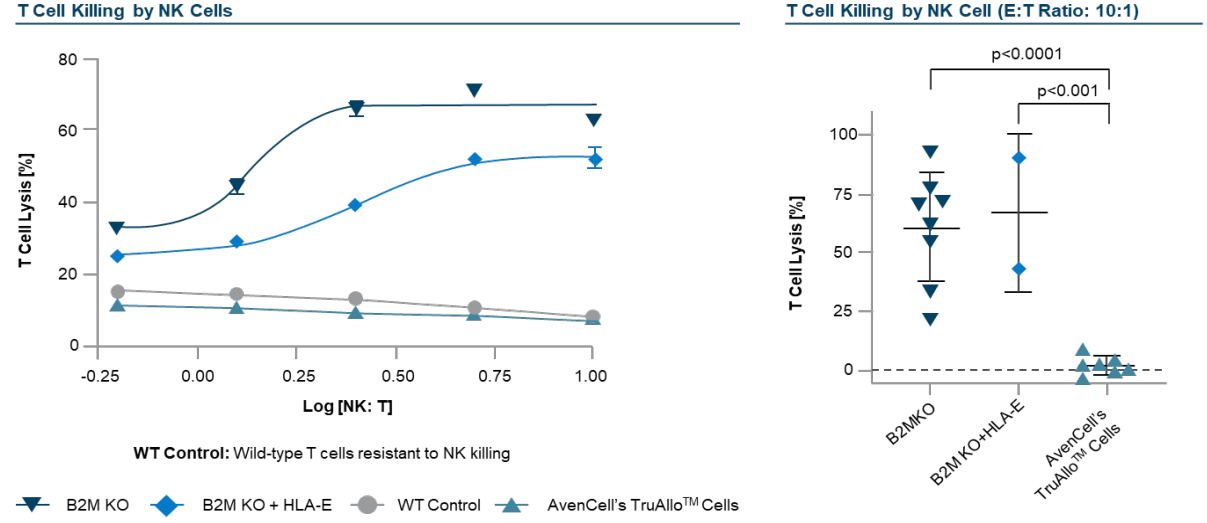


Source: CRBU company reports; William Blair Equity Research

To eliminate the need for HLA matching, **Caribou** is developing an immune cloaking platform that uses a B2M-HLA-E-peptide fusion to reduce NK-cell–mediated rejection. This modification has been incorporated into its BCMA (CB-011) and CLL1 (CB-012) allogeneic CAR-T assets. The company plans to share initial clinical data from the ongoing CaMMouflage Phase 1 clinical trial of CB-011 in r/r MM in the first half of 2025, which could provide clinical proof of concept for its immune cloaking platform.

In contrast, **AvenCell** is selectively knocking out HLA-A while retaining other HLA class I molecules, thereby protecting its allogeneic cell products from the patient's adaptive immune system while avoiding NK-cell–mediated death. However, since expression of the other HLA class I molecules is retained, the company matches patients to donors based on HLA-B or HLA-C expression. Based on preclinical research, the company believes this method provides even greater immune protection than the most common B2M KO modification (exhibit 36).

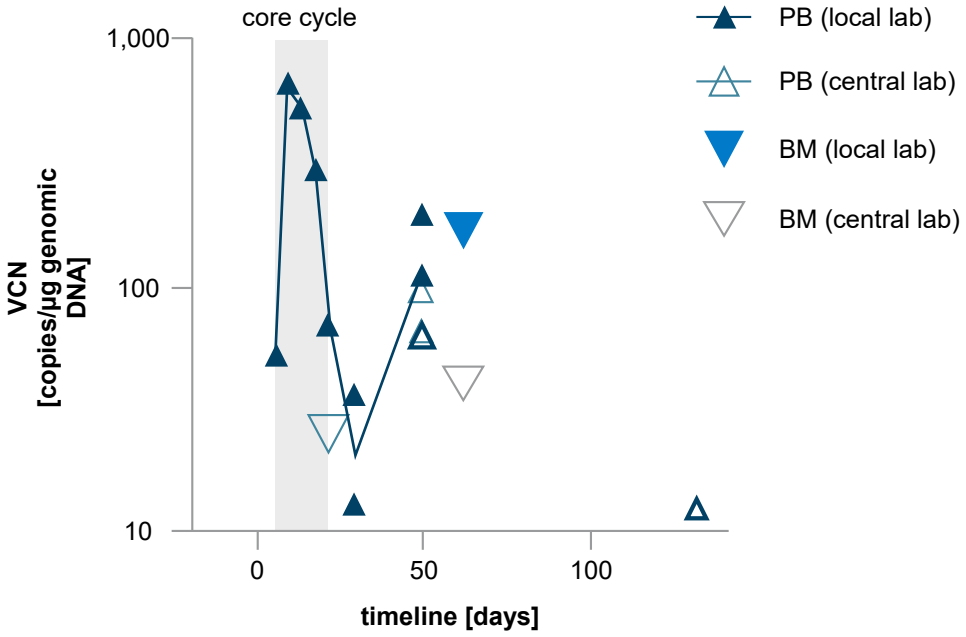
Exhibit 36
CELLect Horizons
AvenCell's TruAllo Cells Evade NK-Cell Killing



