T-cell Redirection in Oncology: Advancing Roles of Bispecific T-Cell Engagers and CAR T

Executive Summary

The field of oncology has experienced a significant wave of innovation in the next generation of T-cell directed approaches, including both chimeric antigen receptor T-cell therapies (CAR T) and bispecific antibody T-cell engagers (bispecific TCEs). These modalities have similar biological goals in harnessing cytotoxic T-cells to target and kill tumor cells and therefore compete for similar patient populations, particularly in the malignant hematology landscape, where both modalities have multiple approvals.

However, while both modalities promise transformational value to the care of cancer patients, they diverge on several key attributes based on what has been demonstrated in hematologic malignancies to date. Overall, CAR T has demonstrated more robust efficacy, with greater response rates and more durable responses than bispecific TCEs in similar patient populations. Beyond these efficacy benefits, CAR T also offers the potential for one-time dosing. However, bispecific TCEs have relatively easier-to-manage safety profiles, do not require the toxic pre-conditioning therapy of CAR T, and are logistically easier to deliver relative to the complex CAR T manufacturing and administration process (i.e., are available "off the shelf"). This leads bispecific TCEs to have a lower resource burden and makes them better positioned to be incorporated into non-academic hospitals, which treat the majority of cancer patients in the U.S.

Over time, innovation will lead both modalities to improve their respective profiles and therefore they are likely to become increasingly similar. Bispecific TCEs will aim to bridge the efficacy gap vs. CAR T through novel combinations and engineering approaches such as logic gating, which may also contribute to minimization of off-tumor, on-target safety challenges. Conversely, CAR Ts will seek to become safer, through enhanced editing approaches, and more logistically convenient, through reductions in turnaround time and potentially allogeneic or in vivo options which could increase accessibility across treatment settings. For both modalities, these innovation priorities become even more critical for advancing CAR T and bispecific TCEs to solid tumors, where faster disease progression and greater heterogeneity of the tumor microenvironment pose significant challenges. Given this backdrop, it is critical for biotech and pharma companies to carefully evaluate their approach to innovation, and the corresponding tradeoffs that exist, as part of investing in either modality.

Introduction

Background On T-cell Redirecting Therapy Development

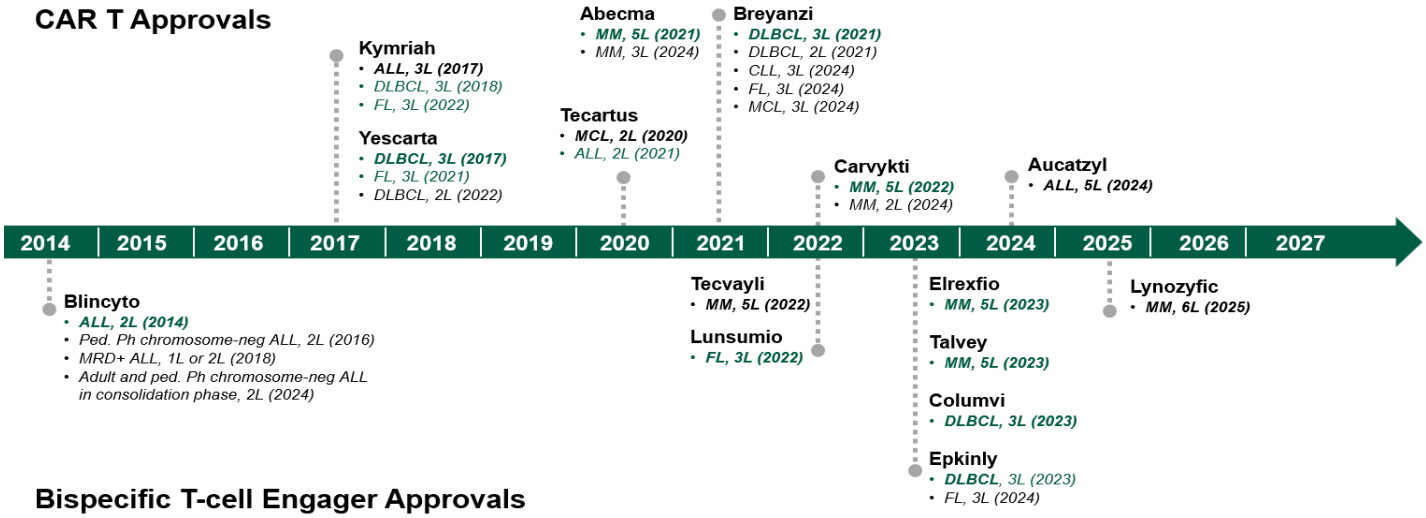
While checkpoint inhibitor immunotherapies have significantly improved treatment outcomes in over 20 malignancies, many patients unfortunately do not have the durable responses that we would hope for. To continue to advance outcomes, a significant amount of innovative R&D effort aims to address challenges faced by current immunotherapies including the ability to more directly activate T cells and help them infiltrate the tumor microenvironment. CAR T cell therapy and bispecific T-cell engagers exemplify this trend, as both approaches "redirect" and prime T-cells to attack cancer cells expressing specific cellular markers.

