Advances in cellular therapies for children and young adults with solid tumors

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Purpose of review
Adoptive immunotherapy brings hope to children and young adults diagnosed with high-risk solid tumors. Cellular (cell) therapies such as chimeric antigen receptor (CAR) T cell, CAR natural killer (NK) cell, and T cell receptor (TCR) T cell therapy are potential avenues of targeted therapy with limited long-term toxicities. However, development of cell therapies for solid tumors is in its nascent stages. Here, we will review the current clinical experience, barriers to efficacy, and strategies to improve clinical response and patient access.

Recent findings
Cell therapies are shown to be generally safe and well tolerated. Strategies to optimize antitumor activity have now moved into early-phase trials. The immunosuppressive tumor microenvironment remains a major barrier to efficacy, and efforts are underway to gain better understanding. This will inform future treatment strategies to enhance the antitumor activity of cell therapies.

Summary
Clinical experiences to date provide important insights on how to leverage cell therapies against solid tumors. Key factors in advancing the field include a better understanding of immune cell biology, tumor cell behavior, and the tumor microenvironment. Lastly, improving access to novel cell therapies remains an important consideration in the conduct of clinical trials and for future implementation into standard practice.

Keywords
chimeric antigen receptor, clinical trial access, solid tumors, T cell receptor, tumor microenvironment

INTRODUCTION

Relapsed or refractory (R/R) solid tumors remain difficult to treat with minimal improvement in outcomes in recent decades. The advent of CD19-specific chimeric antigen receptor (CAR) T cell therapy has significantly improved outcomes for patients with R/R B-cell acute lymphoblastic leukemia, bringing hope for other difficult-to-treat malignancies [1,2]. Unsurprisingly, there have been efforts to develop adoptive cellular (cell) therapies for high-risk solid tumors, which present a unique set of challenges.

CAR T cells are engineered by isolating and transducing a patient's own T cells to express tumor-associated antigen (TAA)-binding receptors derived from monoclonal antibodies. This allows for major histocompatibility complex (MHC)-independent T cell recognition, activation, and cytotoxicity [3]. First-generation CAR T cells are composed primarily of the extracellular CAR linked to the intracellular cytotoxicity domain. However, experience from CD19-CAR T cells demonstrate the importance of including a costimulatory domain such as CD28 or 4-1BB to improve CAR T cell survival and persistence, resulting in the second-generation CAR [3–5]. Cell therapy utilizing CAR technology extends to other immune cells such as natural killer (NK) cells and macrophages [6]. NK cells are a part of the innate immune system and do not require additional activation to induce cytotoxicity [7]. Similarly to T cells, NK cells can be engineered to express a CAR, thereby directing its antitumor activity. Use of NK cells is an attractive alternative due to their lack of alloreactivity, which

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KEY POINTS

- Early-phase clinical trials have demonstrated that second-generation chimeric antigen receptor (CAR) T cell and natural killer (NK) cell therapies are generally safe for pediatric patients with relapsed/refractory solid tumors. However, efficacy has been limited.
- Current clinical trials explore various strategies to improve CAR T cell expansion and persistence.
- Future studies should include strategies to overcome or leverage the tumor microenvironment to improve the effectiveness of adoptive cell therapies.
- Access to cellular therapies remain inequitable due to cost of manufacture and logistics of clinical trials- there is a call to close these gaps in care which involve not only providers and scientists, but systems-based policy change.

allows manufacturing from universal healthy donors. However, NK cells lack persistence, with a lifespan of about two weeks, and this may contribute to limited tumor response [6,8]. Alternatively, CAR macrophages have a hypothetical advantage of improved tumor trafficking and infiltration, with less potential to be impacted by the immunosuppressive tumor microenvironment (TME). However, efficient transduction of the CAR construct into macrophages remains a challenge and thus, this approach remains in early stages of clinical development [6,9].

Additional adoptive cellular therapy approaches include T cell receptor-engineered (TCR) T cells as well as tumor infiltrating lymphocytes (TILs). TCR T cells utilize a modified version of the natural T cell receptor to recognize target antigens within the context of typical MHC-dependent presentation. A major advantage of TCR T cells is the wider range of targetable epitopes which can be derived from both membrane as well as intracellular proteins [10]. Furthermore, TCR T cells have a lower activation threshold compared to CAR T cells which require exposure to a higher target density to become activated. However, TCR T cells require epitope presentation by certain human leukocyte antigen (HLA) alleles, which in turn limits the number of patients eligible for therapy [10,11]. Alternatively, TILs are lymphocytes isolated from resected tumor tissue which are expanded *ex vivo*. The advantage of TILs includes oligoclonal T cell activation by a variety of tumor-associated antigens. Unfortunately, high rates of adverse effects in addition to cost and logistics of TIL manufacturing remain an obstacle.

