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REVIEW

Cancer Focus

# T cell engagers emerge as a compelling therapeutic modality

P.A. Baeuerle[1,2*], K. Sauer[1,3*], R. Grieshaber-Bouyer[4], and J.S. Michaelson[1]

**T cell engagers (TCEs) are antibody-based constructs designed to transiently reprogram cytotoxic T lymphocytes for target cell elimination by simultaneously binding the T cell receptor and a specific surface antigen on the target cell. Over the past 12 years, 10 TCEs were approved by the US Food and Drug Administration, and an additional two by the European Medicines Agency. Nine TCEs treat hematologic malignancies, and three target solid tumors. Over 150 TCEs are being investigated in clinical trials, recently also in autoimmune diseases. Here, we discuss the learnings from the 12 approved TCEs. A surprising variety of molecular designs and biochemical characteristics appear suitable for approval. On the clinical side, we review targets, indications, dosing, schedules, side effects, mitigation strategies for adverse events, and efficacy. High flexibility in design and choice of target, scalability, high response rates as a monotherapy in hematologic malignancies, and emerging efficacy against solid tumors and in autoimmune diseases make TCEs an attractive therapeutic modality.**

## Introduction

Cytotoxic T lymphocytes (CTLs) have the potential to find, recognize, and eradicate pathogenic target cells in most parts of the body. They do so through binding of their T cell receptor (TCR; Fig. 1) to antigenic peptides presented by major histocompatibility complex (MHC) proteins on the surface of target cells, termed pMHCs. The resulting assembly of an iummunological, cytolytic synapse triggers signaling events within a CTL, leading to target cell lysis via the transfer of cytotoxic proteins (Fig. 2). The highly effective search and destroy behavior of CTLs can eventually provide the basis for a cure for diverse cancers and, by lysis of disease-driving autoreactive cells, a profound modification of autoimmune diseases (AIDs).

An increasingly popular approach to employ CTLs in the clinic is bispecific antibody-based constructs called T cell engagers (TCEs; Fig. 1). By simultaneously binding to the TCR—usually its CD3ε subunit—on a T cell and a surface antigen on a target cell, TCEs reprogram the T cells to recognize a target cell independently of their TCR specificity and the target cell's pMHC peptidome (Fig. 2). As evidenced by a surge in approvals since 2021 (Fig. 3), TCEs have recently expanded the clinical practice routine in cancer therapy (Bergamaschi et al., 2025; Clynes and Desjarlais, 2019). Here, we review TCE therapies, which have gained approval by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). We believe that learnings from approved molecules are best suited to showcase advantageous properties of first-generation TCEs. We provide an in-depth characterization and comparison of all 10 FDA-approved TCEs (Table 1). We also include odronextamab and catumaxomab, which have recently been approved by the EMA (Blair, 2024; Syed, 2025). Catumaxomab has a unique history with a first approval in the European Union in 2009 for prevention of malignant ascites in EpCAM-expressing carcinomas, followed by a withdrawal in 2017 for commercial reasons, and renewed approval in February 2025. This history might reflect both its niche application and its limited impact on survival (EMA, 2025; Syed, 2025).

Given the focus herein on approved TCEs, we will not discuss in depth the numerous TCEs currently in clinical trials or preclinical development, and will only briefly describe TCE applications in AIDs, design of conditional and costimulatory TCEs, and engagers for subsets of T cells or non-T immune cells. Instead, we refer to in-depth recent reviews on these topics (Ai et al., 2025; Bergamaschi et al., 2025; Nolan-Stevaux and Smith, 2024; Robinson et al., 2024; Wei et al., 2022; Wu et al., 2020).

The currently approved TCEs can engage all cytotoxic T cell subsets because those all share CD3ε and possess secretory granules containing cytolytic perforin and granzymes. This enables CD8, CD4, γδ, NKT, and even regulatory T ($T_{reg}$) cells to

[1]Cullinan Therapeutics, Cambridge, MA, USA; [2]Institute for Immunology, Faculty of Medicine, Biomedical Center, Ludwig-Maximilians-Universität München, Martinsried-Planegg, Germany; [3]Department of Immunology and Microbiology, The Scripps Research Institute, La Jolla, CA, USA; [4]Department of Internal Medicine 3, Rheumatology and Immunology, Deutsches Zentrum Immuntherapie (DZI), Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.

*P.A. Baeuerle and K. Sauer contributed equally to this paper. Correspondence to J.S. Michaelson: jmichaelson@cullinantx.com.







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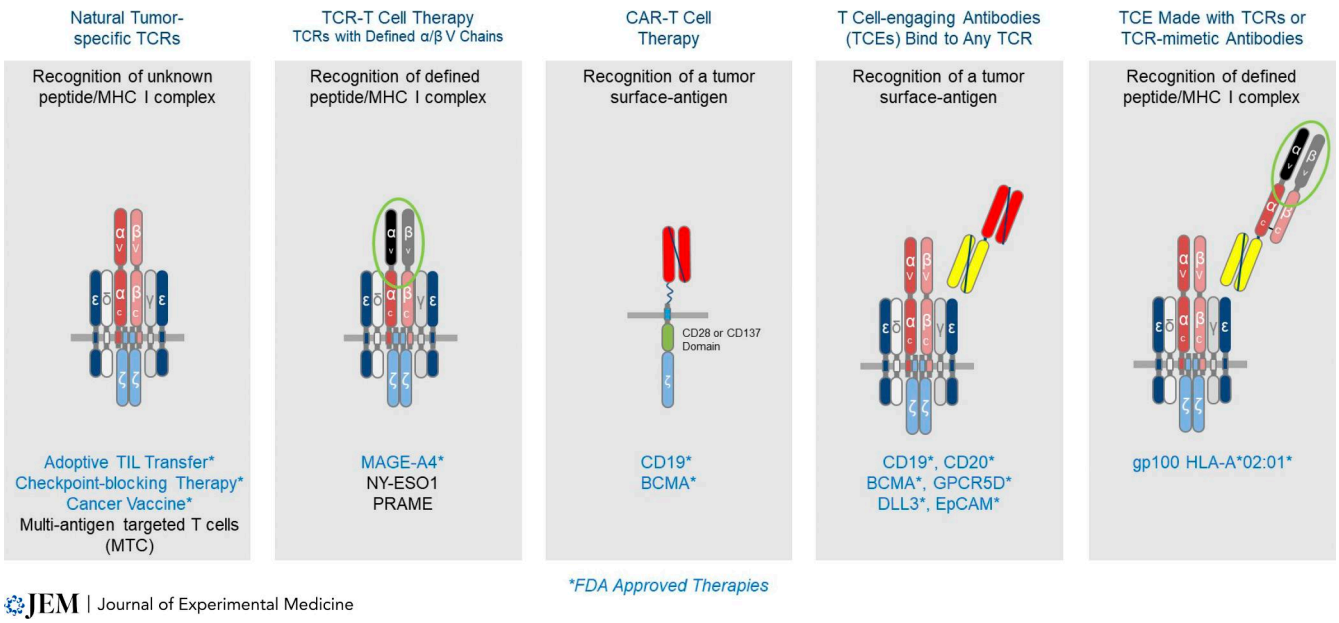


Figure 1. **Comparison of approved T cell therapies.** Shown from left to right are the principles by which T cell therapies take advantage of the TCR: by leveraging natural T cells, which through their TCR recognize a tumor-associated antigen peptide/MHC complex (pMHC); by employing T cells with a transgenic TCR recognizing a defined pMHC target; by utilizing genetically engineered T cells expressing a recombinant CAR; and by engaging T cells whereby the TCR is connected via a TCE to a surface antigen or pMHC on target cells. Therapeutics are listed below each modality with asterisks denoting FDA-approved drugs. Each T cell naturally expresses only one TCR specific for a peptide presented by MHC molecules on the surface of target cells. Recognition is through heterodimeric α/β chains of the TCR, each of which comprises an antigen-binding variable (V) domain followed by a constant (C) domain, a transmembrane (TM) domain, and a short cytoplasmic domain. TM and cytoplasmic domains associate with intracellular, signal-transducing TCRζ subunits and CD3εδ and εγ heterodimeric subunits. TCR-T cells harbor engineered TCRs whereby defined α and β chain V regions are selected to bind predefined pMHC molecules, such as MAGE-A4 peptide in the case of Tecelra (Keam, 2024). CAR-T cells employ antibody-derived domains to recognize surface antigens such as CD19 or BCMA on target cells. The antibody fragments are fused to a TM and signal-transducing domains derived from costimulatory CD28 or CD137 receptors, and only use TCRζ for T cell activation. TCEs are soluble antibody-based constructs that are bispecific for an antigen on target cells and the CD3ε subunit shared by all TCRs. TCEs using TCR fragments or TCR-mimetic antibodies are bispecific for CD3ε on T cells and a defined pMHC on target cells. An example is tebentafusp whose TCR moiety binds gp100 peptide/HLA-A*02:01 MHCs on melanoma cells (Liddy et al., 2012; Lowe et al., 2019).

qualify as effectors for TCEs, provided they express granzymes (Haas et al., 2009). The clinical efficacy of the approved TCEs indicates that $T_{reg}$ engagement does not prevent activity, although some data may suggest a limiting effect under certain circumstances (Duell et al., 2017; Duffy et al., 2025). Other data suggest that CD4 T cell activation may promote efficacy, e.g., by providing help to CTL and through their own lytic activity (Duffy et al., 2025). It is not well understood to what extent circulating,

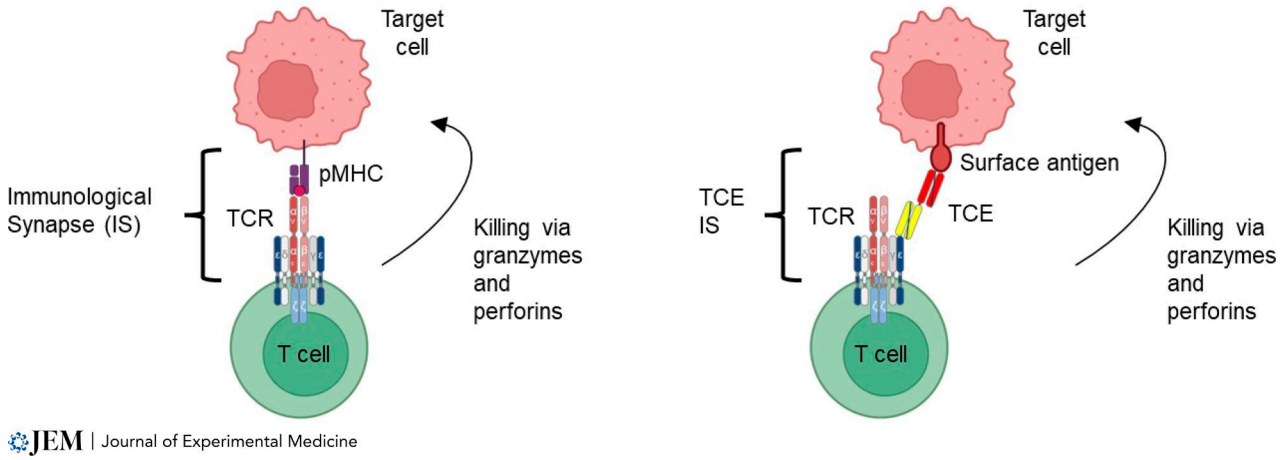


Figure 2. **TCEs enable formation of an immunological, cytolytic synapses (IS) between T cells and target cells.** Shown are simplified IS formed by (left) a TCR on a T cell and a cognate peptide–MHC (pMHC) on a target cell and (right) a tandem scFv-format TCE (e.g., blinatumomab, Fig. 4) simultaneously bound to the CD3ε subunit of the TCR on a cytotoxic T cell and a specific surface antigen on a target cell (CD19 for blinatumomab). IS formation employs additional receptor–ligand interactions between T cell and target cell (not shown) to activate the T cell and kill the target cell (Chen et al., 2021; Leithner et al., 2025; Offner et al., 2006). The IS induced by a TCE differs from the natural IS in that it does not require TCRαβ chains or pMHC molecules. Created in BioRender. Sauer, K. (2025) https://BioRender.com/c27rh9f.