Source: AvenCell company reports; William Blair Equity Research

AvenCell recently shared initial PK data from one patient treated with its allogeneic CD123-targeted CAR-T, AVC-201, that showed CAR-T persistence in the bone marrow at day 61 and in the peripheral blood at day 132 despite the targeting module being administered for only the first 20 days (exhibit 37). Overall, the CAR-T expansion observed in the first patient was similar to results observed with the company's autologous CAR-T product (AVC-101), highlighting its allogeneic TruAllo platform's potential for successful immune evasion and persistence.

Exhibit 37
CELLect Horizons
One Patient's CAR-T Expansion After Treatment With AvenCell's TruAllo CAR-T Cells

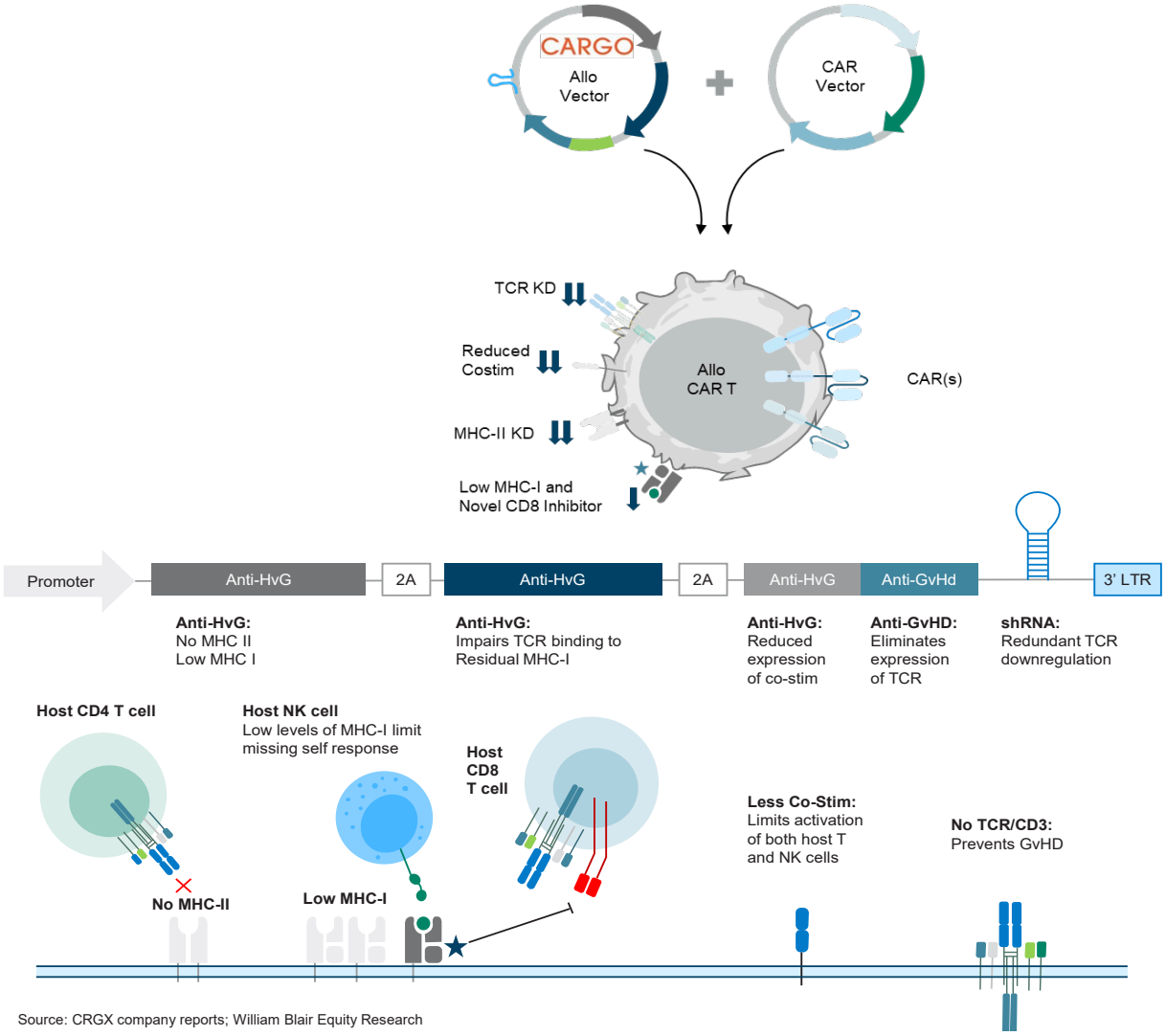


Source: AvenCell company reports; William Blair Equity Research

Alternatively, **Roche (formerly Poseida Therapeutics)** implements a partial knockdown of B2M as opposed to a complete knockout to limit NK-cell–mediated rejection while avoiding the need to HLA match.

