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STATE-OF-THE-ART REVIEW

Immune Checkpoint Inhibitor Therapy in Oncology

Current Uses and Future Directions: *JACC: CardioOncology* State-of-the-Art Review

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ABSTRACT

Immune checkpoint inhibitors (ICIs) are a major class of immuno-oncology therapeutics that have significantly improved the prognosis of various cancers, both in (neo)adjuvant and metastatic settings. Unlike other conventional therapies, ICIs elicit antitumor effects by enhancing host immune systems to eliminate cancer cells. There are 3 approved ICI classes by the U.S. Food and Drug Administration: inhibitors targeting cytotoxic T lymphocyte associated antigen 4, programmed death 1/programmed death-ligand 1, and lymphocyte-activation gene 3, with many more in development. ICIs are commonly associated with distinct toxicities, known as immune-related adverse events, which can arise during treatment or less frequently be of late onset, usually relating to excessive activation of the immune system. Acute cardiovascular immune-related adverse events such as myocarditis are rare; however, data suggesting chronic cardiovascular sequelae are emerging. This review presents the current landscape of ICIs in oncology, with a focus on important aspects relevant to cardiology. (J Am Coll Cardiol CardioOnc 2022;4:579–597)

The development of immune checkpoint inhibitors (ICIs) culminated decades of searching for the elusive keys to activating host immunity to regulate cancer growth. These agents have dramatically changed the landscape of cancer treatment in the past decade. The success of ICIs was recognized by the awarding of the 2018 Nobel Prize in Medicine or Physiology to 2 immunologists who developed the concept of ICIs, James Allison and Tasuku Honjo.[1] As of April 2022, therapies targeting 3 immune checkpoints: cytotoxic T lymphocyte associated antigen 4 (CTLA-4), programmed death-1 (PD-1) and its ligand (PD-L1), and lymphocyte-activation gene 3 (LAG-3), are approved by the U.S. Food and Drug Administration (FDA) for use as anticancer agents, either as monotherapy or in combination with other ICIs or with chemotherapy and/or molecularly targeted agents. Currently, almost half of all patients with metastatic cancer in high-income countries are being treated with ICIs.[2] However, there are a number of cancers in which ICIs are minimally effective; understanding primary and secondary resistance is a major focus of research. In this State-of-the-Art Review, we discuss the broad principles of ICI cancer treatment for solid tumors, including mechanisms of action, clinical indications,

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ABBREVIATIONS AND ACRONYMS

CTLA-4 = cytotoxic T lymphocyte associated antigen 4

ICI = immune checkpoint inhibitors

irAE = immune-related adverse event

LAG-3 = lymphocyte-activation gene 3

MSI = microsatellite instability

PD-L1 = programmed death-ligand 1

TMB = tumor mutational burden

TME = tumor microenvironment

immune-related adverse effects (irAEs), predictive biomarkers, contemporary issues and future directions, and emerging cardiovascular issues (**Central Illustration**).

MECHANISM OF ACTION

IMMUNE RESPONSE TO CANCER. Current ICIs were developed based on the cancer immunosurveillance hypothesis, which stipulated that the immune system is capable of detecting and eliminating nascent cancer cells.[3] Harnessing the host's own immunity to recognize and eliminate cancer cells as "foreign" has been a goal for decades, although the clinical utility of earlier cytokine-based immunotherapies such as interleukin-2 and interferon alpha were hampered by lack of specificity, causing low efficacy and high toxicity.[4]

Success of immunotherapies is reliant on tumor immunogenicity (ie, the ability of a tumor to induce a host immune response). Tumors with poor immunogenicity, simplistically denoted as "cold" tumors, such as primary brain, pancreatic and most colorectal cancer have poor response rates to immunotherapy[5,6]; conversely, "hot" tumors such as melanoma and squamous cell carcinomas, can respond dramatically.[5] Tumor immunogenicity is affected by intrinsic characteristics such as tumor antigen expression and tumor-infiltrating cytotoxic CD8 lymphocytes,[5,6] as well as the tumor microenvironment (TME), which consists of anatomical and physiological properties extrinsic to cancer cells (**Figure 1**). The host's gut microbiome is also proving to be an important determinant of response, with mechanisms still poorly understood.

IMMUNE CHECKPOINT INHIBITORS. ICIs are monoclonal antibodies that achieve immune activation by inhibiting key regulatory mechanisms known as checkpoints. Immune checkpoints are physiologically designed to limit immune responses within the body, and thus their inhibition restores host T cell immunity toward cancer cells that have adapted toward immune evasion. The processes involved in cytotoxic CD8 T cell-mediated immunity are summarized in **Figure 2**.

CTLA-4 inhibitors. CTLA-4 is an inhibitory receptor present on T cells that downregulates T cell activity and prevents unnecessary T cell activation (**Figure 2**).[7-9] Inhibition of CTLA-4 receptors blocks these inhibitory signals and upregulates T cell activation and response toward cancer cells.[10]

Ipilimumab, a CTLA-4 inhibitor, was the first ICI to enter clinical use, approved in 2011 by the U.S. FDA following demonstration of an overall survival benefit in a randomized phase III trial in metastatic melanoma, a previously treatment-resistant, highly fatal malignancy with median survival <1 year[11]; with modern immunotherapy at least 50% of patients, even with widespread metastatic disease including brain secondaries, appear to be cured.[12,13] This is the only CTLA-4 inhibitor commonly used in standard practice, either as monotherapy or in combination with PD-1/PD-L1 inhibitors. Ipilimumab is usually prescribed a total of 4 cycles (termed induction) and not continually like PD-1/PD-L1 inhibitors, mainly due to toxicity. An adjustment of dose from initial schedules has made this a far more tolerable treatment.[14]

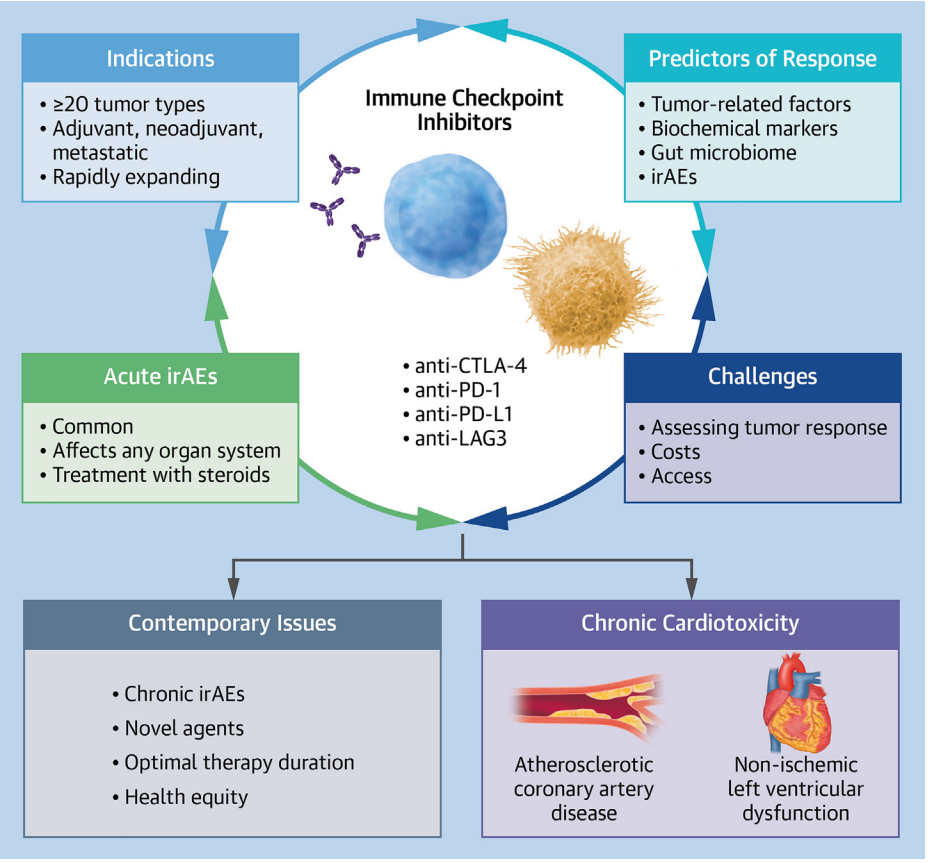
PD-1 and PD-L1 inhibitors. PD-L1 is a protein on target cells that binds to PD-1 receptors on CD8 T cells to limit inflammation and prevent healthy tissue from damage (**Figure 2**).[15] Tumor cells have the ability to express PD-L1 to cause T cell anergy and evade immune response. ICIs targeting PD-1 receptors or PD-L1 prevent tumor escape from overexpression of PD-L1, leading to cytotoxic CD8 T cell-mediated tumor cell destruction.