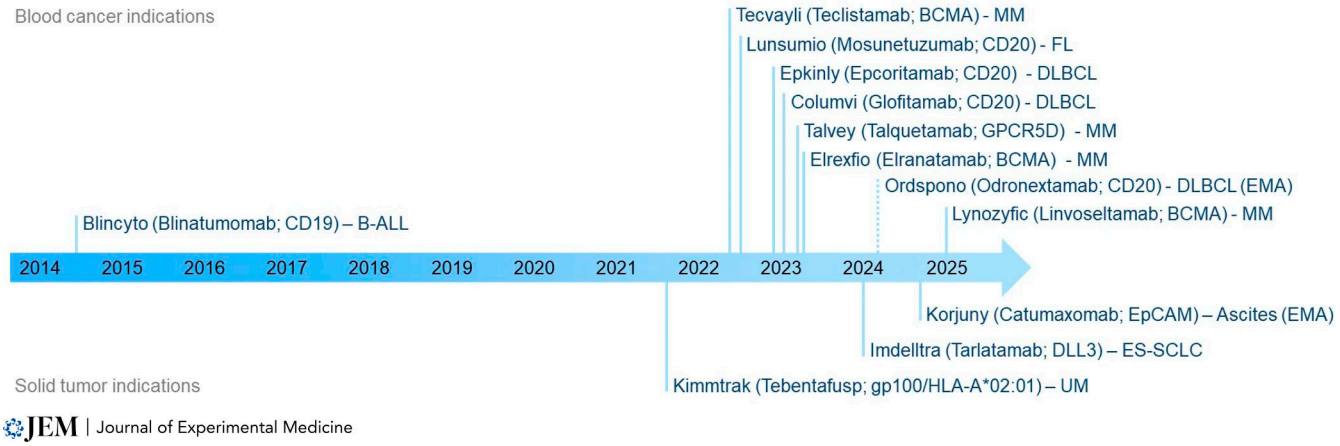


Figure 3. **Timeline showing approval dates of TCEs.** Vertical lines mark approximate dates of approval by the FDA or the EMA for the indicated TCE drugs. Also provided in parentheses are international nonproprietary/generic names (INN) and target antigen and indications (acronyms). Approval dates were obtained from https://www.fda.gov/drugs/drug-approvals-and-databases/resources-information-approved-drugs, EMA (2024), EMA (2025).

lymphoid, normal tissue-resident, or tumor-infiltrating lymphocytes (TILs) are recruited by TCEs for tumor cell lysis and which T cell subsets are most critical for efficacy. The transient decrease in circulating T cells after TCE treatment, likely reflecting vessel adherence and margination, supports a role for circulating T cells (Bucci et al., 2024; Hagen et al., 2024). Likely, TILs may be engaged by TCEs in "hot" tumors, consistent with clonal expansion of both bone marrow and circulating T cells in multiple myeloma (MM) patients by a BCMAxCD3 TCE (Friedrich et al., 2023). Finally, TCE efficacy in "cold" tumor indications lacking TILs, such as prostate cancer, is consistent with recruitment of peripheral T cells (Lowe et al., 2019; Nathan et al., 2021; Hassel et al., 2023; Kelly et al., 2024, Janux Therapeutics, 2024a, Janux Therapeutics, 2024b).

Selective engagement of T cell subsets, including γδ T cells and CD8 T cells, and engaging T cells through their costimulatory receptors like CD28, 4-1BB, or CD2 are all being tested. To date, no clinical superiority of such approaches has been established, and no drugs selectively engaging T cell subsets or costimulatory receptors have thus far been approved. Engagers for NK cells or macrophages are interesting avenues but out of scope for this review.

Engagement and activation of T cells for cancer therapy has a long history. First was the cytokine interleukin-2 (IL-2), which promotes T cell growth and survival, but is not commonly used in the clinic today due to toxicities and limited efficacy (Rokade et al., 2024). Next were monoclonal antibodies (mAbs) targeting checkpoint inhibitory circuits of T cells, most notably the PD1-PDL1 axis. Such mAbs can effectively treat a multitude of cancers by binding either T cells expressing PD-1 or cancer cells expressing the PD-L1 ligand. They can reinvigorate precursors of exhausted T cells in models of chronic virus infection, and tumor-specific T cells in human tumors (Blackburn et al., 2008; Fritz and Lenardo, 2019; Im et al., 2016; Paul et al., 2024; Tsui et al., 2022). More elaborate approaches include genetic engineering of a patient's T cells to express predefined TCRs (TCR-T cells) or chimeric antigen receptors (CAR-T cells; Fig. 1). This creates living cell therapies whereby very small numbers of genetically engineered T cells can elicit potent clinical efficacy in liquid and solid tumors, although the latter remain challenging (Escobar et al., 2025; Harris et al., 2022; Sanomachi et al., 2025). Afamitresgene autoleucel TCR-T cells targeting MAGE-A4 peptides presented by HLA-A*02:01 MHC molecules were FDA-approved for unresectable or metastatic synovial sarcoma in 2024. The pivotal trial, which enrolled 44 patients, showed an overall response rate (ORR) of 39% (D'Angelo et al., 2024). CAR-T cells have shown clinical efficacy in brain, gastric, liver, sarcoma, neuroblastoma, pleural, claudin 6–positive, and glypican 3–positive tumors. However, most clinical trials only enrolled small patient numbers, efficacy was limited, and no CAR-T cell therapy has been approved to date for solid tumors (Escobar et al., 2025). Yet, another cell therapy, TIL therapy, employs cytotoxic T cells that are isolated from a patient's solid tumor, expanded and reinvigorated *ex vivo*, and then infused back into the patient (Harris et al., 2022). Lifileucel TILs have been approved by the FDA for metastatic melanoma based on an ORR of 31.4% in 153 patients (Turcotte et al., 2025).

Fig. 1 compares the role of the TCR in various approved T cell–engaging therapies. Except for CAR-T cells, all rely on activation of the TCR. Of note, CAR-T and TCE modalities can recognize target cells independently of pMHC expression and TCR specificity (Clynes and Desjarlais, 2019). They can target cell surface–expressed target antigens through antibodies or fragments thereof. An exception are TCEs using a soluble TCR fragment or a TCR-mimetic antibody fragment for recognizing a pMHC (Fig. 1). Several such "TCR-TCEs" are currently in clinical trials (Isaacs, 2025). Tebentafusp was the first example approved for treating a solid tumor indication, uveal melanoma (UM) (FDA, 2025; Immunocore, 2024). A unique property of TCEs—unlike any other T cell–based therapy—is that they can potentially leverage all phenotypes of cytotoxic T cells in the body for target cell lysis.

## TCEs as an emerging drug modality

The appreciation of TCEs as a novel cancer immunotherapy lagged behind the alluring emergence of CAR-T cell and

Table 1. **Approved TCEs**

| INN | Brand name | Target | Company | Approval date | Indication | Dose and schedule | Route | References |
|---|---|---|---|---|---|---|---|---|
| Blinatumomab | Blincyto | CD19 | Amgen | December 3, 2014 | MRD⁺ or r/r or CP CD19⁺ B-ALL | MRD⁺, ≥45 kg body weight: four cycles of days 1–28, 28 µg/day continuous infusion; days 29–42, no treatment. r/r: induction cycle 1, days 1–7, 9 µg/day; days 8–28, 28 µg/day; days 29–42, no treatment. Induction cycle 2, days 1–28, 28 µg/day; days 29–42, no treatment. Consolidation cycles 3–5, days 1–28, 28 µg/day; days 29–42, no treatment. Cycles 6–9, days 1–28, 28 µg/day, days 29–84, no treatment.<br>CP: consolidation cycle, days 1–28, 28 µg/day; days 29–42, no treatment. | IV infusion | Amgen (2024a), FDA (2025), Herrera et al. (2024) |
| Tebentafusp-tebn | Kimmtrak | gp100/HLA-A*02:01 | Immunocore | January 25, 2022 | HLA-A*02:01⁺ unresectable or metastatic UM | Weekly. Day 1, 20 µg; day 8, 30 µg; then 68 µg weekly. | IV infusion | FDA (2025), Hassel et al. (2023), Herrera et al. (2024), Immunocore (2024) |
| Teclistamab-cqyv | Tecvayli | BCMA | Janssen | October 25, 2022 | r/r MM | Weekly cycles. Cycle 1 step-up, 0.06–1.5 mg/kg; week 2+, 1.5 mg/kg. Patients with CR ≥ 6 m: 1.5 mg/kg every 2 wk. | SC injection | FDA (2025), Herrera et al. (2024), Janssen Biotech (2024) |
| Mosunetuzumab-axgb | Lunsumio | CD20 | Roche/Genentech | December 22, 2022 | r/r FL | 21 day cycles. Cycle 1 step-up, 1–60 mg; cycle 2, 60 mg, cycle 3+, 30 mg. | IV infusion | Budde et al. (2022b), FDA (2025), Genentech (2024), Herrera et al. (2024), Strohl (2024) |
| Epcoritamab-bysp | Epkinly | CD20 | AbbVie/Genmab | May 19, 2023 | r/r DLBCL, r/r FL | 28 day cycles. Cycle 1 step-up, 0.16–48 mg weekly. Cycles 2/3, 48 mg weekly. Cycles 4–9, 48 mg biweekly. Cycle 10+, 48 mg every 4 wk. | SC injection | FDA (2025), Genmab (2024), Herrera et al. (2024), Strohl (2024) |
| Glofitamab-gxbm | Columvi | CD20 | Roche/Genentech | June 15, 2023 | r/r DLBCL, NOS DLBCL, LBCL | 21 day cycles. Cycle 1, day 1, obinutuzumab 1,000 mg pretreatment; day 8, 2.5 mg Columvi, day 15, 10 mg. Cycle 2–12, day 1, 30 mg. | IV infusion | FDA (2025), Genentech (2023), Herrera et al. (2024), Strohl (2024) |
| Talquetamab-tgvs | Talvey | GPRC5D | Janssen | August 9, 2023 | r/r MM | Two schedules. Weekly schedule: Cycle 1 step-up, day 1, 0.01 mg/kg; day 4, 0.06 mg/kg; day 7, 0.4 mg/kg. Then 0.4 mg/kg once weekly. Biweekly schedule: Cycle 1 as above. Day 10, 0.8 mg/kg; then 0.8 mg/kg every 2 wk. | SC injection | Janssen Biotech (2023), FDA (2025), Herrera et al. (2024), Strohl (2024) |