Similarly, **Cargo Therapeutics'** Allo vector platform contains multiple transgenes that produce novel proteins designed to regulate protein expression, one of which reduces HLA-I expression to low levels. The other Allo vector transgenes eliminate expression of HLA-II, reduce expression of costimulatory domains to limit activation of host NK and T cells, and express a novel CD8 inhibitor to further limit host T-cell activation (exhibit 38). Cargo expects to select a lead allogeneic candidate in the first half 2025.

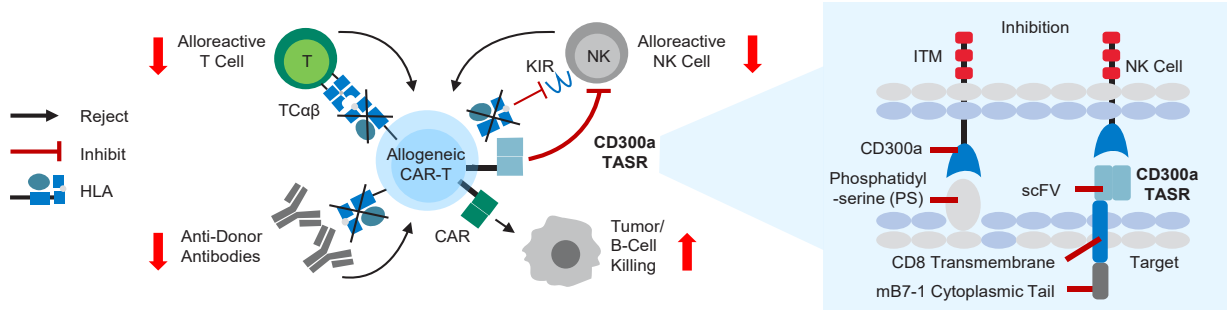
Exhibit 38
CELLect Horizons
Design of Cargo's Allo Vector Platform



Source: CRGX company reports; William Blair Equity Research

Century Therapeutics has also developed an immune evasion strategy that is incorporated into its Allo-Evasion technology. Its Allo-Evasion platform has undergone a series of iterations and its Allo-Evasion 5.0 platform is being applied to its iPSC-derived CAR-αβT cells pipeline, which it acquired from Clade Therapeutics in April 2024 (Acquisition of Clade Expands iPSC Toolbox; Increased Focus on Autoimmune Indications Expected in Second Half 2024). The Allo-Evasion 5.0 edits include genetic knockouts of B2M and CIITA, the expression of CD300a (a pan-NK inhibitory ligand), and expression of a cell surface enzyme responsible for degradation of IgG antibodies (exhibit 39).