This review will outline results from early-phase clinical trials studying the use of adoptive cell therapies in children and young adults with solid tumors, current challenges in development of effective therapies, as well as considerations for pursuing investigational cellular therapies for patients with R/R solid tumors.

CLINICAL EXPERIENCE

Clinical experience in pediatric solid tumors has mainly focused on investigation of CAR T cell therapy. Targetable tumor-associated antigens (TAA) for CAR therapy historically have been identified based on the homogeneity and level of surface antigen expression. Ideal TAAs also have little or no expression on normal tissue to reduce the risk of on-target, off-tumor toxicity. TAAs currently being targeted include disialoganglioside (GD2), human epidermal growth factor receptor 2 (HER2), glypican-3 (GPC3), and B7-H3 (CD276) which are expressed on multiple solid tumors [12▪,13–16,17▪,18▪]. There have been several phase 1/2 clinical trials evaluating CAR T or NK cell therapy targeting these antigens (Table 1).

Results to date demonstrate overall safety and tolerability of adoptive cell therapies in children and young adults [12▪,13–16,17▪,18▪]. Notable adverse effects reported from these studies include cytokine release syndrome (CRS) and hepatotoxicity after CAR T cell administration. Severe CRS (defined as grades 3 and 4) has been associated with higher dose levels of CAR T cells, while reported hepatotoxicity was associated with CAR T cell engraftment [17▪,18▪]. In addition to safety, these early experiences have highlighted several strategies to improve treatment efficacy. Lymphodepletion, or the delivery of myelosuppressive chemotherapy prior to cell infusion, aim to modulate the immunologic milieu and allow for *in vivo* CAR T cell expansion [12▪,13,16,17▪]. Addition of lymphodepletion has been associated with better clinical response due to improved CAR T cell persistence, with one group reporting persistence of up to 30 months [17▪]. Another consideration is the amount of disease at time of CAR T cell infusion, with some groups demonstrating improved response and survival in patients treated with lower disease burden [14,17▪,19]. Lastly, available data demonstrate that multiple T cell infusions are safe with manageable adverse effects [14,17▪,18▪]. However, further studies are needed to investigate the optimal number of doses, need for lymphodepletion prior to subsequent doses, and time interval between doses.

Clinical experience to date has been more limited for CAR NK cell therapy, with only one trial reported to date for treatment of R/R neuroblastoma [15]. This trial demonstrated GD2-CAR NK safety as well as evidence of CAR NK cell tumor trafficking and subsequent clinical response across all dose

Table 1. Pediatric cellular therapy clinical trial results to date

NCT (reference)	CAR construct	Diseases treated	Patients treated (no.)	LD	MTD	DLT	Best clinical response
CAR T cell therapy							
NCT02761915 [12▪]	GD2.CD28.z	R/R neuroblastoma	12	Flu 125 mg/m^2 CPM 1200 mg/m^2	1 × 10^9 CAR + T cells/m^2	None reported	Mixed response ($n=2$) Near CR ($n=1$)
NCT01822652 [13]	GD2.CD28.OX40.z + Pembrolizumab	R/R neuroblastoma	11	Flu 60 mg/m^2 CPM 1500 mg/m^2	1.5 × 10^8 CAR + T cells/m^2	None reported	SD ($n=3$)
NCT03373097 [14]	GD2.CD28.41BB.z	R/R neuroblastoma	27	Flu 75 mg/m^2 CPM 1500 mg/m^2	1 × 10^7 CAR+ T cells/kg	Grade 4 ICH ($n=1$)	CR ($n=9$) PR($n=8$) SD($n=5$)
NCT00902044 [16,17▪]	HER2.CD28.z	R/R HER2-positive non-CNS solid tumors	19, 13	Flu 125 mg/m^2 CPM 60 mg/kg	1 × 10^8 T cells/m^2	Grade 3 CRS ($n=1$), Grade 4 CRS ($n=1$) with 1 x 10^8 CAR+ T cells/m^2	CR ($n=2$) SD ($n=3$)
NCT04483778 [18▪]	B7H3.41BB.z	R/R solid tumors	9	Flu 120 mg/m^2 CPM 1000 mg/m^2	1 × 10^6 CAR+ T cells/kg	None reported	SD ($n=3$)
CAR NK cell therapy							
NCT03294954 [15]	GD2-CAR.15 NK	R/R neuroblastoma	12	Flu 60 mg/m^2 CPM 1500 mg/m^2	Not reached- (DL4: 1 × 10^8 CAR+ NK cells/m^2	None reported	PR ($n=3$; one of which achieved CR after 2nd infusion) SD ($n=4$)

