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STATE-OF-THE-ART REVIEW

Cancer Immunotherapy Beyond Checkpoint Blockade

JACC: CardioOncology State-of-the-Art Review

Nathan E. Welty, MD, PhD,[a,b] Saar I. Gill, MD, PhD[a,b]

ABSTRACT

Avoidance of immune destruction is recognized as one of the hallmarks of cancer development. Although first predicted as a potential antitumor treatment modality more than 50 years ago, the widespread clinical use of cancer immunotherapies has only recently become a reality. Cancer immunotherapy works by reactivation of a stalled pre-existing immune response or by eliciting a de novo immune response, and its toolkit comprises antibodies, vaccines, cytokines, and cell-based therapies. The treatment paradigm in some malignancies has completely changed over the past 10 to 15 years. Massive efforts in preclinical development have led to a surge of clinical trials testing innovative therapeutic approaches as monotherapy and, increasingly, in combination. Here we provide an overview of approved and emerging antitumor immune therapies, focusing on the rich landscape of therapeutic approaches beyond those that block the canonical PD-1/PD-L1 and CTLA-4 axes and placing them in the context of the latest understanding of tumor immunology. (J Am Coll Cardiol CardioOnc 2022;4:563–578) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A fundamental challenge for cancer treatments such as chemotherapy and targeted therapies is that cancers undergo natural selection. Genetic and epigenetic modifications accumulate in cancer subclones during treatment, and those that provide a selective advantage enable tumor growth or recurrence despite continued drug therapy. The power of immune therapy over other forms of treatment therefore rests on several fundamental features of the adaptive immune system: 1) antigen specificity: immune receptors are competitively tuned to produce exquisite specificity for particular antigens; 2) clonal selection: cells that obtain positive signaling via these receptors expand and mature to become more adept at eliminating foreign antigens; and 3) memory: antigen-specific clones persist over the lifetime of the host, serving as a long-term reservoir to control foreign antigens. The combination of specificity, adaptation, and durability offered by immune-based therapies thus combats cancer clonal evolution through natural selection and offers the potential for long-term control without prohibitive off-target toxicities.

A basic principle of cancer immunotherapy is that oncogenesis requires escape from immune surveillance.[1] Because of immune ignorance (de novo

From the [a]Center for Cellular Immunotherapies, University of Pennsylvania, Philadelphia, Pennsylvania, USA; and the [b]Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

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ABBREVIATIONS AND ACRONYMS

alloHCT = allogeneic hematopoietic stem cell transplantation

BiTE = bispecific T cell engager

CAR = chimeric antigen receptor

CRS = cytokine-release syndrome

FDA = U.S. Food and Drug Administration

HLA = human leukocyte antigen

ICI = immune checkpoint inhibitor

IL = interleukin

mAb = monoclonal antibody

NK = natural killer

NSCLC = non-small cell lung cancer

TIL = tumor-infiltrating lymphocyte

absence of mutation-specific immune recognition), tolerance (acquired absence of mutation-specific immune recognition), or suppression (development of counter-regulatory mechanisms that prevent immune recognition), cancers that progress from precancerous lesions toward growth and metastasis are de facto insensitive to normal mechanisms of immunologic pressure against non-self-antigens. This process is known as cancer immunoediting.[2,3] Successful cancer immunotherapies must overcome cancer immunoediting, either by provoking a de novo antitumor immune response or by reactivating an existing immune response that has become ineffective. In this review we provide an overview of approved and emerging antitumor immune therapies as they fit within these 2 broad mechanisms of action, discussing both cell-based and noncellular therapies, their mechanisms of action, and toxicities (**Central Illustration**). We emphasize the most recent and clinically advanced approaches apart from immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 or CTLA-4, which are amply covered in numerous other dedicated reviews.

HIGHLIGHTS

- Cancer immunotherapies have undergone rapid commercialization over the past decade.
- Immunotherapy mechanisms, responses, and toxicities diverge from prior treatments.
- Future advances must build on these unique traits to address immunotherapy resistance.