Exhibit 39
CELLect Horizons
Design of Century's Allo-Evasion 5.0 Platform



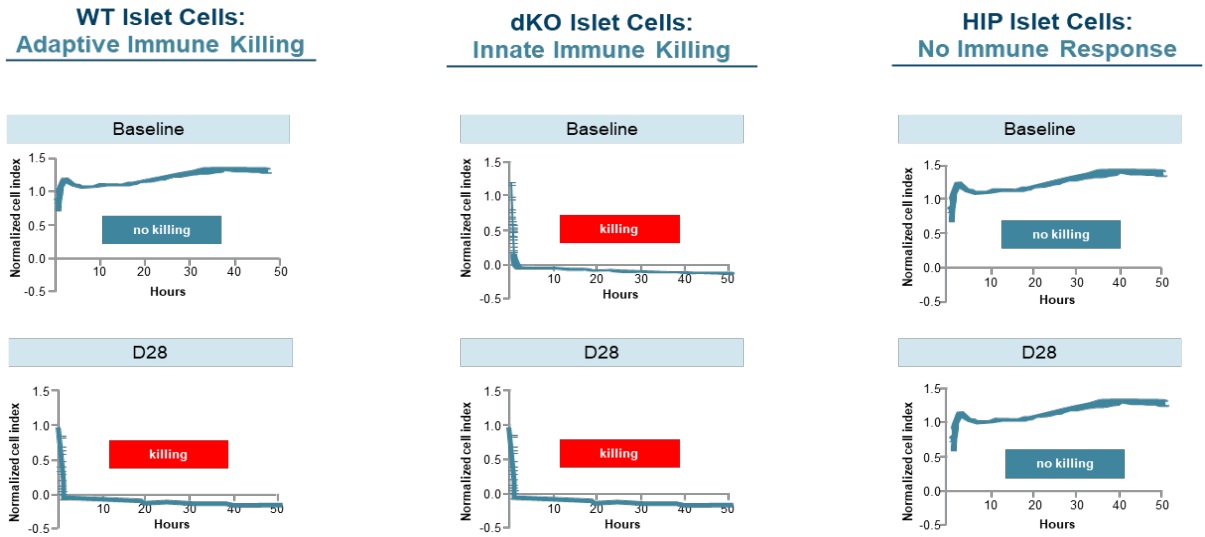
Source: IPSC company reports; William Blair Equity Research

At ASH 2024, Century presented a poster on the use of trans antigen signaling receptors (TASRs) specific for CD300 to aid in in the persistence of allogeneic T cells. Similar to other "don't eat me" signals (e.g., CD47 and HLA-E), cell surface expression of CD300 antigens (CD300a) protects cells against NK cell and macrophage-mediated response. In vitro, CD300a TASR expression enhanced allogeneic T-cell survival when co-cultured with donor NK cells. Notably, CD300a TASRs T cells outperformed the in vitro persistence of T cells expressing HLA-E, CD47, and SIRPα. Century identified several variable domains of heavy chain (VHH) binders that demonstrate comparable protection and donor universality to scFv fragments targeting CD300a, with no CD300c overlapping binding. Century plans to provide additional details on the company's preclinical pipeline prioritization in the first quarter of 2025.

Sana Biotech's hypoimmune cell platform (HIP) uses CD47 overexpression, in addition to B2M and CIITA knockouts, to cloak against rejection by host macrophages and NK cells. Sana is applying its HIP across its iPSC-derived cell therapies, including SC262, a CD22 CAR-T for the treatment of r/r NHL.

Although Sana has not yet shared clinical data from the Phase I VIVID trial of SC262, in January 2025, Sana presented initial clinical data from its allogeneic, donor-derived, pancreatic islet cell asset, UP421, for the treatment of type 1 diabetes, which also uses its HIP. Data of the first patient treated with UP421 without the use of immunosuppression demonstrated graft survival and no safety or inflammation signals 28-days post-transplantation, suggesting that the HIP islet cells were able to evade both the patient's adaptive and innate immune systems. Furthermore, the drug product tested in the first patient contained a mixture of HIP islet cells (HLA I/II KOs, CD47 overexpression), along with wild-type (WT) islet (no genetic modifications) and double knockout (dKO) islet cells, (only HLA I/II KOs) allowing for additional detailed immune analysis. The patient's immune response was monitored at several time points after transplantation (days 7, 14, 21, 28), which showed that while both the HIP islet cells and dKO islet cells overcame the adaptive immune barrier (as assessed by IgM and IgG antibodies from days 7-28), CD47 overexpression was needed to avoid the innate immune system, and the patient's NK cells killed the dKO islets within 5 hours of transplantation (exhibit 40). While we see the initial T1D data as having potential positive readthrough to its CAR-T platform, we highlight the different immune environments between muscle (which UP421 is implanted into) compared with the peripheral blood (used for SC262) as a possible caveat.