CNS, central nervous system; CPM, cyclophosphamide; CR, complete response; DL, dose level; DLT, dose-limiting toxicities; Flu, fludarabine; ICH, intracranial hemorrhage; LD, lymphodepletion; MTD, maximum tolerated dose; PR, partial response; R/R, relapsed/Refractory; SD, stable disease.

levels. Similar to the CAR T cell experiences, clinical response was most apparent in patients who received the highest dose level, with one patient achieving a CR after a second infusion [15]. These results provide encouraging data to support future efforts in advancing CAR NK cell therapy for solid tumors.

Lastly, published clinical data for TILs and TCR T cells have been limited to adult patients, though with encouraging results [20]. Most notably, melanoma-associated antigen 4 (MAGE-A4) TCR T cells or afamitresgene autoleuecel (afami-cel) has demonstrated significant clinical efficacy in treating unresectable or metastatic synovial sarcoma in a phase 2 trial (NCT03132922), accelerating the first FDA-approval for an engineered TCR T cell therapy [21,22▪▪]. This brings hope for pediatric and young adult patients with synovial sarcoma, with a pediatric focused study now underway (NCT05642455). Another target of interest for TCR T cell therapy against synovial sarcoma as well as other solid tumors is New York esophageal squamous cell carcinoma 1(NY-ESO-1) with promising results from an early-phase clinical trials in adults and a recently completed pediatric study (NCT03967223) [23▪▪,24].

BARRIER TO EFFECTIVE CELLULAR THERAPIES

Although great progress has been made advancing adoptive cell therapies, clinical experiences to date also provide important insight on obstacles that must be addressed to improve efficacy. Some of these barriers are being addressed by strategies adopted into current clinical trials (Table 2). One identified barrier to clinical success is inadequate T cell expansion and persistence. As such, current efforts are focused on improving CAR T cell fitness. Approaches to mitigate this obstacle include addition of a second costimulatory domain (third-generation CAR), co-expression of CD19-specific receptor to CAR constructs aimed at utilizing $CD19^+$ B cells to promote CAR T cell expansion, and incorporation of constitutive cytokine signaling by interleukin (IL)-7 or IL-15 to promote T cell expansion [14,18▪,25]. Another strategy is to decrease T cell exhaustion by combining treatment with immune checkpoint inhibition (ICI) such as pembrolizumab, a PD-1 monoclonal antibody. A preliminary study reports on three patients with R/R neuroblastoma who received GD2-CAR T cells in combination with lymphodepletion and pembrolizumab and subsequently achieved stable disease, the best clinical response amongst the treated cohort [13].

Another obstacle in effective adoptive cell therapies is difficulty identifying TAAs with tumor-restricted expression, as many TAAs are also expressed at low levels on normal tissue. This raises concern for potential on-target, off-tumor effect leading to toxicity [26]. Various strategies exist to ameliorate this challenge, such as working to identify novel tumor-specific antigens, adjusting target affinity to reduce binding at low expression levels, and including an "AND-gate" or requiring co-recognition of two antigens for immune cell activation [27]. These strategies have yet to be evaluated clinically.

The tumor microenvironment (TME) is perhaps the greatest barrier to effective antitumor activity of cell therapies in solid tumors and is thus the focus of much of the current research in the field of solid tumor immunotherapy. Notably, the presence of three distinct inhibitory immune cells- regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs)- use different mechanisms to inhibit the ability of adoptive immune cells to invade the tumor and eliminate malignant cells. Tregs are a subset of $CD4^+$ T cells which counteract potentially harmful, uncontrolled helper T cell activity [28]. Unfortunately, this natural safety mechanism counteracts the desired effect of adoptive T cells. Current strategies to eliminate Tregs include lymphodepleting chemotherapy and co-administration of ICI [17▪,29,30].