Table 1. **Approved TCEs (*Continued*)**

| INN | Brand name | Target | Company | Approval date | Indication | Dose and schedule | Route | References |
|---|---|---|---|---|---|---|---|---|
| Elranatamab-bcmm | Elrexfio | BCMA | Pfizer | August 14, 2023 | r/r MM | Two schedules. Weekly schedule: Cycle 1 step-up, day 1, 12 mg; day 4, 32 mg; day 8, 76 mg. Then 76 mg weekly through week 24. Biweekly schedule: responders only. Starting at week 25, 76 mg every 2 wk. | SC injection | FDA (2025), Herrera et al. (2024), Pfizer (2023), Strohl (2024) |
| Tarlatamab-dlle | Imdelltra | DLL3 | Amgen | May 16, 2024 | Pretreated ES-SCLC | Biweekly cycles. Cycle 1 step-up, day 1, 1 mg; day 8, 10 mg; day 15, 10 mg. Cycle 2+, days 1 and 15, 10 mg each. | IV infusion | Amgen (2024b), FDA (2025), Herrera et al. (2024) |
| Odronextamab | Ordspono | CD20 | Regeneron | August 22, 2024 (EMA) | r/r DLBCL, r/r FL | Four 21-day cycles followed by biweekly or monthly maintenance. Cycle 1 step-up, day 1, 0.2 mg, day 2, 0.5 mg, days 8 and 9, 2 mg, days 15 and 16, 10 mg. Cycles 2–4, 80 mg (r/r FL) or 160 mg (r/r DLBCL) on days 1, 8 and 15. Maintenance, 160 mg (r/r FL) or 320 mg (r/r DLBCL) biweekly. Reduce to monthly after CR duration of 9 mo. | IV infusion | Blair (2024), EMA (2024), Regeneron Pharmaceuticals (2025b) |
| Catumaxomab | Korjuny | EpCAM | Lindis Biotech, licensed to Pharmanovia | February 10, 2025 (EMA) | Malignant ascites in adults with EpCAM$^+$ carcinomas | Four IP infusions of 10, 20, 50, and 150 µg on days 0, 3, 7, and 10, respectively. | IP infusion | EMA (2025), Syed (2025) |
| Linvoseltamab-gcpt | Lynozyfic | BCMA | Regeneron | July 2, 2025 | r/r MM | Step-up: three ascending doses of 5 mg on week 1 day 1, 25 mg on week 2 day 1, and 200 mg on week 3 day 1. Then 200 mg weekly in week 4–13, followed by 200 mg every 2 wk. Patients who have received at least 17 doses of 200 mg and shown confirmed very good PRs or better at or after week 24 can switch to once every 4 wk. | IP infusion | FDA (2025), Regeneron Pharmaceuticals (2025a) |

CP, consolidation phase; HLA, human leukocyte antigen; NOS, not otherwise specified; PR, partial response; r/r, relapsed or refractory.

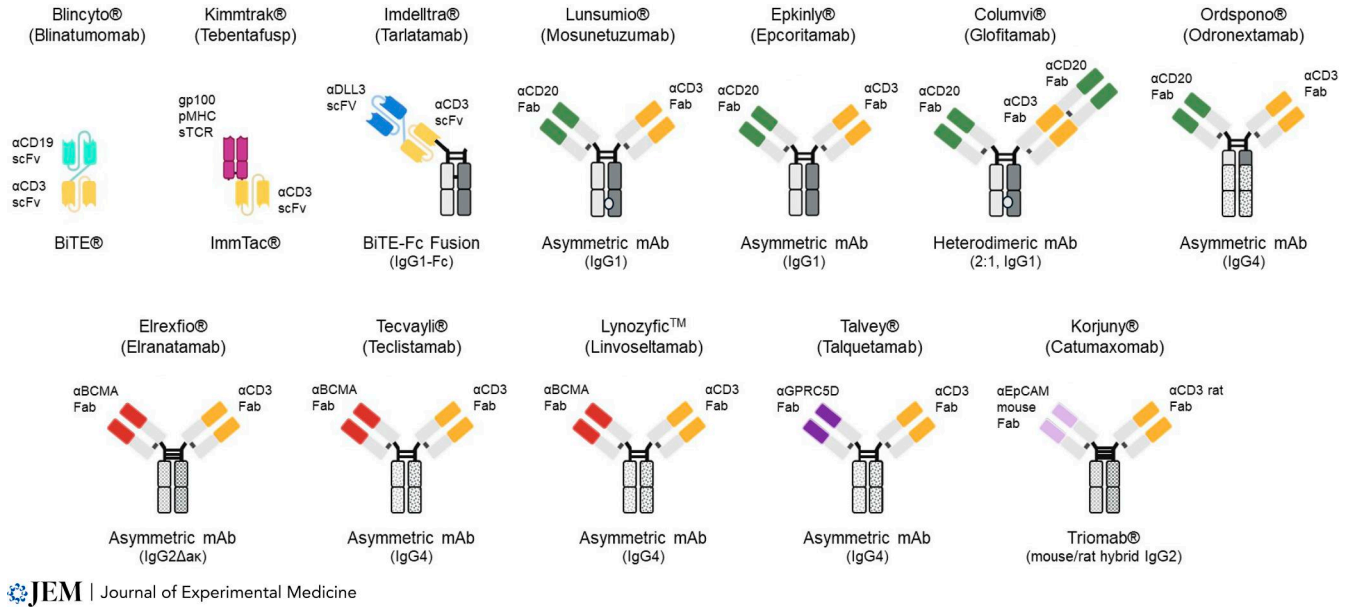




Figure 4. **Designs of approved TCEs.** Brand names, INN, schematic structures, and design principles of approved TCEs. Smaller formats include scFv-based bispecific TCEs (BiTE) where two scFvs are joined in tandem. In Kimmtrak (tebentafusp), the tumor antigen-binding scFv is replaced by a soluble TCR (sTCR) (Liddy et al., 2012; Lowe et al., 2019). In Imdelltra (tarlatamab), a BiTE is fused to a Fc moiety for half-life extension. Larger formats are usually asymmetric 1:1-format mAbs where one Fab arm binds a tumor antigen and the other Fab arm binds CD3. Columvi (glofitamab) is a 2:1-format mAb where one Fab arm binds the tumor antigen (CD20) and the other arm contains two fused Fab fragments. The proximal Fab binds CD3, whereas the distal Fab binds CD20. This format increases the avidity for CD20. BCMA, B cell maturation antigen, also known as tumor necrosis factor receptor superfamily member 17 (TNFRSF17); CD19, cluster of differentiation 19; CD20, cluster of differentiation 20; Fc, fragment crystallizable; gp100, glycoprotein 100, also known as premelanosome protein (PMEL); GPRC5D, G protein–coupled receptor family C group 5 member D; HLA, human leukocyte antigen; scFv, single-chain fragment variable.

checkpoint inhibitor therapies. This is somewhat surprising given the significant single-agent activity and approval back in 2014 of blinatumomab (Blincyto), a CD19xCD3-bispecific TCE for the treatment of relapsed or refractory acute lymphoblastic leukemia (r/r ALL) and respective minimal residual disease (MRD, Table 1; and Figs. 2 and 4) (Herrera et al., 2024; Nagorsen et al., 2012; Sanford, 2015).

In hindsight, much of the sentiment regarding TCEs as a new modality was likely based on shortcomings of blinatumomab, including its very short serum half-life of 2.1 h necessitating burdensome continuous intravenous (IV) administration through a port that also increased infection risk, and a fatal treatment-related serious adverse event (TRSAE) rate of 3% (Tables 2 and 3). Among adverse events, cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) are both now regarded to be modality-related adverse events of both TCEs and CAR-T cell therapies (Tables 2 and 3) (Gurumurthi et al., 2023; Herrera et al., 2024; Shah et al., 2023; Subklewe, 2021; van de Donk and Zweegman, 2023). As discussed below, many TCEs are now being administered subcutaneously (SC). This and various other mitigation strategies can substantially decrease the frequency and grade of adverse events of TCEs, potentially enabling outpatient administration. Overcoming the shortcomings of blinatumomab through novel TCE designs and administration regimen, and expansion into novel target antigens and indications have increased attention toward TCEs in recent years.

The TCE mode of action is surprisingly simple. TCEs function as adaptor proteins with at least two binding arms, one for a surface antigen on target cells and one for the TCR on T cells. Out of six TCR subunits (Fig. 1), CD3ε is usually targeted, given the availability of several suitable antibodies. TCEs can physically connect a cytotoxic T cell with a target cell (Fig. 2) without using pMHC or TCR αβ chains. By solely binding CD3ε, TCEs can induce formation of a functional cytolytic synapse that effectively triggers T cell activation and target cell lysis (Chen et al., 2021; Leithner et al., 2025; Offner et al., 2006). TCR engagement by pMHC or TCE is thought to induce T cell membrane bending, pushing the cytoplasmic tails of CD3 subunits into the cytoplasm and enabling their activating phosphorylation by the protein tyrosine kinase Lck (Al-Aghbar et al., 2022). Concurrently, the antagonistic protein tyrosine phosphatase CD45 with its large extracellular domain is displaced from the synapse, promoting CD3ζ phosphorylation and recruitment of the protein tyrosine kinase ZAP-70 (Razvag et al., 2019). Lck and ZAP-70 then phosphorylate adaptor proteins, including LAT and SLP-76, which recruit additional effectors to ultimately activate downstream kinase cascades and transcription factors and activate all T cell effector functions. For CTLs, this involves degranulation of vesicles containing proteolytic granzymes and pore-forming perforin, granzyme delivery into the cytosol of target cells, and proteolytic activation of procaspases, which then cause target cell death (Baeuerle and Wesche, 2022).