U.S. FDA approval for this ICI subclass followed shortly after the success of ipilimumab. Widespread use of these agents as standard therapies has rapidly been adopted after reporting of large scale randomized controlled trials across a broad range of cancers. Generally this subclass of ICI has demonstrated less toxicity than CTLA-4 inhibitors.[16]

HIGHLIGHTS

- Immune checkpoint inhibitors (ICIs) stimulate and enhance host immunity to eliminate cancer cells.
- Indications are rapidly broadening across various cancer types and settings (cure, palliation, adjuvant).
- Although generally well tolerated, ICIs cause immune-related adverse events (irAEs), related to excessive immune activation.
- Attention should be directed toward the detection and management of chronic irAEs.

CENTRAL ILLUSTRATION **Current Landscape and Contemporary Issues of Immune Checkpoint Inhibitors**



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The use of immune checkpoint inhibitors in oncology has grown significantly in the past decade, with significant focus on expanding indications, determining predictors for response, treating immune-related adverse events (irAEs), and developing methods to assess tumor response. Further efforts are required to address emerging contemporary issues surrounding potential chronic cardiotoxicities, optimal length of therapy, and health equity. CTLA-4 = cytotoxic T lymphocyte associated antigen 4; LAG-3 = lymphocyte-activation gene 3; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1.

Commonly used PD-1 inhibitors include nivolumab, pembrolizumab, and cemiplimab; PD-L1 inhibitors include atezolizumab, avelumab, and durvalumab.

Lymphocyte-activation gene 3 inhibitors. LAG-3 is a co-inhibitory protein that is uniquely present on both cytotoxic CD8 T cells as well as immunosuppressive regulatory T cells. Inhibition of LAG-3 increases CD8 T cell response both directly and indirectly through reduced regulatory T cell mechanisms (**Figure 2**),[17,18] with additive antitumor effects when combined with PD-1 inhibition.[19]

LAG-3 inhibitors are the latest class of ICIs to be granted approval by the U.S. FDA. Currently, there is 1 LAG-3 inhibitor in clinical use, relatlimab, which is only available in a fixed dose combination with nivolumab in the treatment of advanced melanoma.[20]

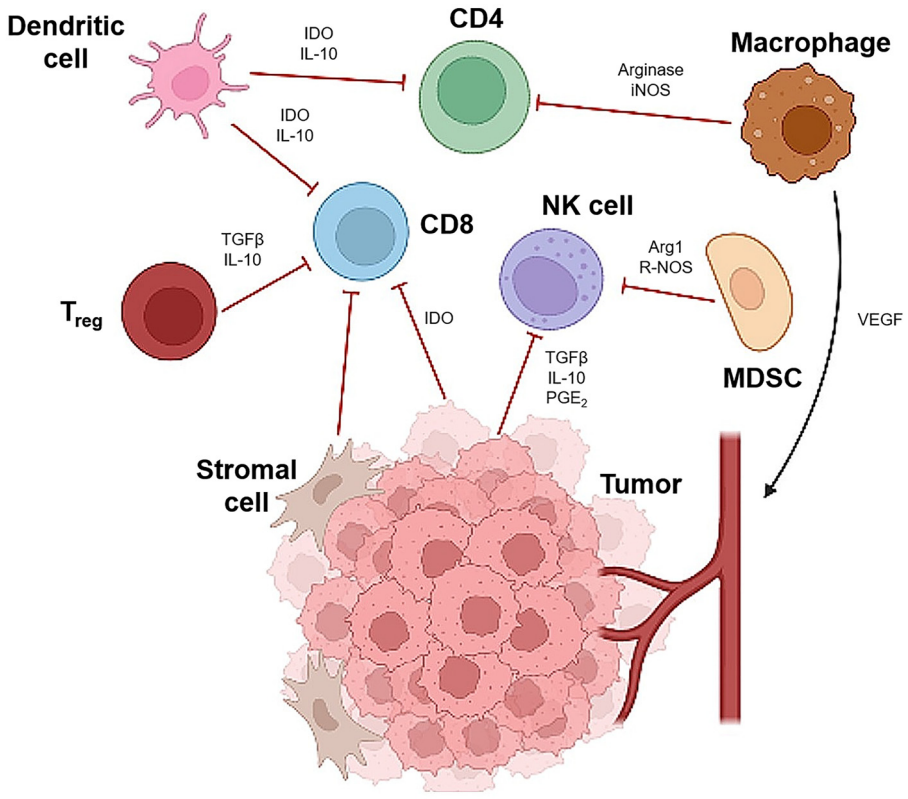
KEY POINTS.

- ICIs utilize host immunity to eliminate cancer cells.
- Response to ICIs is reliant on tumor immunogenicity.
- ICIs in use include anti-CTLA-4, anti-PD-1/PD-L1, and anti-LAG-3 antibodies.

PRACTICAL APPLICATIONS

CLINICAL INDICATIONS. ICIs are routinely used in patients across approximately 20 tumor types, with