Adoptive cell therapies require pro-inflammatory cytokines to proliferate and expand. These cytokines are secreted by activated CAR T cells upon binding to its target and by nearby macrophages and endothelial cells [31]. However, tumor-associated macrophages (TAMs) counteract pro-inflammatory cytokine signaling in the TME, and associations between the presence of macrophages and poor outcome have been reported [32,33]. Preclinical studies are underway to better understand the role of TAMs in the TME and mitigate their immunosuppressive consequences on CAR T cells. One potential strategy being investigated is TRUCKs, or T cells redirected toward universal cytokine-initiated killing. TRUCKs are designed to release IL-18 upon activation, resulting in increased number of pro-inflammatory M1 macrophages and NK cells which in turn promote augmented CAR T cell antitumor activity [25,34–36]. Another approach includes blocking the tumor cells' "don't eat me" signal with anti-CD47 antibodies, which could have a synergistic effect with CAR T cell therapy [37,38]. Finally, approaches to reduce the immunosuppressive effects of TAMs have also been considered, including CAR T cell-mediated depletion of TAMs

Table 2. Current clinical trials evaluating adoptive cellular therapies against solid tumors in pediatric and young adult patients

NCT	Cell therapy	Co-stimulation	"Armor"	Lymphodepletion	Disease
Active, not recruiting					
NCT02311621	CD171-CAR T	4-1BB CD28 + 4-1BB	N/A	Yes	R/R neuroblastoma, ganglioneuroblastoma
NCT04483778	B7-H3 (CD276)-CAR T	4-1BB	Bi-specific to CD19 Add pembrolizumab	Yes	R/R solid tumors
NCT02932956	Glypican-3 (GPC3)-CAR T	Not specified	N/A	Yes	R/R solid tumors ($GPC3^+$)
NCT03635632	GD2-CAR T	Not specified	IL-7 receptor	No	R/R neuroblastoma R/R osteosarcoma R/R solid tumor ($GD2^+$)
NCT03967223	NY-ESO-1	N/A	N/A	Yes	Synovial sarcoma, Myxoid/Round cell liposarcoma
Active, recruiting					
NCT03618381	EGFR-CAR T	4-1BB	Bi-specific to CD19	Yes	R/R solid tumor (EGFR+)
NCT05312411	Fluorescein (FITC-E2)- CAR T	Not specified	UB-TT170 (Folate-Fluorescein) tumor label	Yes	R/R osteosarcoma
NCT04995003	HER2-CAR T	CD28	Pembrolizumab or Nivolumab	Yes	R/R solid tumor ($HER2^+$)
NCT04377932	GPC3-CAR T	Not specified	IL-15	Yes	R/R solid tumors ($GPC3^+$)
NCT04897321	B7-H3-CAR T	Not specified	N/A	Yes	R/R solid tumors ($B7\text{-}H3^+$)
NCT03721068	GD2-CAR T	2^{nd} generation (not specified)	IL-15	Yes	R/R neuroblastoma or R/R osteosarcoma
NCT03294954	GD2-CAR NK	N/A	IL-15	Yes	R/R neuroblastoma
NCT05642455	MAGE-A4 TCR T	N/A	N/A	Yes	Synovial sarcoma, MPNST, Neuroblastoma, Osteosarcoma ($MAGE\text{-}A4^+$)
Not yet recruiting					
NCT04715191	GPC3-CAR T	Not specified	IL-15, IL-21	Yes	R/R solid tumors ($GPC3^+$)

CAR, chimeric antigen receptor; HER2, human epidermal growth factor receptor 2; IL, interleukin; Lymphodepletion, fludarabine/cyclophosphamide; MPNST, malignant peripheral nerve sheath tumor.

prior to administration of tumor-targeted CAR T cells [39].

Lastly, myeloid-derived suppressor cells (MDSC) are another major component of the TME known to play an immune suppressive role [40]. MDSC are derived from the bone marrow but accumulate in peripheral lymphoid organs and tumor tissue. In tumor tissue, MDSC induce immune suppression through multiple mechanisms, such as producing nitric oxide, reactive oxygen species, and anti-inflammatory cytokines in response to its interaction with the TME. Strategies to mitigate MDSC-induced immune suppression include targeting chemokines such as CSF-1, which recruit myeloid cells into the tumor [30,37]. Other measures to counteract MDSC recruitment include the use of tyrosine kinase inhibitors such as sunitinib [41]. Future studies may draw from further investigations describing the tumor microenvironment and its impact on adoptive cell therapies, allowing for multipronged approach to successfully treat solid tumors.