Substantial amplification of the initial TCR signal (Huang et al., 2013) may explain how extremely low TCE concentrations—often

Table 2. **Characteristics of approved TCEs**

| TCE | Format | TAA: CD3 ratio | Fc silencing mutations | MW | $T_{1/2}$ | TAA | TAA mAb | CD3 mAb (target) | Target cell affinity | $CD3^+$ T cell affinity | CD3 affinity/ Target affinity ratio | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Blinatumomab | BiTE (tandem scFv, no effector function) | 1:1 | NA | ~54 kDa | 2.1 h | CD19 | HD37 | TR66 (OKT3 variant) | 1.49 nM | 260 nM | 1:175 | Amgen (2024a), Dreier et al. (2002), Löffler et al. (2000) |
| Mosunetuzumab | Asymmetric mAb (humanized IgG1, KIH, attenuated Fc) | 1:1 | N297G, aglycosylated, no FcγR binding | 146 kDa | 6–11 d | CD20 | 2H7 | UCHT1 (CD3ε) | 68 nM | 40 nM | 1.7:1 | Budde et al. (2022a), Choi et al. (2024), Genentech (2024), Limb et al. (2022), Sun et al. (2015) |
| Epcoritamab | Asymmetric mAb (humanized IgG1, Mab-like DuoBody, controlled $F_{ab}$-arm exchange, silenced Fc) | 1:1 | L234F, L235E, D265A (FEA), no FcγR and C1q binding | 149 kDa | 22 d | CD20 | 7D8 | SP34 variant (CD3ε) | 2.4 nM | 4.7 nM | 1:2 | Choi et al. (2024), Engelberts et al. (2020), Genmab (2024) |
| Glofitamab | Asymmetric mAb (humanized IgG1, KIH heterodimeric CrossMab with head-to-tail fusion $F_{ab}$s, silenced Fc) | 2:1 | L234A, L235A, P329G (LALAPG), no FcγR and C1q binding | 197 kDa | 6–11 d | CD20 | B-ly1 (obinutuzumab) | SP34-like (CD3ε) | 4.8 nM | >20 nM | ~1:4.2 | Bacac et al. (2018), Falchi et al. (2023), Genentech (2023), Hutchings et al. (2021), Mössner et al. (2010) |
| Odronextamab (REGN1979) | Asymmetric mAb (human IgG4, hinge-stabilized heterodimer, controlled arm exchange, attenuated Fc) | 1:1 | Effector function-minimized IgG4 | ~150 kDa | 19–24 w time to LLOQ | CD20 | 3B9-10 | REG1250 (CD3δε) | Not found | Not found | | Blair (2024), Falchi et al. (2023), Regeneron Pharmaceuticals (2025b), Smith et al. (2015) |
| Teclistamab | Asymmetric mAb (humanized IgG4 DuoBody, hinge-stabilized, controlled arm exchange, silenced Fc) | 1:1 | L234A, L235A (IgG4-PAA, minimized FcR binding) | 147 kDa | 15 d | BCMA | OMT rat anti-BCMA Ab | SP34 variant (CD3ε) | 180 pM | 28 nM | 1:156 | Choi et al. (2024), Janssen Biotech (2024), Moreau et al. (2022), Pillarisetti et al. (2020b), Strohl (2024) |
| Elranatamab (PF-06863135) | Asymmetric mAb (humanized IgG2Δaκ, heterodimerizing Fc mutations, silenced Fc) | 1:1 | G2ΔA, D265A (reduce FcγR binding) | 149 kDa | 22 d | BCMA | PF-06863058 | PF-06863059 (CD3ε) | 40 pM | 17 nM | 1:425 | Grosicki et al. (2023), Panowski et al. (2019), Pfizer (2023), Strohl (2024) |

Table 2. **Characteristics of approved TCEs (*Continued*)**

| TCE | Format | TAA: CD3 ratio | Fc silencing mutations | MW | $T_{1/2}$ | TAA | TAA mAb | CD3 mAb (target) | Target cell affinity | $CD3^+$ T cell affinity | CD3 affinity/ Target affinity ratio | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Linvoseltamab-gcpt (REGN5458) | Asymmetric mAb (human IgG4, hinge-stabilized heterodimer, controlled arm exchange, attenuated Fc) | 1:1 | Effector function-minimized IgG4 | 146 kDa | 6.5–7.7 d in monkeys | BCMA | Velocimmune mouse-derived | Velocimmune mouse-derived, likely REG1250 (CD3δε) | Not found | 120 nM | | Crawford et al. (2019), DiLillo et al. (2021), Regeneron Pharmaceuticals (2025a), Smith et al. (2015) |
| Talquetamab (JNJ-64407564) | Asymmetric mAb (humanized IgG4 DuoBody, controlled arm exchange, silenced Fc) | 1:1 | S228P, F234A, L235A (IgG4-PAA, minimized FcR binding) | 147 kDa | 8.4–12.2 d | GPRC5D | Not found | SP34-like (CD3ε) | 9.7–14 nM | 25 nM | 1:1.8–2.6 | Pillarisetti et al. (2020a), Janssen Biotech (2023) |
| Tebentafusp | ImmTAC (BiTE-like, disulfide bond-stabilized, soluble TCR fused to α-CD3 scFv, no effector function) | 1:1 | NA | ∼77 kDa | 7.5 h | gp100/ HLA-A*02:01 | Affinity-matured TCR | UCHT1 (CD3ε) | 24 pM | 38 nM | 1:1,583 | Choi et al. (2024), Immunocore (2024), Liddy et al. (2012) |
| Tarlatamab (AMG 757) | HLE-BiTE (BiTE fused to attenuated IgG1-Fc with engineered CH2 disulfide bond) | 1:1 | N297G | ∼105 kDa | 11.2 d | DLL3 | XenoMouse-derived scFv | SP34-like (CD3ε) | 640 pM | 14.9 nM | 1:23 | Amgen (2024b), Giffin et al. (2021), Jacobsen et al. (2017) |
| Catumaxomab (LP-000, Removab) | Triomab trifunctional mAB (rat/mouse hybrid IgG2, quadroma technology, $Fc_\gamma R$ binding enabled) | 1:1 | None | 150 kDa | 2.5 d (plasma) | EpCAM | Mouse IgG2a Ho-3 | Rat IgG2b 26/II/6 | Not found. 560 pM (SPR) | Not found | Not found | Chelius et al. (2010), EMA (2025), Ruf et al. (2007), Syed (2025) |

Additional discussions are in references Choi et al. (2024), Falchi et al. (2023), and Strohl (2024). d, day(s); BCMA, B cell maturation antigen, also known as tumor necrosis factor receptor superfamily member 17 (TNFRSF17); CD19, cluster of differentiation 19; CD20, cluster of differentiation 20; h, hour(s); gp100, glycoprotein 100, also known as premelanosome protein (PMEL); GPRC5D, G protein–coupled receptor family C group 5 member D; hIgG1, humanized IgG1; HLA, human leukocyte antigen; HLE, half-life extension; KIH, knobs-into-holes (Spiess et al., 2013); LLOQ, lower limit of quantification; MW, molecular weight; NA, not applicable; SPR, surface plasmon resonance; $T_{1/2}$, serum half-life; TAA, tumor-associated antigen; w, week(s).

Table 3. **Clinical performance of approved TCEs**

| TCE | Target | Indication | Efficacy | | | | Safety | | | | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Responses | mDOR | mPFS | mOS | CRS or ICANS | | TRSAE | Specific AE | |
| | | | | | | | All grades | ≥ grade 3 | | | |
| Blinatumomab | CD19 | r/r B-ALL, phase 3 | CR 34% vs. 16% SOC | | 7.3 vs. 4.6 m SOC | 7.7 vs. 4 m SOC | 14.2% CRS | 4.9% CRS, 9.4% neurologic events | 3% fatal, 4% CRS | CRS, neurologic events, infusion reactions, sepsis, infections, cytopenias | Kantarjian et al. (2017), Pulte et al. (2018) |
| | | r/r B-ALL, real-world data | $Ph^-$, 46% CR, $Ph^+$, 41% CR | | $Ph^-$, 11 m, $Ph^+$, 6.7 m | $Ph^-$, 12.2 m, $Ph^+$, 16.3 m | | | | | Boissel et al. (2023) |
| Mosunetuzumab | CD20 | r/r FL | 80% ORR, 60% CR | 22.8 m | 17.9 m | 89.6% (18 m) | 43% CRS, 5% mild ICANS | 2% CRS | 47% | CRS, neurologic events, infections, cytopenias | Budde et al. (2022b) |
| Epcoritamab | CD20 | r/r LBCL, 2-year follow-up | 63.1% ORR, 40.1% CR | 17.3 m | 4.4 m | 18.5 m | 51% CRS, 6.4% ICANS | 3.2% CRS, 0.6% ICANS | 11.5%. 0.6% fatal ICANS, 0.6% COVID-19 pneumonia, 0.6% bacterial pneumonia | CRS, neurologic events, neutropenia, infections | Thieblemont et al. (2023, 2024) |
| | | r/r FL | r/r FL, optimization cohort: 91% ORR, 68% CR | | | | r/r FL, optimization cohort: 49% CRS, 0% ICANS | r/r FL, optimization cohort: 0% CRS, 0% ICANS | | | Linton et al. (2024), Vose et al. (2024) |
| Glofitamab | CD20 | r/r B-NHL | 53.8% ORR, 36.8% CR (at RP2D: 65.7 and 57.1%) | 5.5 m | 2.9 m | | 50.3% CRS, 5.2% ICANS, 43.3% neurologic AE | 3.5% CRS, 1.2% ICANS | 45%, none fatal | CRS, neurologic, infections, neutropenia | (Hutchings et al., 2021) |
| | | r/r MCL | 85% ORR, 78.3% CR | 16.2 m | 16.8 m | 29.9 m | 70% CRS, 11.7% neurologic AE | 11.6% CRS, no neurologic AE | 60%, none grade 5 (fatal) | | (Phillips et al., 2025) |
| Odronextamab | CD20 | r/r FL | 80% ORR, 73% CR | 22.6 m | 20.7 m | NR | 56% CRS, 0.8% ICANS | 0.8% CRS, no ICANS | 44.5%, 3% fatal | CRS, cytopenias, infections, pyrexia | Blair (2024), Kim et al. (2024) |
| | | r/r DLBCL | 52% ORR, 31% CR | 10.2 m | | | 55% CRS, no ICANS | 1% CRS, no ICANS | 4% fatal COVID-19 infections | CRS, cytopenias, infections, pyrexia | Ayyappan et al. (2023), Blair (2024) |
| Teclistamab | BCMA | r/r MM, 2-year follow-up | Original ORR 63%, 58.8% VGPR or better; 2-year follow-up: 43% CR | 24 m | 12.5 m | 21.9 m | 72% CRS, 14.5% neurologic events, 3% ICANS | 0.6% CRS, 0.6% neurologic events, 0% ICANS | 3.6% deaths | CRS, neurologic events, infections, cytopenias, hypogammaglobulinemia | Donk et al. (2023), Moreau et al. (2022) |

