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Conventional cancer immunotherapies: assessing progress and envisioning future possibilities

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Abstract

Cancer immunotherapy aims to modify and improve the immune system's fight against cancer, it is a highly promising and evolving field. It is effective at treating a wide range of cancers, suppressing tumor growth and improving survival rate of cancer patients. Despite the promise and fervor around cancer immunotherapy, many challenges have limited their widespread use and efficacy. In this review article, we consider novel cancer immunotherapies, encouraging clinical trials and innovative strategies employed in developing safe and effective cancer immunotherapies. It is safe to say that cancer immunotherapy has revolutionized cancer therapy, but there are hurdles and challenges (toxicity concerns being the most notable) that must be overcome for safer and more effective treatment strategies. The battle against cancer is an arduous and prolonged affair. We aim to point out what we have achieved in recent times and outline potential strategies to mitigate our losses and chart a course of victory.

Keywords: Cancer, Immunotherapy, Clinical trials, T-cells, Antibody

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Introduction

Cancer, normal cells in mad pursuit of immortality, causing unprecedented mortality and affecting so many families, remains a thorn in the flesh despite numerous and varying onslaughts on it. The focus on cancer treatment research has shifted from surgery, radiotherapy, and chemotherapy to immunotherapy (1). The immune system has the ability to identify and get rid of rogue cells. Cancer can develop when rogue cells pick up mutations that allow them to avoid the immune system (2). These mutations enable the cancer cells to: down-regulate tumor antigen MHC I expression; suppress effector T-cells through increased checkpoint ligands; aid regulation of immune cells through activation of suppressor immune cells and molecules; and nurture a hostile tumor microenvironment (3). The approval of several immunotherapies for the treatment and management of many cancers (majorly haematological malignancies) has generated much interest and promise in the endless possibilities cancer immunotherapies possess (1). But many roadblocks limit their widespread adoption and efficacy in many tumors, and we still have a long way to go. Newer strategies and modifications to cancer immunotherapies aim to mitigate these challenges, inadvertently boosting the immune system's capacity to remove malignancies and improving the safety profile of immunotherapies. Researchers are optimizing existing immunotherapies with molecular technologies, newer sequencing tools, the evaluation of other immune cells or molecules, and the discovery of novel tumor target antigens. The explorative and progressive nature of scientific research ensures endless possibilities in cancer immunotherapy. In this article, we review recently approved cancer immunotherapies and outstanding clinical trials (CTs), their challenges, and potential ways of optimizing cancer immunotherapy.

Antibody Therapy and Immune Checkpoint Inhibitors (ICIs)

Antibodies are an essential part of the body's immune defense system. In certain conditions, antibodies can become ineffective or insufficient, hence the development of specific and effective antibodies *in vitro* (4). This has led to the emergence of antibody diagnostics and therapeutics, which include monoclonal antibodies, pro-antibodies, antibody-drug combinations, and bi- and tri-specific antibodies (4). Many diseases, most notably cancer, have benefited significantly from the use of antibody-based treatments (5). They have demonstrated success in eliminating or suppressing many tumors, but it is not without limitations. In this section, we consider newly approved antibody-based therapies and efforts made to mitigate challenges encountered with this form of cancer therapy.

Monoclonal antibody

Monoclonal antibodies (mAbs) are antibodies that possess the same receptor and are produced from the same B-cell line. mAbs have found use in several immunotherapies, either in their soluble form or bound to a membrane. Several mAbs that target overexpressed growth factors, CD20, immune checkpoints, and CD3 have been authorized for the treatment of cancer by the Food and Drug Administration (FDA). Antibodies are being developed for newly discovered tumor-specific antigens (TSA). Recently, mAbs (dinutuximab and naxitamab) against disialoganglioside GD2 have been approved for treating neuroblastoma (6). This has increased the survival rate of neuroblastoma patients, but relapse has been observed in 50% of patients (6). Monoclonal IgE antibodies that target chondroitin sulfate proteoglycan 4 (CSPG4), which is implicated in melanoma, induce all IgE effector functions against melanoma in human xenograft models (7). All antibodies approved for cancer therapy are IgG; other antibodies are now being trialed, most notably IgE, with encouraging outcomes from CTs.

Bispecific antibodies (BsAbs)

BsAbs possesses the ability to bind to two specific antigens, which improves its specificity. BsAb can function in diverse ways; it helps bind immune cells to tumor cells, bind to certain molecules to reduce their expression and block immune checkpoints (8). Clinical BsAb can target either an antigen and CD3 in T-cells or CD3 and immune checkpoint molecules to enhance T-cell activation (the latter combination has demonstrated significant efficiency at T-cell activation) (9). BsAbs that target tumor antigens and CD3 molecules are mostly used for hematological malignancies. Recently, BsAb, mosunetuzumab-axgb,

and teclistamab-cqyv have received FDA approval for treating refractory follicular lymphoma and refractory multiple myeloma, respectively (10,11). Mosunetuzumab binds to CD20 on follicular lymphoma cells and CD3 on T-cells, which aids in the destruction of the lymphoma cells (10), while Teclistamab binds to B cell maturation antigen (BCMA) on myeloma cells and CD3 on T-cells, leading to an effective T-cell response against myeloma cells (11). Early in 2022, the FDA granted approval for tebentafusp-tebn usage, which binds to CD3 on T-cells and the gp100 peptide-HLA complex instead of the tumor antigen on cancer cells, for metastatic uveal melanoma (12). Cadonilimab, a BsAb that targets PD-1 and CTLA-4, received approval in China for relapsed or metastatic cervical cancer (13). MEDI5752 and ABL501 are some of the BsAb directed against immune checkpoints in clinical trials, while HLX301 targets molecules expressed on exhausted T-cells and natural killer (NK) cells (13).

Other combinations can be explored to fully maximize BsAb. One of which, amivantamab-vmjw, simultaneously blocks multiple growth factor signaling molecules to limit resistance. It has been authorized for use in metastatic non-small cell lung cancer (NSCLC) patients (14). Two bispecific T-cell engagers (BiTEs), epcoritamab-bysp and Glofitamab-gxbm, received approval by the FDA in 2023 for refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma patients. They bind to CD3 on T-cells and CD20 on lymphoma cells or healthy B-cells, leading to the activation of T-cells and subsequent destruction of these cells (15). Pasotuxizumab, a BiTE antibody that binds to both prostate-specific membrane antigen (PSMA) on prostate cancer cells and the T-cell receptor (TCR) CD3, showed promise during CTs in reducing the tumor. It is being modified and clinically tested to overcome the short half-life and neutralize Abs against it (16) (Figure 1).