ACCESS TO CELLULAR THERAPY TRIALS

There are many prospective questions left to be answered regarding optimal utility of cellular therapies for solid tumors. When faced with limited treatment options upon developing relapsed or refractory disease, clinicians and patients are motivated to explore novel therapies. However, there are important factors to consider when pursuing an early-phase clinical trial involving engineered cell therapies (Fig. 1). Due to the logistics of cell product manufacturing, patients are often required to travel to the study site for trial enrollment and apheresis. This may occur over multiple days, which incurs

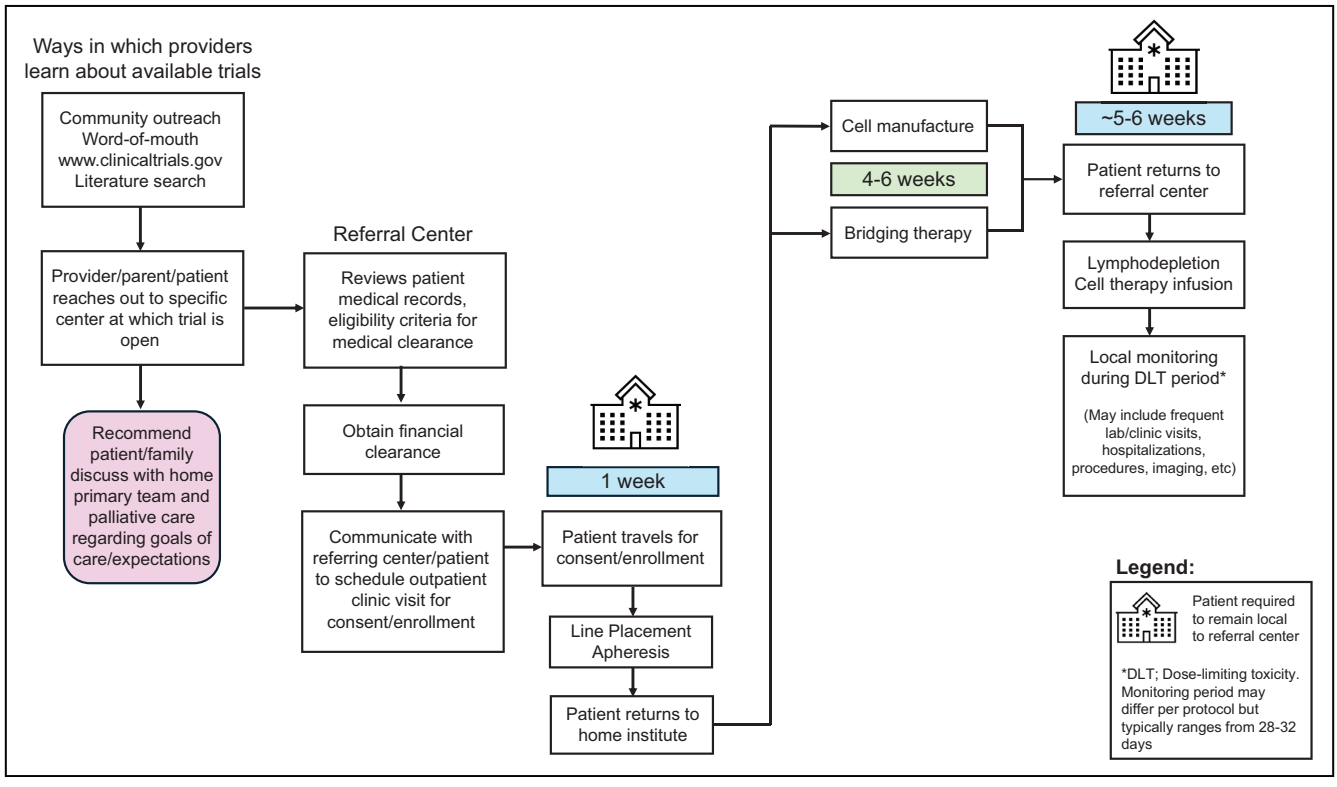

FIGURE 1. Schematic and timeline of clinical trial enrollment and treatment.