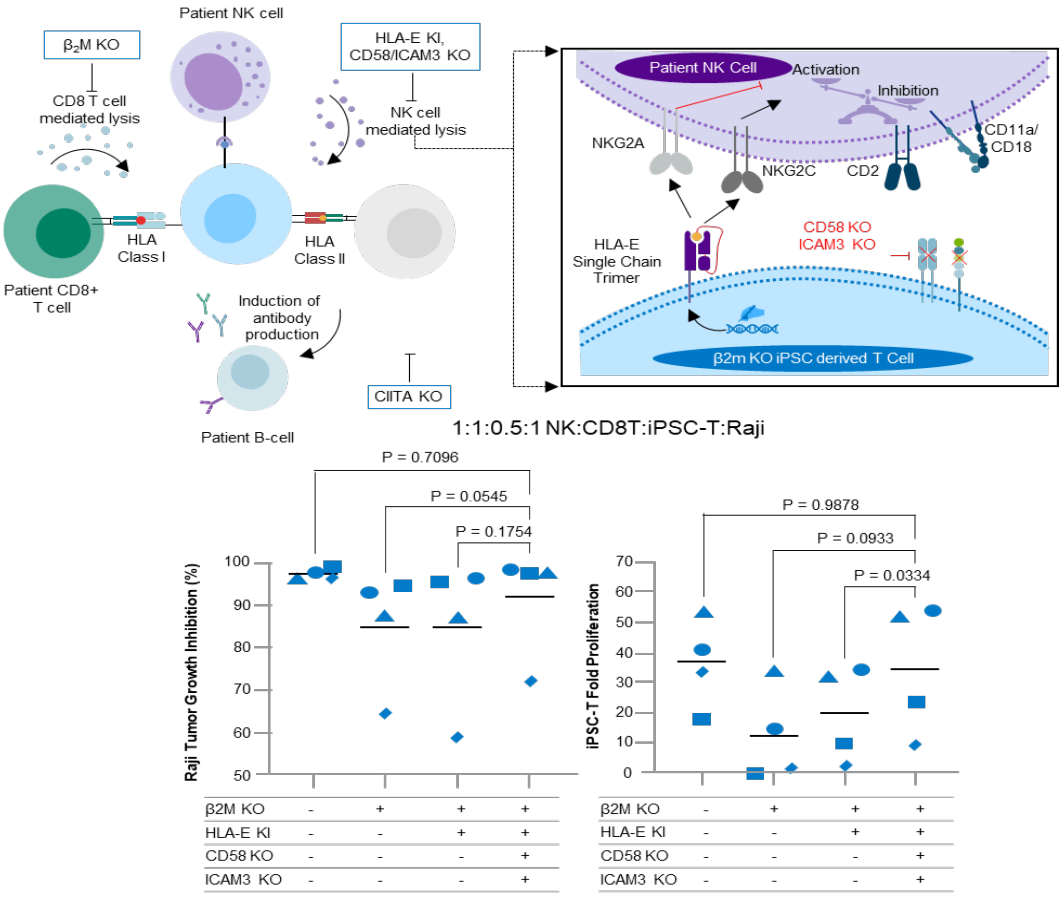
Exhibit 40
CELLect Horizons
Sana's HIP Islet Cells Demonstrated Adaptative and Innate Immunity in T1D Patients



Source: Sana company reports; William Blair Equity Research

At the 2024 ASH meeting, private company **Notch Therapeutics** introduced its "layered cloaking strategy," which it is applying to its iPSC-derived CD8 T cells. In addition to B2M and CIITA knock-outs, its novel approach knocks out adhesion ligands CD58 and ICAM3 and knocks in a modified HLA-E single chain trimer to prevent the formation of a stable immune synapse between allogeneic cells and patient NK cells. Preclinical data presented at ASH supports the additional edits' potential to further provide immune evasion support and enhance persistence, while retaining its potency, compared to HLA-E knock-in alone in a co-culture with NK and CD8 T cells (exhibit 41).

Exhibit 41
CELLect Horizons
Notch's Layered Cloaking Strategy to Evade NK-Cell Killing



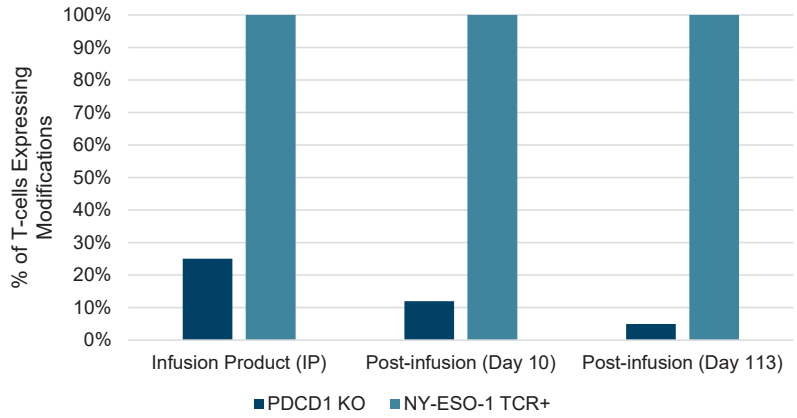
Source: Notch ASH 2024; William Blair Equity Research