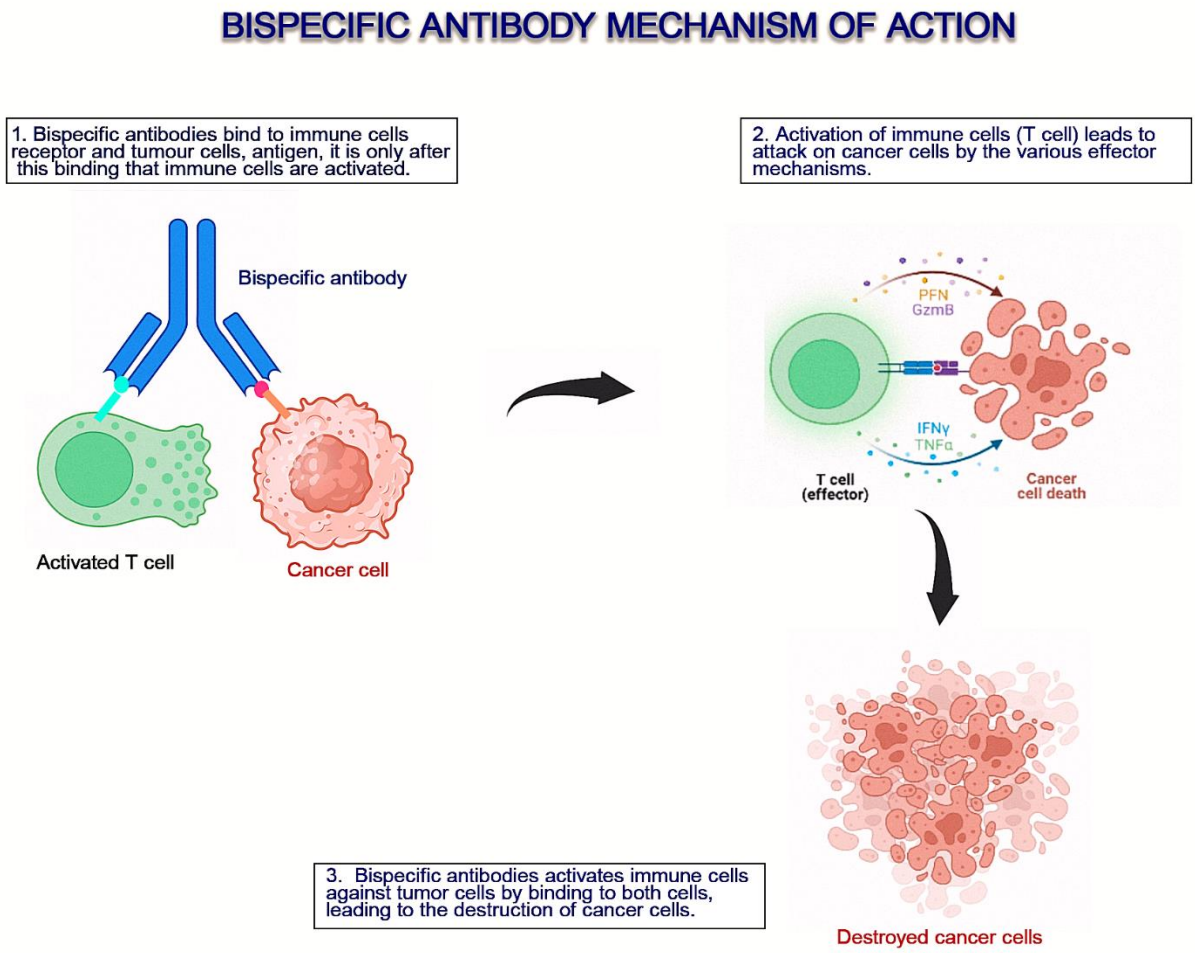

Figure 1. An overview of the mechanism of action of bispecific antibodies (9).

Antibody-drug conjugates (ADC)

ADC are cytotoxic agents conjugated with tumor antigen-specific antibodies, leading to destructive effects on targeted tumor cells (17,18). About 10 ADCs have received FDA approval for mostly hematological cancers, while about 80 ADCs are in development (19). The major challenge with ADCs is the tendency to attack body cells expressing the target antigen. This challenge is being addressed by extensive screening of the target antigen, unmasking of paratopes in tumors by TME enzymes, targeting antigens exclusively located in the TME, and adoption of novel TSA (20). The following ADC modifications are actively being explored to increase its efficiency: target antigen choice, chemistry of the linkers, cytotoxic agents with greater efficiency, enhancements of conjugation techniques, and better ADC internalization (5). In October 2022, the FDA approved Elahere, an ADC that targets folate receptor alpha (FRα) to treat ovarian, fallopian tube, and peritoneal cancers that are resistant to platinum chemotherapy and express FRα (21). Sacituzumab govitecan, containing anti-Trophoblast cell-surface antigen (TROP-2) Ab and the antineoplastic drug SN-38, has been recently authorized for triple-negative breast cancer (TNBC) and metastatic hormone receptor $(HR)^+$, human epidermal growth factor 2 (HER2)-negative breast cancer (22,23). Sacituzumab govitecan is highly effective at targeting cancer cells and releasing its toxic payload (23).

Immune checkpoint inhibitors (ICIs)

Immune checkpoints regulate the immune system to protect against an uncontrolled immune response. Cancer uses this mechanism of regulation to prevent an immune attack on it (5). FDA authorized mAbs are available that block immune checkpoints (most notably programmed cell death 1 ligand 1 (PD-L1) (atezolizumab, avelumab, and durvalumab), programmed cell death protein 1 (PD-1) (pembrolizumab, nivolumab, and cemiplimab), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (ipilimumab, tremelimumab)), thereby allowing immune cells to attack cancerous cells (24,25). These approved antibodies have also been combined for higher efficacy, but only FDA-approved combinations are available for use. Poor lymphocyte tumor infiltration and T-cell activation are some of the challenges faced with this approach; coupling the anti-PD-L1 mAbs with photothermal agents has proven to be effective in overcoming this challenge (26). The FDA authorized the combo drug Opdualag in March 2022, a combination of two ICI antibodies, nivolumab and relatlimab-rmbw, which block PD-L1 and lymphocyte activation gene 3 (LAG3) activity, respectively. It is used for metastatic melanoma (27). CD24 is another immune checkpoint target; it is involved in B and T-cell regulation (28,29), cell migration (30), inhibition of phagocytosis, and crucially contributes to the development of tumors (31). Overexpression of CD24 has been observed in many cancers (31). mAbs targeting CD24 have been approved for use; ALB9, G7, and SWA11 mAbs have all limited various types of cancer growth and metastases (32,33). They have also been used in conjunction with chemotherapy and other immunotherapies. Docosahexaenoic acid (DHA) also reduces the manifestation of PD-L1 in cancer cells by degrading the PD-L1 ubiquitin-proteasome and promoting C5N5-dependent PD-L1 degradation, resulting in reduced PD-L1-mediated immunosuppression in tumor models (34). Recently, another immune checkpoint target, Galectin-9 (an immunosuppressive regulator), has also been targeted in CTs. Inhibition by mAbs is done in conjunction with Ataxia telangiectasia mutated (ATM) inhibition, which leads to remarkably suppressed tumor growth in mouse (35). Triggering receptors expressed on myeloid cells 2 (TREM2) on monocyte-derived macrophages have been shown to cause NK cell dysfunction in lung cancer. mAb TREM2 inhibtion coupled with an NK cell stimulator restores antitumor immunity in mice (36). mAbs against some innate immune checkpoints, co-inhibitory molecules, and co-stimulatory agonists have also been explored, but toxicity issues have hampered progress (37,38).

Antibody-based therapies are stable, specific to the target protein, and can induce antibody-dependent T-cellular cytotoxicity (ADCC) by innate immune cells (39,40). The challenges encountered in antibody-related cancer therapy include tumor antigen mutation, immune-related adverse effects, activation of other growth signaling pathways by tumor cells, hostility of the tumor microenvironment (TME), poor antibody

penetration, few TSA to target, immune checkpoints, and system toxicity due to the ubiquitous nature of the target antigen (5,41). Antibody combination therapies with other cancer therapies, wider screening for TSA, and effective antibody delivery systems can help eliminate some of these challenges (5). The most common way of surmounting the systemic toxicity challenges due to the ubiquitous nature of most target antigens is masking the antibodies to avoid binding to normal cells. Once in the tumor environment, the antibodies are unmasked by tumor protease, thereby activating their therapeutic functions (42). Reduced system toxicities have been confirmed when this strategy is used, as evidenced in anti-CTLA4 DVD-Ig (43). Other drugs under CTs include pacmilimab for anti-PD1-L1, CX-904, EGFRxCD3, and BMS-986249 for anti-CTLA4 (5,44). Novel tumor-specific antigens (neoantigens) are actively being investigated for different types of cancers in order to enable the testing and development of immunotherapeutic solutions. Circulating tumor DNA (ctDNA), major histocompatibility complex (MHC)-II expression on tumor cells, and gene expression profiles (GEPs) are being considered in TNBC (45). While research is also ongoing to develop and test mAbs and BsAb against six-transmembrane epithelial antigen of prostate (STEAP), human carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) and delta-like protein 3 (DLL3) expressed in different types of prostate cancer (46,47). Additionally, studies are being conducted to ascertain the effectiveness and safety of inhibiting the immune checkpoint B7-H3, which is significantly expressed in neuroblastoma, as a treatment option (48). Preclinical and clinical studies using mAbs against anaplastic lymphoma kinase (ALK) for neuroblastoma are already in motion (49). The innovative and explorative research methods for improving cancer antibody therapy are commendable and will help increase the diversity of treatment options.

Adoptive T-Cell Therapy

Adoptive T-cell Therapy (ACT) uses normal or engineered T-cells to identify a particular antigen on the tumor cells and eliminate them (50). ACT aims to expand and equip T-cells with the necessary battle armaments to eliminate elusive cancer cells (51). ACT has brought relief and remission to many cancer patients, mainly those with hematological malignancies, but it has yet to find therapeutic use in solid tumors (52). The main forms of ACTs are tumor-infiltrating lymphocytes (TILs) therapy, engineered T-cell receptor therapy (TCR-T), and chimeric antigen receptor (CAR)-T-cell therapy (50).