additional costs for travel and accommodations. After enrollment procedures, patients can return home to receive bridging therapy while awaiting cell product manufacturing, often 4–6 weeks. Patients subsequently return to the study site for lymphodepletion and cell therapy infusion, after which they are usually required to stay within proximity to the treatment site during the toxicity evaluation period, typically several weeks. During this time, patients and their families may be separated from their support system and medical home. This emotional burden becomes especially challenging with unexpected toxicities, hospitalizations, and acute illnesses, and can be an obstacle to many who may otherwise consider pursuing treatment. It is critical that the patient's medical team, which may include a palliative care team, be aware of this timeline and logistical complexity when counseling patients and discussing potential cell therapy trials. Additionally, discussions around the expectations of a phase I trial (focused on treatment safety rather than efficacy) and how this aligns with the patient's goals of care and end-of-life wishes is recommended prior to referral and enrollment.

With only a limited number of centers offering cell therapy, the logistical and financial barriers impact equitable access to cell therapies. It is estimated that the real-world cost of CAR T cell therapy ranges from $700 000 to $1 million when considering both the cost of product manufacturing as well as cost of travel and lodging while patients receive therapy [42▪▪]. Experts have proposed mainstreaming late-stage development and commercialization of cell therapy products by utilizing strategies including automated manufacturing processes, optimizing current regulatory procedures, and amending current licensing practices which often serve as barrier to timely access to novel therapies [43▪▪]. There are additional identified disparities in access to cell therapy. It has been reported that male patients of higher socioeconomic status, and who live closer to a center offering cell therapy are more likely to receive cell therapy [44]. Additionally, documented racial disparity in clinical trial enrollment impacts the ability to effectively study the safety and clinical utility of these therapies [45]. There is a call for continued efforts and research to mitigate biases prior to study referral and to improve community outreach raising awareness of clinical trials and FDA-approved cellular therapies [42▪▪,46▪▪].

CONCLUSION

Adoptive cell therapies remain an exciting opportunity to provide therapy to patients with relapsed

or refractory disease and limited treatment options. To date, cellular therapies have been safe and well tolerated while demonstrating signals of clinical activity. Various modalities of adoptive cell therapies are being developed and investigated, and there is a specific focus on strategies to overcome the immunomodulatory tumor microenvironment. Clinicians and investigators must also consider the logistical and financial burden of current cellular therapy trials for patients, and efforts must be undertaken to reduce the cost and ensure equitable access to treatment.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Maude SL, Frey N, Shaw PA, *et al.* Chimeric antigen receptor T cells for sustained remissions in leukemia. http://dx.doi.org/10.1056/NEJMoa1407222. [Accessed 10/15/2014].
2. Maude SL, Laetsch TW, Buechner J, *et al.* Tisagenlecleucel in children and young adults with b-cell lymphoblastic leukemia. N Engl J Med 2018; 378:439–448.
3. Rababah F, Alabduh T, Awawdeh A, *et al.* Chimeric antigen receptor T cells therapy in solid tumors. Clin Transl Oncol 2023; 25:2279–2296.
4. Harding FA, McArthur JG, Gross JA, *et al.* CD28-mediated signalling costimulates murine T cells and prevents induction of anergy in T-cell clones. Nature 1992; 356:607–609.
5. Smith R, Shen R. Complexities in comparing the impact of costimulatory domains on approved CD19 CAR functionality. J Transl Med 2023; 21:515.
6. Pan K, Farrukh H, Chittepu V, *et al.* CAR race to cancer immunotherapy: from CAR T, CAR NK to CAR macrophage therapy. J Exp Clin Cancer Res 2022; 41:119.
7. Vojdani A, Koksoy S, Vojdani E, *et al.* Natural killer cells and cytotoxic T cells: complementary partners against microorganisms and cancer. Microorganisms 2024; 12:230.
8. Dash CP, Sonowal D, Dhaka P, *et al.* Antitumor activity of genetically engineered NK-cells in nonhematological solid tumor: a comprehensive review. Front Immunol 2024; 15:1390498.
9. Lu J, Ma Y, Li Q, *et al.* CAR Macrophages: a promising novel immunotherapy for solid tumors and beyond. Biomark Res 2024; 12:86.
10. Baulu E, Gardet C, Chuvin N, Depil S. TCR-engineered T cell therapy in solid tumors: State of the art and perspectives. Sci Adv 2023; 9:eadf3700.
11. Albarran V, San Roman M, Pozas J, *et al.* Adoptive T cell therapy for solid tumors: current landscape and future challenges. Front Immunol 2024; 15:1352805.
12. ■ Straathof K, Flutter B, Wallace R, *et al.* Antitumor activity without on-target off-tumor toxicity of GD2–chimeric antigen receptor T cells in patients with neuroblastoma. Sci Transl Med 2020; 12:eabd6169.