Enhancing Antitumor Activity

Genetic modifications are also being used to enhance the activity of allogeneic CAR-T cells, which can become exhausted after excessive stimulation or exhibit reduced activity due to tumor suppression factors. Knocking out inhibitory receptors, which are overexpressed in exhausted T cells, has been a key focus for improving allogeneic CAR-T activity and persistence. Several preclinical studies have demonstrated that an antibody blockade of PD-1, or disruption/knockdown of the gene encoding PD-1 (i.e., PDCD1), improves CAR-T cell-mediated killing of tumor cells in vitro and enhanced clearance of PD-L1+ tumor xenografts in vivo (Rupp et al. *Sci. Rep.* 2017).

However, **Tmunity Therapeutics' (acquired by Gilead's Kite)** NY-ESO-1 TCR therapy was an autologous T-cell product that was CRISPR edited to eliminate expression of PD-1. While the product was ultimately discontinued due to poor efficacy, a publication in *Science* noted that expression of the NY-ESO-1 TCR in the infusion product that had mutations in the PDCD1 locus decreased from 25% to about 5% four months after infusion (Stadtmauer et al. *Science.* 2020, exhibit 42). The *Science* publication suspected this occurred because PD-1–deficient T cells are less likely to establish memory and noted that T-cell exhaustion can still occur in the absence of PD-1, possibly indicating that additional methods are needed to promote persistence.

Exhibit 42
CELLect Horizons
Frequency of Cells With PDCD1 Edits Decreases Over Time



Source: Stadtmauer et al. *Science* 2020; adapted by William Blair Equity Research

Despite Tmunity's results, **Beam Therapeutics, Caribou Biosciences,** and **Antion Biosciences** are all incorporating PD1 knockouts into their allogeneic cell products. Caribou has shared the most clinical data to date on an allogeneic product with a PDCD1 KO in the oncology setting. However, given that only 8 of the 46 patients treated with CB-010 (18%) achieved a CR at 6 months post-infusion, along with the company's decision to implement partial HLA matching, the incorporation of a PDCD1 KO does not seem to be sufficient to compensate for the reduced CAR-T persistence due to host-versus-graft rejection.

Beam Therapeutics also includes a PDCD1 KO in its multiplex base-edited anti-CD7 CAR-T-cell therapy, BEAM-201. At the 2024 ASH meeting, the company shared data from four patients dosed with BEAM-201, with three of the four patients achieving CR or CRi (CR with incomplete hematologic recovery); however, PK data shared was limited with three of the four patients showing good persistence with detectable CAR-T up to 28 days post-infusion. Thus, overall, we believe it has yet to be seen clinically if a PDCD1 knockout modification leads to greater persistence of allogeneic CAR-T products.

In contrast, **CRISPR Therapeutics'** next-generation allogeneic CAR-T candidates, CTX112 targeting CD19 and CTX131 targeting CD70, include two additional knockouts aimed at increasing cell potency: Regnase-1 (to help prevent T-cell exhaustion) and TGFBR2 (to increase T-cell antitumor activity). The company describes the Regnase-1 KO as "removing an intrinsic brake on T cell function" as it increases functional persistence, cytokine secretion and sensitivity, and effector function of T cells, while the TGFBR2 KO is described as "removing a key extrinsic brake on T cell antitumor activity" as it reduces tumor microenvironment inhibition of multiple CAR-T cell functions, including preservation of memory functions to enhance antitumor activity. Regnase-1 has also been validated by research out of the lab of Dr. Carl June from the University of Pennsylvania, which demonstrated disruption of Regnase-1 in T cells results in the induction of hyperinflammation and an increased antitumor response (Mai et al. PNAS 2023).

This past December, CRISPR Therapeutics shared initial data from the Phase I/II trial of CTX112 for patients with r/r B-cell malignancies, allowing for a comparison of CTX112 to its first-generation, allogeneic product CTX110. The additional two edits (Regnase-1 KO and TGFBR2 KO) led to higher CAR-T expansion and functional persistence compared to CRISPR's first-gen CAR-T product as measured by mean AUC and C_{max} (exhibit 43). Furthermore, a patient case study highlighted

the potential of persisting CAR-T cells to combat disease reemergence. One patient experienced disease progression at the six-month assessment after achieving a CR with CTX112 at dose level 1. A "watch and wait" approach was taken, wherein the patient received no additional anticancer therapies. Strikingly, at the nine-month assessment, the patient demonstrated an MRD-negative PR and achieved a CR at month 12, which remained durable through 15 months. We believe this case study further highlights how the improved expansion and functional kinetics of the CAR-T cells can translate to recurrent antitumor activity in the clinic compared to CTX110.