TIL therapy

TILs was the first ACT to be developed and adopted. It involves the harvesting and isolation of mainly T-cells exposed to tumor antigens from metastatic lesions, expanding them, and reinfusing them with repeated doses of interleukin-2 (IL-2) into cancer patients (1). Steve Rosenberg was the first to experiment with this therapy in murine models; it was later clinically trialed on metastatic melanoma patients with encouraging results (53). The effort to extend TIL therapy is currently being expanded to treat other solid tumors. There are currently numerous CTs of TILs for diverse solid cancer types (advanced breast cancer, metastatic cholangiocarcinoma, melanoma, cervical cancer, and colorectal cancer) that have remarkable therapeutic benefits (54). A phase I CT involving the combo of TILs, IL-2, and pembrozulimab produced an effective response in metastatic NSCLC (55). TILs therapy has a better safety profile than other ACTs, and unlike other ACTs, it has also shown greater potential in treating solid tumors (1).

TILs therapy is faced with many challenges, which are being mitigated with available technology and novel strategies. Few TILs identify autologous tumor cells; some TILs are dysfunctional with high expression of inhibitory molecules, while others have low affinity for tumor sites (56). With a greater understanding of cell composition, sequencing technologies, and the utility of gene editing, the ability to modify and improve TILs harvesting, sorting, expansion, efficacy, and safety has greatly improved (56). Strategies aimed at countering immunosuppression and improving TILs function in CTs include the use of recombinant safer IL-2, knockout of transforming growth factor-β (TGF-β) receptor-2 in TILs using CRISPR/Cas9, and knockout of TILs negative regulators such as cytokine-induced SH2 protein (CISH), cbl-b, and AKT1/2 (57-62). Specific phenotypes of tumor-reactive TILs (possessing PD-1, CD39, and CD103) are being targeted to improve tumor immune responses of TILs

(63). Studies assessing the engineering of TILs to produce IL-12 (which improves antitumor response) in small quantities are in different phases of CTs, to particularly determine the safety of this approach (64). Combining TILs with oncolytic viral therapy helps attract T-cells (TILs) to the TME; two studies have confirmed the effectiveness of this strategy in mouse models (65,66). The efforts put into addressing the difficulties encountered in TIL therapy are remarkable.

T-cell Receptor Engineered T-cells

T-cell receptor (TCR) identifies antigens attached to MHC on cells or phagocytes and initiates T-cell effector functions. TCRs are either αβ TCRs or γδ TCRs, depending on the peptide chain combination (67). Some TCRs are specific to certain tumor antigens; the concept of TCR-T-cell therapy is based on transferring tumor-antigen TCR gene sequence onto other T-cells through genetic modifications; this confers the engineered T-cells with the capacity of targeting and eliminating cells that possess that tumor antigen (68). These TCRs are isolated from high affinity TILs or healthy T-cells induced with tumor antigens (67). Unlike conventional CAR-T-cells (which target only extracellular antigens), TCR-T-cells, can also target intracellular antigens owing to their recognition of antigens bound to MHC I/II (69). The FDA has not granted approval for any TCR-T-cell therapy; most CTs involving TCR-T are either in phase I/II. Fatal cross-reactivity of TCR-T cells with similar or even dissimilar antigens, insufficient T cell persistence, a paucity of suitable TCR-T antigens, and the hostile TME are some of the obstacles hindering the emergence of TCR-T-approved therapies. The TCR-T-cell therapies currently in CTs mainly target NY-ESO-1, with many encouraging outcomes (1). Increased TCR-T-cells tumor infiltration, proliferation, and effectiveness were observed in an advanced soft tissue sarcoma treatment in a phase I trial using TCR-T cells in combination with a nanoparticle peptide vaccine to target NY-ESO-1 (70). Melanoma antigens recognized by T cells-1 (MART-1), MAGE-A3, MAGE-A4, MAGE-A10, gp100, WT1, E7, and E6 are some of the other targets being explored in CTs (71). A new gene editing technique simultaneously swaps the initial TCR for the new one, improving the speed of clinical TCR-T production (72). This technique has already found application in the clinical setting (72). TCR-T has been observed in CTs to target similar antigens or tumor-associated antigen (TAA) on normal tissues, resulting in toxicity. A thorough preclinical assessment of TAA and the HLA is mandatory to prevent adverse events (71).

CAR-T-cell Therapy

Chimeric antigen receptors (CARs) are engineered surface receptors that target a specific antigen. They are usually attached to T-cells, but they have also found use in NK cells and macrophages (73). Since they were first introduced, CARs have undergone and are still undergoing various optimizations to optimize their safety and effectiveness. They have the ability to bind to antigens in the absence of MHC molecules (74). Additionally, CARs blend T-cell regenerative and effector functions and the antigen-binding capacity of mAbs (75). CAR-T cells identify varying forms of tumor antigens (proteins, glycolipids, and carbohydrates), unlike conventional TCRs that recognize only peptides (73). In contrast to conventional cancer therapies like chemotherapy and radiation, CAR-T-cell therapy is a compelling substitute because of how specifically it attacks tumors (76). CARs possess the following main domains: the extracellular antigen binding domain (usually a modified mAb); the hinge region (which determines the length of the antigen binding domain and provides flexibility); the transmembrane domain (essential for CAR stability and surface expression); and the intracellular domain (involved in intracellular signaling and co-stimulation) (77). All four domains are essential in determining the efficiency of CAR-T-cell therapy; these domains are constantly optimized for greater potency and therapeutic effect (78). The intracellular domain divides CARs into five progressive generations, targeted at optimizing their function (79-81). The signaling pathways, functional capabilities, effectiveness, and safety of CAR-T-cell therapy are influenced by their composition and architecture (Figure 2).