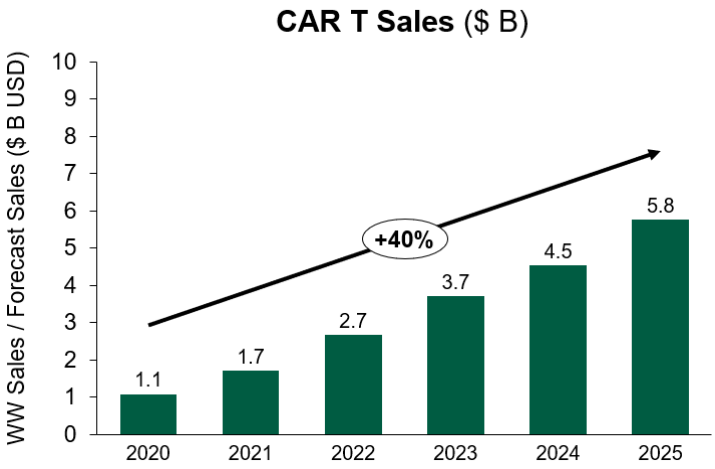
What is a CAR T?

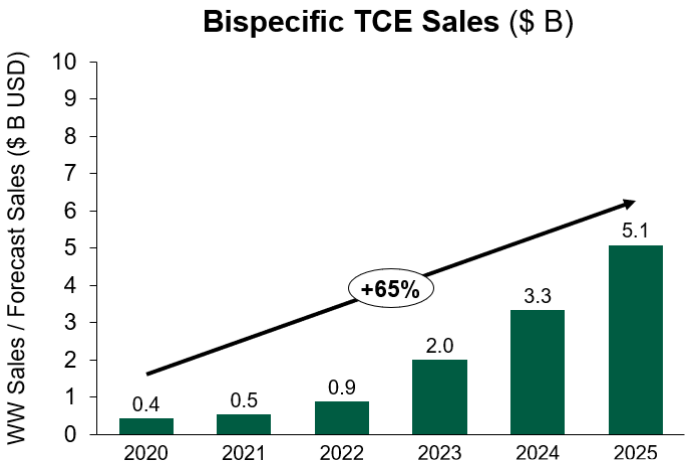
CAR T cell therapy uses human T-cells modified to express CARs (Chimeric Antigen Receptors), which are genetically engineered receptors specific to a tumor cell surface antigen. Currently approved CAR T therapies are all autologous and therefore require apheresis of T-cells from a patient, ex-vivo modification to insert the CAR, T-cell activation & expansion, and then re-administration to the patient. In all, this manufacturing process takes several weeks but once administered, modified CAR T cells are primed to target cancer cells and have demonstrated robust and durable clinical responses. Seven CAR T therapies have been approved to date, all for hematologic malignancies, with the first approval occurring in 2017. Approved CAR Ts all target one of two antigens: CD19 for B-cell lymphomas / B-cell acute lymphoblastic leukemia or BCMA (B-cell Maturation Antigen) for multiple myeloma. Beyond CAR T, there are also other approaches to cell therapy which have shown promise, such as tumor-infiltrating lymphocyte therapy (e.g., AMTAGVI in melanoma). However, these will not be covered in this paper.

What is a Bispecific T-cell Engager?

In contrast, bispecific T-cell engagers (TCEs) are antibodies engineered to form an immunological synapse between T-cells and tumor cells through two distinct binding sites. The bivalent structure allows one arm to target the tumor antigen (e.g., BCMA, GPRC5D, CD20) while the other recruits and activates T-cells (e.g., CD3) at the tumor site, enabling T-cell mediated tumor cell killing. The first bispecific TCE, Blincyto, was approved in 2014. Since then, a new wave of bispecific TCE development has targeted largely the same malignancies as CAR T (e.g., multiple myeloma, non-Hodgkin's lymphoma), though approvals have lagged CAR T. Bispecific T-cell engagers have also now been approved for solid tumors, including IMDELLTRA in small cell lung cancer and KIMMTRAK in uveal melanoma. Additionally, significant bispecific research is ongoing outside of TCEs (e.g., dual-pathway antagonism) , though given these are not T-cell redirecting approaches, they will not be the focus of this paper.