FIGURE 1 Tumor Microenvironment

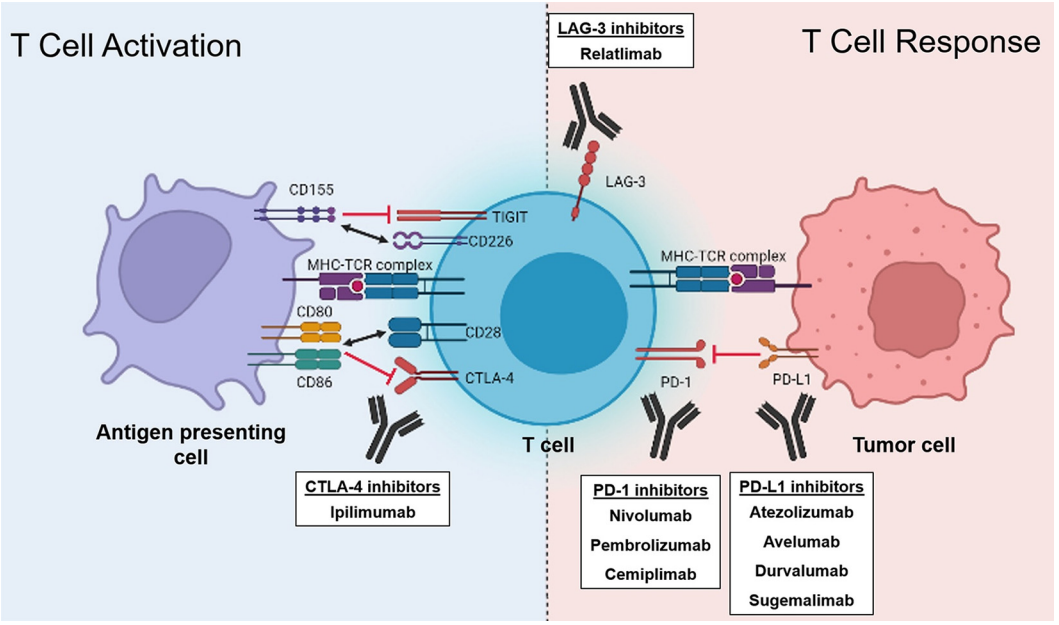


The tumor microenvironment consists of immune cells (CD8 T cells, CD4 T cells, regulatory T cells [T_{regs}], natural killer [NK] cells, dendritic cells, macrophages, myeloid-derived suppressor cells [MDSCs]) within the extracellular matrix, stromal cells, surrounding vascular supply, and numerous cytokines.[6,113] Through expression of various cytokines (inhibitory cytokines shown by **red lines**, stimulatory cytokines shown by **black arrows**), the tumor microenvironment can promote tumor growth and immune evasion. Created with BioRender. Arg1 = arginase 1; IDO = indoleamine 2,3-dioxygenase; IL = interleukin; iNOS = inducible nitric oxide synthase; PGE_2 = prostaglandin E2; R-NOS = reactive nitric oxide species; TGF = transforming growth factor; VEGF = vascular endothelial growth factor.

rapidly broadening indications as numerous ongoing trials are reported (Figure 3). All ICIs in clinical use are only available as intravenous formulations. PD-1/PD-L1 inhibitors are the most widely used, commonly as monotherapy, or as the backbone of combination regimens with ipilimumab or relatlimab, cytotoxic chemotherapy, and/or molecularly targeted therapies. Current indications for patients with metastatic cancer are summarized in Table 1, while current indications in the adjuvant (defined as systemic therapy to eliminate micrometastases and reduce risk of recurrence after definitive cancer treatment, usually surgery or [chemo]radiotherapy) and neoadjuvant (defined as systemic therapy to downsize tumors prior to definitive therapy) settings are summarized in Table 2.[21]

MEASURING TUMOR RESPONSE. Response to standard anticancer treatment has been defined in clinical trials using serial measurements of tumor size and/or volume by conventional radiological imaging, predominantly computed tomography, positron emission tomography–computed tomography, or magnetic resonance imaging. Compared with conventional systemic treatments, lesions may sometimes increase in size early after commencement of ICIs (usually at first tumor assessment at 6-8 weeks). This

FIGURE 2 **Mechanisms of T Cell Activation, Response, and Immune Checkpoint Inhibitors**

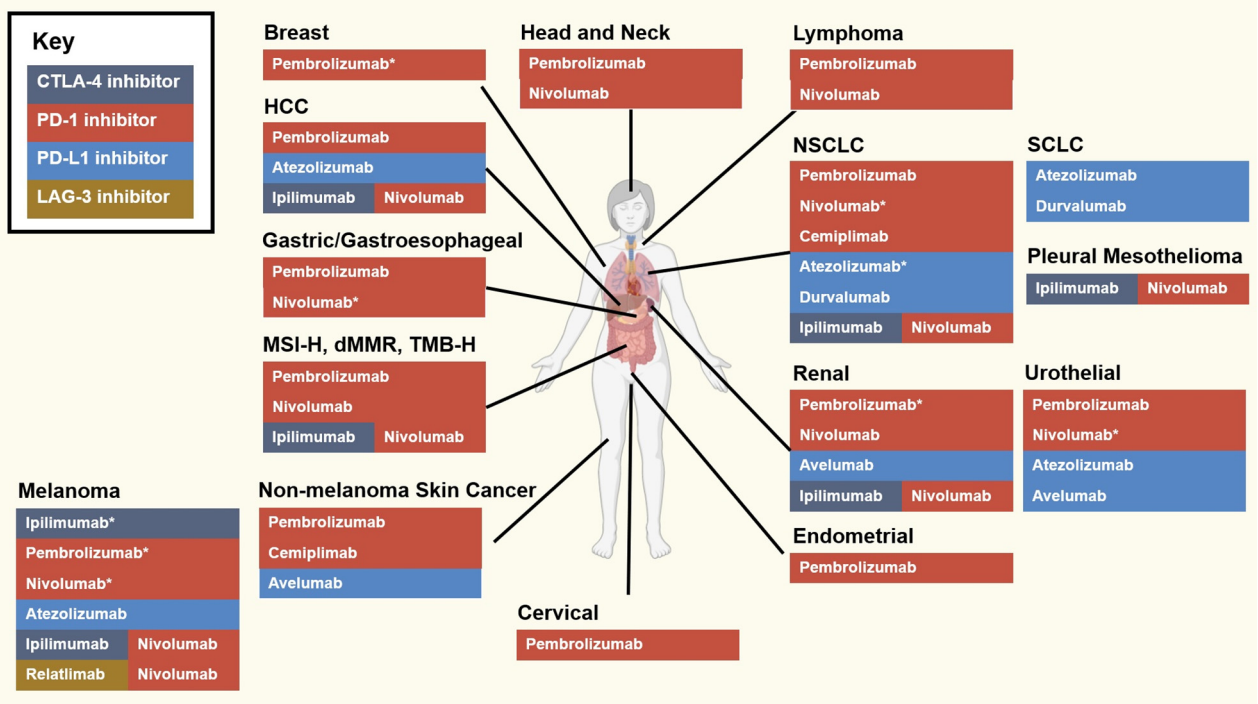


T cell activation is a multiple signal process that begins with tumor antigen presentation by antigen-presenting cells (APCs) from the innate immune system to T cells via the major histocompatibility complex (MHC). A second co-stimulatory signal from the binding of CD80 and CD86 on APCs to CD28 on T cells is also required.[114,115] The intracellular cascade from these signals results in the differentiation of resting CD8 T cells into activated cytotoxic CD8 T cells, which have the ability to recognize tumor cells and promote tumor cell apoptosis through secretion of various cytotoxins. This process is further assisted by additional co-stimulatory signals **(black 2-way arrows)** or inhibited by co-inhibitory signals **(red lines)** that are both present in T cell activation and response. Cytotoxic T lymphocyte associated antigen 4 (CTLA-4), programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1), and lymphocyte-activation gene 3 (LAG-3) are co-inhibitory signal targets for immune checkpoint inhibition, allowing increased T cell activation and response toward tumor cells. Additional nonimmune mechanisms of immune checkpoint inhibitors (not depicted) may be involved in the treatment of lymphoma. Created with BioRender. TCR = T cell receptor; TIGIT = T cell Immunoreceptor with Ig and ITIM domains.

phenomenon, known as pseudoprogression, is postulated to be due to initial massive recruitment of immune cells/inflammatory response.[12] Although uncommon, pseudoprogression can be difficult to distinguish from early tumor progression. Standardized radiological response criteria, RECIST (Response Evaluation Criteria in Solid Tumors),[22] used in early clinical trials failed to account for this phenomenon, leading to the development of modified versions in current use, denoted iRECIST (immune RECIST).[23] Current guidelines recommend considering radiological assessment in context with clinical status (improvement in symptoms, weight), however evaluation of early tumor response can remain challenging.[23]

OPTIMAL THERAPY DURATION. One remarkable feature of treatment with ICIs is the possibility of durable stable disease, or response (including complete response) and "clinical cure" for patients with metastatic disease.[12] Sixteen percent of 655 patients with metastatic melanoma treated with PD-1 inhibitors with or without anti-CTLA-4 had complete response and after cessation of ICI, <10% relapsed over 5-year follow-up.[24] Even better results were demonstrated with PD-1 inhibition in a pooled cohort of patients with advanced melanoma, renal cell cancer, and non-small cell lung cancers, with 5 year survival rates of 34%, 28% and 16%, respectively, after achieving either complete or partial response.[25] This has led to substantial hope for a possible cure for metastatic cancers in some patients treated with ICIs, although it is important to acknowledge that durable response has only been reported in a minority of patients (more frequently seen in patients who