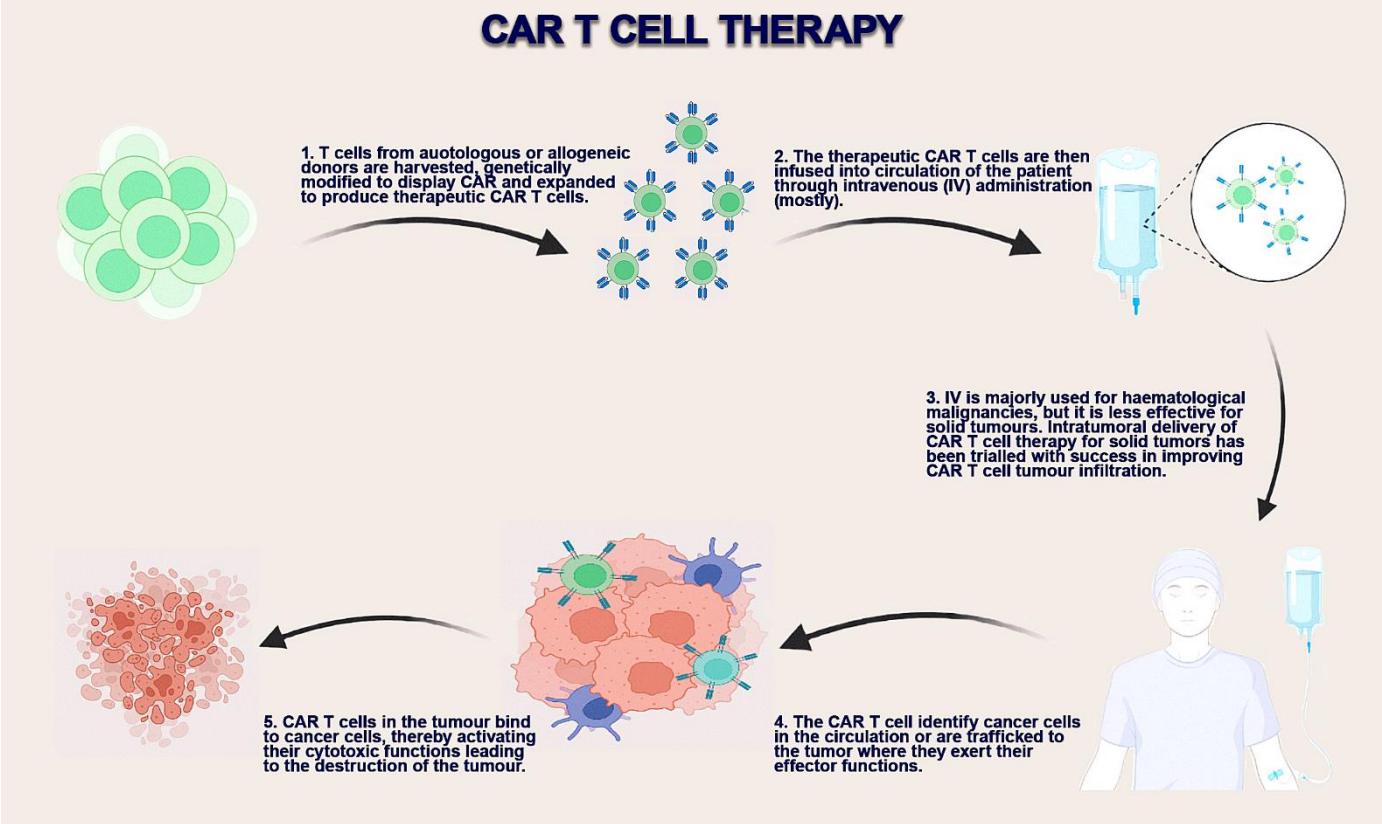

Figure 2. CAR-T-cell production, delivery methods, and mechanism of action (75).

The FDA has granted approval to six CAR-T-cell therapies for heamatological cancer; these therapies are mostly used as second-line or last resort treatments because of their high toxicity. Recent modifications have improved the safety and effectiveness of CAR-T-cell therapies, thereby expanding their range of use, prolonging remission, and improving survival outcomes. Ciltacabtagene autoleucel was granted FDA approval in 2022 for usage in relapsed multiple myeloma patients (82). The CAR-T-cell possesses two single-domain antibodies that target BCMA on myeloma cells (82). Approved therapies are shown in Table 1. Most of these therapies target either BCMA or CD19. Cytopenia and hypogammaglobulinaemia are the two prominent long-term toxic effects seen in approved CAR-T-cell therapies, while cytokine release syndrome (CRS) and neurotoxicity driven by immune effector cells are the prominent acute toxicities (83). CTs exploring CAR-T-cell therapies for non-haematological cancers are burgeoning, with mixed outcomes from initial results.

Table 1. Approved CAR-T-cell therapies with their brand name, therapeutic use and indications (82,83).

S/no	CAR-T-cell therapy	Brand name	Therapeutic use	Indications
1	Idecabtagene vicleucel	ABECMA	Relapsed or refractory Multiple myeloma	For adult patients, to be used after four or more prior lines of therapy.
2	Lisocabtagene maraleucel	BREYANZI	Relapsed or refractory B-cell lymphoma and follicular lymphoma	For adult patients, to be used after two or more lines of systemic therapy.
3	Ciltacabtagene autoleucel	CARVYKTI	Relapsed or refractory multiple myeloma	For patients, to be used after four prior lines of therapy.
4	Tisangenlecleucel	KYMRIAH	Relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) and DLBCL	For adult patients.

5	Brexucabtagene autoleucel	TECARTUS	Relapsed or refractory mantle cell lymphoma and B-cell precursor acute lymphoblastic leukemia	For adult patients. It can be used to treat mantle cell lymphoma in other patients.
6	Axicabtagene ciloleucel	YESCARTA	Relapsed or refractory B-cell lymphoma and Follicular lymphoma	For patients, to be used after two or more lines of systemic therapy.

Widespread adoption of CAR-T-cell therapy is restricted by some hurdles, which include mutation or veiling of tumor antigens, effects on normal tissues that express TAA, poor CAR-T-cell tumor invasion, hostile TME, and toxicities (84). These issues are being addressed with innovative strategies in CTs. Studies targeting multiple antigens have demonstrated promising efficacy, reducing the chances of tumor antigen escape (84). CAR-T-cell extracellular ligand domains are also being explored in preclinical and clinical studies as an alternative to modified antibody domains to increase CAR-T-cell efficacy (85). Combination treatment regimens with ICIs, mainly, are another vital solution to mitigating the suppressive TME. In some studies, CAR-T-cells are genetically modified to produce ICIs, significantly improving the efficiency of CAR-T-cell therapy (86). Knocking out the checkpoint molecule in CAR-T-cells by CRISPR/Cas9 is another method being explored in CTs (86). CAR-T-cells are also being genetically modified to possess their own immunostimulatory and migratory cytokines to resist immunosuppressive TME and improve T-cell trafficking/tumor infiltration, respectively (84). Another method of improving CAR-T-cell tumor infiltration is direct administration into the tumor; this has been trialed in several studies with satisfactory outcomes (75). Non-viral vectors (mRNA and DNA transposons systems) are being evaluated for transducing T-cells with CAR, considering the toxicity concerns associated with viral vectors (87). Culture expansion techniques lead to some epigenetic changes in CAR-T-cells, which affect therapeutic outcomes. Effective expansion techniques and less cultivation time are some of the ways to mitigate this challenge (88).

In addition, many CTs depend on autologous T-cells as the source of CAR-T-cells which is time-consuming and technical; the ensuing delay could be fatal for patients with aggressive tumors (89). Chemotherapy also affects the quantity and quality of autologous T-cells (90). Allogeneic T-cells provide large numbers of fully operational cells and also multivalent CAR-T-cell products (89). Despite the advantages of allogeneic CAR-T-cells, graft-versus-host disease (GVHD) and allorejection limit their clinical applications, but not for long (91). Eliminating the donor's TCR with genetic engineering can be utilized to attenuate the GVHD (91). All three adoptive T-cell therapies share similar challenges; a breakthrough solution addressing one of these challenges can be modified and adopted in all T-cell therapies.

Oncolytic Virus Therapy

Oncolytic viruses (OVs) are modified or wild viruses that infect and kill cancer cells. They release more viruses and toxic substances that destroy cancer cells without killing normal cells (92). Mutations in cancer cells leave them susceptible to viral infection due to an altered antiviral defense system (93). OVs kill infected cancer cells through toxic viral activities and numerous immune-killing functions (94). The OV alters the cell death processes of the tumor cells and uses the cells resources for its own survival and reproduction before moving on to infect the next tumor cell (95). OVs also release pathogen-associated molecular patterns (PAMPs) and death-associated molecular patterns (DAMPs) to amplify specific antitumor immune responses or through the effects of proteins encoded in engineered OVs (94). The OVs selected are weakened strains or harmless viruses that are capable of infecting cancer cells and stimulating the immune system (96).

OVs promote inflammation in the tumor, which is an excellent way of attracting and activating immune cells. Phagocytes engulf tumor antigens and present them to T-cells, thereby activating T-cell antitumor activity (97). CTs on OVs or combination therapies (especially with ICIs) are increasing due to the therapy's safe profile. In Japan, Teserpaturev, a recombinant oncolytic herpes simplex virus type-1 (HSV-1), was granted provisional regulatory approval for stereotactic intratumoral therapy of patients with inoperable glioma (97). Approval has been granted to

four OVs in various countries, but talimogene laherparepvec (T-VEC) is the sole universally authorized OV therapy. It received approval in 2015 for usage in recurrent melanoma patients, but it is still being optimized and trialed for use in other cancers (98). Telomelysin (monotherapy and combinational therapy) for head and neck cancer patients is another OV in phase II CT in the United States of America but has been approved for use in Canada and the Asia-pacific region (98). Telomelysin is an adenoviral OV that possesses the human telomerase reverse transcriptase gene (hTERT) promoter, which is prominent in cancer cells (99). Canerpaturev, a mutant HSV-1, is another OV that awaits FDA approval; its' efficacy at eliciting an immune response and destroying tumor cells is well documented in several studies (100). OVs are also engineered to act as viral vectors. Nadofaragene firadenovec-vncg (Adstiladrin), an adenoviral vector for gene therapy (containing Interferon-α2b gene) was granted FDA approval in December 2022 for use in non-muscle-invasive bladder cancer patients (101). Many other viral vectors are at different stages of CTs. Genetic engineering of OVs has increased the possibilities and potential of OVs therapy. The modifications include the surface display of antitumor antibodies, the incorporation of immunomodulatory genes (97) and the introduction of cell death-inducing factors. Arakai et al. showed that Ad OBP-702, an engineered OV expressing p53, enhanced ICD (102). Recombinant Newcastle disease virus (NDV), NDV-MIP3α equipped with the macrophage inflammatory protein-3α (MIP-3α) enhanced tumor killing as well as improved the maturation and stimulation of dendritic cells (DCs) (103), 4-1BBL, a T-cell immunostimulator incorporated into the VACV/MVA vaccine, enhanced CD8 T-cell activation and also destroyed tumor cells (104). OVs penetrate solid tumors, which is an important advantage as it improves the efficacy of other immunotherapies, which are usually ineffective against solid tumors. The few challenges encountered with OVs therapy include attacks on OVs by the immune system, safety concerns, an insufficient immune response, OV delivery systems, and OV tumor penetration (105). These challenges would have to be addressed before widespread adoption and clinical usage of OVs materialize.