Table 3. **Clinical performance of approved TCEs (*Continued*)**

| TCE | Target | Indication | Efficacy | | | | Safety | | | | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Responses | mDOR | mPFS | mOS | CRS or ICANS | | TRSAE | Specific AE | |
| | | | | | | | All grades | ≥ grade 3 | | | |
| Elranatamab | BCMA | r/r MM | Original, 56% VGPR or better, 35% CR; Prolonged follow-up: 61% ORR, 37.4% CR | NR | 17.2 m | 24.6 m | 57.7% CRS, 4.9% ICANS | 0% CRS, 0% ICANS | 3.25% deaths (2.4% lethal infections) | CRS, cytopenias, neutropenia, infections | Lesokhin et al. (2023), Tomasson et al. (2024) |
| Linvoseltamab-gcpt | BCMA | r/r MM | 70% ORR, 45% CR or better, 19% VGPR | NR. Bumma: 29.4 m | Bumma: NR | Bumma: 31.4 m | 46% CRS, 8% ICANS | 0.9% CRS, 2.6% ICANS | 74% SAE, 7% fatal: 3.4% sepsis, 0.9% chronic kidney disease, 0.9% pneumonia, 0.9% TLS, 0.9% encephalopathy | CRS, neurologic events, infusion reactions, infections, cytopenias | Bumma et al. (2024), Regeneron Pharmaceuticals (2025a) |
| Talquetamab | GPRC5D | r/r MM | 73–74% ORR, 57–59% VGPR or better; Phase 1: 64–70% ORR, 52–57% VGPR or better, 23% CR | | 7.5–11.9 m | | 75–79% CRS, 11% ICANS | Phase 1: 0–3% CRS | No deaths | CRS, neurologic, infections, skin-related, nail-related, dysgeusia, cytopenias, hypogammaglobulinemia | Chari et al. (2022), Schinke et al. (2023) |
| Tebentafusp | gp100/ HLA-A*02:01 | Uveal melanoma, phase 3, 3-year follow-up | ORR 11% vs. 5% IC; CR <1% vs. 0% | 11.1 vs. 9.7 m | 3.4 vs. 2.9 m | 21.6 vs. 16.9 m | 89% CRS | 1% CRS | | CRS, skin events | Hassel et al. (2023), Nathan et al. (2021) |
| Tarlatamab | DLL3 | Pretreated ES-SCLC | 10 mg: 40% ORR, 1% CR. 100 mg: 32% ORR, 8% CR | | 10 mg: 4.9 m. 100 mg: 3.9 m | 10 mg: 14.3 m. 100 mg: NE | 10 mg: 51% CRS, 8% ICANS. 100 mg: 61% CRS, 28% ICANS | 10 mg: 1% CRS, 0% ICANS. 100 mg: 6% CRS, 5% ICANS | 10 mg: 1% fatal respiratory failure | CRS, neurologic events, cytopenias | Ahn et al. (2023), Herrera et al. (2024) |
| Catumaxomab | EpCAM | Malignant ascites in adults with EpCAM⁺ carcinomas | | | mPuFS, OC: 48 vs. 11 d (control)*. mPuFS, non-OC: 30 vs. 14 d (control)* | 72 vs. 71 d (control)* | 23% CRS | 11/41 CRS episodes | 15%. Integrated analysis of 11 studies: SIRS, hepatic failure | CRS, SIRS, abdominal pain, cytopenias, elevated liver enzymes, infections | EMA (2025), Syed (2025) |

Data are from published pivotal trials, including recent updates and select real-world data. Additional discussions are in references Falchi et al. (2023), Herrera et al. (2024), and Strohl (2024). Specific AE are AE considered specific for the respective TCE. * indicates that the trial compared catumaxomab + paracentesis treatment with paracentesis-only controls. However, the control group included crossover patients and thus may overestimate efficacy in that group. AE, adverse effects; BCMA, B cell maturation antigen, also known as tumor necrosis factor receptor superfamily member 17 (TNFRSF17); d, day(s); gp100, glycoprotein

in the single-digit picomolar range—can potently trigger redirected target cell lysis. However, in contrast to the scarcity of cognate pMHC targets of the TCR, TCEs typically find abundant numbers of surface target antigens, often ranging from 1,000 to 100,000 molecules per target cell. This may allow the formation of much larger synapses containing unusually high numbers of TCRs. As a result, redirected lysis by TCEs may be more efficient, faster, and less prone to negative regulation than is possible with natural synapses. Moreover, multiple T cells may engage in elimination of a single target cell.

The functionality of the synapse formed by a TCE likely depends on the specific target antigen, the bound epitope, and the design and biophysical properties of the TCE. Key determinants for synapse formation are thought to be the strength of cell adhesion, the distance between the engaged cell surfaces, and the conformational flexibility of the TCE connection (Chen et al., 2021; Leithner et al., 2025; Offner et al., 2006). Interestingly, the approval of TCEs with very different formats, biochemical/biophysical features, and target antigens (Tables 1 and 2) suggests that there is substantial tolerance regarding the synapse configurations for achieving safety and efficacy. Indeed, identifying the optimal format for a TCE remains largely empirical.

Another key feature of a TCE is the capacity to induce serial lysis (Hoffmann et al., 2005). This may require cycles of CTL engagement and disengagement supported by not overly adhesive synapses. TCE-activated T cells also express Fas ligand and thereby can kill target-negative bystander cells expressing Fas receptor. Fas ligand and Fas are both upregulated by cytokines from activated T cells, most notably TNFα and IFNγ (Ross et al., 2017). Bystander killing may be critical for complete tumor eradication and prevention of relapses from target-negative or target-low cancer cells.

Of note, all TCEs must be conditional in that they exclusively activate T cells in the presence of target cells. This is usually achieved by limiting the number of functional CD3ε-binding domains within a TCE to just one and by tuning its affinity to avoid TCR clustering in the absence of target antigen-mediated cross-linking. In addition, the fragment-crystallizable (Fc) portions of immunoglobulin-like TCEs are usually silenced to avoid TCE binding to $Fc_\gamma$ receptors on other immune cells, which otherwise can cause T cell lysis by those other immune cells, lysis of $Fc_\gamma$ receptor-expressing immune cells by T cells, and undesired T cell activation in the process (Table 2 and Fig. 4) (Lee et al., 2023; Robertson et al., 2024). One exception is catumaxomab (Korjuny), a trifunctional TCE whose Fc domain binds and co-engages myeloid cells. Their effector mechanisms are thought to synergize with T cell–mediated tumor cell killing (TDCC) for enhanced efficacy, although catumaxomab clinical efficacy appears limited with no significant survival impact (Chelius et al., 2010; EMA, 2025; Syed, 2025). In animal models, TCEs typically elicit a high rate of cures, tumor eradication, and a memory effect (Bacac et al., 2018; Engelberts et al., 2020; Giffin et al., 2021; Liddy et al., 2012; Mössner et al., 2010; Panowski et al., 2019; Pillarisetti et al., 2020a; Pillarisetti et al., 2020b; Smith et al., 2015; Sun et al., 2015).

Because TCEs can engage any phenotype of cytotoxic T cell for redirected target cell lysis (Haas et al., 2009), TCEs can

100, also known as premelanosome protein (PMEL); GPRC5D, G protein–coupled receptor family C group 5 member D; HLA, human leukocyte antigen; IC, investigator's choice therapy; m, months; MCL, mantle cell lymphoma; mDOR, median duration of response; mPuFS, median puncture-free survival; mPFS, median progression-free survival; NE, not evaluated; NR, not reached; OC, ovarian cancer; ORR, objective response rate; OS, overall survival (duration in parentheses); Ph, Philadelphia chromosome; r/r, relapsed or refractory; RP2D, recommended phase 2 dose; SIRS, systemic inflammatory response syndrome; SOC, standard of care; TLS, tumor lysis syndrome; VGPR, very good partial response.

leverage an essentially unlimited source of effector T cells in the body. This may limit exhaustion, a potential issue for the low numbers of genetically engineered CAR-T or TCR-T cells. T cell exhaustion by TCEs is, however, possible where there is a limited number of local T cells in a target compartment and an insufficient influx of peripheral, nonexhausted T cells (Devasia et al., 2024; Friedrich et al., 2023; Hutter-Karakoc et al., 2025; Letouzé et al., 2024; Subklewe, 2021).

Their independence from the TCR specificity of the engaged T cell and from target cell MHC expression makes TCEs resistant to pMHC downregulation, a frequent mechanism of immune escape, although some T cell clones may undergo MHC-dependent expansion (Friedrich et al., 2023). Additionally, other immune escape mechanisms, including overexpression of PD-L1, serpin 9, indoleamine 2,3-dioxygenase, and target cell secretion of TGFβ, adenosine, or IL-10, had little if any impact on the performance of TCE-engaged T cells even when co-expressed (Deisting et al., 2015).

TCEs share many of the advantages of mAb therapies regarding ease of manufacturing and administration and predictability of pharmacokinetic/pharmacodynamic (PK/PD) properties. TCE manufacturing employs standard processes for biologics, and TCEs can be stored and administered like typical mAbs without requirements for individualized and complicated processes as required for engineered T cell therapies. The off-the-shelf availability of TCEs allows for flexibility of dosing, including readministration as needed. In contrast to engineered T cells, TCE redosing enables engagement of fresh, unexhausted T cells.

Modality-based PD effects of TCEs are quite predictable and occur most prominently upon treatment start. They entail the transient release of cytokines and chemokines, and a transient activation and sequestration of peripheral lymphocytes leading to cytopenias. Often, subsequent doses of TCEs no longer show these initial PD effects, called tachyyphylaxis (Falchi et al., 2023; Herrera et al., 2024).

A particular challenge for TCE development is their very high potency. Often, single-to-low double-digit picomolar concentrations can elicit *in vitro* TDCC, T cell activation, and cytokine release (Bacac et al., 2018; Engelberts et al., 2020; Giffin et al., 2021; Liddy et al., 2012; Mössner et al., 2010; Panowski et al., 2019; Sun et al., 2015). This can be explained by the fact that full T cell activation may only require low double-digit copy numbers of surface-bound TCEs (Ma et al., 2008). An illustration is the ability of the CD3xBCMA TCE teclistamab to deplete circulating naive B cells despite their lack of appreciable BCMA surface levels as assessed by flow cytometry (Hagen et al., 2024). In many cases, TDCC has proven to be much more sensitive than flow cytometry and other detection methods. The most drug-sensitive pharmacologic readout is typically used to determine the "minimum anticipated biological effect level" (MABEL). This often leads to extremely low starting doses for TCEs in clinical trials and, consequently, lengthy dose escalation until clinically effective levels are reached. A further technical challenge associated with low starting doses is the difficulty in measuring low TCE concentrations in patients' peripheral blood for PK analysis, necessitating the development of ultra-sensitive assays. Aiming to mitigate these issues, quantitative system pharmacology has recently been employed to arrive at higher starting doses that were accepted by regulatory authorities (Elmeliegy et al., 2024).

## Recent surge in TCE approvals

After an eight-year hiatus following the 2014 approval of blinatumomab, the last four years have seen the addition of nine more FDA approvals of TCEs, plus two additional EMA approvals (Table 1 and Fig. 3). This suggests that new TCE developments did not start in earnest in the industry until blinatumomab was approved. TCEs now outperform CAR-T cell therapies in terms of the number of approvals in both hematologic and solid tumor indications, and of the number of target antigens pursued. Several reasons may explain the recent surge in TCE approvals.

### Feasibility

A major attraction of TCEs versus cell therapies is their ease of manufacturing, off-the-shelf availability, mAb-like IV or SC administration, flexibility of dose and schedule, control of PK, and the possibility for repeat-dosing and prolonged treatment and exposure (Falchi et al., 2023; Gurumurthi et al., 2023; Herrera et al., 2024; Subklewe, 2021).