FIGURE 3 U.S. Food and Drug Administration–Approved Immune Checkpoint Inhibitors as of April 2022



There are ≥20 approved indications for immune checkpoint inhibitors at time of writing, although this is expected to expand significantly in the future. Created with BioRender. *Also approved for use in adjuvant or neoadjuvant settings. dMMR = deficient mismatch repair; HCC = hepatocellular carcinoma; MSI-H = microsatellite instability-high; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; TMB-H = tumor mutational burden-high; other abbreviations as in Figure 2.

achieve complete rather than partial response), with many still succumbing to cancer.[12] Observations of durable response have led to current studies to define optimal duration of ICI therapy, particularly in complete or partial responders. In practice, a 2-year treatment duration is commonly used based on consensus opinion.[26] The small proportion of patients with disease progression after ICI discontinuation may be retreated, although observational studies have reported variable response rates on rechallenge.[24,27]

Duration of ICI in adjuvant settings is also of interest due to balancing survival benefit with ICI-related morbidity from acute and chronic irAEs, especially in low-risk patients in which surgery alone could be curative. Further research is currently directed at evaluating this challenging paradigm, with postulation that shorter regimens could reduce the occurrence of irAEs without compromising cancer-related survival.[28] Costs and use of health care resources are also factors to be considered in this regard.

INTERACTION WITH OTHER THERAPIES.

Corticosteroids. High-dose and chronic low-dose corticosteroids are relatively contraindicated during ICI therapy, particularly early in the treatment course due to potential to negate antitumor efficacy, although definitive evidence is lacking.[29] Steroid use for antiemesis particularly for concurrent chemotherapy is tolerated but should be minimized by use of alternate agents where practical.

Cytotoxic chemotherapy. Cytotoxic chemotherapy can synergistically enhance ICI activity by triggering release of tumor antigen from dying cancer cells for immune cell recognition.[30] Combination ICI and cytotoxic chemotherapy, in particular platinum or taxane-based regimens, are employed in the treatment of non-small cell cancer[31-33] and small cell lung cancer,[34,35] head and neck cancer,[36] triple negative breast cancer,[37,38] and esophageal cancer.[39-42] Further trials in other cancer types are ongoing.

Targeted therapies. Vascular endothelial growth factor (VEGF) inhibitors are targeted therapies which inhibit angiogenesis signatures within the TME and

TABLE 1 U.S. Food and Drug Administration Approved Immune Checkpoint Inhibitors as of April 2022: Advanced or Metastatic Cancers

Organ	Cancer	Immune Checkpoint Inhibitor	Line of Therapy	Schedule
Skin	Melanoma	Ipilimumab[116]	First	Every 3 wk
		Pembrolizumab[16]	First	Every 3 or 6 wk
		Nivolumab[117]	First or second	Every 2 or 4 wk
		Atezolizumab[118]	First	Every 2-4 wk
		Ipilimumab and Nivolumab[13]	First	Every 3 wk
		Relatlimab and Nivolumab[20]	First	Every 4 wk
	Cutaneous squamous cell carcinoma	Pembrolizumab[119]	First	Every 3 or 6 wk
		Cemiplimab[120]	First	Every 3 wk
	Basal cell carcinoma	Cemiplimab[121]	Second	Every 3 wk
	Merkel cell carcinoma	Pembrolizumab[122]	First	Every 3 or 6 wk
		Avelumab[123]	First	Every 2 wk
Lung	Non-small cell lung cancer	Pembrolizumab[31,32,124]	First	Every 3 or 6 wk
		Nivolumab[125,126]	First or second	Every 2 or 4 wk
		Cemiplimab[127]	First	Every 3 wk
		Atezolizumab[33,128]	First	Every 2-4 wk
		Ipilimumab and Nivolumab[129]	First	Every 3 wk
	Small cell lung cancer	Atezolizumab[34]	First	Every 2-4 wk
		Durvalumab[35]	First	Every 3-4 wk
	Pleural mesothelioma	Ipilimumab and Nivolumab[130]	First	Every 6 wk
Urological	Renal cell cancer	Pembrolizumab[44,45]	First	Every 3 or 6 wk
		Nivolumab[46]	First or second	Every 2 or 4 wk
		Avelumab[47]	First	Every 2 wk
		Ipilimumab and Nivolumab[131]	First	Every 3 wk
	Urothelial carcinoma	Pembrolizumab[132,133]	Second	Every 3 or 6 wk
		Nivolumab[134]	Second	Every 2 or 4 wk
		Atezolizumab[135-137]	First or second	Every 2-4 wk
		Avelumab[138]	Second	Every 2 wk
Head and neck	Squamous cell carcinoma	Pembrolizumab[36]	First	Every 3 or 6 wk
		Nivolumab[139]	Second	Every 2 or 4 wk
Gastrointestinal	Hepatocellular carcinoma	Pembrolizumab[140]	Second	Every 3 or 6 wk
		Atezolizumab[48]	First	Every 2-4 wk
		Ipilimumab and Nivolumab[141]	Second	Every 3 wk
	MSI-H or dMMR colorectal cancer	Pembrolizumab[80]	First	Every 3 or 6 wk
		Nivolumab[81]	Second	Every 2 or 4 wk
		Ipilimumab and Nivolumab[142]	Second	Every 3 wk
	Gastric and gastroesophageal cancer	Pembrolizumab[39,41]	First	Every 3 or 6 wk
		Nivolumab[40,42]	First or second	Every 2-4 wk
Gynecological	Cervical cancer	Pembrolizumab[143]	First or second	Every 3 or 6 wk
	Endometrial cancer	Pembrolizumab[49,144]	Second	Every 3 or 6 wk
Breast	Triple negative breast cancer	Pembrolizumab[37]	First	Every 3 or 6 wk
Lymphoma	Classical Hodgkin's lymphoma	Pembrolizumab[145]	Third	Every 3 or 6 wk
		Nivolumab[146]	Fourth	Every 2 or 4 wk
	Mediastinal B cell lymphoma	Pembrolizumab[147]	Third	Every 3 or 6 wk
Others	MSI-H, dMMR, or TMB-H solid organ tumors	Pembrolizumab[82,148]	Salvage therapy	Every 3 or 6 wk

Source: U.S. FDA.[21]

dMMR = deficient mismatch repair; MSI-H = microsatellite instability-high; TMB-H = tumor mutational burden-high.

improve tumor response to ICI therapy.[43] VEGF inhibitors are commonly prescribed with ICIs in the treatment of renal cell carcinoma,[44-47] with clinical benefit also demonstrated in hepatocellular carcinoma[48] and endometrial cancer.[49]

Radiotherapy. Radiotherapy has been shown to enhance tumor immunogenicity by increasing tumor antigen release and inflammatory cytokine signaling within the TME.[50] Several preclinical studies have shown radiotherapy to enhance T cell activation and

TABLE 2 U.S. Food and Drug Administration Approved Immune Checkpoint Inhibitors as of April 2022: Adjuvant and Neoadjuvant Therapies

Organ	Cancer	Immune Checkpoint Inhibitor	Scenario	Cancer Stage	Schedule
Skin	Melanoma	Ipilimumab[149]	Adjuvant	III	Every 3 wk
		Pembrolizumab[150]	Adjuvant	II-III	Every 3 or 6 wk
		Nivolumab[151]	Adjuvant	III	Every 2 or 4 wk
Lung	Non-small cell lung cancer	Nivolumab[152]	Neoadjuvant	I-III	Every 3 wk
		Atezolizumab[153]	Adjuvant	II-III	Every 2-4 wk
		Durvalumab[154]	Adjuvant	III	Every 2 or 4 wk
Urological	Renal cell cancer	Pembrolizumab[155]	Adjuvant	II-IV	Every 3 or 6 wk
	Urothelial carcinoma	Nivolumab[156]	Adjuvant	III	Every 2 or 4 wk
Gastrointestinal	Gastric and gastroesophageal cancer	Nivolumab[157]	Adjuvant	II-III	Every 2 or 4 wk
Breast	Triple negative breast cancer	Pembrolizumab[38]	Adjuvant and neoadjuvant	II-III	Every 3 or 6 wk

Abbreviations as in Table 1.

response, suggesting a synergistic potential if used in combination with ICIs.[50] Clinical studies investigating ICI treatment with radiotherapy are underway.