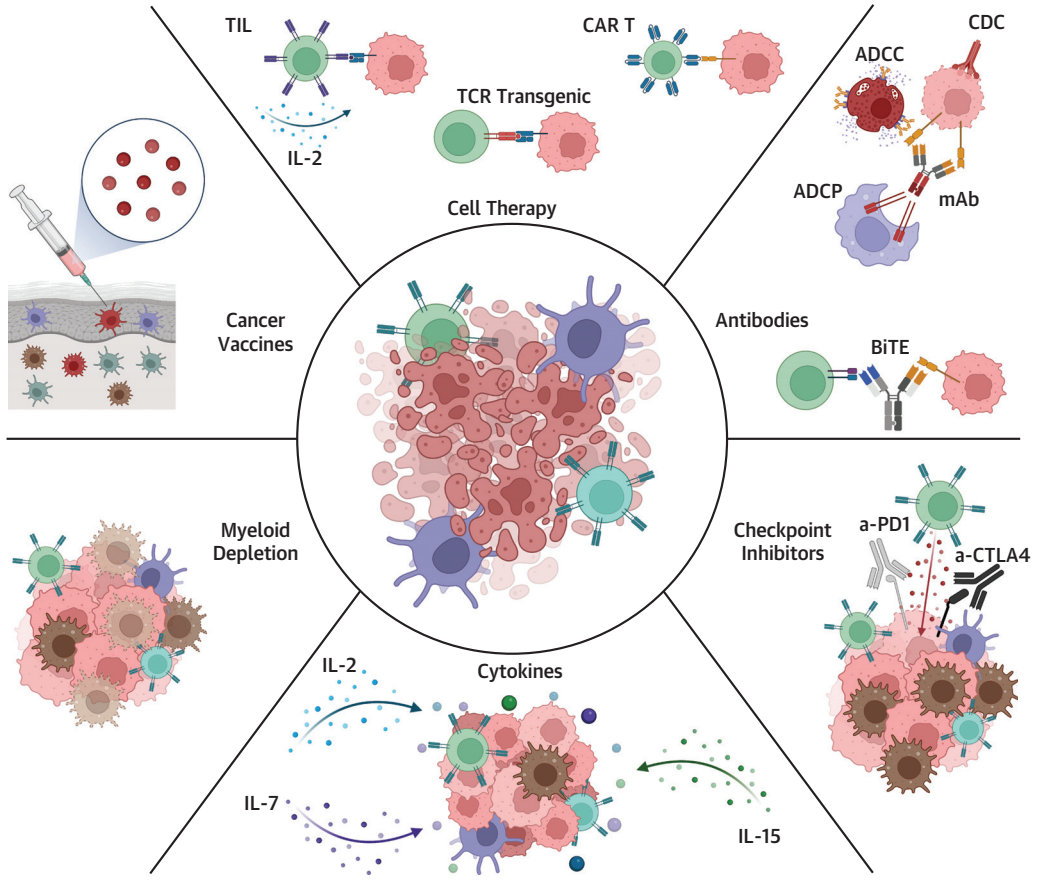
PROVOKING AN ANTITUMOR IMMUNE RESPONSE

TUMOR-SPECIFIC ANTIGENS. Cancer cells exhibit genetic instability and accumulate somatic mutations, gene fusions, chromosomal copy number variations, and other genomic, epigenetic, and post-transcriptional modifications.[4] These events generate an intracellular pool of altered, potentially immunogenic peptides that are processed and presented on human leukocyte antigen (HLA) molecules to T cells, thereby stimulating immune responses[5] (**Figure 1**). Peptides that are present only in malignant cells, known as neoantigens, can also act as therapeutic targets, demonstrated by data showing that neoantigen burden is a biomarker for response to immune checkpoint blockade.[6-9] Neoantigens represent attractive targets because they are not expressed in normal tissues and therefore have higher potential immunogenicity and lower potential toxicity. However, they have also been challenging targets for several reasons. First, these mutations are generally private (ie, not shared between individuals), and drug development therefore requires intensive personalized medicine strategies such as whole-exome sequencing and bioinformatic analyses at the individual patient level.[10,11] Second, neoantigen peptides are immunogenic only when presented by particular HLA molecules. HLA loci are among the most highly polymorphic regions of the human genome,[12,13] presenting difficulties for drug development at the population level as well. Nonetheless, vaccine- and cell-based therapies targeting tumor-specific neoantigens are in early-phase development.[11]

Cancer vaccines. Clinical trials targeting tumor-specific neoantigens largely use cancer vaccines to generate new immune responses for cancer prevention or treatment. In initial trials in melanoma, neoantigen-based cancer vaccines could expand existing antitumor T cells and elicit de novo T cell responses.[14-16] However, results from phase 3 cancer vaccine trials, which include both neoantigen and non-neoantigen targets, have been disappointing.[17] Failure of the elicited neoantigen immune responses to control cancer is multifactorial, and antigen target selection is only one of many barriers. However, an emerging strategy to improve neoantigen selection is to target mutated peptides in genes that are obligate for cancer development. These "driver" mutations are potentially favorable for a few reasons. Because they are oncogenic, these mutations are present in all cancer subclones and indispensable for continued cancer growth. Thus, further genetic aberrations that permit cancer cells to lose the mutation are unlikely. Additionally, these mutations are shared across individuals and tumor types, circumventing challenges of entirely personalized therapy.[5,18-20]

Early-phase trials of neoantigen vaccination targeting driver mutations are currently recruiting (eg, NCT03592888, NCT04117087, NCT05202561, NCT04853017). However, the HLA restriction of neoantigens remains a potential limitation.[13]

CENTRAL ILLUSTRATION **Landscape of Cancer Immunotherapy**



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Cancer immunotherapies can be divided into those that aim to stimulate a direct antitumor response **(top half)**—which include vaccines, cell therapies, and antibody-based therapies—and those that aim to reactivate host immunity **(bottom half)** by targeting immune inhibitor checkpoints, stimulating immune cells with activating cytokines, or depleting immune-suppressive cells. ADCC = antibody-dependent cell-mediated cytotoxicity; ADCP = antibody-dependent cell-mediated phagocytosis; BiTE = bispecific T cell engager; CAR T = chimeric antigen receptor–modified T cell; CDC = complement-dependent cytotoxicity; IL = interleukin; mAb = monoclonal antibody; TCR = T cell receptor; TIL = tumor-infiltrating lymphocyte. Created with BioRender.com.

Additionally, HLA loss of heterozygosity in cancer cells is a known mechanism of immune escape,[21] occurring, for instance, in up to 40% of patients with non-small cell lung cancer (NSCLC),[22] and can prevent T cell recognition. Avoiding this phenomenon may require vaccination against multiple neoepitopes presented on different HLAs, as is under way in a trial of vaccination against hundreds of recurrent mutations in patients with DNA mismatch repair-deficient cancers[23] (NCT04041310), which have a high neoantigen burden. This approach may be less effective in cancers with a lower neoantigen burden, although several clinical trials of messenger RNA-based vaccines targeting multiple neoantigens are under way in melanoma, head and neck cancers, colorectal cancer, and others (eg, NCT03313778, NCT03897881, NCT03815058, NCT03289962). Ultimately the optimal strategy for anticancer vaccination against any antigen type remains unclear, despite trials of cell-based and acellular approaches using DNA, RNA, and peptides with various adjuvant strategies.[11,17] Generally, vaccines work best in

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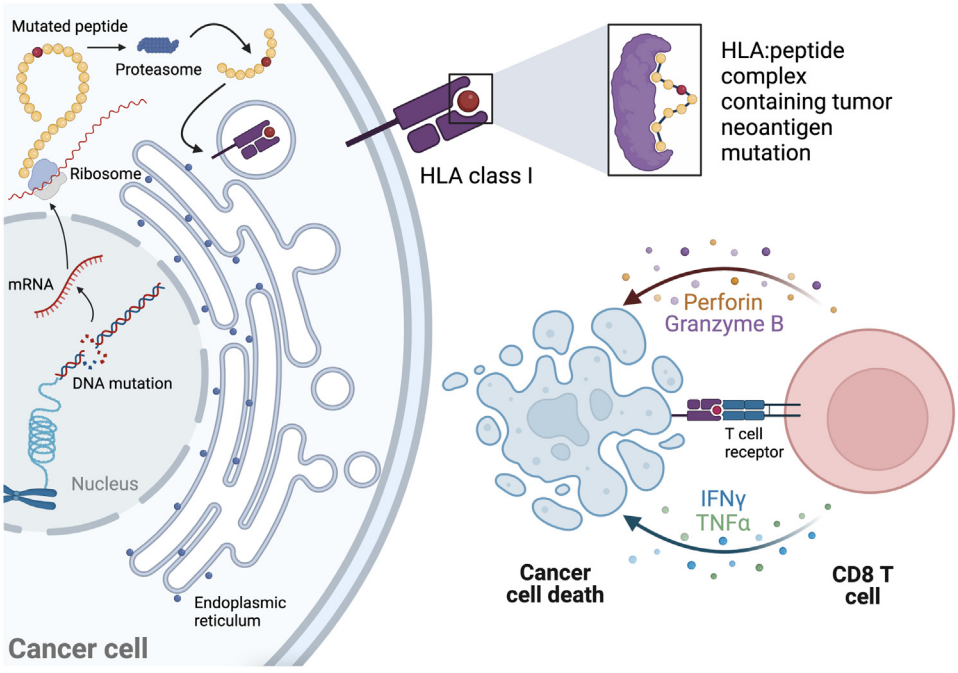
FIGURE 1 Immune Recognition of Tumor Neoantigens