What is the Market for CAR T and Bispecifics Today?

The markets for both CAR T and bispecific TCE antibodies have grown meaningfully in recent years. In 2025, CAR T sales are projected to be ~$6 B, representing a ~40% CAGR since 2020, while bispecific TCE sales are projected to be ~$5 B, representing a ~65% CAGR over the same period. For both modalities, growth since 2020 has been driven by new entrants, continued uptake, and expansions to earlier lines of therapy with both approaches focusing on multiple myeloma and non-Hodgkin lymphoma[1].

Clinical Tradeoffs to Current CAR T and Bispecific T-cell Engager Therapies

Given their similarities in mechanistic approach, targets, and disease focus, understanding the strengths and weaknesses of these classes is key to inform treatment decisions and R&D investment.

What are the Advantages of CAR T?

Efficacy

CAR T has set the bar for efficacy relative to bispecific TCEs. CAR Ts have demonstrated a more robust response rate and an impressive duration of response. Considering BCMA targeting for relapsed / refractory multiple myeloma as an example, Carvykti (CAR T) demonstrated more than double the complete response rate and median progression free survival when compared to Tecvayli (bispecific TCE), despite being tested in a slightly more heavily pretreated and refractory population (Table 1 – Appendix).

Potential for One-time Dosing

CAR T one-time dosing may offer attractive convenience to patients compared to bispecific TCEs, which require ongoing dosing ranging from weekly to every 4 weeks depending on the specific regimen or indication. Therefore, following initial dosing and monitoring requirements, CAR T eliminates the need for repeated visits to receive treatment in addition to potential exposure to therapy adverse events experienced over the treatment duration.

What are the Advantages of Bispecific TCEs?

Safety

Similar adverse events are observed in both CAR T and bispecific TCE treatment. However, TCEs have been associated with lower levels of G3+ adverse events, particularly in key immune-related adverse events such as cytokine release syndrome (CRS) and Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS). Table 1 (Appendix) illustrates an example in RRMM, where CRS and ICANS were more frequent and severe with Carvykti than Tecvayli. Additionally, bispecific TCEs use does not require toxic lymphodepleting pre-conditioning therapy, which current CAR T patients must undergo.

[1]EvaluatePharma.

Ease of Logistics (Off-the-shelf)

CAR T utilization is significantly hindered by the complex manufacturing required. The process requires significant time (vein-to-vein time averaging ~1 month), toxicity for patients (toxic bridging therapy), and risk of treatment failure (manufacturing failures occur in 5 – 15% of all CAR T products). Patients must also undergo lymphodepletion prior to treatment and receive extensive monitoring post-treatment (e.g., 1-week monitoring, 4-week restriction on daily activities), expanding the patient burden. These complexities preclude use outside of specialized centers currently equipped to handle these logistics. Bispecific TCEs, on the other hand, are available for use "off-the-shelf", eliminating manufacturing wait times and making these therapies less logistically burdensome. This lack of wait time also allows patients to rapidly receive therapy and begin to benefit, limiting the time the disease has to progress, without the need for bridging therapy.

Broader Settings of Care

Given easier administration logistics and improved safety, bispecific TCEs have greater potential for uptake in a wider range of hospital settings than CAR T. Bispecific TCEs still have risk of serious AEs that necessitate significant patient monitoring, institutional protocol development, and physician / nurse training for AE management. However, growing clinical experience and institutional capabilities are already driving broader use today compared to current CAR T.

Future of CAR T and Bispecifics

Addressing the respective challenges of CAR T and bispecific TCE therapies creates significant opportunity for patients and it is therefore the focus of significant R&D investment. Illustrating this key point, there are ~200 CAR T and ~100 bispecific TCEs in the clinical pipeline, with the majority of investment focused on hematologic malignancies. A review of the pipeline suggests a few key trends that manufacturers aiming to invest in the space will need to consider.