Cancer Vaccine

Vaccines are molecules or organisms that stimulate the immune system to provide protection against a particular antigen or organism (106). In 1980, the inaugural cancer vaccine was devised, comprising cancer cells and extracts (106). Cancer vaccines artificially expose the immune system to cancer antigens, thereby priming the body's defenses against future exposure to that antigen (107). The human papillomavirus (HPV) vaccine and the hepatitis B virus (HBV) vaccine are the two approved prophylactic cancer vaccines. They avert HPV and HBV infection, which are associated with an incidence of cervical and hepatic cancer, respectively (107). Bacillus calmette-guerin (BCG) vaccine, which is used for tuberculosis, has been approved for bladder cancer, while Sipuleucel-T helps treat prostate cancer (107). Both therapeutic and prophylactic vaccines have limited uses considering the multiplicity and plasticity of cancer antigens and the fact that the immune system they aim to stimulate is easily evaded or repressed by tumors. Cancer vaccine research was considered a failure by some, but there has been renewed interest in the use of neoantigens in cancer vaccines. There are many forms of cancer vaccines (peptide-based, nucleic acid, and DC vaccines) based on neoantigens in CTs. Peptide-based vaccines are specific, cost-friendly, and safe, with many studies exploring its utility, one recent study showcased the inducement of antitumor T-cell immune responses in NSCLC models treated with personalized peptide vaccine (108). In a single-patient study, the administration of DNAJB1-PRKACA-peptide vaccine with a poly-ADP-ribose polymerase inhibitor induced a specific and efficient T-cell response against DNAJB1-PRKACA, the oncogenic driver in fibrolamellar hepatocellular carcinoma (109). There was no relapse in the patient 21 months after vaccination (109), which is remarkable. The main challenge with peptide vaccines is moderate immunogenicity (110). Recent studies have made headway in solving this challenge with the conjugation of nanoparticles or immunostimulatory adjuvants (heat shock protein 70, C-terminal of diphtheria toxin) with the vaccine, and the results from the CTs are impressive (110). Nucleic acid vaccines are relatively cheap; they also induce cellular and humoral immunity, but the immune response induced is disappointing most of the

time. Personalized DNA and RNA vaccines are being explored by researchers with modifications to improve their formulation and efficacy. The success of SARS-CoV-2 mRNA vaccines has led to renewed interest in mRNA solutions for cancer. Over 30 mRNA solutions are in different stages of CTs with mixed initial outcomes (111). BNT112, encoding 5 prostate-specific antigens, recorded positive immune outcomes in metastatic castration-resistant prostate cancer (mCRPC) from initial data in phase I/IIa CT (112). BNT121, BNT122, and CV9201 are other mRNA vaccines inducing favorable immunological responses in CT (113). It should be noted that a good number of mRNA vaccines do not elicit a significant immunological response (111). As with other cancer immunotherapy solutions, combination therapy enhances immune responses. mRNA encoding immune costimulatory molecules, Toll-like receptor (TLR)-4, and TAA incorporated into dendritic cells administered with ipilimumab, a mixture identified as Trimix DC-MEL, elicited robust T-cell responses (particularly CD8 T-cells) in melanoma patients during phase II CT (113). DC-based vaccines induce potent immune responses but are expensive to produce. DCs are harvested and pulsed with neoantigens. mRNA or peptides can be incorporated into the DC and infused into cancer patients. Other DC fusion techniques include DC-tumor fusion and electrofusion. Several mRNA-loaded DC vaccines in CTs elicit potent antitumor T-cell immune responses with an excellent safety profile in various cancers (114). Reduced tumor antigen exposure through mutation or low expression, the heterogeneous nature of tumors/tumor antigen, appropriate vaccine platforms, and insufficient immunostimulation are some of the challenges encountered in cancer vaccine development (115). These challenges do not deter research aimed at optimizing cancer vaccines for safe and efficient cancer therapy (Figure 3).

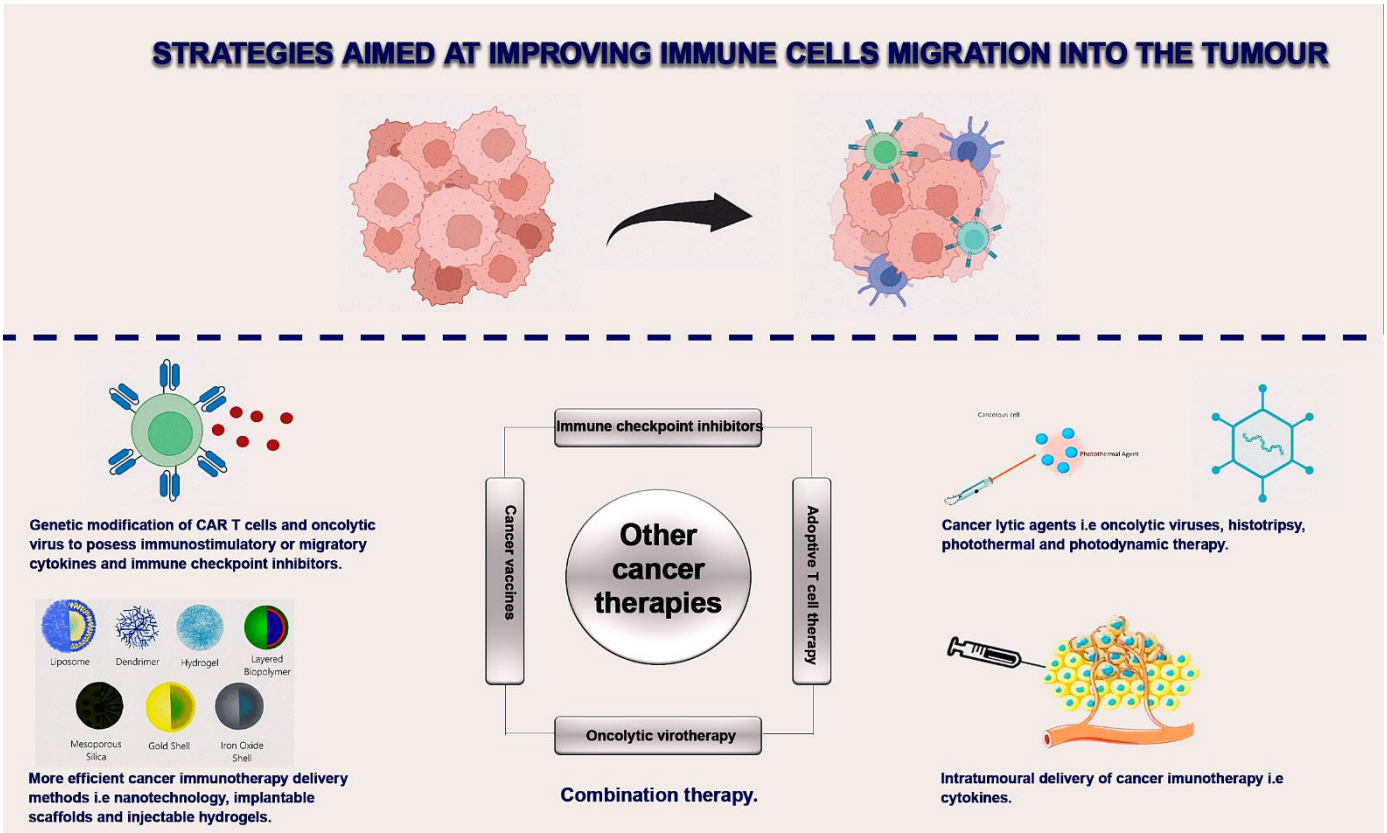

Figure 3. Improving immune cell trafficking and migration to tumours. The hostile tumour microenvironment is one of the major challenges limiting the efficacy of cancer immunotherapies. A summary of the various strategies employed to mitigate these challenges is outlined in the diagram (1,110).