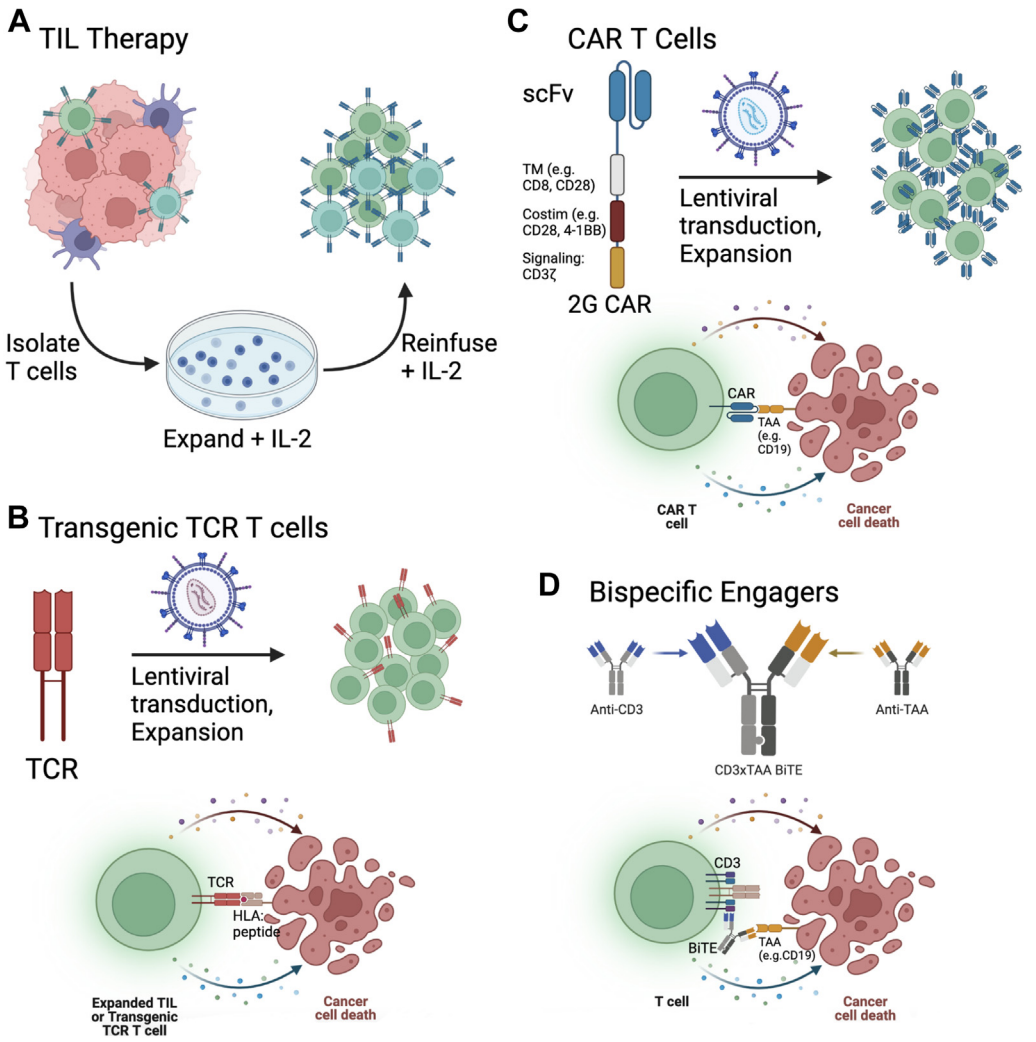


Nonsynonymous mutations within a cancer cell result in mutated peptide neoantigens that are degraded, processed, and loaded on human leukocyte antigen (HLA) class I molecules intracellularly prior to cell surface presentation. Mutated peptide:HLA complexes are recognized as foreign by T cell receptors, triggering downstream signaling and effector molecule production that results in cancer cell killing. IFN = interferon; mRNA = messenger RNA; TNF = tumor necrosis factor. Created with BioRender.com.

combination with therapies that counteract immune suppression and in settings of low-volume disease, limiting use in patients with the most advanced cancers.[17] Indeed, the only U.S. Food and Drug Administration (FDA)-approved vaccine for metastatic malignancy, sipuleucel-T, though well tolerated, shows only minimal clinical benefit[24] and is most effective in those patients with low-volume prostate cancer.[25] The only cardiovascular toxicity associated with sipuleucel-T is a low incidence of hypertension around the time of infusion[24]; cardiotoxicities in phase 3 trials of other vaccines were uncommon and not clearly treatment related.[26-28]

Nonengineered cell therapies. One of the earliest cancer immunotherapies was autologous tumor-infiltrating lymphocytes (TILs) that were harvested from resected melanomas, expanded in vitro with interleukin (IL)-2, and then reinfused back into patients after lymphodepleting chemotherapy and in conjunction with additional in vivo IL-2 treatment[29] (**Figure 2A**). Later work demonstrated that antigens targeted by TIL therapy and associated with clinical responses are in fact neoantigens.[30] Despite its early start, TIL therapy was overshadowed by the development of ICIs, which have an improved toxicity profile compared with systemic IL-2 and do not require the prolonged manufacturing process for personalized cellular therapy. Nonetheless, TIL therapies show a response rate of about 30% to 40%, even in patients with melanoma previously treated with checkpoint inhibitors,[31-33] suggesting nonoverlapping mechanisms of action. Responses are associated with high-dose IL-2, higher infused TIL number, and possibly with lack of prior anti-CTLA-4 treatment.[31-33] Responses can be very durable, and toxicities are typically within the first few weeks of treatment.[31-33] Although no phase 3 data have been reported for any TIL product, the first commercial TIL product for melanoma, lifileucel, has shown response rates of approximately 30% and received fast-track designation from the FDA.[33] TIL therapy is also an emerging treatment modality for other epithelial cancers, with early-phase clinical trials completed or ongoing in NSCLC (NCT04614103), cervical cancer (NCT03108495