Exhibit 43
CELLect Horizons
CAR-T Cell Expansion Kinetics of CTX112 vs. CTX110

	CTX110 DL3 (n=5)	CTX112 DL3 (n=3)	Fold-increase
Mean AUC	13,830	133,701	9.7x
Mean C_{max}	3,773	26,235	7.0x

DL3, dose level 3 (300 million cells)
Source: CRISPR Therapeutics ASH 2024; William Blair Equity Research

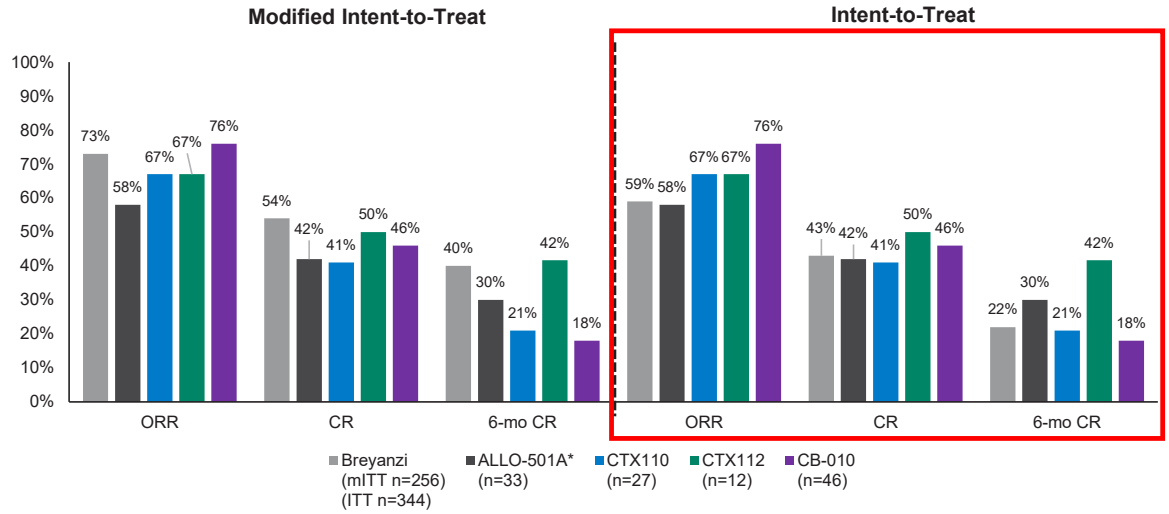
However, while the pharmacokinetic data and patient case study are highly encouraging, we cannot definitively say the edits and increased expansion are driving increased efficacy compared to CTX110 and other allogeneic CD19 CAR-T products given the limited number of patients and differences in baseline patient disease and demographics (exhibits 44 and 45). We look forward to additional updates from this program in 2025, as well as initial data for CTX131, to further validate these edits.

Exhibit 44
CELLect Horizons
Clinical Data for Autologous CAR-T Cell Therapies in DLBCL and B-NHL