Conclusions

For years now, treatment options for cancer conditions have consistently gained much attention, with increased life expectancy among affected patients and a better understanding of immunosurveillance against cancer cells. Cancer immunotherapy has revolutionized the treatment of different types of cancer conditions with remarkable success. Several cancer immunotherapy regimens have been developed, including adoptive T-cell therapy, immune checkpoint inhibitors, antibody therapies, oncolytic virus therapy, and cancer vaccines, with significant breakthroughs and concomitant increases in patient's quality of life and survival. However, it is important to note that patient responsiveness to immunotherapy does not cut across all patients due to differences in human genetic composition, tumor antigen heterogeneity, stage of the cancer, and the fitness of the immune system. Considering this, further research is ongoing on improving the effectiveness of immunotherapies and reducing their toxicity concerns. It is worth noting that the next generation of cancer immunotherapies will greatly change the status quo in the battle against cancer progression and metastasis.

Limitations of the study

1. The study excluded other non-conventional immunotherapies including cytokine cancer immunotherapy.
2. Emerging technologies intended to enhance cancer immunotherapy delivery were not covered in the study.

Author contribution

PYN wrote the antibody-based therapy section and part of the other sections. He also reviewed the corrections and drafted the figures and table. **MAI** wrote the oncolytic virus and cancer vaccine sections. **AAI** wrote the conclusion and handled the plagiarism and grammar checks. **GSE** wrote the introduction and adoptive cell therapy sections. All authors contributed to the manuscript revision and approved the final draft.

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Conflict of interest

All authors declare that they have no conflicts of interest.

References

1. Liu C, Yang M, Zhang D, Chen M, Zhu D. Clinical cancer immunotherapy: Current progress and prospects. Front Immunol. 2022; 13: 961805.

2. Tan AC, Bagley SJ, Wen PY, et al. Systematic review of combinations of targeted or immunotherapy in advanced solid tumors. J Immunother Cancer. 2021; 9 (7): e002459.

3. Chang H, Qiu J, Buck MD, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell. 2015; 162 (6): 1229-1241.

4. Liu L, Chen J. Therapeutic antibodies for precise cancer immunotherapy: current and future perspectives. Med Rev. 2023; 2 (6): 555-569.

5. Carter PJ, Rajpal A. Designing antibodies as therapeutics. Cell. 2022; 185: 2789–2805.

6. Chan GC, Chan CM. Anti-GD2 directed immunotherapy for high-risk and metastatic neuroblastoma. Biomolecules. 2022; 12 (3): 358.

7. Chauhan J, Grandits M, Palhares L, et al. Anti-cancer pro-inflammatory effects of an IgE antibody targeting the melanoma-associated antigen chondroitin sulfate proteoglycan 4. Nat Commun. 2023; 14: 2192.

8. Ma J, Mo Y, Tang M, et al. Bispecific Antibodies: From Research to Clinical Application. Front Immunol. 2021; 12: 626616.

9. Goebeler ME, Bargou RC. T-cell-engaging therapies - BiTEs and beyond. Nat Rev Clin Oncol. 2020; 17: 418–434.

10. Moreau P, Garfall AL, van de Donk N, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2022; 387: 495–505.

11. Budde LE, Assouline S, Sehn LH, et al. Single-agent mosunetuzumab shows durable complete responses in patients with relapsed or refractory B-cell lymphomas: phase I dose escalation study. J Clin Oncol. 2022; 40: 481–491.

12. Nathan P, Hassel JC, Rutkowski P, et al. Overall survival benefit with tebentafusp in metastatic

uveal melanoma. N Engl J Med. 2021; 385: 1196–1206.

13. Zhang T, Lin Y, Gao Q. Bispecific antibodies targeting immunomodulatory checkpoints for cancer therapy. Cancer Biol Med. 2023; 20 (3): 181-195.

14. Moores SL, Chiu ML, Bushey BS, et al. A novel bispecific antibody targeting EGFR and cMet is effective against EGFR inhibitor-resistant lung tumors. Cancer Res. 2016; 76: 3942–3953.

15. Riaz R, Khan A, Siddiqui T. Epcoritamab-bysp (Epkinly)-A phenomenal breakthrough in the treatment of diffuse large B-cell lymphoma. Rare Tumors. 2023; 15: 20363613231193566.

16. Deegen P, Thomas O, Nolan-Stevaux O, et al. The PSMA-targeting half-life extended BiTE Therapy AMG 160 has potent antitumor activity in preclinical models of metastatic castration-resistant prostate cancer. Clin Cancer Res. 2021; 27: 2928-2937.

17. Tong J, Harris PWR, Brimble MA, Kavianinia I. An insight into FDA approved antibody-drug conjugate for cancer therapy. Molecules. 2021; 26 (19): 5847.

18. Su D, Zhang D. Linker design impacts antibody-drug conjugate pharmacokinetics and efficacy via modulating the stability and payload release efficiency. Front Pharmacol. 2021; 12: 687926.

19. Dean AQ, Luo S, Twomey JD, Zhang B. Targeting cancer with antibody drug conjugates: promises and challenges. mAbs. 2021; 13 (1): 1951427.

20. Boni V, Sharma MR, Patnaik A. The resurgence of antibody drug conjugates in cancer therapeutics: Novel targets and payloads. Am Soc Clin Oncol Educ Book. 2020; 40: 1-17.

21. Matulonis UA, Lorusso D, Oaknin A, et al. Efficacy and safety of Mirvetuximab Soravtansine in patients with platinum-resistant ovarian cancer with high folate receptor alpha expression:results from the SORAYA study. J Clin Oncol. 2023; 41 (13): 2436-2445.

22. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021; 384: 1529–1541.

23. Rugo HS, Bardia A, Marme F, et al. Sacituzumab Govitecan in Hormone receptor-positive/Human epidermal growth factor 2-negative metastatic breast cancer. J Clin Oncol. 2022; 40 (29): 3365-3376.

24. Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: an overview of FDA approved immune checkpoint inhibitors. Int Immunopharmacol. 2018; 62: 29–39.

25. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015; 348: 56–61

26. Huang L, Li Y, Du Y, et al. Mild photothermal therapy potentiates anti-PD-L1 treatment for immunologically cold tumors via an all-in-one and all-in-control strategy. Nat Commun. 2019; 10: 4871.

27. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022; 386 (1): 24-34.

28. Wu H, Su Z, Barnie PA. The role of B regulatory (B10) cells in inflammatory disorders and their potential as therapeutic targets. Int Immunopharmacol. 2020; 78: 106111.

29. Shi Y, Zhu J, Liu J-Q, Talebian F, Li M, Bai X-F. CD24 is expressed on FoxP3+ regulatory T-cells and regulates their function. Am J Transl Res. 2022; 14: 2291–2300.

30. Runz S, Mierke CT, Joumaa S, Behrens J, Fabry B, Altevogt P. CD24 induces localization of β1 integrin to lipid raft domains. Biochem Biophys Res Commun. 2008; 365: 35–41.

31. Altevogt P, Sammar M, Hüser L, Kristiansen G. Novel insights into the function of CD24: A driving force in cancer. Int J Cancer. 2021; 148: 546–559.

32. Bretz NP, Salnikov AV, Perne C, et al. CD24 controls Src/STAT3 activity in human tumors. Cell Mol Life Sci. 2012; 69: 3863–3879.

33. Chen Z, Wang T, Tu X, Xie W, He H. Antibody-based targeting of CD24 enhances antitumor effect of cetuximab via attenuating phosphorylation of Src/STAT3. Biomed. Pharmacother. 2017; 90: 427–436.

34. Zhang H, Chen H, Yin S, et al. Docosahexaenoic acid reverses PD-L1 mediated

immune suppression by accelerating its ubiquitin-proteasome degradation. J Nutr Biochem. 2023; 112: 109186.

35. Zheng S, Song J, Linghu D, et al. Galectin-9 blockade synergizes with ATM inhibition to induce potent anti-tumor immunity. Int J Biol Sci. 2023; 19 (3): 981-993.

36. Park MD, Reyes-Torres I, LeBerichel J, et al. TREM2 macrophages drive NK cell paucity and dysfunction in lung cancer. Nat Immunol. 2023; 24 (5): 792-801.