FIGURE 2 T Cell-Targeted Immunotherapies



(A) Tumor-infiltrating lymphocyte (TIL) therapy expands autologous T cells from tumor biopsies prior to reinfusion for cancer targeting. **(B)** T cells are engineered via lentiviral transduction to express a transgenic T cell receptor (TCR). TILs and transgenic TCRs require human leukocyte antigen (HLA)–restricted recognition of tumor peptides. **(C)** Chimeric antigen receptor (CAR)–modified T cells are created by lentiviral transduction of a CAR, containing an antibody-like single-chain variable fragment (scFv) fused to transmembrane (TM), (costim), and signaling domains. All currently approved CAR products are second generation (2G). Infused CAR T cells recognize tumor-associated antigens (TAAs). **(D)** Bispecific T cell engagers (BiTEs) are synthetic molecules containing scFvs that activate T cells via CD3, a component of the TCR complex, against a target TAA. Created with BioRender.com. IL = interleukin.

), and others (NCT03449108).[34-36] Cardiotoxicities observed with TIL therapy are common and include hypotension, arrhythmias, and edema (**Table 1**), with a major contribution from systemic IL-2 administration, although conditioning chemotherapy and TIL factors may also contribute.[33,37,38]

Engineered cell therapies. While TILs are a non-engineered T cell therapy, advances in molecular biology have enabled cell therapies that are augmented through genetic modification to enhance antitumor activity (**Figure 2**). Engineered cell therapies are usually generated by viral transduction with synthetic or naturally occurring molecules capable of modifying immune cell activity, although other approaches, such as clustered regularly interspaced short palindromic repeats-based gene editing, are

TABLE 1 Cardiovascular Toxicities Associated With Selected Immunotherapies

Agent(s)	Disease	Toxicity (Frequency)	Ref. #
Lifileucel (TIL) + chemotherapy + IL-2	Melanoma	Hypotension (36%), tachycardia (35%), edema (26%)	33
High-dose IL-2	RCC	Hypotension (96%), arrhythmia (14%), myocardial ischemia (2%), myocardial infarction (2%), cardiac arrest (2%), myocarditis (1%)	150
Tebentafusp	Uveal melanoma	CRS (89%), hypotension (38%), hypertension (6%)	68
Margetuximab	Breast cancer	Hypertension (5.3%), grade 3+ LV dysfunction (1.1%)	53
Obinutuzumab	NHL, CLL	Cardiac events (10.7%)[a]	54,174
Blinatumomab	B-ALL	CRS (14.2%), hypotension (12%), cardiac disorders (2.2% with blinatumomab vs 2.8% with chemotherapy)	175
CAR T (various products)	NHL (88%), myeloma (8%)	CRS (59%), elevated troponin (54%), decreased LVEF (28%), decompensated HF (3%-10%), arrhythmia (3%-4%), CV death (4%)	98-101
Allogeneic HCT	Various	Ischemic heart disease (5.4%), cardiomyopathy (12.3%), rhythm disorder (15.2%), hypertension (31.6%), cardiovascular death (5.2%)	114
PD-1 inhibitor ± CTLA-4 inhibitor (various products)	Various	Myocarditis (0.06%-0.15% for PD-1 vs 0.26%-0.27% for combination)	141,142
Pexidartinib	TGCT	Hypertension (15%)	162

[a]Defined as any preferred term in the System Organ Class cardiac disorders.

B-ALL = B cell acute lymphoblastic leukemia; CAR T = chimeric antigen receptor–modified T cell; CLL = chronic lymphocytic leukemia; CRS = cytokine-release syndrome (any grade, various grading systems); CV = cardiovascular; HCT = hematopoietic stem cell transplantation; HF = heart failure; IL = interleukin; LV = left ventricular; LVEF = left ventricular ejection fraction; NHL= non-Hodgkin lymphoma; RCC = renal cell carcinoma; TGCT = tenosynovial giant cell tumor; TIL = tumor-infiltrating lymphocyte.

also rapidly developing.[39-42] For instance, T cells are readily harvested from peripheral blood by apheresis and virally transduced to express a receptor targeting known neoantigens prior to expansion and reinfusion into patients, thereby stimulating an antitumor immune response (**Figure 2B**). Clinical trials using this method to target driver neoantigen mutations in solid tumors are ongoing (eg, NCT03745326, NCT03190941, NCT04146298). These T cells are engineered to express an HLA-restricted murine T cell receptor recognizing mutated Kristen rat sarcoma viral oncogene homologue peptides complexed with HLA-A*11:01.[43] Similarly, a recent case report described a clinical response in a patient treated with engineered autologous T cells transduced with an HLA-C*08:02-restricted receptor targeting a mutant Kristen rat sarcoma viral oncogene homologue G12D peptide.[44] Further discovery efforts to identify antigen recognition domains that specifically bind neoantigen:HLA complexes are ongoing.[45,46] These may enable the development of neoantigen-targeting chimeric antigen receptor (CAR) T cells (**Figure 2C**), which typically use antibody-derived single-chain variable fragments to recognize their targets, or even noncellular immunotherapies, such as bispecific T cell engagers (BiTEs)[47] (**Figure 2D**). Important safety concerns with these agents include cross-recognition of alternative peptides presented by HLA molecules, as occurred with MAGE-A3-targeted transgenic T cell receptor T cells that caused cardiogenic shock and early mortality in 2 patients through recognition of a titin peptide in beating cardiac tissue.[48,49] Developing preclinical model systems that can predict such toxicities has been challenging.[50]

TUMOR-ASSOCIATED ANTIGENS. As opposed to tumor-specific neoantigens, most immunotherapy targets are shared surface antigens that are highly expressed on tumor cells but are not necessarily cancer specific. In hematologic malignancies, these targets are typically lineage-associated maturation antigens that are expressed during development of both normal and malignant cells, for instance, CD19 and CD20 in B cell neoplasms and CD33 in myeloid neoplasms. In some malignancies, they may be oncofetal (also known as "cancer germline" or "cancer testis") antigens that are typically expressed during fetal development and in cancer but not on normal adult tissues, antigens that are overexpressed on tumor cells, or normal antigens with aberrant post-transcriptional modifications, such as glycosylation variants, in the context of cancer.[20] Unlike neoantigens, these targets present higher potential for on-target, off-tumor toxicities because of expression on normal cells in addition to malignant ones. Despite these drawbacks, their more uniform expression both within tumors and across individuals, and the lack of HLA restriction, have been more amenable for drug development.