KEY POINTS.

- Three ICI classes (9 agents) are currently approved for use across 20 tumor types as monotherapy and in various combinations, with anti-PD-1/PD-L1 antibodies being the most commonly used.
- Durable response can be observed in patients with metastatic disease.
- The optimal duration of treatment with ICIs in both metastatic and adjuvant settings is under investigation.

IMMUNE-RELATED ADVERSE EVENTS

IrAEs refer to autoimmune-like adverse reactions that can occur in any organ, particularly those with extensive environmental exposure (eg, skin, gastrointestinal tract, lungs) or predisposition to autoimmunity (eg, thyroid) (**Figure 4, Tables 3 and 4**).[51] Although irAEs mirror de novo autoimmune disease, the timing in relation to treatment is usually diagnostic, with manifestation usually within the first 3 months of ICI initiation, although more rarely at later time points, including after ICI discontinuation.[52] Severity is graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (**Table 5**).[53]

Each subclass of ICIs has subtly different patterns but often quite different incidence of individual irAEs.[54] In general, high grade (grade ≥3) irAEs occur most frequently in patients treated with combination anti-CTLA-4 and anti-PD-1/PD-L1, followed by anti-CTLA-4 monotherapy, combination anti-LAG-3 and anti-PD-1, and PD-1/PD-L1 monotherapy. Combination anti-CTLA-4 with anti-PD-1/PD-L1 is associated with increased incidence and severity of irAEs, with an estimated 55% incidence of high-grade irAEs, leading to significantly higher rates treatment discontinuation.[55,56] In a meta-analysis of 22 trials including 1,265 patients, CTLA-4 inhibition was associated with a 72% overall incidence of irAEs, of which 24% were high grade and 0.9% were fatal.[57] In contrast, a meta-analysis of 46 studies and 12,808 patients treated with PD-1/PD-L1 inhibitors reported an overall irAE incidence of 27%, of which 6% were high grade and mortality was 0.2%.[58] The risk of CTLA-4 inhibitor-associated toxicities increases with dose, which is not the case with PD-1/PD-L1 inhibitors, which are used at fixed dosing schedules.[57,58]

MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS. Guideline-directed recommendations for managing irAEs have been developed by oncological societies such as the American Society of Clinical Oncology, National Comprehensive Cancer Network, and European Society of Medical Oncology (**Figure 5**).[59-62] These are categorized into affected organ systems (**Table 4**) and specific recommendations are available for each individual irAE. Mild-to-moderate (grade 1 or 2) irAEs may be observed or managed symptomatically while continuing therapy; however, intolerable low grade irAEs may require treatment interruption or cessation. Corticosteroids form the mainstay of treatment for high-grade irAEs, including high-dose methylprednisolone, with rapid escalation to other immunosuppressive therapies,

TABLE 3 Cardiovascular Immune-Related Adverse Events

Cardiac Immune-Related Adverse Events[60,108]	Incidence[a]	Grading	Management
Myocarditis Pericarditis Arrhythmias Heart failure Myocardial infarction Ischemic stroke	0.3%-0.5% 0.8% 1% 0.9% 0.7% 0.9%	Grade 1: Abnormal cardiac biomarker without symptoms or ECG abnormalities Grade 2: Abnormal cardiac biomarker with mild symptoms or new ECG abnormalities without conduction delay Grade 3: Abnormal cardiac biomarker with moderate symptoms or new conduction delay Grade 4: Life-threatening conditions with moderate-severe decompensation requiring intervention or intravenous medications	Grade 1: • Withhold ICI and recheck cardiac biomarker • Consider resuming once normalized or if believed not to be related to ICI Grade ≥2: • Withhold and cease ICI • Admission to hospital for monitoring • High-dose corticosteroids (1-2 mg/kg/d prednisone, oral or intravenous) • If unresponsive to high-dose corticosteroids, consider methylprednisolone 1 g/d and addition of other immunosuppressants (mycophenolate, infliximab, antithymocyte globulin, abatacept, alemtuzumab) • Consider pacemaker if conduction delay
Venous thromboembolism	12.9%	Grade 1: Superficial thrombosis Grade 2: Uncomplicated deep vein thrombosis Grade 3: Uncomplicated pulmonary embolism Grade 4: Life-threatening conditions	Grade 1: • Continue ICI • Warm compresses Grade 2: • Continue ICI • Anticoagulation Grade 3: • Withhold ICI • Anticoagulation • Consider recommencing ICI depending on risk-benefit assessment Grade 4: • Withhold ICI • Admission for respiratory and/or hemodynamic support • Anticoagulation • Consider recommencing ICI depending on risk-benefit assessment
Dyslipidemia	2%	Not applicable	Treat as per standard guideline-directed recommendations

[a]Incidences primarily derived from a meta-analysis (108) of ICI clinical trials of patients treated during a follow-up ranging from 3.2 to 32.8 months.
ECG = electrocardiography; ICI = immune checkpoint inhibitor.

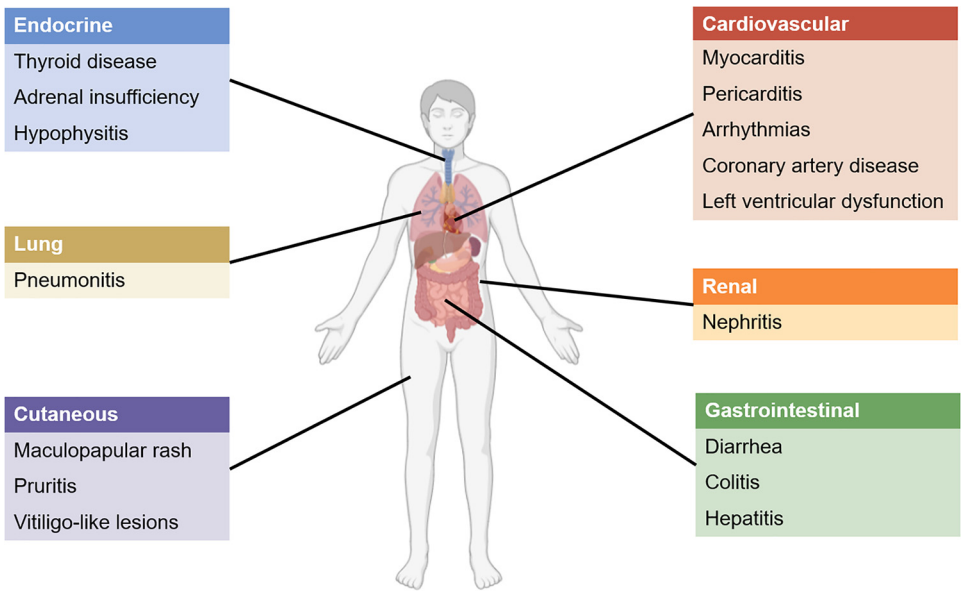
such as infliximab, mycophenolate mofetil, or cyclophosphamide, if severe or recalcitrant.[60] Consultation with organ-based specialties is frequently required for high grade toxicities, particularly if diagnostic investigations are required (eg, colonoscopy in setting of colitis).