This is a clinical trial demonstrating safety and efficacy of a 3rd-generation GD2-CAR T cell for treatment of relapsed/refractory neuroblastoma. This article highlights the signal of clinical response in a disease with poor prognosis, particularly when CAR T cells are administered at low levels of disease burden.

13. Heczey A, Louis CU, Savoldo B, *et al.* CAR T cells administered in combination with lymphodepletion and PD-1 inhibition to patients with neuroblastoma. Mol Ther 2017; 25:2214–2224.
14. Del Bufalo F, De Angelis B, Caruana I, *et al.* GD2-CART01 for relapsed or refractory high-risk neuroblastoma. N Engl J Med 2023; 388:1284–1295.
15. Heczey A, Xu X, Courtney AN, *et al.* Anti-GD2 CAR-NKT cells in relapsed or refractory neuroblastoma: updated phase 1 trial interim results. Nat Med 2023; 29:1379–1388.
16. Ahmed N, Brawley VS, Hegde M, *et al.* Human epidermal growth factor receptor 2 (HER2)–specific chimeric antigen receptor–modified T cells for the immunotherapy of HER2-positive sarcoma. J Clin Oncol 2015; 33:1688–1696.
17. ■ Hegde M, Navai S, DeRenzo C, *et al.* Autologous HER2-specific CAR T cells after lymphodepletion for advanced sarcoma: a phase 1 trial. Nat Cancer 2024; 5:880–894.

This is the first HER2-CAR T cell trial in pediatric solid tumors. This article highlights the importance of lymphodepletion prior to CAR T cell administration to optimize T cell persistence.

18. ■ Pinto N, Albert CM, Taylor MR, *et al.* STRIvE-02: a first-in-human phase I study of systemically administered B7-H3 chimeric antigen receptor T cells for patients with relapsed/refractory solid tumors. J Clin Oncol 2024; JCO2302229. doi:10.1200/JCO.23.02229.

This clinical trial describes the first-in-human experience using B7-H3 CAR T cells in pediatric patients with relapsed/refractory solid tumors. This article highlights the safety as well as unique toxicities associated with CAR T cell administration.

19. Hegde M, Joseph SK, Pashankar F, *et al.* Tumor response and endogenous immune reactivity after administration of HER2 CAR T cells in a child with metastatic rhabdomyosarcoma. Nat Commun 2020; 11:3549.
20. Klebanoff CA, Chandran SS, Baker BM, *et al.* T cell receptor therapeutics: immunological targeting of the intracellular cancer proteome. Nat Rev Drug Discov 2023; 22:996–1017.
21. Mullard A. FDA approves first TCR-engineered T cell therapy, for rare soft-tissue cancer. Nat Rev Drug Discov 2024; 23:731.
22. ■■ D'Angelo SP, Araujo DM, Abdul Razak AR, *et al.* Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial. Lancet 2024; 403:1460–1471.

This article describes the early-phase clinical trial evaluating Amfi-cel, the first FDA-approved adoptive cellular therapy for solid tumors in adults. This publication highlights the clinical efficacy of MAGE-A4 TCR T cells in the treatment of solid tumors in adults.

23. ■■ Pan Q, Weng D, Liu J, *et al.* Phase 1 clinical trial to assess safety and efficacy of NY-ESO-1-specific TCR T cells in HLA-A ∗02:01 patients with advanced soft tissue sarcoma. Cell Rep Med 2023; 4:101133.

This is the first clinical trial investigating safety and efficacy of NY-ESO-1 TCR T cells. This article demonstrates promising clinical response in patients with advance soft tissue sarcoma.