Monoclonal antibodies. Monoclonal antibodies (mAbs) directed at cell membrane antigens form the largest class of FDA-approved cancer immunotherapies. By "creating" antigens for immune recognition

from normally nonimmunogenic cell surface proteins, mAbs induce antitumor immunity through their Fc domains, which engage myeloid, natural killer (NK) cells, and other immune cells to cause antibody-dependent cellular cytotoxicity, antibody-dependent cell phagocytosis, and/or complement-dependent cytotoxicity of targeted cells[51] (**Central Illustration**). Although in hematologic malignancies direct immune-mediated cytotoxicity is appreciated as the major mechanism of action of mAbs, in solid tumors attention has focused more on their disruption of cancer cell signaling pathways rather than their immune effects.[52] However, the clinical importance of these immune effects in solid tumors is recently highlighted by the FDA approval of margetuximab-cmkb, a mAb targeting the same HER-2 epitope as trastuzumab, which was previously approved to treat HER-2-positive breast cancer, but with a redesigned Fc domain to enhance immune-mediated cytotoxicity. Margetuximab showed modest but significantly improved progression-free survival compared with trastuzumab (5.8 months vs 4.9 months) given with chemotherapy in patients with previously treated breast cancer. Despite a small increase in infusion reactions, rates of cardiotoxicity (**Table 1**) were similar to those seen with trastuzumab, which is known to be associated with decreased left ventricular ejection fraction.[53] However, other trials of engineered mAbs designed to enhanced immune activity have been less successful. For instance, the newer engineered anti-CD20 mAbs obinutuzumab and ofatumumab showed no improvement over standard rituximab for the treatment of non-Hodgkin lymphomas despite increased immune toxicities and infusion reactions. Overall cardiac events are also increased with these agents compared with rituximab, although these were not well defined in the registration trials, and the mechanism remains unclear (**Table 1**).[54,55]

Naked mAbs have limited single-agent activity, and most regimens combine antibodies with traditional chemotherapy.[56-59] This finding is somewhat counterintuitive given the immunosuppression caused by traditional chemotherapy. This synergy may relate to immunogenic cell death, depletion of immune-suppressive cells, or other immune stimulatory effects of chemotherapy.[60-63] Beyond naked mAbs, numerous antibody-drug conjugates have received FDA approval. Antibody-drug conjugates exploit the tumor-targeting capacity of mAbs; upon cross-linking their antibody target antigen, these drugs deliver high intracellular doses of chemotherapy, radiation, or other cytotoxic payloads directly to cancer cells,[52] expanding the therapeutic window and avoiding prohibitive toxicities that would otherwise be associated with these agents. Although antibody-drug conjugates have much higher single-agent activity, their mechanism of action is due chiefly to the cytotoxicity of the drug conjugate. Antibody-drug conjugates and their toxicities, including cardiotoxicities, have been extensively reviewed in other publications.[64,65]

Bispecific engagers. Although most antibody-based treatments target a single tumor-associated antigen, there is increasing research and development of antibody-like bispecific products that simultaneously bind 2 different targets to mediate antitumor immunity (**Figure 2D**). Amivantamab-vmjw is one such agent that simultaneously targets epidermal growth factor and mesenchymal-epithelial transition factor receptors on the surface of NSCLC via single-chain variable fragment domains, mediating antitumor activity via its Fc domain. This drug received FDA approval for the treatment of patients with NSCLC with epidermal growth factor receptor exon 20 insertion mutations, showing a response rate of 40% in a population that does not respond to drugs that treat most epidermal growth factor receptor–mutated lung cancers.[66] Peripheral edema and hypoalbuminemia, known class effects of mesenchymal-epithelial transition factor inhibition, occur with this agent, but cardiac toxicities are not seen.[66] Like mAbs, this Fc-mediated mechanism of action only indirectly leads to T cell activation, as T cells generally do not express Fc receptors. However, other bispecific products, known as BiTEs, use antibody fragments to directly activate T cells. BiTEs typically contain a domain recognizing CD3, a component of the T cell receptor, linked to a second domain targeting a cancer cell surface antigen.[67] Binding of the BiTE to both targets mimics the action of T cell receptor HLA-peptide binding and activates T cell effector functions against the target cell, "redirecting" T cells to kill tumor targets they would not otherwise recognize.

Tebentafusp-tebn is a bispecific molecule that redirects $CD3^+$ T cells to kill tumor cells displaying a peptide from the melanoma antigen gp100 in the context of HLA-A*02:01. It is the only FDA-approved BiTE for solid tumors, with 1-year overall survival of 73% compared with 59% in the control group in treated patients with uveal melanoma.[68] However, cutaneous toxicities with this medication are also observed, likely due to on-target, off-tumor toxicity, as gp100 is not a neoantigen but is also expressed in normal melanocytes.[68,69] The only BiTE to receive FDA approval to date for hematologic malignancies is blinatumomab, a CD3 × CD19-targeting molecule that

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TABLE 2 Current FDA-Approved CAR T Cell Products

Product (Brand Name)	Target	Costimulation/Unique Features	FDA Indication	ORR (CRR)	Ref. #
Tisagenlecleucel (Kymriah)	CD19	4-1BB	B-ALL, LBCL	82% (60%), 52% (40%)	176,177
Axicabtagene cioleucel (Yescarta)	CD19	CD28	LBCL, FL	82% (40%), 92% (74%)	178,179
Brexucabtagene autoleucel (Tecartus)	CD19	CD28/T cell enrichment of apheresis product	B-ALL, MCL	71% (56%), 93% (67%)	180,181
Lisocabtagene maraleucel (Breyanzi)	CD19	4-1BB/separate manufacture/infusion of CD4/CD8 T cells	LBCL	73% (53%)	182
Idecabtagene vicleucel (Abecma)	BCMA	4-1BB	MM	73% (33%)	183
Ciltacabtagene autoleucel (Carvykti)	BCMA	4-1BB/two VHHs targeting distinct BCMA epitopes	MM	97% (67%)	184