ASSOCIATION WITH CLINICAL RESPONSE. The occurrence of irAEs has been postulated to reflect a robust immune reaction with ICIs and has been demonstrated to modestly correlate with increased antitumor efficacy characterized by greater response rate, progression-free survival, and overall survival.[52,63-65] This association has only been observed with PD-1/PD-L1 inhibitors[63-65] but not CTLA-4 inhibitors.[66] Although the association between antitumor benefits with irAE type, timing, treatment and course have yet to be described, the event of minor or treatable irAEs should provide clinicians with reassurance to persist with treatment.

RECHALLENGE. Most acute irAEs resolve with discontinuation of ICI. Current guidelines recommend permanent cessation only in patients with grade 4 irAEs,[59-61] with the majority eligible for rechallenge after irAE resolution, particularly if anticancer efficacy has been demonstrated and/or in which few alternative treatments are available. In patients who experience limiting irAEs with combination ICI therapy, treatment can often be continued with a single-agent PD-1 inhibitor. ICI rechallenge following irAE resolution was reported to have a recurrence rate of 28.8% in an observational pharmacovigilance cohort study of 24,079 irAE cases.[67] Colitis, hepatitis, and pneumonitis were associated with a higher recurrence with rechallenge.[67] Similar results were demonstrated in a meta-analysis of 77 studies, with all-grade and high-grade recurrent irAEs being 34.2% and 11.7% respectively.[68]

Strategies for rechallenge include switching ICI classes, rechallenging with the same ICI as

FIGURE 4 Main Organs Affected by Immune-Related Adverse Events



Any organ system can be affected. Most common are skin, endocrine, gastrointestinal tract, kidney and lung. Cardiovascular immune-related adverse events are rare but carry significant mortality and morbidity. Created with BioRender.

monotherapy, and prophylaxis with antihistamines and steroids.[69] Importantly, no loss of antitumor efficacy has been reported in the specific scenario for ICIs used with concurrent immunosuppression for toxicity.[69]

CARDIOVASCULAR irAEs. Cardiovascular irAEs are rare but carry significant morbidity and mortality (**Table 3**).[51,60] Acute fulminant myocarditis represents the most concerning irAE, with reported estimated incidence of up to 1% and mortality rates of up to 50%.[70] Patients often present within 6 weeks of ICI commencement, with presentations ranging from abnormal results on cardiovascular surveillance (usually being performed for other reasons such as concurrent cardiotoxic therapy) to fulminant heart failure with cardiogenic shock.[51,60] Diagnosis may not be straightforward and requires clinical correlation with 12-lead electrocardiography, biomarkers such as troponin, echocardiography, negative coronary angiography, magnetic resonance imaging, and in some cases endomyocardial biopsy.[70,71] Depending on the combination of these features, patients may be classified into 3 groups—definite, probable and possible myocarditis.[71] Positively adjudicated cases of myocarditis may be subclassified into fulminant, clinically significant nonfulminant, and subclinical disease.[71]

Current guidelines recommend treatment for all cases of myocarditis, including cessation of ICI, cardiology consultation, high-dose corticosteroids, and supportive treatments such as diuretics and inotropes where required.[60] In cases of steroid-refractory myocarditis, other immunosuppressive agents such as mycophenolate, infliximab, antithymocyte globulin, abatacept, and alemtuzumab have been used, although evidence is limited.[60,70] With increasing awareness, there is growing identification of milder and subclinical cases, with management in the context of ongoing need for ICI therapy the subject of ongoing investigation.

Additional acute cardiovascular irAEs during treatment include pericarditis, arrhythmias, heart failure, coronary artery disease, venous thromboembolism, and dyslipidemia, which are managed similarly to non-immune-mediated cases, with additional considerations to suspend or cease treatment depending on severity.[60]

KEY POINTS.

- ICIs can cause irAEs which may mimic autoimmune disease.
- Systemic corticosteroids are essential in the management of high-grade irAEs.
- Acute myocarditis is a rare but potentially fatal cardiovascular irAE.

TABLE 4 Noncardiovascular Immune-Related Adverse Events

Organ System	Immune-Related Adverse Events[60,158-160]	Estimated Incidence
Skin	Maculopapular rash, pruritis, vitiligo-like lesions, erythema multiforme, lichenoid, eczematous, psoriasiform, morbilliform, palmar-plantar erythrodysesthesia, bullous dermatoses, hand-foot syndrome	Overall: 71.5% Maculopapular rash: 14%-24%
Gastrointestinal	Immune-related diarrhea, colitis, hepatitis, gastritis, enterocolitis	Diarrhea: 25%-54% Colitis: 3% Hepatitis: 10%-30%
Endocrine	Hypothyroidism, hyperthyroidism, primary adrenal insufficiency, hypophysitis, diabetes	Hypothyroidism: 6.6% Hyperthyroidism: 2.9% Primary adrenal insufficiency: 0.7% Hypophysitis: 1.3%
Lung	Pneumonitis	2.7%-10%
Musculoskeletal	Arthralgia, myalgia, inflammatory arthritis, myositis, polymyalgia-like syndrome	Arthralgia or myalgia: 40%
Renal	Nephritis, acute kidney injury	Acute kidney injury: 1%-5%
Neurological	Headache, myasthenia gravis or myasthenic syndrome, aseptic meningitis, encephalitis, Guillain-Barré syndrome, peripheral neuropathy, demyelinating disorders	Overall: 3%-12% High-grade: <1%
Hematologic	Hemolytic anemia, acquired thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, aplastic anemia, lymphopenia, immune thrombocytopenia	Anemia: 9.8% Thrombocytopenia: 2.8%
Ocular	Uveitis, iritis, episcleritis	Uveitis: 1% Episcleritis: <1%

Incidences provided are for both monotherapy and combination immune checkpoint inhibitor regimens.

PREDICTIVE BIOMARKERS

Predictive biomarkers of ICI activity is an area of intensive research with 3 in clinical use: PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability (MSI) (**Figure 6**); under investigation are markers of TME, genomic mutational profile, gut microbiome, and neutrophil-to-lymphocyte ratio (NLR). Conceptually, these biomarkers evaluate elements of tumor and host immunogenicity, although none have been validated to be completely clinically reliable. Characterization of host immunogenicity may likely require composite biomarkers in future.

PD-L1 EXPRESSION. The degree of PD-L1 expression on tumor cells and antigen-presenting cells measured using immunohistochemistry has been shown to enrich for responders to treatment with PD-1/PD-L1 inhibitors.[72] Many clinical trials evaluating PD-1/PD-L1 inhibitors utilized PD-L1 expression for target population selection, stratification, or to correlate with clinical efficacy, which led to PD-L1 expression being included by the FDA as an eligibility criterion for PD-1/PD-L1 inhibitor use in certain cancers.[73] However, its predictive utility and the threshold level for clinical benefit seem to be tumor-specific; while high expression predicts for treatment efficacy in certain tumor types, lack of PD-L1 expression may not preclude clinical response entirely, and in other tumor types, it lacks predictive ability altogether. In addition, the available commercial immunohistochemistry assays are not interchangeable, tissue staining can be heterogeneous, and there can be significant interobserver variability.[74]

TUMOR MUTATIONAL BURDEN AND MICROSATELLITE INSTABILITY. TMB, defined as the total number of mutations per coding area of tumor DNA,[75] is predictive of response to CTLA-4 inhibitors[76-78] and PD-1/PD-L1 inhibitors.[75] It has been hypothesized that increased TMB leads to increased expression of different tumor neoantigens (peptides unique to cancer cells), thus enhanced recognition by cytotoxic CD8 T cells and increased tumor immunogenicity.[77] However, the correlation is imperfect, postulated to be due to expression of less immunogenic tumor-specific antigens and genetic heterogeneity within individual tumors.[79] Although TMB alone may not predict treatment response in all patients,[73] the use of PD-1 inhibitors in patients with high-TMB advanced solid tumors, as determined by companion diagnostic tests, has been approved by the FDA in patients who have exhausted all other treatment options.