37. Segal NH, Logan TF, Hodi FS, et al. Results from an integrated safety analysis of urelumab, an agonist anti-CD137 monoclonal antibody. Clin Cancer Res. 2017; 23: 1929–1936.

38. Pietsch EC, Dong J, Cardoso R, et al. Antileukemic activity and tolerability of anti-human CD47 monoclonal antibodies. Blood Cancer J. 2017; 7 (2): e356.

39. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol. 2007; 7: 715–725.

40. Nimmerjahn F, Ravetch JV. Fc gamma receptors: old friends and new family members. Immunity 2006; 24: 19–28.

41. Shankar B, Zhang J, Naqash AR, et al. Multisystem immune-related adverse events associated with immune checkpoint inhibitors for treatment of non-small cell lung cancer. JAMA Oncol. 2020; 6: 1952–1956

42. Vasiljeva O, Hostetter DR, Moore SJ, Winter MB. The multifaceted roles of tumor-associated proteases and harnessing their activity for prodrug activation. Biol Chem. 2019; 400: 965–977.

43. Pai CS, Simons DM, Lu X, et al. Tumorc onditional anti-CTLA4 uncouples antitumor efficacy from immunotherapy-related toxicity. J Clin Invest. 2019; 129: 349–363.

44. Naing A, Thistlethwaite F, De Vries EGE, et al. CX-072 (pacmilimab), a Probody ((R)) PD-L1inhibitor, in advanced or recurrent solid tumors (PROCLAIM-CX-072): an open-label dose finding and first-in-human study. J Immunother Cancer. 2021; 9 (7): e002447.

45. Garufi G, Carbognin L, Schettini F, et al. Updated Neoadjuvant Treatment Landscape for Early Triple Negative Breast Cancer: Immunotherapy, Potential Predictive Biomarkers, and Novel Agents. Cancers. 2022; 14: 4064.

46. Lin TY, Park JA, Long A, Guo HF, Cheung NV. Novel potent anti-STEAP1 bispecifc antibody to redirect T-cells for cancer immunotherapy. J Immunother Cancer. 2021; 9 (9): e003114.

47. Dorff TB, Narayan V, Forman SJ, Zang PD, Fraietta JA, June CH. Novel redirected T-cell immunotherapies for advanced prostate cancer. Clin Cancer Res. 2022; 28: 576-584.

48. Pulido R, Nunes-Xavier CE. Hopes on immunotherapy targeting B7-H3 in neuroblastoma. Transl Oncol. 2023; 27: 101580.

49. Furman WL. Monoclonal antibody therapies for high risk neuroblastoma. Biologics 2021; 15: 205–219.

50. Feldman SA, Assadipour Y, Kriley I, Goff SL, Rosenberg SA. (2015). Adoptive Cell Therapy—Tumor-Infiltrating Lymphocytes, T-Cell Receptors, and Chimeric Antigen Receptors. Semin oncol. 2015; 42 (4): 626-639.

51. Alnefaie A, Albogami S, Asiri Y, et al. Chimeric Antigen Receptor T-Cells: An Overview of Concepts, Applications, Limitations, and Proposed Solutions. Front Bioeng Biotechnol. 2022; 10: 797440.

52. Rohaan MW, Wilgenhof S, Haanen JBAG. Adoptive cellular therapies: the current landscape. Virchows Arch. 2019; 474 (4): 449–461.

53. Rosenberg SA, Packard BS, Aebersold PM, et al. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. a preliminary report. N Engl J Med. 1988; 319: 1676–1680.

54. Zhao Y, Deng J, Rao S, et al. Tumor infiltrating lymphocyte (TIL) therapy for solid tumor treatment: progressions and challenges. Cancers. 2022; 14 (17): 4160.

55. Creelan BC, Wang C, Teer JK, et al. Tumor-infiltrating lymphocyte treatment for anti-PD-1-resistant metastatic lung cancer: a phase 1 trial. Nat Med. 2021; 27 (8): 1410–1418

56. Tasa L, Jedemaa I, Haanen J. Novel strategies to improve efficacy of treatment with tumor-infiltrating lymphocytes (TILs) for patients with solid cancers. Curr Opin Oncol. 2023; 35: 107–113.

57. Fix SM, Forget MA, Sakellariou-Thompson D, et al. CRISPR-mediated TGFBR2 knockout renders human ovarian cancer tumor-infiltrating lymphocytes resistant to TGF-beta signaling. J Immunother Cancer. 2022; 10: e003750.

58. Palmer DC, Webber BR, Patel Y, et al. Internal checkpoint regulates T-cell neoantigen reactivity and susceptibility to PD1 blockade. Med. 2022; 3 (10): 682–704.

59. Kumar J, Kumar R, Kumar Singh A, et al. Deletion of Cbl-b inhibits CD8(þ) T-cell exhaustion and promotes CAR-T-cell function. J Immunother Cancer. 2021; 9 (1): e001688.

60. Liu Y, Zhou N, Zhou L, et al. IL-2 regulates tumor-reactive CD8(þ) T-cell exhaustion by activating the aryl hydrocarbon receptor. Nat Immunol. 2021; 22: 358–369.

61. Feng H, Qiu L, Shi Z, et al. Modulation of intracellular kinase signaling to improve TIL stemness and function for adoptive cell therapy. Cancer Med. 2022; 12 (3): 3313-3327.

62. Deak CL, Nicolini V, Hashimoto M, et al. PD-1-cis IL-2R agonism yields better effectors from stem-like CD8(þ) T-cells. Nature. 2022; 610: 161–172.

63. Hanada KI, Zhao C, Gil-Hoyos R, et al. A phenotypic signature that identifies neoantigen-reactive T-cells in fresh human lung cancers. Cancer Cell. 2022; 40: 479–493,

64. Jones DS, Nardozzi JD, Sackton KL, et al. Cell surface-tethered IL-12 repolarizes the tumor immune microenvironment to enhance the efficacy of adoptive T-cell therapy. Sci Adv. 2022; 8 (17): eabi8075.

65. Ye K, Li F, Wang R, et al. An armed oncolytic virus enhances the efficacy of tumor-infiltrating lymphocyte therapy by converting tumors to artificial antigen presenting cells in situ. Mol Ther. 2022; 30: 3658–3676.

66. Feist M, Zhu Z, Dai E, et al. Oncolytic virus promotes tumor-reactive infiltrating lymphocytes for adoptive cell therapy. Cancer Gene Ther. 2021; 28: 98–111.

67. Shah K, Al-Haidari A, Sun J, Kazi JU. T-cell receptor (TCR) signaling in health and disease. Signal Transduct Target Ther. 2021; 6 (1): 412.

68. Chandran SS, Klebanof CA. T-cell receptor-based cancer immunotherapy: emerging efficacy and pathways of resistance. Immunol Rev. 2019; 290 (1): 127–147

69. Chen L, Qiao DJ, Wang JT, Tian G, Wang MJ. Cancer immunotherapy with lymphocytes genetically engineered with T-cell receptors for solid cancers. Immunol Lett. 2019; 216: 51–62.

70. Ishihara M, Nishida Y, Kitano S, et al. A phase 1 trial of NY-ESO-1-specific TCR-engineered T-cell therapy combined with a lymph node-targeting nanoparticulate peptide vaccine for the treatment of advanced soft tissue sarcoma. Int J cancer, 2023; 152 (12): 2554–2566.

71. Shafer P, Kelly LM, Hoyos V. Cancer therapy with TCR-engineered T-cells: current strategies, challenges and prospects. Front Immunol. 2022; 13: 835762.

72. Zhang Y, Liu Z, Wei W, Li Y. TCR engineered T-cells for solid tumor immunotherapy. Exp Hematol Oncol. 2022; 11 (1): 38.

73. Abbott RC, Cross RS, Jenkins MR. Finding the Keys to the CAR: Identifying Novel Target Antigens for T-cell Redirection Immunotherapies. Int J Mol Sci. 2020; 21 (2): 515.

74. Lim WA, June CH. The Principles of Engineering Immune Cells to Treat Cancer. Cell. 2017; 168: 724–740.

75. Kozani SP, Kozani SP, Najafabadi AM, Yousefi F, Mirarefin SM, Rahbarizadeh F. Recent Advances in solid tumor CAR-T-cell Therapy: Driving tumor Cells from Hero to Zero? Front Immunol. 2022; 13: 795164.