BCMA = B cell maturation antigen; CRR = complete response rate; FDA = U.S. Food and Drug Administration; FL = follicular lymphoma; LBCL = large B cell lymphoma; MCL = mantle cell lymphoma; MM = multiple myeloma; ORR = overall/objective response rate; VHH = heavy chain variable domain; other abbreviations as in Table 1.

activates killing of B cells, for the treatment of B cell acute lymphoblastic leukemia, with a response rate of 69% in relapsed/refractory patients.[70-72] Additional agents targeting CD20, CD38, or BCMA in B cell and plasma cell malignancies and CD33 or CD123 in myeloid leukemias are in clinical trials.[67] Contrasting with treatments whose mechanism of action is based on Fc recognition, which typically have low immune toxicity,[66,73] immune-related adverse events with BiTEs are more common. Both cytokine-release syndrome (CRS) and neurotoxicity are observed, likely because of direct T cell engagement.[68,74,75] Although cardiotoxicities were observed with blinatumomab, rates were not significantly higher compared with the chemotherapy treatment group (Table 1). Mechanisms of resistance to BiTEs remain underexplored, although CD19 loss by tumor cells can occur in patients treated with blinatumomab.[71,76]

Cell therapies. Nonengineered T cell products enriched for tumor-associated antigen specificity can be generated by exposing peripheral blood–derived T cells to autologous antigen presenting cells loaded with peptides selected from a list of known tumor-associated antigens (eg, PRAME, MAGEA4, NYESO1, survivin), followed by ex vivo manufacturing with activating cytokines. Treatment with these products has generated interesting antitumor responses in patients with hematologic malignancies, with few toxicities and no cardiotoxicities.[77,78] However, the most clinically advanced approaches to cell therapy involve the use of immune effector cells that are genetically engineered to target tumor-associated antigens. Immune effector cells include T cells, NK cells, NK/T cells, and macrophages. Of these, T cells bearing CARs represent the most advanced technology to date. CAR T cells are typically manufactured from autologous T cells isolated from peripheral blood and lentivirally transduced to express a CAR, which redirects their specificity toward a tumor-associated antigen, prior to reinfusion after lymphodepleting chemotherapy (Figure 2C). CAR T cells have FDA labels for the treatment of pediatric and adult B cell acute lymphoblastic leukemia, adults with B cell non-Hodgkin lymphomas, and multiple myeloma (Table 2) and are in clinical trials for other hematologic and solid tumors, with encouraging early data in T cell malignancies,[79] Hodgkin lymphoma,[80] acute myeloid leukemia,[81] and some gastrointestinal,[82] prostate,[83] and brain[84] cancers. Two recent publications of CAR-modified NK cells[85] and NK/T cells[86] have also shown promise. Overall, as of September 2022, 347 clinical trials of CAR-modified immune effector cells were registered as actively recruiting on ClinicalTrials.gov, including 152 in the United States, 165 in China, and 31 in Europe. Most use T cells, whereas 6 use NK cells, 2 use NK/T cells, and 1 uses macrophages. An excellent recent review of the therapeutic landscape for CAR-engineered cells identified 64 different targets for T, NK, or NK/T cells in more than 500 clinical trials encompassing more than 20,000 patients.[87] The potential of genetically engineered cell therapies to be a “one and done” treatment for cancer is underscored by reports of deep and durable responses in patients with multiply relapsed hematologic malignancies such as chronic lymphocytic leukemia,[88] results that may justify the high initial cost of these therapies.[89]

Novel toxicities have emerged with the implementation of CAR T cell therapies. These include expected on-target, off-tumor toxicities from depletion of healthy cells that share the targeted antigen. For instance, anti-CD19-targeted CAR T cells cause aplasia of normal $CD19^+$ B cells, which is therefore a pharmacodynamic marker of CAR T persistence.[90] CAR T cells also cause previously unanticipated toxicities, including CRS, immune cell-associated neurotoxicity syndrome, and prolonged bone marrow aplasia. CRS is a potentially life-threatening immune activation syndrome occurring in the first days to 2 weeks after infusion associated with elevated serum

inflammatory markers and cytokines. CRS can cause pyrexia, hypoxia, and vasodilatory shock.[91] It occurs in 60% to 90% of patients because of inflammatory cytokine (IL-6 and IL-1) production by myeloid cells in response to T cell cytokines and inflammatory tumor cell death.[92-94] Risk factors for severe CRS include higher disease burden and high infused CAR T dose,[91] with severity graded per consensus guidelines from the American Society of Transplantation and Cell Therapy.[95] The mainstay of management is the IL-6 receptor inhibitor tocilizumab, which was empirically effective in initial registration trials, although steroids, IL-1 antagonists, and other agents are also used.[91,92,96,97] Retrospective studies have identified cardiovascular toxicities in patients treated with CAR T cells (**Table 1**). The chief cardiotoxicity is heart failure, although arrhythmias are also observed, with the main risk factor being grade 2 or higher CRS.[98] Other risk factors include delayed tocilizumab administration and elevated baseline creatinine.[98,99] Left ventricular ejection fraction recovery is seen in most patients with the resolution of CRS, although increased cardiovascular mortality is observed.[98-101] Like CRS, immune cell-associated neurotoxicity syndrome was not originally predicted as a toxicity of CAR T therapy, but it occurs in up to 40% to 50% of patients and can have serious sequelae.[91] The pathophysiology of immune cell-associated neurotoxicity syndrome is less well understood but involves endothelial damage and blood-brain barrier permeabilization due to IL-1 and tumor necrosis factor-α but not IL-6 production.[92-94] Immune cell-associated neurotoxicity syndrome management includes steroids and supportive care, although the efficacy of steroids has not been well established. Tocilizumab is not effective.[91,92,96] Finally, prolonged bone marrow suppression is emerging as a frequent complication of CAR T cell therapy even when the targeted antigen is not expressed on bone marrow stem cells and is seen in up to 40% of patients. The etiology remains unclear; however, risk factors include degree and duration of CRS.[102-105]