### Efficacy in hematologic and solid tumors

TCEs showed compelling single-agent clinical activities against various malignant diseases, often supporting an accelerated approval path (Table 3). A recent study suggests that TCEs, including talquetamab or teclistamab, can furthermore be highly effective in treating patients with relapsed MM after CAR-T cell therapy, supporting their potential use as an effective salvage therapy (Merz et al., 2024). Unlike cellular therapies, TCEs do not require prior lymphodepletion by chemotherapy. Approved TCEs can also effectively treat certain solid tumors like UM, extensive-stage small cell lung cancer (ES-SCLC), or malignant ascites, although response rates tend to be lower than in hematologic cancers. Of note, TCEs can exhibit significant single-agent response rates in cancers resistant to checkpoint inhibitors, including UM and hormone-refractory metastatic, castration-resistant prostate cancer (mCRPC), both considered cold tumors with minimal T cell infiltration (Nathan et al., 2021; Hassel et al., 2023; Kelly et al., 2024, Janux Therapeutics, 2024).

### Improved management of side effects

There has been substantial progress in managing and mitigating the common side effects of TCEs, most notably CRS. A toolbox of strategies is now available, including prior tumor debulking with mAbs to lower target cell burden (e.g., glofitamab preceded by obinutuzumab), step-up dosing, SC delivery, and the use of preventive steroids, antipyretics, antihistamines, and anti-IL-6 mAbs at treatment start (Falchi et al., 2023; Herrera et al., 2024).

### High need for therapies profoundly depleting malignant and autoreactive B cells

A scarcity of "clean" target antigens is a limitation for most targeted T cell therapies, including TCEs. One exception are B lineage antigens, including CD19, CD20, BCMA, or GPRC5D,

where long-term depletion of normal B cells is manageable and acceptable when treating leukemias, lymphomas, or myelomas with TCEs or CAR-T cell therapies. This has led to the approval of eight TCEs targeting B cells in the past 4 years (Fig. 3). More recently, numerous clinical trials currently explore TCEs, mostly directed against CD19 or BCMA, for the treatment of various AIDs. In such diseases, only few patients will be eligible for the complex and expensive CAR-T cell therapies.

### Flexibility of design

Another reason for the upsurge in TCEs lies in their flexibility of design. As detailed below, multiple TCE formats have been developed in parallel that demonstrated safety and clinical efficacy (Fig. 4). They ultimately all met the criteria for regulatory approval and could all be manufactured to support treatment of large patient populations (Table 1). This situation is not unlike that for antibody drug conjugates (ADCs) where different target antigens, antibodies, payloads, linkers, modes of payload attachment, and drug-to-antibody ratios led to many approvable products (Maecker et al., 2023).

## Approved TCE designs

The range of designs for all 12 approved TCEs is highlighted in Fig. 4 and summarized in Table 2. The molecular formats can be divided into immunoglobulin G (IgG)–like and non–IgG-like TCEs (Choi et al., 2024; Falchi et al., 2023; Strohl, 2024). To achieve bispecific binding, the IgG-like TCEs are typically made asymmetric by either using knobs-in-holes, IgG4-based DuoBody, or IgG2Δaκ- or mouse/rat hybrid IgG2-based technologies that serve to heterodimerize the Fcγ domain (Spiess et al., 2013). For CD3ε and target antigen binding, regular "fragment antigen-binding" (Fab) arms are employed. An exception is glofitamab with its so-called 2+1 format whereby two Fab arms bind CD20, and one binds CD3ε. Here, two Fab arms are arranged in tandem but bind different antigens. Most IgG-like TCEs are based on the human (h) IgG1, IgG2, or IgG4 subtype and bear mutations that eliminate binding to immune cells expressing Fcγ receptors. Silenced Fcγ domains still retain binding to the so-called neonatal FcR on endothelial cells, which provides them with a long, IgG-like serum half-life. Reported serum half-lives between 6 and 22 days for IgG-like TCEs support infrequent dosing (Table 2).

Non–IgG-like TCEs blinatumomab and tebentafusp use either tandemly arranged single-chain Fv fragments (scFvs, blinatumomab) or a soluble TCRα/β fragment fused to a CD3-binding scFv (tebentafusp; Fig. 4 and Table 2). Tebentafusp's format is also referred to as "immune mobilizing monoclonal TCRs against cancer" (ImmTAC) (Oates and Jakobsen, 2013). Blinatumomab has a very short serum half-life of 1–2 h and therefore requires continuous IV infusion to achieve high clinical activity. Tebentafusp, with a half-life of 7.5 h, is given once weekly by IV infusion. The molecular weights of approved TCE formats range from 54 kDa (blinatumomab) to 197 kDa (glofitamab; Table 2). Their shelf life for storage ranges between 1 and 3 years.

The 12 approved TCEs address a total of seven different target antigens, four for hematological malignancies and three for solid tumors (Tables 1 and 2). Four TCEs (mosunetuzumab, glofitamab, epcoritamab, and odronextamab) target the B cell antigen CD20 for the treatment of non-Hodgkin's lymphoma (NHL), and one (blinatumomab) targets CD19 for treatment of ALL. Three target BCMA (teclistamab, elranatamab, and linvoseltamab) and one GPCR5D (talquetamab) for treatment of MM. For treatment of solid tumors (UM), tebentafusp targets a glycoprotein 100 (gp100) peptide/HLA-A*02:01 MHC protein complex. Tarlatamab targets delta-like ligand 3 (DLL3) for treatment of ES-SCLC. Catumaxomab targets epithelial cell adhesion molecule (EpCAM) for treatment of malignant ascites. All approved TCEs target CD3ε on T cells. Odronextamab and likely linvoseltamab are claimed to target CD3ε in a heterodimer with CD3δ.

Cross-reactivity to nonhuman primates (NHP) is an important TCE feature, because it enables preclinical studies that can inform and derisk clinical development. The anti-CD3ε mAb SP34 and derivatives, and other antibodies that bind the flexible N-terminal sequence of CD3ε, are typically cross-reactive with NHP CD3ε. Two other anti-CD3ε antibodies derived from OKT3 (blinatumomab) and UCHT1 (tebentafusp) bind overlapping conformational epitopes in the center of CD3ε and are not cross-reactive with NHP CD3ε (Lee et al., 2025). Likewise, 26/II/6, the CD3-binder used in catumaxomab (Bokemeyer, 2010), is not cross-reactive. Overall, it is apparent that TCEs allow for flexibility regarding their binding moieties for both target and CD3. A host of novel TCEs are currently in clinical development, which may further expand the target space for TCEs (Wei et al., 2022).

## Biochemical characteristics of approved TCEs

One might expect that the binding affinities for target antigen and CD3ε and the ratio of such affinities matter greatly for TCE biological and clinical activity. Indeed, reducing the affinity for CD3ε ("detuning") can reduce cytokine release while preserving cytotoxicity (Zuch de Zafra et al., 2019). However, these preclinical results do not necessarily translate into the clinic. Indeed, the necessity of a specific affinity ratio is not supported by the characteristics of approved TCEs (Table 2). $K_D$ values for monovalent binding to target antigens can vary over a thousand-fold, from 24 pM (tebentafusp) up to 68 nM (mosunetuzumab). $K_D$ values for monovalent binding to CD3ε can range from 4.7 nM (epcoritamab) to 260 nM (blinatumomab). The ratios of affinities for CD3 binding versus target binding can vary anywhere between 1.7:1 (mosunetuzumab) and 1:1,583 (tebentafusp). Hence, it seems difficult to predict which affinities and affinity ratios will ultimately support the activity, developability, and approval of a TCE.

The clinical doses of approved TCEs also vary greatly (Table 1). The lowest maintenance dose of 28 µg per day is given for blinatumomab, and the highest weekly maintenance dose of 200 mg per week or biweekly for linvoseltamab. Odronextamab can be dosed up to 320 mg biweekly. Most other TCEs use weekly doses between 30 and 76 mg. Somewhat unique is catumaxomab, which is infused intraperitoneally (IP) in four ascending doses of 10–150 µg within one cycle of 10 days. The steady-state serum concentration of blinatumomab is the lowest at 0.6 ng/ml, whereas elranatamab reaches the highest maximal serum

concentration ($C_{max}$) of all FDA-approved TCEs at 33.6 mg/ml (Clements et al., 2020; Pfizer, 2023). This may reflect different $EC_{50}$ values for TDCC, a commonly used preclinical potency assay, and suggests that while format and affinities may matter for dose, they may not matter as much for clinical efficacy, which is relatively comparable among TCEs in their respective target indications (Table 3). In other words, low *in vitro* TDCC activity does not necessarily predict low clinical activity, and vice versa. As long as a TCE can be safely dosed up to levels supporting complete target cell lysis, its absolute $EC_{50}$ value for TDCC may not have much impact. Additional studies suggest that TCE design and valency for tumor antigens may have an impact on discriminating between cells with high versus low antigen expression (Moore et al., 2019). The differences in dosing and activity might also reflect the quality of the cytolytic synapse formed by a TCE between T cell and target cell, as discussed above (Chen et al., 2021; Leithner et al., 2025; Offner et al., 2006). In some cases, sufficient activity may not require many TCE molecules, while in other cases, high TCE concentrations may be required to ultimately overcome suboptimal synapse formation. The approval of TCEs with very different formats, biochemical and biophysical features (Tables 1 and 2), suggests that there is considerable flexibility to achieve clinical safety and efficacy.

## Clinical experience

Approved TCEs are administered to patients either by continuous IV infusion for 4 wk (blinatumomab), by weekly short-term IV infusion (tebentafusp, mosunetuzumab, glofitamab, tarlatamab, odronextamab, and linvoseltamab), or by weekly bolus SC administration (teclistamab, elranatamab, epcoritamab, and talquetamab) (Table 1). An exception is the IP route used for catumaxomab. Where compared, the SC route exhibited lower grade CRS upon treatment start than the IV route (Falchi et al., 2023; Herrera et al., 2024). This may be related to lower $C_{max}$ values reached at treatment start and a slower rise to $C_{max}$ by the SC versus IV route. Despite its safety advantage, SC administration does have the potential to cause injection site reactions and to augment the frequency of anti-drug antibodies, which can potentially limit efficacy by neutralizing TCE activity. For B cell–depleting TCEs, the latter risk is reduced via elimination of normal B cells.

For all TCEs, low step-up or "priming" doses are being employed that are escalated to maintenance doses typically after 1 wk (Table 1). Like SC administration, this is a measure to curb $C_{max}$ values at treatment start. Step-up dosing has been shown to reduce cytokine secretion, likely by priming the immune system to prevent an initial inflammatory response. In combination with preemptive administration of steroids and antihistamines, approved TCEs rarely show CRS of grade 3 and higher (Table 3) (Herrera et al., 2024; Le et al., 2025; Strohl, 2024). Nevertheless, all approved TCEs have black box warnings for CRS, and some have an additional warning regarding ICANS, but both are mostly manageable (Herrera et al., 2024; Le et al., 2025). An exception may be glofitamab, which is associated with 11.6% grade 3 or higher CRS in r/r MCL patients and showed high rates of other TRSAE. However, safety was considered manageable, and the events might reflect the IV administration route, confounding COVID-19 infections, and some instances of overdosing (Phillips et al., 2025).