One critical determinant of TMB is whether there are defects in DNA damage repair pathways, which are innate cellular mechanisms responsible for repairing genetic aberrations during replication. Defects such as deficient mismatch repair (from germline mutations or somatic epigenetic changes in DNA mismatch repair genes) lead to increased genetic

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TABLE 5 National Cancer Institute Common Terminology Criteria for Adverse Events Grading for Immune-Related Adverse Events

Grade	Severity	Definition[53]
1	Mild	Asymptomatic or mild symptoms Clinical or diagnostic observation only Intervention not indicated
2	Moderate	Limiting age-appropriate instrumental activities of daily living Minimal, local, or noninvasive intervention indicated
3	Severe	Disabling or limiting self-care activities of daily living Medically significant but not immediately life-threatening Hospitalization or prolongation of hospitalization indicated
4	Life-threatening	Urgent intervention indicated
5	Fatal	Death related to adverse event

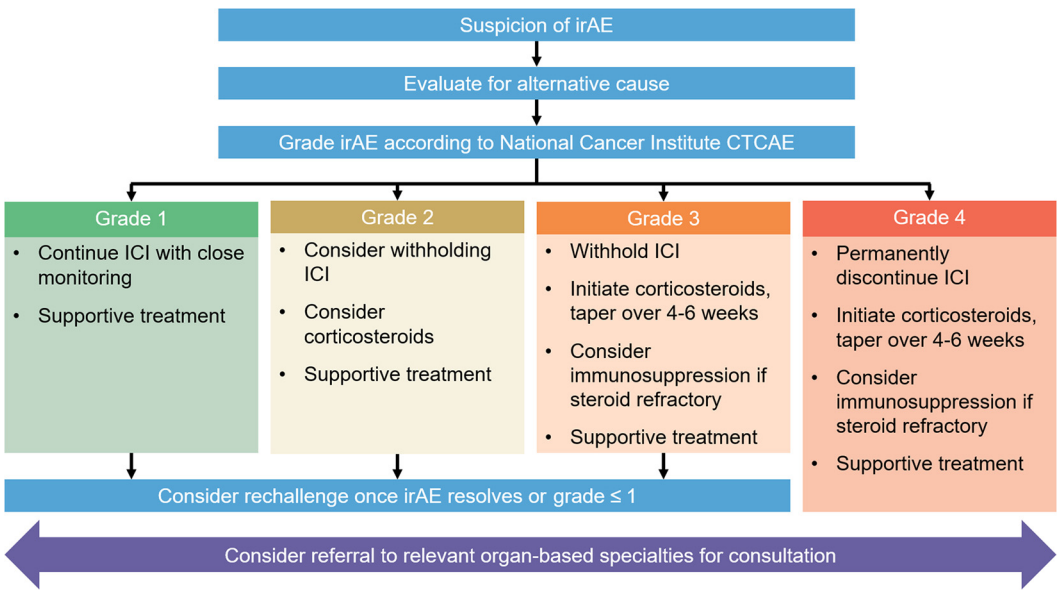
hypermutability in short repeated sequences of DNA called microsatellites. Tumors with deficient mismatch repair or its characteristic genetic signature of high MSI are highly sensitive to ICIs,[80-82] resulting in the first biomarker-driven tumor-agnostic cancer treatments approved by the FDA.

TUMOR MICROENVIRONMENT. Potential novel biomarkers for TME employ transcriptomic analysis to profile messenger ribonucleic acids and identify immune and angiogenesis signatures within the TME.[43] TME profiles can guide rational drug partners for ICI (eg, antiangiogenesis agents) to improve tumor response. Early studies evaluating these biomarkers are promising and further investigations are ongoing.[83,84]

GENOMIC MUTATIONAL PROFILE. Variations in oncogenes, tumor suppressors, and natural immune signaling pathways, such as MAPK, PI3K-AKT-mTOR, WNT-β, and IDO1, have been postulated as biomarkers to predict response to ICIs.[73] Serial tumor biopsy studies to understand evolution of tumor mutational profile during ICI treatment are underway to outline mechanisms of resistance.

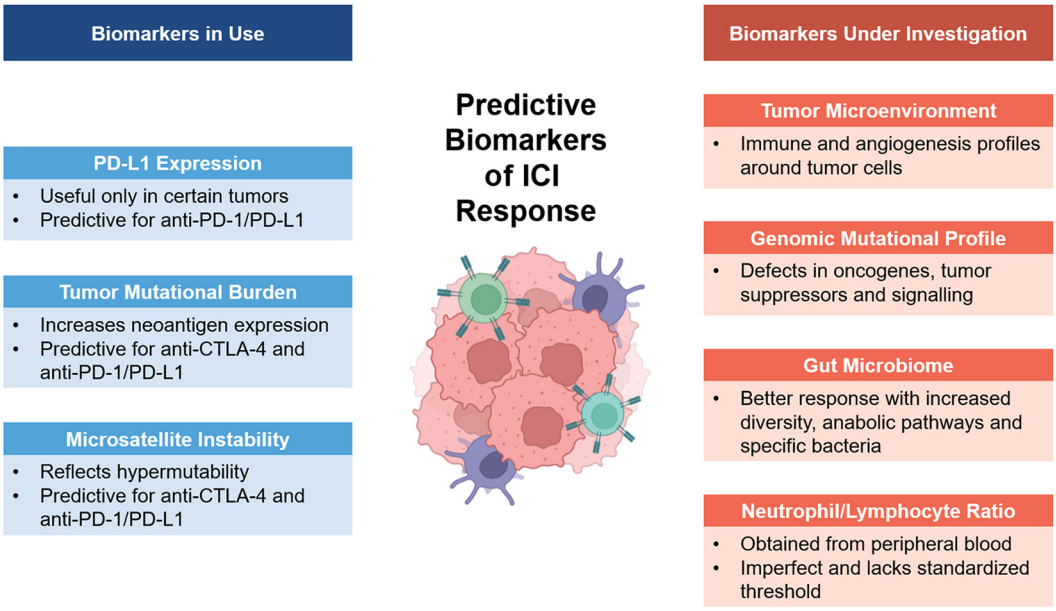
GUT MICROBIOME. Human gut microbiomes with increased diversity, enriched anabolic pathways, and specific bacteria such as *Ruminococcus*, *Firmicutes*, and *Akkermansia muciniphila* have been associated with better response to ICIs.[85,86] Conversely, medications that can alter microbiome composition such as antibiotics,[86] proton pump inhibitors,[87] histamine

FIGURE 5 General Management Principles of irAEs



The management of immune-related adverse events (irAEs) depends on severity and involves consideration for suspension of therapy, corticosteroids, and/or immunosuppression.[59-61] Management of some organ-specific irAEs may differ from the provided flow chart. CTCAE = Common Terminology Criteria for Adverse Events; ICI = immune checkpoint inhibitor.