24. Kawai A, Ishihara M, Nakamura T, *et al.* Safety and efficacy of NY-ESO-1 antigen-specific T-cell receptor gene-transduced T lymphocytes in patients with synovial sarcoma: a phase I/II clinical trial. Clin Cancer Res 2023; 29:5069–5078.
25. Steffin D, Ghatwai N, Montalbano A, *et al.* Interleukin-15-armored GPC3-CAR T cells for patients with solid cancers. Res Sq 2024; doi:10.21203/rs.3.rs-4103623/v1. [Preprint]
26. Morgan RA, Yang JC, Kitano M, *et al.* Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. Mol Ther 2010; 18:843–851.
27. Zhao Z, Sadelain M. CAR T cell design: approaching the elusive AND-gate. Cell Res 2023; 33:739–740.
28. Corthay A. How do regulatory T cells work? Scand J Immunol 2009; 70:326–336.
29. Lickefett B, Chu L, Ortiz-Maldonado V, *et al.* Lymphodepletion – an essential but undervalued part of the chimeric antigen receptor T-cell therapy cycle. Front Immunol 2023; 14:1303935.
30. Terry RL, Meyran D, Fleuren EDG, *et al.* Chimeric antigen receptor T cell therapy and the immunosuppressive tumor microenvironment in pediatric sarcoma. Cancers 2021; 13:4704.
31. Lindo L, Wilkinson LH, Hay KA. Befriending the hostile tumor microenvironment in CAR T-cell therapy. Front Immunol 2020; 11:618387.
32. Yang M, McKay D, Pollard JW, Lewis CE. Diverse functions of macrophages in different tumor microenvironments. Cancer Res 2018; 78:5492–5503.
33. Yan ZX, Li L, Wang W, *et al.* Clinical efficacy and tumor microenvironment influence in a dose-escalation study of anti-CD19 chimeric antigen receptor T cells in refractory B-cell non-Hodgkin's lymphoma. Clin Cancer Res 2019; 25:6995–7003.
34. Lin FY, Stuckert A, Tat C, *et al.* Phase I trial of GD2.CART cells augmented with constitutive interleukin-7 receptor for treatment of high-grade pediatric CNS tumors. J Clin Oncol 2024; 42:2769–2779.
35. Ma L, Zhang K, Xu J, *et al.* Building a novel TRUCK by harnessing the endogenous IFN-gamma promoter for cytokine expression. Mol Ther 2024; 32:2728–2740.
36. Chmielewski M, Abken H. CAR T cells releasing IL-18 convert to T-Bet(high) FoxO1(low) effectors that exhibit augmented activity against advanced solid tumors. Cell Rep 2017; 21:3205–3219.
37. Wessel KM, Kaplan RN. Targeting tumor microenvironment and metastasis in children with solid tumors. Curr Opin Pediatr 2022; 34:53–60.

38. Majeti R, Chao MP, Alizadeh AA, *et al.* CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell 2009; 138:286–299.

39. Rodriguez-Garcia A, Lynn RC, Poussin M, *et al.* CAR-T cell-mediated depletion of immunosuppressive tumor-associated macrophages promotes endogenous antitumor immunity and augments adoptive immunotherapy. Nat Commun 2021; 12:877.

40. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The nature of myeloid-derived suppressor cells in the tumor microenvironment. Trends Immunol 2016; 37:208–220.

41. Guislain A, Gadiot J, Kaiser A, *et al.* Sunitinib pretreatment improves tumor-infiltrating lymphocyte expansion by reduction in intratumoral content of myeloid-derived suppressor cells in human renal cell carcinoma. Cancer Immunol Immunother 2015; 64:1241–1250.

42. Odstrcil MS, Lee CJ, Sobieski C, *et al.* Access to CAR T-cell therapy: focus on ■■ diversity, equity and inclusion. Blood Rev 2024; 63:101136.

This article explores and highlights the current barriers in access to cell therapies and offer future considerations to bridge these gaps.

43. Mackall CL, Bollard CM, Goodman N, *et al.* Enhancing pediatric access to cell ■■ and gene therapies. Nat Med 2024; 30:1836–1846.

This article describes infrastructural barriers and ways to address them by proposing a new and unique entity to improve pediatric access to cell and gene therapies.

44. Ahmed N, Sun F, Teigland C, *et al.* Chimeric antigen receptor T-cell access in patients with relapsed/refractory large B-cell lymphoma: association of access with social determinants of health and travel time to treatment centers. Transplant Cell Ther 2024; 30:714–725.

45. Ahmed N, Shahzad M, Shippey E, *et al.* Socioeconomic and racial disparity in chimeric antigen receptor T cell therapy access. Transplant Cell Ther 2022; 28:358–364.

46. Ruella M. CAR-T therapy for all: addressing the access gap. Transplant Cell ■■ Ther 2024; 30:644–645.

This article highlights specific factors such as race, ethnicity, and socioeconomic status found to be associated with access to cell therapy in the "real-world' experience.