76. Sadelain M, Brentjens R, Rivière I. The Basic Principles of Chimeric Antigen Receptor Design. Cancer Discov. 2013; 3: 388–398.

77. Lindner SE, Johnson SM, Brown CE, Wang LD. Chimeric antigen receptor signaling: Functional consequences and design implications. Sci Adv. 2020; 6 (21): eaaz3223.

78. Jayaraman J, Mellody MP, Hou AJ, et al. CAR-T design: Elements and their synergistic function. EBioMedicine. 2020; 58: 102931.

79. Guedan S, Calderon H, Posey AD, Maus MV. Engineering and Design of Chimeric Antigen Receptors. Mol Ther Methods Clin Dev. 2019; 12: 145–156.

80. Chmielewski M, Abken H. TRUCKS, the Fourth-generation CAR-T-cells: Current Developments and Clinical Translation. Adv. Cell. Gene Ther. 2020; 3 (3): 1145-1154.

81. Tokarew N, Ogonek J, Endres S, von Bergwelt-Baildon M, Kobold S. Teaching an Old Dog New Tricks: Next-Generation CAR-T-cells. Br. J. Cancer. 2019; 120: 26–37.

82. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021; 24 (398): 314-324.

83. Cappell KM, Kochenderfer JN. Long term outcomes following CAR-T-cell therapy: what we know so far. Nat Rev Clin Oncol. 2023; 20: 359-371.

84. Sterner RC, Sterner RM. CAR-T-cell therapy: current limitations and potential strategies. Blood Cancer J. 2021; 11 (4): 69.

85. Ramirez-Chacon A, Betriu-Mendez S, Bartolo-Ibars A, Gonzalez A, Marti M, Juan M. ligand-based CAR-T-cell: Different strategies to drive T-cells in future new treatments. Front Immunol. 2022; 13: 932559.

86. Gumber D, Wang LD. Improving CAR-T immunotherapy: overcoming the challenges of T-cell exhaustion. EBioMedicine 2022; 77: 103941.

87. Martinez M, Moon EK. CAR-T-cells for solid tumors: new strategies for finding, infiltrating and surviving in the tumor microenvironment. Front Immunol. 2019; 10: 128.

88. Salz L, Seitz A, Schafer D, et al. Culture expansion of CAR-T-cells results in aberrant DNA methylation that is associated with adverse clinical outcome. Leukaemia. 2023; 37 (7): 1-11.

89. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. 'Off-the-shelf' Allogeneic CAR-T-cells: Development and Challenges. Nat Rev Drug Discov. 2020; 19: 185–199.

90. Zhao Z, Chen Y, Francisco NM, Zhang Y, Wu M. The Application of CAR-T-cell Therapy in Hematological Malignancies: Advantages and Challenges. Acta Pharm Sin B. 2018; 8: 539–551.

91. Martínez-Bedoya D, Dutoit V, Migliorini D. Allogeneic CAR-T-cells: An Alternative to Overcome Challenges of CAR-T-cell Therapy in Glioblastoma. Front Immunol. 2021; 3 (12): 506.

92. Jennings VA, Scott GB, Rose AMS, et al. (2019). Potentiating Oncolytic Virus-Induced Immune-Mediated Tumor Cell Killing Using Histone Deacetylase Inhibition. Mol. Ther. 2019; 27 (6): 1139–1152.

93. Harrington K, Freeman DJ, Kelly B, Harper J, Soria JC. Optimizing Oncolytic Virotherapy in Cancer Treatment. Nat. Rev. Drug Discov. 2019; 18 (9): 689–706.

94. Russell SJ, Peng KW, Bell J. Oncolyticytic virotherapy. Nat Biotechnol. 2012;30(7):658-670.

95. Cattaneo R, Miest T, Shashkova EV, Barry MA. Reprogrammed viruses as cancer therapeutics: targeted, armed and shielded. Nat Rev Microbiol. 2008; 6: 529–540.

96. Mondal M, Guo J, He P, Zhou D. Recent advances of oncolytic virus in cancer therapy. Hum Vaccin Immunother. 2020; 16 (10): 2389-2402.

97. Russell SJ, Bell JC, Engeland CE. et al. Advances in oncolytic virotherapy. Commun Med. 2022; 2: 33.

98. Shalhout SZ, Miller DM, Emerick KS, Kaufman HL. Therapy with oncolytic viruses: Progess and challenges. Nat Rev Clin Oncol. 2023; 20: 160-177.

99. Shah MA, Eads JR, Sarkar S, et al. Phase II study of telomelysin (OBP-310) in combination with pembrolizumab in gastroesophageal (GEA) adenocarcinoma. J Clin Oncol. 2023; 41 (16): 4052.

100. Eissa IR, Mukoyama N, Abdelmoneim M, et al. oncolytic herpes simplex virus HF10 (canerpaturev) promotes accumulation of CD8+ PD-1- enriched tumor

microenvironment. Int J Cancer. 2021; 1 (149): 214-227.

101. Boorjian SA, Alemozaffar M, Konety BR, et al. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-non-invasive bladder cancer: A single-arm, open-label, repeat-dose clinical trial. Lancet. 2021; 1: 107-117.

102. Araki H, Tazawa H, Kanaya N, et al. Oncolytic virus-mediated p53 overexpression promotes immunogenic cell death and efficacy of PD-1 blockade in pancreatic cancer. Mol Ther Oncolytics. 2022; 27: 3–13.

103. Huang FY, Wang JY, Dai SZ, et al. A recombinant oncolytic Newcastle virus expressing MIP-3a promotes systemic antitumor immunity. J Immunother Cancer. 2020; 8 (2): e000330.

104. Hinterberger M, Giessel R, Fiore G, et al. Intratumoral virotherapy with 4-1BBL armed modified vaccinia Ankara eradicates solid tumors and promotes protective immune memory. J Immunother Cancer. 2021; 9 (2): e001586.

105. Rahman MM, McFadden G. Oncolytic viruses: newest frontier for cancer immunotherapy. Cancers. 2021; 13 (21): 5452.

106. Liu, J, Fu, M, Wang, M. et al. Cancer vaccines as promising immuno-therapeutics: platforms and current progress. J Hematol Oncol. 2022; 15 (1): 28.

107. Sobhani, N, Scaggiante, B, Morris, R, et al. Therapeutic cancer vaccines: From biological mechanisms and engineering to ongoing clinical trials. Cancer Treat Rev. 2022; 109: 102429.

108. Li, L. et al. Optimized polyepitope neoantigen DNA vaccines elicit neoantigen specific immune responses in preclinical models and in clinical translation. Genome Med. 2021; 13 (1): 56.

109. Bauer J, Kohler N, Maringer Y, et al. the oncogenic fusion protein DNAJB1-PRKACA can be specifically targeted by peptide-based immunotherapy in fibrolamellar hepatocellular carcinoma. Nat Commun. 2022; 13: 6401.

110. Fritah H, Rovelli R, Chiang CL, Kandalaft LE. The current clinical landscape of personalized cancer vaccines. Cancer Treat Rev. 2022; 106: 102383.

111. Krause, W. mRNA—From COVID-19 Treatment to Cancer Immunotherapy. Biomedicines. 2023; 11 (2): 308.

112. Linch M, Papai Z, Takacs I, et al. 421 A first-in-human (FIH) phase I/IIa clinical trial assessing a ribonucleic acid lipoplex (RNA-LPX) encoding shared tumor antigens for immunotherapy of prostate cancer; preliminary analysis of PRO-MERIT. J. Immunother. Cancer. 2021; 9 (2): 451.

113. Jansen Y, Kruse V, Corthals J, et al. A randomized controlled phase II clinical trial on mRNA electroporated autologous monocyte-derived dendritic cells (TriMixDC-MEL) as adjuvant treatment for stage III/IV melanoma patients who are disease-free following the resection of macrometastases. Cancer Immunol. Immunother. 2020; 69: 2589–2598.

114. Beck JD, Reidenbach D, Salomon N, et al. mRNA therapeutics in cancer immunotherapy. Mol. Cancer. 2021; 20 (1): 69.

115. Bowen WS, Svrivastava AK, Batra L, Barsoumian H, Shirwan H. Current challenges for cancer vaccine adjuvant development. Expert Rev Vaccines. 2018; 17 (3): 207–215.