Reduced Vein-to-vein Time of CAR T

Recent investment by large pharma in technologies that reduce vein-to-vein time signals a strategic shift toward faster, more scalable CAR T models that preserve the quality of autologous material for next generation CAR T products. Currently, the shortest median CAR T vein-to-vein time is ~1 month[2], but a shorter turnaround time may reduce risk of progression events and spare toxicity associated with bridging therapy, creating a critical clinical advantage. Multiple assets are aiming to meet this need by a variety of approaches, for example:

- Kite-partnered Arcellx BCMA CAR T, anito-cel, touts a maximum 17-day turnaround time[3], leveraging Kite's manufacturing infrastructure and authorized treatment center network
- Novartis/Legend's T-Charge platform stimulates T-cell proliferation and stem-like differentiation in vivo, dramatically reducing need for extended culture time ex vivo, demonstrating similar response rates with a manufacturing process of <2 days[4]
- Gracell's FastCAR technology, the focus of their acquisition by AstraZeneca for $1 B, is a rapid autologous manufacturing platform that streamlines T-cell activation and transduction into a single concurrent step via a proprietary lentivirus-derived vector, enabling potential for next-day manufacturing in a preliminary in-human study[5].

Investment Interest in In-vivo CAR T

In vivo CAR T is more nascent and lacks significant clinical PoC data (first in-human studies commenced in late 2024). The technology aims to generate CAR T-cells within a patient's body by delivering CAR-encoding material via LNPs or viral vectors to T-cells, though the relative transduction/transfection efficiency and ability to mitigate off-target delivery remains unclear. Ultimately, if successful, these approaches may enable true "off-the-shelf" CAR T, though the potential efficacy tradeoff to existing autologous CAR Ts (and benefit over bispecific TCEs) remains uncertain[6].

[2]Locke. Blood Advances. 2025. [3]Arcellx Inc. Corporate Presentation. 2025. [4]Ikegawa. Blood. 2023. [5]Yang. Blood Cancer Journal. 2022.

Nonetheless, these approaches have attracted significant investment interest from large pharma in 2025 – including Gilead's acquisition of Interius ($350 M), AstraZeneca's acquisition of EsoBiotec (up to $1 B), and AbbVie's acquisition of Capstan (up to $2.1 B). These deals signal the substantial promise of in vivo CAR T approaches if technical success is achieved.

Bispecific TCEs in Combination Regimens

Along with improved safety, dosing of bispecific TCEs makes them more conducive to combination with other SOC regimens to enhance their clinical profile. While a review of the pipeline shows this approach is being leveraged increasingly often, it is worth noting that bispecific TCEs have already shown potential for strong efficacy in combination with current SOC agents (e.g., TALVEY + DARZALEX achieved an ORR of 82% and mPFS of 20.3 months in RRMM[7]). Further, bispecific TCEs may even be combined with each other as shown with TECVAYLI + TALVEY in triple-class refractory MM patients which yielded an 80% ORR, though faced safety challenge with 64% of patients experiencing grade 3 or 4 infections[8]. Importantly, as bispecific TCEs move into earlier lines of therapy, a wide range of combination strategies are being explored—not only to enhance efficacy to levels approaching those seen with CAR Ts, but also to optimize safety and tolerability in broader patient populations.

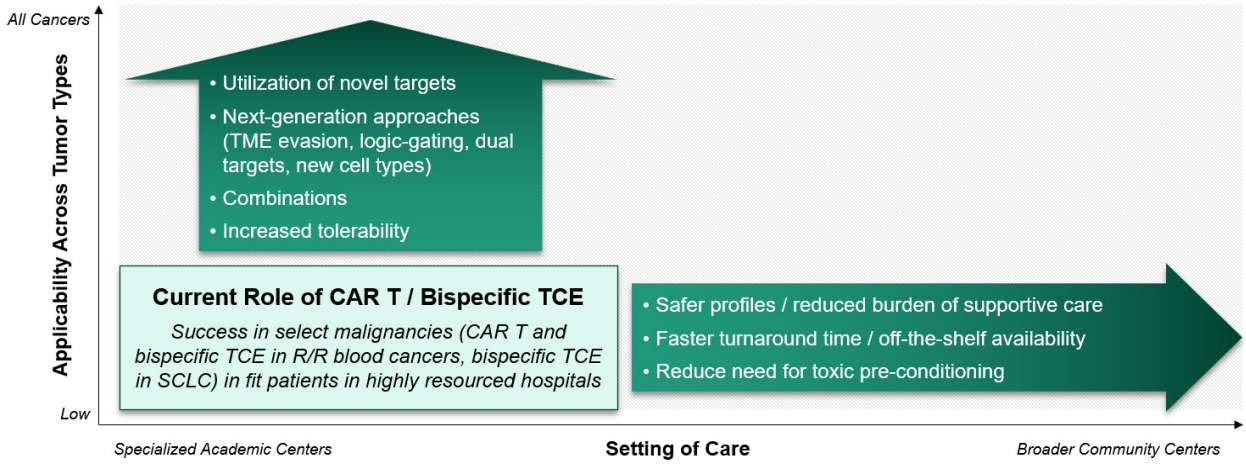
Expansion to Solid Tumors

To date, most of the clinical success for T-cell redirection has been in hematologic malignancies. However, success in solid tumors represents a transformative opportunity for the field, as these cancer types account for ~90%[9] of all incident patients and remain largely untapped by current T-cell redirection approaches. However, solid tumors introduce several novel challenges to T-cell redirection, including:

- The need to circumvent immunosuppressive tumor microenvironments
- Selection of an appropriate target that is highly expressed on cancer cells, ideally across malignancies, but not on healthy tissues

Despite these challenges, both bispecific TCEs and CAR T have demonstrated recent progress in solid tumors. At ASCO this year, cell therapies demonstrated clear responses and promising data in forms of kidney cancer, gastric cancer, and brain cancer though toxicity remains a challenge. Conversely, bispecific TCEs have already been approved in solid tumors, placing the current progress of bispecific TCEs ahead of that for CAR T. One example is IMDELLTRA, which achieved accelerated approval in small cell lung cancer based on 40% ORR and 9.7-month duration of response that far exceeded efficacy of single agent chemo SOC (24% ORR; 3.3-month duration of response)[10].

Oncology Landscape



[5]Additional technological innovations such as the use of healthy donor cell material (allogeneic CAR T) and in vivo CAR T technology altogether obviate vein-to-vein delay and represent potential "off-the-shelf" CAR T products. The allogeneic approach uses healthy donor T-cells genetically modified to encode a CAR domain and edited to minimize alloreactivity (e.g., via knockout of TCR domain). Though this approach enables off-the-shelf dosing, preliminary allogeneic data indicates a more modest depth and durability of response relative to auto CAR T. [7]Johnson & Johnson. Press Release. 2024. [8]Cohen. New England Journal of Medicine. 2025. [9]Surveillance, Epidemiology, and End Results Program. Accessed August 2025. [10]FDA. Press Release. 2024.

Conclusion

CAR T and bispecific T-cell engager therapies in hematologic malignancies have set new expectations for cancer treatment as innovation continues to raise the bar for what is possible within each modality. At the same time, improved CAR T and bispecific TCE profiles are likely to become increasingly similar to one another as their respective profile challenges are addressed. Combined with the other market dynamics noted above, this trend raises several strategic questions for biotech and pharmaceutical companies as they consider investments in either approach, including:

- What is the appropriate balance of innovation in terms of novel biology (targets, sub-populations) vs. modality (bispecific logic gating, allogeneic and in-vivo vs. autologous CAR T)? How should these evolve as a portfolio size increases?
- How can differentiation be achieved both within and across each class that will increasingly compete?
- For companies pursuing both modalities, what is the optimal co-positioning strategy? What is the best way to think about pursuing the same vs. different targets for each?
- For a given asset, what is the appropriate level of data needed for sufficient derisking? How should this be balanced against a competitive landscape where being first in class often has a significant impact on brand share thereby incentivizing speed to market?
- How can the profile of the asset be optimized to reach the broadest set of patients? How is this impacted by sequencing considerations between modalities, including T-cell redirecting approaches and beyond, within and across malignancies?
- What level of site support is needed to maximize adoption of the asset and potentially differentiate from entrenched manufacturers?

As manufacturers have multiple investment paths to consider for each modality, enabling an opportunity to drive lasting impact for increasingly more patients, carefully considering the implications of the evolving landscape on the above questions is critical.

Appendix

Table 1

Illustrative Data Comparison: *BCMA-Targeting Agents in RRMM*		
	CARVYKTI (BCMA CAR T) (CARTITUDE-1)	TECVAYLI (BCMA TCE) (MajesTEC-1)
Patient Population		
Median Number of Prior LoT	6	5
% Triple-Class Refractory	88%	76%
Efficacy		
Overall Response Rate (ORR)	98%	68%
Complete Response (CR)	80%	31%
Median Progression-free Survival (mPFS)	24.9 months	11.4 months
Median Overall Survival (mOS)	mOS not reached (62.9% at 36 months)	22.2 months
Safety and Tolerability		
CRS Rate: *All Grade % (G3+ %)*	94.5% (5.1%)	72% (0.6%)
ICANS Rate (Gr3+ %)	21.6% (12.3%)	14.5% (0.6%)
Treatment Logistics		
Median Time from Leukapheresis to Product Availability	32 days (range: 27 – 66)	N/A
Received Bridging Therapy	75%	N/A
Dosing		
Dosing Schedule	One-time Infusion	3x in ~1 week for Step-Up, then QW or Q2W until progression or unacceptable toxicity

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