Specific adverse events associated with TCEs include CRS, neurologic events and ICANS, infusion reactions, and cytopenias (Table 3). The underlying mechanisms involve T cell activation and redistribution, cytokine release, immune cell depletion, and occasionally tumor lysis syndrome (Choi et al., 2024; Falchi et al., 2023; Herrera et al., 2024; Strohl, 2024). Treatment with a B cell– or plasma cell–depleting TCE is often associated with infections, in some cases severe, likely due to disease-associated or TCE-promoted immune suppression, and exacerbated by COVID-19 infection. Prior treatments, which can be immunosuppressive, may also contribute to an increased infection risk in hematologic cancer patients. Of note, the 34% rates of grade 3 or higher infections reported for blinatumomab IV–treated patients in one study might be related to an increased infection risk from the use of ports for prolonged continuous IV infusion of the drug. Importantly, these rates were notably lower than the 52% reported in the chemotherapy-treated group (Tables 1 and 3) (Kantarjian et al., 2017). Infections are less common for TCEs targeting solid tumors, where both underlying disease and other therapies are less likely to promote immune suppression and associated infections. Obviously, toxicities can be related to the specific TCE target. Tebentafusp-associated skin events and talquetamab-associated skin and nail toxicities presumably reflect expression of respective target antigen on normal skin cells (Hassel et al., 2023; Le et al., 2025).

A comprehensive analysis of the FDA Adverse Event Reporting System database recently confirmed the prominence of CRS and infections as adverse events associated with approved TCE in real-world datasets. It also supported the relatively low risk of neurologic events and ICANS (Le et al., 2025). Interestingly, the study also found statistical associations of certain TCEs with previously undescribed safety signals. However, causality, mechanisms, and clinical relevance remain to be established, and some of the observations may be secondary to CRS, other toxicities, or the reemergence of drug-resistant cancers. All in all, vigilant clinical monitoring of TCE-treated patients is warranted.

TCEs are being used as a monotherapy for a wide variety of diseases. Among the more frequent hematologic cancers, only acute myelogenous leukemia, chronic lymphocytic leukemia, and T cell lymphoma lack approved TCE therapies. This may have to do with the lack of appropriate target antigens, unique disease biology, a more exhausted T cell phenotype, and the risk of fratricide with targets for T cell malignancies. TCEs have demonstrated significant ORR and complete response (CR) rates for the treatment of ALL, various NHL subtypes, and MM (Table 3). For instance, CD20-targeting TCEs had CR rates of 60%–73% in follicular lymphoma (FL), and of 31%–57% in diffuse large B cell lymphoma (DLBCL) (Ayyappan et al., 2023; Blair, 2024; Budde et al., 2022b; Hutchings et al., 2021; Kim et al., 2024; Linton et al., 2024; Phillips et al., 2025; Thieblemont et al., 2024; Thieblemont et al., 2023; Vose et al., 2024). BCMA- and GPRC5D-targeting TCEs had CR rates of 23%–45%

and very good partial response rates of 19%–59% (Chari et al., 2022; Donk et al., 2023; Lesokhin et al., 2023; Moreau et al., 2022; Schinke et al., 2023; Tomasson et al., 2024). A combination of teclistamab and talquetamab increased response rates to 80% with 52% CRs and durability, but also increased the risk of grade 3/4 infections, although r/r MM patients have an inherently elevated risk of infections due to immunodeficiency and pretreatments (Cohen et al., 2025; Moreau et al., 2022).

The only TCE approved for ALL is blinatumomab. Depending on study and patient population, CR rates of 34–46% in r/r B cell precursor acute lymphoblastic leukemia (B-ALL) and 78–91% in patients with MRD were achieved (Boissel et al., 2023; Gökbuget et al., 2020; Kantarjian et al., 2017; Pulte et al., 2018). TCEs also increased median progression-free (mPFS) and median overall survival (mOS) relative to controls, exemplified by an mOS of 7.7 mo for blinatumomab vs. 4 mo for standard-of-care (SOC) chemotherapy in a registrational Philadelphia chromosome-negative ($Ph^-$) r/r B-ALL phase 3 trial. OS in $Ph^-$ patients increased to 12.2 mo in real-world data (Table 3) (Boissel et al., 2023; Kantarjian et al., 2017; Pulte et al., 2018). Recently, a survival benefit was shown for blinatumomab even in MRD-negative patients, highlighting that depletion of residual malignant B cell clones via TCE is more sensitive than methods employed to quantify MRD (Litzow et al., 2024). In other examples, CD20-targeting TCEs yielded mPFS and mOS durations of 17.9–20.7 mo and up to 18.5 mo, respectively, in r/r FL (Blair, 2024; Budde et al., 2022b; Kim et al., 2024). In DLBCL/large B cell lymphoma (LBCL), they achieved a mPFS of 2.9–4.4 mo, and epcoritamab achieved a mOS of 18.5 mo (Hutchings et al., 2021; Thieblemont et al., 2024; Thieblemont et al., 2023). In r/r MM, BCMA- or GPRC5D-targeting TCEs achieved mPFS and mOS rates of 7.5–17.2 and 21.9–31.4 mo, respectively (Bumma et al., 2024; Chari et al., 2022; Donk et al., 2023; Lesokhin et al., 2023; Moreau et al., 2022; Schinke et al., 2023; Tomasson et al., 2024).

TCE response rates in solid tumor indications, namely, UM and SCLC, were lower than for blood cancers (Table 3). Tebentafusp's ORR was only 9% in phase 3, but it was approved due to a robust OS benefit, even in patients without decreases in tumor size (Nathan et al., 2021). At a 3-year follow-up, the ORR increased to 11% vs. 5% for investigator's choice treatment, and mOS reached 21.6 vs. 16.9 mo (Hassel et al., 2023). At 10 mg, tarlatamab showed a 40% ORR and 14.3-mo mOS as a single agent in pretreated ES-SCLC, a very difficult-to-treat cancer (Ahn et al., 2023). Interestingly, the ORR dropped, and toxicities increased at a higher dose of 100 mg. Catumaxomab combined with paracentesis extended median puncture-free survival to 48 days in ovarian cancer and 30 days in other indications versus the respective 11 or 14 days achieved by paracentesis alone. mOS was not changed in the overall group (EMA, 2025; Syed, 2025).

## Potential limitations of TCEs

Like other antibody-based therapeutics, TCEs encounter limitations regarding efficacy and safety. Suboptimal pharmacokinetics and other limitations may have contributed to disappointing clinical outcomes with several TCEs (Dewaele and Fernandes, 2025; Falchi et al., 2023; Herrera et al., 2024).

Reduced efficacy may derive from target antigen loss on therapy, or from heterogeneous antigen expression on target cells. For instance, target antigen loss from the cell surface can occur through shedding, genetic or epigenetic alterations, or the outgrowth of antigen-negative tumor cells under treatment pressure (Letouzé et al., 2024). Examples include CD19 loss in TCE- or CAR-T cell–treated patients (Subklewe, 2021), CD20 loss in NHL patients who relapsed after glofitamab treatment (Grigg et al., 2024), and BCMA shedding in MM patients where soluble antigen can reduce TCE efficacy (Letouzé et al., 2024). This limitation is likely shared with all therapies targeting BCMA and presumably other shed antigens. Co-administration of gamma secretase inhibitors, which can inhibit BCMA shedding, increased response rates to teclistamab in MM patients, but was also associated with high-grade immune events (Letouzé et al., 2024). MHC downregulation is a tumor escape mechanism relevant for TCEs targeting pMHC (Herrera et al., 2024; Letouzé et al., 2024).

Approaches to counter target loss include binding multiple antigens in an OR logic–gated fashion with multispecific TCEs, or employing conditional TCEs which—through their wider therapeutic window—allow much higher drug concentrations in tumor tissue to enable targeting cells with very low antigen copy numbers. It is also possible to combine or sequentially administer TCEs against different target antigens. Sequential administration of the same TCE is a possible mitigation for an "antigen sink" effect, where antigen abundance may limit tumor exposure and thus efficacy.

TCE efficacy can also be limited by preexisting or treatment-induced T cell exhaustion, activation-induced T cell death (AICD), or an immunosuppressive tumor microenvironment (TME) (Friedrich et al., 2023; Hutter-Karakoc et al., 2025; Letouzé et al., 2024; Subklewe, 2021). However, TCE-induced exhaustion or AICD are likely limited since TCEs only engage a small fraction of total T cells and incapacitated T cells are, in theory, replaced through homeostatic local expansion or influx of peripheral, nonexhausted T cells. Retreatment and drug-free intervals may also mitigate T cell exhaustion by TCEs (Subklewe, 2021). Likewise, co-administration of checkpoint-blocking mAbs, costimulatory agonists, or T cell invigorating small molecules may overcome exhaustion (Falchi et al., 2023; Letouzé et al., 2024; Subklewe, 2021). Costimulatory moieties could also be engineered into next-generation TCEs. Importantly, the TCE efficacy seen in MM patients who had relapsed after CAR-T cell therapy suggests that TCE can overcome some resistance mechanisms specific for CAR-T cell therapies (Merz et al., 2024).

Another potential limitation of TCEs is that the T effector cell compartment may be compromised from preceding chemotherapy or other SOC treatments. In one study, chemotherapy induced T cell exhaustion and exclusion from tumors (Launonen et al., 2024). However, in preclinical models of MM, combination of a TCE with cyclophosphamide improved T cell persistence and function (Letouzé et al., 2024). Preliminary findings with CD20-specific TCEs in lymphoma and with blinatumomab in first-line ALL suggest that combination with SOC augments rather than reduces TCE efficacy in patients (Falchi et al., 2023; Jabbour et al., 2024; Litzow et al., 2024).

Currently, TCEs only leverage a rather small number of suitable target antigens. This may limit their utility to treat more cancers. Most approved TCEs target antigens which are exclusively expressed on B cell malignancies and normal B/plasma cells whose transient depletion can be tolerated (Table 1). In contrast, most solid tumor antigens show some expression in normal tissues. Since TCEs kill target cells very potently, many targets for mAbs and ADCs, including HER-2, EGFR, or nectin-4, are not suitable for TCEs because their low-level expression on critical organs can cause on-target toxicities. The discovery of novel antigens, targeting of pMHCs, AND logic–gated multi-targeting, and conditional TCE approaches, may considerably increase the target space for TCEs.

CRS, ICANS, and cytopenia are regarded as class toxicities for both TCEs and engineered T cell–based therapies (Anyfanti et al., 2025; Falchi et al., 2023; Herrera et al., 2024; Subklewe, 2021). While these may not substantially restrict the use of TCEs in oncology, they could be showstoppers for treating large numbers of AID patients in an outpatient setting. However, the lower target cell and antigen load in AID versus cancer patients have been associated with reduced adverse events (Anyfanti et al., 2025). Moreover, several strategies may improve safety and broaden treatable autoimmune patient populations, e.g., step-up dosing, SC administration, TCE design, and premedications or on-treatment therapies such as antipyretics and anti-IL-6 therapy already used in oncology.

Finally, TCEs targeting B/plasma cell antigens in patients with MM or AIDs reduce humoral immunity and thereby increase the risk of opportunistic infections, with likely contributions of transient cytopenia (Anyfanti et al., 2025; Herrera et al., 2024). This necessitates appropriate patient screening, monitoring, prophylactic treatment with antibiotics, and, eventually, revaccination.