	CRISPR			Allogene		Caribou
Generic Name	CTX112	CTX110		ALLO-501/A	Phase II Regimen ALLO-501/A (Single dose + FCA90)	CB-010
Clinical Trial	Phase I/II trial	CARBON		ALPHA/ALPHA2	ALPHA/ALPHA3	ANTLER
Phase	Phase I/II	Phase I Part A	Phase I Part B	Phase I	Phase I	Phase I
Indication	r/r B-NHL (FL, MZL, MCL, CLL/SLL, DLBCL)	r/r LBCL		r/r LBCL	r/r LBCL	r/r B-NHL (DLBCL, PMBCL, FL, MCL)
Baseline Characteristics	Median Age: 62 ECOG 0 or 1: 100% Stage IV disease: 67% Median prior therapies: 3 (1-7) Patient breakdown: FL:3; MZL: 3; MCL:1; LBCL: 5	Median Age: 64 ECOG 0 or 1: 100% Stage IV disease: 53.1% IPI 3-5: NR Median prior therapies: 2 (2-10) Prior SCT: 34.4%		Median Age: 66 ECOG 0 or 1: 79% Stage IV disease: 58% IPI 3-5: 58% Mean prior therapies: 3 Prior SCT: 21% Double or triple hit: 30%	Median Age: 60 ECOG 0 or 1: 92% Stage III/IV disease: 67% IPI 3-5: 50% Mean prior therapies: 3 Prior SCT: 50% Double or triple hit: 33%	Median age: 65 IPI 3-5: 39% Patient breakdown; LBCL:40, MZL:1, FL:2, MCL:3 Mean prior therapies: 1 (1-8)
Dose Level	Single dose with optional re-dosing $30x10^6$ - $600x10^6$	Single dose with optional re-dosing $30x10^6$ - $300x10^6$	Consolidating dosing $600x10^6$	$4x10^7$ - $3.6x10^8$	$4x10^7$ - $3.6x10^9$	40, 80, or $120x10^6$
Conditioning Chemotherapy	Fludarabine (30 mg/m^2) and Cyclophosphamide (500 mg/m^2) for 3 days	Fludarabine (30 mg/m^2) and Cyclophosphamide (500 mg/m^2) for 3 days		Fludarabine (90 or 30 mg/m^2), Cyclophosphamide (900 or 300 mg/m^2) and ALLO-647 90mg	Fludarabine (90 mg/m^2), Cyclophosphamide (900 mg/m^2) and ALLO-647 90mg	Fludarabine (25 mg/m^2) for 5 days and Cyclophosphamide (60 mg/kg/d) for 2 days
Treated Patients	12 Patients	27 Patients	31 Patients	33 patients	12 patients	46 patients
Best Objective Response Rate	**ORR = 67% (8/12)** **CR = 50% (6/12)**	**ORR = 66.7% (18/27)** **CR = 40.7% (11/27)**	**ORR = 65% (20/31)** **CR = 39% (12/31)**	**ORR = 58% (19/33)** **CR in LBCL (mITT)= 42% (14/33)**	**mITT ORR = 67% (8/12)** **CR in LBCL (mITT)= 58% (7/12)**	**ORR:76% (35/46)** **CR: 46% (21/46)**
Response at 6 Months	**6-mo CR= 42% (5/12)**	**6-mo CR= 19% (5/27)** **3 patients ongoing CR at 24 months**	**6-mo CR= 23% (7/31)**	**CR in LBCL (mITT)= 33% (10/30)**	**CR in LBCL (mITT)= 45%**	**CR: 18% (8/45) at 6 mos** **4 patients ongoing CR over 18 months**
Grade 3+ CRS	0%	0%		0%	0%	0%
All grade CRS	58% (7/12)	56.3% (18/32)		24%	33%	57% (26/46)
Grade 3+ Neurotoxicity	0%	6.2% (2/32)		6%	0%	7% (3/46)
All grade Neurotoxicity	33% (4/12)	9.3% (3/32)		39%	33%	22% (10/46)
Reference	ASH 2024	ASH 2022	December 2023	ICML June 2023		ASCO 2024

Sources: Company reports and William Blair Equity Research

Exhibit 45
CELLect Horizons
Comparison of Response Rates Between Autologous and Allogeneic CD19 CAR-T Therapies



Modified intent-to-treat population excludes patients who undergo randomization but do not start treatment due to disease progression, product manufacturing failure, or patient death. Intent-to-treat population includes all participants enrolled in a given study.
*ALLO-501A is currently being evaluated as a consolidation therapy in large B-cell lymphoma (LBCL) patients in the first-line setting

Sources: Company reports; adapted by William Blair Equity Research

The prices of the common stock of public companies mentioned in this report follow:

Allogene Therapeutics (Outperform)	$1.60
Arcellx (Outperform)	$68.24
AstraZeneca	$72.36
Autolus (Outperform)	$2.10
Beam Therapeutics (Outperform)	$27.65
Bristol Myers Squibb (Market Perform)	$57.42
Cargo Therapeutics (Market Perform)	$3.70
Caribou BioSciences	$1.42
Cellectis	$1.59
Celyad Oncology	€0.42
Century Therapeutics (Market Perform)	$0.76
CRISPR Therapeutics (Outperform)	$40.61
Gilead	$98.04
Legend Biotech (Market Perform)	$36.11
Lyell Immunopharma	$0.59
Johnson & Johnson	$153.51
Roche	$39.61
Sana Biotechnology	$3.26

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DOW JONES: 44303.40
S&P 500: 6025.99
NASDAQ: 19523.40

Additional information is available upon request.

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Outperform (Buy)	71	Outperform (Buy)	9
Market Perform (Hold)	29	Market Perform (Hold)	1
Underperform (Sell)	1	Underperform (Sell)	0

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