UNKNOWN OR POORLY CHARACTERIZED ANTIGENS. Arguably the cellular immunotherapy modality in widest routine clinical use is allogeneic hematopoietic stem cell transplantation (alloHCT), also known as bone marrow transplantation, for the treatment of hematopoietic cancers. Minor histocompatibility mismatches between the donor and host hematopoietic systems, among other potential immunogenic antigens, leads to a graft-vs-leukemia effect, whereby donor lymphocytes attack and eliminate the tumor-bearing host hematopoietic system.[106-108] The corollary of this desired graft-vs-leukemia effect is graft-vs-host disease; maintaining graft-vs-leukemia effects without exacerbating graft-vs-host disease is the key challenge of alloHCT.[107,108] Sources for alloHCT donor grafts include bone marrow, peripheral blood (following administration of recombinant granulocyte colony-stimulating factor to induce $CD34^+$ hematopoietic stem cell egress into peripheral blood), or umbilical cord blood, and donor source can affect the incidence of graft-vs-host disease.[109,110] The etiology of cardiovascular complications after alloHCT is multifactorial given intensive pretransplantation chemotherapy and/or radiation that predisposes to cardiac dysfunction, with anthracycline dose representing a strong predictor.[111,112] Nonetheless, graft-vs-host disease also predisposes cardiovascular complications, which include pericardial effusions or tamponade,[113] arrhythmias,[114,115] and other morbidities related to long-term cardiac risk factor modification, suggesting immune-mediated mechanisms as well. The increasing use of haploidentical (half-matched) alloHCT grafts has also led to the development of CRS-like reactions, with significant impacts on mortality.[116] Further cardiac complications of alloHCT are more fully discussed in other recent publications.[117,118]

(RE)ACTIVATING EXISTING ANTITUMOR IMMUNITY

In contrast to tumor target-specific strategies to generate a de novo antitumor immune response, many cancer immunotherapies aim to reverse general pre-existing immune suppression (**Central Illustration**). The most well-established examples of this approach are the ICIs, mAbs directed against PD-1, PD-L1, and CTLA-4, as well as other emerging targets. These antibodies block immune inhibitory signals from cancer, stromal, and immune-suppressive myeloid elements within the tumor microenvironment to T cells, thus reactivating dysfunctional antitumor T cell responses. Since their first approvals in melanoma, ICIs have garnered numerous additional indications in a variety of tumor types, including lung cancer, genitourinary cancers, gastrointestinal malignancies, Hodgkin lymphoma, and all solid tumors with DNA mismatch repair deficiency or high tumor mutational burden regardless of tissue origin.[119,120] As PD-1/PD-L1 and CTLA-4 checkpoint inhibitors, their mechanism of action, and toxicities have been covered in depth in prior publications,[121] we focus on novel immune checkpoints and combination therapies as well as noncheckpoint strategies to activate existing antitumor immune responses.

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NOVEL ICIs AND COMBINATIONS. Although the PD-1 and CTLA-4 pathways are the most well studied, they are not the only immune-suppressive checkpoints exerted on T cells within the tumor microenvironment. Both PD-1 and CTLA-4 are early T cell activation markers that are up-regulated as a counter-regulatory mechanism against overactivation. Their prolonged expression during long-term T cell stimulation is eventually associated with an "exhausted" and dysfunctional T cell state.[122] LAG-3 is a similar T cell inhibitory receptor, and high LAG-3 expression is associated with T cell exhaustion.[123] Recently, in a phase 3 first-line study for unresectable or metastatic melanoma, treatment with the LAG-3 inhibitor relatlimab in combination with nivolumab, a PD-1 inhibitor, significantly improved progression-free survival compared with PD-1 inhibition alone (10.1 months vs 4.6 months)[124] and has now received FDA approval for this indication. A key advantage of this combination over the previously approved combination of PD-1/CTLA-4 inhibitors is the lower rate of grade 3 or 4 immune-related toxicities, which were >50% with combined PD-1/CTLA-4 blockade and 18.9% for PD-1/LAG-3 inhibition.[124-126] Myocarditis was uncommon, occurring in 1.7% of patients with PD-1/LAG-3 inhibition, consistent with other ICI studies. Numerous other products, both mono- and bispecific, targeting LAG-3 or other noncanonical immune checkpoints are in preclinical and early-phase development.[123] The durability of responses with these novel agents compared with existing ICIs, which can allow treatment discontinuation in some patients,[127,128] remains unclear.

ICIs have also been combined with other drug classes, which has steadily expanded the population of patients with cancer eligible for these therapies. The most illustrative example is NSCLC, for which the PD-1 inhibitor pembrolizumab has single-agent FDA approval for PD-L1-positive patients.[129] Subsequently, even patients with negative PD-L1 staining became eligible for pembrolizumab plus chemotherapy, which showed a 12-month overall survival benefit compared with chemotherapy alone (69.2% vs 49.4%).[130] ICI and chemotherapy combinations have also been approved in gastroesophageal and biliary tract cancers.[131,132] ICIs have also been found to synergize with angiogenesis inhibitors, and these combinations are approved in several solid tumors, including hepatocellular carcinoma,[133] endometrial cancer,[134] and renal cell carcinoma.[135-137] The exact mechanism for this synergy is unclear, particularly as many antiangiogenic agents are multikinase inhibitors that affect several different pathways.[138,139] Last, newly engineered versions of existing ICIs may improve responses in presently immune-refractory tumor types, as was shown recently in a phase 1 trial of botensilimab, an Fc-engineered CTLA-4 inhibitor, which when combined with a PD-1 inhibitor achieved a 24% response rate (73% disease control) with high durability in patients with heavily pretreated microsatellite-stable colorectal cancer who are resistant to traditional ICIs.[140]

Cardiovascular toxicities are rare with ICI monotherapy, with myocarditis occurring in <1% of patients, though more commonly with dual ICI treatment (**Table 1**). These rates may be underestimates, as increased recognition has led to increases in reporting over time.[141-143] Despite its rarity, this is a feared complication that carries a high mortality rate.[141,144] Additionally, emerging evidence shows that ICI combination with anti-VEGF or multikinase targeted agents is associated with major adverse cardiovascular events.[141,145] As these agents alone lead to a known increase in cardiovascular risk factors such as hypertension, thromboembolism, and cardiomyopathy,[146-148] the contribution of immune toxicity to major adverse cardiovascular event risk remains unclear, particularly given that these are mostly nonmyocarditis events,[141] although recent retrospective data have suggested that ICIs are also associated with major adverse cardiovascular events, particularly in predisposed patients.[149]