## Future directions

With hundreds of clinical trials ongoing with novel TCEs, we anticipate seeing a wave of additional TCE approvals over the coming years for both hematologic cancers and solid tumor indications. A particularly interesting advance is the development of double-conditional TCEs (Baeuerle and Wesche, 2022; Bergamaschi et al., 2025). While all TCEs are conditional in that they only activate T cells in the presence of target cells, selective activation in the TME would provide another layer of control with the potential to widen the therapeutic index. A variety of approaches have been developed that exploit intratumoral conditions for activation of otherwise inactive TCE precursors (Ai et al., 2025; Nolan-Stevaux and Smith, 2024). Most popular is the use of protein or peptide masks that are flexibly joined to TCEs by protease-sensitive linkers. Masks cover the adjacent CD3-binding domain, and in some cases also the target-binding domain of the TCE. Masks are designed to only be released in the uniquely protease-rich TME, sparing normal tissues expressing the target antigen. When activated TCEs exit the tumor, they are diluted into a large plasma volume, and some by design lose their half-life extending domain upon cleavage, further reducing systemic exposure. An interesting example is mCRPC, a tumor with very low T cell infiltration. Here, TCEs targeting the "dirty" antigen PSMA have been challenging to successfully develop until JANX007 incorporated a masked CD3-binding domain. Initial clinical data suggest robust JANX007 single-agent activity in a small phase 1 cohort of 16 patients, where the ORR in 8 RECIST-evaluable patients was 50%. JANX007 was well tolerated with mostly transient, predictable treatment-related adverse events (Janux Therapeutics, 2024a, Janux Therapeutics, 2024b). Given the small patient cohort of this trial, it will be important to determine JANX007 safety and efficacy in larger trials.

Other conditional TCE approaches use antibodies that only bind target or CD3 at an acidic pH between 6 and 7, or in the presence of high ATP concentrations, conditions largely restricted to the TME. Yet, other approaches employ split designs that conditionally assemble a functional CD3 binder only in the TME. An additional approach to optimize tumor selectivity are AND-gated TCEs, whereby two target-binding domains recognize different target antigens that must be co-expressed on a target cell for TDCC to occur (Ai et al., 2025; Nolan-Stevaux and Smith, 2024). Individual target antigens may be expressed on healthy organs and tissues, but their combination is restricted to cancer cells (Janux Therapeutics, 2024a, Janux Therapeutics, 2024b).

Another opportunity for expanding the TCE target space is targeting pMHCs. These display peptide antigens from essentially all subcellular locations, most of which are not accessible to antibodies. Moreover, tumor-specific, frequent mutant peptides from oncogenes become targets. Tebentafusp is the first approved TCE using soluble TCRα/β chains for binding a MHC presenting a peptide derived from cytoplasmic, melanoma-associated gp100 (Figs. 1 and 4) (FDA, 2025; Immunocore, 2024). Several other TCR-TCEs are in clinical trials (Isaacs, 2025). TCR-mimetic antibodies that recognize pMHC similar to TCR fragments may provide a next wave of TCEs (He et al., 2019). Other types of potential new TCE targets include neuronal proteins that cancer cells express outside the CNS, like DLL3 (targeted by tarlatamab), tumor-associated splice variants, intracellular proteins missorted to the cell surface, "dark matter" antigens derived from retroviral antigens, lineage markers, and tissue-specific targets that are no longer present because the organ (such as breast, prostate, ovaries, testes, or stomach) has been surgically removed in the course of tumor therapy.

An interesting development is the exploration of T cell costimulatory receptors like 4-1BB, CD28, and CD2 for enhancing TCE activity. Cotargeting of CD3 and costimulatory receptors on T cells providing signal 2 may help prevent exhaustion and augment tumor infiltration and memory of T cells engaged by TCEs (Bergamaschi et al., 2025; Wu et al., 2020). The first clinical trials are exploring the benefit of either trispecifics, where a fused costimulatory agonist moiety is built into the TCE, or of TCEs co-administered with bispecific costimulatory antibodies. Given the significant single-agent activity of canonical TCEs and the ability of TCEs to engage essentially all cytotoxic T cells in the body, it remains to be seen whether costimulation can greatly enhance TCE efficacy in patients. Additional T cell stimulation by costimulatory agonists may lead to more frequent and higher grade CRS and must be monitored closely in clinical trials.

Significant promise lies in the combination of TCEs with SOC in oncology (Gurumurthi et al., 2023; Hänel et al., 2024). A prime example is the approval of blinatumomab in the first-line therapy of r/r B-ALL in combination with SOC. The combination led to long-term benefit, if not cure, in 85% of patients (Jabbour et al., 2024; Litzow et al., 2024). Blinatumomab incorporation can moreover enable better tolerated, reduced-dose chemotherapy in vulnerable patients, e.g., the elderly (Jabbour et al., 2024; Pourhassan et al., 2023). In newly diagnosed Ph⁺ B-ALL, blinatumomab can replace chemotherapy in combination with tyrosine kinase inhibitors (Pourhassan et al., 2023). Initial tumor debulking followed by blinatumomab may improve safety and efficacy of either combination. Altogether, it appears that the harsh polychemotherapy or tyrosine kinase inhibition leaves sufficient numbers of functional T cells that can be engaged by a TCE. A spate of smaller clinical trials with CD20-specific TCEs in NHL and FL patients have shown that TCEs can be productively combined with essentially all SOCs in these diseases, leading to increased response rates, sometimes up to 100% in FL (Falchi et al., 2023).

TCEs and chemotherapy may synergize through various mechanisms. In particular, chemotherapy used before TCEs can debulk tumors, reducing antigen load. This may prevent excessive T cell activation by the TCE and associated toxicities, while also limiting T cell exhaustion and AICD to improve efficacy (Letouzé et al., 2024). Tumor debulking may also create a MRD-like situation where only low numbers of target cells remain for effective clearance by TCE-engaged T cells. Moreover, chemotherapy can induce immunogenic tumor cell death, antigen presentation, and MHC class I upregulation, which can promote naive T cell priming, epitope spreading, and memory (Friedrich et al., 2023). The seemingly paradoxical ability of chemotherapy to both kill T cells and synergize with them may be reconciled by the orthogonal mechanisms of cell lysis and reduced chemotherapy dosing, which spares T cells (Jabbour et al., 2024; Pourhassan et al., 2023).

A key question is whether to administer chemotherapy and TCEs simultaneously or sequentially. Current data from B cell lymphoma trials suggest that concurrent administration of epcoritamab, mosunetuzumab, or glofitamab with chemotherapy is possible with high response rates and acceptable safety (Falchi et al., 2023). Efficacy may be improved and CRS reduced over single agents, but cytopenias and infection rates may worsen. Safety benefits are not universal, as glofitamab combination with R-CHOP yielded high rates of grade 3 or higher adverse events in one study (Shastri et al., 2025). Co-administration with the ADC polatuzumab vedotin did not affect mosunetuzumab's PK/PD, indicating that co-administration of chemotherapy does not necessarily impair TCE function (Budde et al., 2024). Theoretically, administering chemotherapy before TCEs may preserve efficacy benefits from impacting tumor cells while allowing T cell recovery from possible impairment. This requires identifying the optimal interval between the two treatments. Indeed, although bendamustine can cause prolonged T cell depletion and impaired CAR-T cell outcomes (Shastri et al., 2025), one report found no clear adverse impact of bendamustine on subsequent TCE responses and safety in B cell lymphomas. However, CD4 T cells were reduced and intervals between treatments were mostly over 12 mo (Iacoboni, 2024). Further confirming feasibility, bendamustine combination with epcoritamab and rituximab achieved a high ORR of 96% in FL (Shastri et al., 2025). More studies are needed to determine optimal sequencing regimen for TCEs and SOC.

The question of optimal sequencing also applies to treating patients with CAR-T cells and TCEs, e.g., in a salvage setting or with TCEs entering earlier lines of treatment. Conceivably, antigen loss, T cell exhaustion, or immunosuppressive TMEs induced by prior CAR-T or TCE treatment may reduce the efficacy of the subsequent treatment, particularly when targeting the same antigen. This notwithstanding, sequenced treatment did not impair responses to either modality in LBCL, and subsequent TCE treatment even reinvigorated residual CAR-T cells (Nizamuddin and Ghobadi, 2025). In MM, however, patients with prior BCMA-TCE exposure responded poorly to BCMA CAR-T cells, whereas non-BCMA TCEs had efficacy after BCMA-targeting therapy, indicating the benefit of switching antigens (Devasia et al., 2024). Conversely, TCEs had efficacy in MM patients who had relapsed after CAR-T cell therapy (Merz et al., 2024). A longer interval after CD19 CAR-T exposure correlated with a better response to mosunetuzumab in r/r B cell lymphomas (Chong et al., 2025). Thus, depending on the indication, negative interactions between treatments can occur.

Finally, an exciting new horizon is to expand and explore the therapeutic potential of TCEs for deep B cell depletion in AIDs. An initial study with blinatumomab in rheumatoid arthritis (RA) patients showed a strong albeit transient disease modification (Bucci et al., 2024). Although only a low loading dose of 9 micrograms per day of blinatumomab was used for a brief 2-wk treatment, the ensuing B cell depletion put all patients into treatment-free remission. Blinatumomab also showed efficacy in a patient with systemic sclerosis (Subklewe et al., 2024). Another TCE that showed profound clinical activity by depletion of plasma cells and later stage B cells in patients with systemic sclerosis, primary Sjögren's syndrome, RA, and idiopathic inflammatory myositis is the BCMAxCD3-bispecific antibody teclistamab (Hagen et al., 2024). Beyond strong efficacy even in heavily pretreated patients, the few examples to date indicate the need for robust clinical studies in AID patients to define the optimal doses and schedules that will result in deep B cell depletion and prolonged remission. Indeed, multiple clinical trials are ongoing with approved and novel TCEs in AIDs (Anyfanti et al., 2025; Robinson et al., 2024). One example is CLN-978, a next-generation CD19xCD3-bispecific TCE in clinical trials in systemic lupus erythematosus (NCT06613360), RA (NCT06994143), and Sjögren's Syndrome (NCT07041099) (Meetze et al., 2023; Shouse et al., 2023). Much like TCEs have expanded the treatment paradigm in several cancer indications, the promise for TCEs to become potent therapies for a broad set of AID indications with high unmet medical need is an exciting future direction.

## Conclusions

The 12 TCEs approved to date teach us that a surprising variety of molecular designs and biochemical characteristics appear

suitable for clinical safety and efficacy. High response rates as a monotherapy in hematologic malignancies and emerging efficacy in solid tumor indications make TCEs an attractive therapeutic modality. Novel approaches such as logic-gated binding of multiple antigens, conditional activation in the TME, or combination with SOC therapies promise to expand target and indication space and to further improve efficacy. A broad flexibility in design and scalability, combined with their off-the-shelf availability and ability to redose, also positions TCEs as an attractive therapeutic approach in oncology and, eventually, in AIDs.

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