FIGURE 6 Predictive Biomarkers for Response to ICI Therapy



Biomarkers evaluating tumor and host immunogenicity have the potential to predict response to ICIs. Created with BioRender. Abbreviations as in Figures 2, 3, and 5.

receptor antagonists,[87] and cannabinoids[88] have been associated with worse prognoses in observational studies and post hoc analyses of clinical trials. Trials to improve ICI efficacy using oral probiotics, various diets and supplements, and even fecal microbiota transplantation are ongoing.[89]

NEUTROPHIL-TO-LYMPHOCYTE RATIO. NLR is a potential biochemical tool which reflects the balance between protumoral inflammation and antitumoral immune response.[90] Elevated pretreatment NLR and ratios that decrease during treatment are associated with worse overall and progression-free survival in retrospective studies.[90-93] These observations are similar to that seen in cardiovascular disease, in which elevated NLR has been shown to predict mortality in patients with acute coronary syndrome and heart failure.[94] However, NLR is not routinely used in clinical practice due to its limited predictive utility and lack of standardized thresholds.[91]

KEY POINTS.

- PD-L1 expression, TMB, and MSI/mismatch repair status are biomarkers in use to predict ICI response.
- Other genomic and immunological predictive biomarkers are under investigation.

CONTEMPORARY ISSUES AND FUTURE DIRECTIONS

MANAGEMENT OF CHRONIC TOXICITIES. As cancer survival improves as a result of ICIs, there is increasing focus on long-term sequelae in cancer survivorship care, which is defined as the health and well-being of a person with cancer from time of diagnosis to end of life.[95] In a retrospective study of 387 patients treated with adjuvant PD-1 inhibitors, 43.2% of patients developed chronic irAEs, defined as persisting beyond 12 weeks after ICI discontinuation.[96] Those involving nonvisceral systems such as endocrinopathies, neurotoxicities, and ocular toxicities were the commonest, and approximately one-third of patients required corticosteroids or persistent immunosuppression.[96] Another retrospective study of 437 patients reported 35.7% of irAEs persisting for up to 24 months.[97] Large registry and phase 4 trials are needed to provide more accurate estimates of chronic irAEs in real-world

settings. Studies investigating long-term organ-specific treatments and/or immunosuppression are also needed to guide management. A multidisciplinary approach and development of innovative ICI-specific models of follow-up, posttreatment surveillance, and preventive care is required to address long-term issues that may affect many cancer survivors.

NOVEL AGENTS. In 2019, there were more than 3,000 trials evaluating T cell modulators in oncology, representing two-thirds of all oncology trials.[98] These include other ICIs targeting alternative co-inhibitory signals such as T cell Immunoreceptor with Ig and ITIM domains (TIGIT) (**Figure 2**).[99] Although monotherapy anti-TIGIT has limited activity, preclinical and early efficacy results from combination TIGIT and PD-1/PD-L1 blockade look promising, including in tumors resistant to PD-1/PD-L1 inhibitors, with a more favorable safety profile compared with other ICI combinations.[100]

Agents that activate co-stimulatory signals such as GITR, CD40, CD40L, CD27, CD70, ICOS, and ICOSL, termed immune agonists, are being explored.[99] Other targets are macrophage checkpoint inhibitors, newer-generation cytokines, vaccine approaches, agents targeting the TME, bispecific T cell engagers, and adoptive cell therapies.[5,99]

HEALTH EQUITY. The costs of ICI are substantial and are not expected to reduce for some years due to ongoing patents, a plethora of new agents, and challenges with generating biosimilars for monoclonal antibodies (which is much more complex than for most other drug classes), limiting access in low- and middle-income countries and contributing to ongoing disparities in global cancer care and outcomes. In high-income countries, ICIs are major contributors to the significant economic burden of cancer care, which is projected to approximate $246 billion in the United States by 2030.[101] Global efforts are imperative to accelerate access to ICIs for cancer patients in low- and middle-income countries, as health access and outcome equity is increasingly recognized as a major sociopolitical issue.

Cost effectiveness studies of ICIs have demonstrated highly variable results depending on cancer and treatment type, setting, efficacy, sponsor of research, and study methodology.[102,103] Hence, further research into patient selection and cost-effectiveness using standardized clinical benefit criteria are required to reduce economic burden on health care systems.

KEY POINTS.

- Chronic irAEs are increasingly recognized in cancer survivorship.
- There are over 3,000 ongoing trials evaluating immune-oncological therapies.
- ICI cost is a barrier to broader uptake in low and middle income countries.

EMERGING CARDIOVASCULAR ISSUES

Chronic cardiovascular toxicities from ICIs are of particular concern, as cardiovascular disease is the leading cause of non-cancer-related death in cancer survivors even in the pre-ICI era due to overlapping risk factors as well as treatment-related effects.[104,105] There is growing appreciation of late onset cardiotoxicities such as atherosclerotic coronary artery disease[99] and nonischemic left ventricular dysfunction.[51,106]

The risk of accelerated coronary artery disease with ICIs is biologically plausible due to its proinflammatory mechanisms.[99] In a retrospective single-center analysis of 5,684 patients, ICI treatment resulted in a 7-fold increased risk of myocardial infarction compared with control subjects.[107] Similar findings were reported in a meta-analysis of 48 cancer drug trials and 29,592 patients, with a 1.5 times increased risk of myocardial infarction over a median follow-up of 6.6 to 32.8 months.[108] These estimates may underestimate the real-world risk, due to underreporting of cardiovascular events,[109] relatively short follow-up duration (limited use for >5 and particularly >10 years), and selection bias due to stringent inclusion criteria in cancer trials compared with real-world situations.[110]

Late onset left ventricular dysfunction could occur as a consequence of subclinical myocarditis during ICI treatment.[51,106] In a prospective serial magnetic resonance imaging study of 22 patients, there was evidence of diffuse myocardial edema and reduction in average left ventricular longitudinal strain after 3 months of ICI treatment.[111] Two patients developed new nonischemic late gadolinium enhancement lesions suggestive of myocardial scarring.[111] Despite these findings, 21 of 22 patients remained asymptomatic,[111] suggestive that subclinical ICI-related myocarditis may be more prevalent than expected. High-sensitivity troponin has been suggested as a potential surveillance biomarker[112] that could lead to early detection of subclinical cases and incorporated into several ongoing phase 3 ICI trials, although data supporting its routine use are limited.

Tailored cardiovascular surveillance protocols during and after completion of ICI therapy, which could include routine myocardial imaging and screening of cardiovascular risk factors, may guide monitoring and even commencement of cardiovascular preventive

therapies. Adoption of healthy lifestyle measures should also be encouraged in patients treated with ICIs.

KEY POINTS.

- Potential chronic cardiovascular irAEs include atherosclerotic cardiovascular disease and heart failure.
- Studies evaluating cardiovascular surveillance after ICI therapy are needed.
- Cardiovascular risk reduction should be strongly considered in patients treated with ICIs.

CONCLUSIONS

ICIs are a key component of standard anticancer systemic therapy across multiple cancer types, across (neo)adjuvant and metastatic settings. Currently, ICIs targeting CTLA-4, PD-1/PD-L1, and LAG3 are approved for clinical use, with ongoing studies investigating novel immune-directed agents and combinations. Side effects, known as irAEs, can be acute or chronic. Acute cardiac irAEs during ICI treatment such as myocarditis can potentially be fatal but are rare, while potential chronic cardiac irAEs, such as atherosclerotic cardiovascular disease and left ventricular dysfunction, may increasingly be reported with improving cancer survivorship (a recent *JACC: CardioOncology* review provides a more detailed discussion on cardiovascular irAEs[161]). More comprehensive mechanistic understanding of irAEs coupled with longer term follow-up data will be central to improve prevention and management of irAEs, particularly chronic cardiac sequelae, as this is a major competing cause of death. Attention should be directed toward developing ICI-specific models of follow-up for cancer survivors, with a key focus on a multidisciplinary approach to patient care.

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