CYTOKINES. Cytokines are intercellular communication molecules that are secreted by or act upon immune cells in an autocrine, paracrine, or endocrine manner. The relevance of cytokines for immuno-oncology pertains to their direct antitumor effect or their ability to stimulate effector immune cells (**Central Illustration**). Recombinant human IL-2 (aldesleukin) has an FDA label for the treatment of metastatic renal cell carcinoma and for metastatic melanoma despite the low fraction of responding patients (15% and 16% overall responders, respectively).[150,151] As administration of high doses of IL-2 is an integral component of TIL therapy (as discussed earlier), the high incidence of severe toxicities due to capillary leak syndrome when administered at the requisite dose remains relevant (**Table 1**).[33,152] More recent developments in synthetic biology have resulted in synthetic cytokines with favorable toxicity profiles that can be administered as single agents and are currently in clinical trials.[153] Synthetic cytokines can also be used in cell therapies by creating immune cells that secrete proinflammatory cytokines,[154] synthetic cytokines that act as partial agonists to expand T cells without inducing terminal differentiation,[155] or entirely synthetic cytokine and cytokine receptor

TABLE 3 Selected Cytokines Investigated in Immunotherapy Clinical Trials

Cytokine	Desired Immunologic Activity	Ref. #
IL-2	Stimulation of CD4 and CD8 T cell proliferation and survival	33,152,153
IL-7	Stimulation of CD4 and CD8 T cell proliferation and survival	185-187
IL-10	Increase expansion and cytotoxicity of tumor-infiltrating CD8 T cells	188
IL-12	NK, NK/T, and CD8 T cell proliferation, T cell differentiation to produce IFNγ, enhancement of dendritic cell antigen presentation	189
IL-15	Stimulation of NK and CD8 T cell proliferation	157,190
IL-18	Augmentation of antibody-dependent cellular cytotoxicity in NK cells	191
IL-21	CD8 T cell proliferation, survival, and resistance to regulatory T cell suppression	192,193

IL = interleukin; NK = natural killer.

circuits, such as the IL-2/IL-2 receptor beta chain system, to selectively expand T cells.[156] By engineering synthetic cytokine receptors to be expressed in adoptively transferred CAR T cells that respond only to engineered cytokines, it is possible to achieve a high level of biological specificity, avoiding both on- and off-target effects of the native cytokine on normal immune cells. Although most efforts to stimulate antitumor immunity with cytokines have focused on native or engineered versions of IL-2, other cytokines with immunologic activity are also under investigation in clinical trials, including IL-7, IL-12, IL-15, and others (**Table 3**). Although cardiotoxicities associated with systemic IL-2 are significant (**Table 1**), early-phase trials of these other cytokines have shown lower severity of cardiovascular side effects, for instance, less severe hypotension and capillary leak syndrome in phase 1 trial of systemic IL-15.[157]

TARGETING IMMUNOSUPPRESSIVE CELLS. The tumor microenvironment poses a key hurdle against antitumor immunity. The tumor microenvironment consists of hematopoietic and stromal cells that are recruited by tumor cells and provide negative regulatory signals to T cells to prevent effective antitumor immunity.[158] As myeloid cells, either in the form of tumor-associated macrophages or myeloid-derived suppressor cells, form a significant fraction of these immune-suppressive bystander cells, depletion of myeloid cells or blockade of their recruitment is an emerging objective in cancer immunotherapy (**Central Illustration**).[159] Some of the activity of traditional chemotherapeutic agents has been attributed to their ability to deplete immune-suppressive myeloid cells.[62,160,161] More targeted strategies have included the use of pexidartinib, a small-molecule inhibitor of the macrophage colony-stimulating factor receptor, which showed a response rate of 39% compared with 0% in a placebo-controlled trial and received FDA approval for the treatment of tenosynovial giant cell tumors.[162] Tenosynovial giant cell tumors overexpress macrophage colony-stimulating factor, leading to increased recruitment of myeloid-derived suppressor cells into the tumor microenvironment. This pathway is blocked by pexidartinib, the only systemic therapy to show robust activity in tenosynovial giant cell tumors.[163] Other strategies to block immune-suppressive myeloid cells include targeting other chemokine and receptor pathways involved in myeloid recruitment, such as the C-C chemokine receptor 2 and 5 pathways,[164] or use of a CD33 × CD3 BiTE to redirect T cells for myeloid depletion that has early-phase activity in solid tumors.[165] Use of CAR T cells to deplete components of the immune-suppressive microenvironment rather than tumor cells themselves has also been proposed and tested in preclinical models,[166] although this therapeutic strategy has not yet reached clinical phase development. In addition to myeloid depletion, reactivating myeloid cell intrinsic antitumor immune functions through inhibition of the "don't eat me" signal CD47[167] or through stimulatory engagement with CD40 agonists[168,169] is also under investigation. Pexidartinib is associated with hypertension (**Table 1**); cardiovascular toxicities of other myeloid depletion strategies remain unknown.

CONCLUSIONS

Although predicted as a potential antitumor treatment modality more than 50 years ago,[170] clinically tractable cancer immunotherapies have become a reality only in the past decade. This achievement is based on many decades of research advances elucidating basic mechanisms of both immunity and tumorigenesis. With the identification of new targets and novel combinations, use of immunotherapy in

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oncology is likely to grow in the coming decades because of its distinct advantages over more traditional anticancer drugs in terms of both depth and durability of potential responses. Rapid expansion of the therapeutic arsenal has presented challenges to clinicians, regulators, and the health care system, as mechanisms of action, response patterns, toxicities, and costs of these therapies diverge significantly from prior generations of cancer treatments. However, a few hallmarks of immune-based therapies have emerged from their widespread clinical adoption, including marked and durable survival benefits despite a low initial responding fraction of patients[171,172] as well as loss of immunotherapy sensitivity in some treated patients.[121] These response patterns highlight future directions for research and development, which must continue to address issues of immune priming as well as both primary and secondary immune resistance[121,173] to achieve durable cancer control and cures.

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ADDRESS FOR CORRESPONDENCE: Dr Saar I. Gill, Smilow Center for Translational Research, Room 8-101, 3400 Civic Center Boulevard, Philadelphia, Pennsylvania 19104, USA. E-mail: saar.gill@pennmedicine.upenn.edu.

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