Received: 7 August 2023 | Revised: 27 September 2023 | Accepted: 3 October 2023

DOI: 10.3322/caac.21818

REVIEW ARTICLE

Immunosurveillance in clinical cancer management

Guido Kroemer MD, PhD[1,2,3] | **Timothy A. Chan MD, PhD**[4,5,6,7] | **Alexander M. M. Eggermont MD, PhD**[8,9] | **Lorenzo Galluzzi PhD**[10,11,12]

[1]Centre de Recherche des Cordeliers, Equipe Labellisée par la Ligue Contre le Cancer, Institut National de la Santé et de la Recherche Médicale, Université Paris Cité, Sorbonne Université, Institut Universitaire de France, Paris, France

[2]Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Center, Villejuif, France

[3]Institut du Cancer Paris Carpem, Department of Biology, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpital de Paris, Paris, France

[4]Department of Radiation Oncology, Taussig Cancer Center, Cleveland Clinic, Cleveland, Ohio, USA

[5]Center for Immunotherapy and Precision Immuno-Oncology, Cleveland Clinic, Cleveland, Ohio, USA

[6]National Center for Regenerative Medicine, Cleveland, Ohio, USA

[7]Case Comprehensive Cancer Center, Cleveland, Ohio, USA

[8]University Medical Center Utrecht and Princess Maxima Center, Utrecht, The Netherlands

[9]Comprehensive Cancer Center München, Technical University München & Ludwig Maximilian University, Munich, Germany

[10]Department of Radiation Oncology, Weill Cornell Medical College, New York, New York, USA

[11]Sandra and Edward Meyer Cancer Center, New York, New York, USA

[12]Caryl and Israel Englander Institute for Precision Medicine, New York, New York, USA

Correspondence
Guido Kroemer, Centre de Recherche des Cordeliers, 15 rue de l'Ecole de Médecine, Paris 75006, France.
Email: kroemer@orange.fr

Lorenzo Galluzzi, Department of Radiation Oncology, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA.
Email: log3001@med.cornell.edu

Funding information
National Institutes of Health/National Cancer Institute, Grant/Award Numbers: CA271915, CA274291, CA232097, CA205426, CA274513; US Department of Defense, Grant/Award Numbers: BC180476P1, BC210945, W81XWH2120034; STARR Cancer Consortium, Grant/Award Number: I16-0064; Ligue Contre le Cancer; Agence National de la Recherche; Association pour la Recherche sur le Cancer; Fondation pour la Recherche Médicale; European Research Council Advanced Investigator Award, Grant/Award Numbers: ERC-2021-ADG, 101052444; Crimson; Institut National du

Abstract

The progression of cancer involves a critical step in which malignant cells escape from control by the immune system. Antineoplastic agents are particularly efficient when they succeed in restoring such control (immunosurveillance) or at least establish an equilibrium state that slows down disease progression. This is true not only for immunotherapies, such as immune checkpoint inhibitors (ICIs), but also for conventional chemotherapy, targeted anticancer agents, and radiation therapy. Thus, therapeutics that stress and kill cancer cells while provoking a tumor-targeting immune response, referred to as *immunogenic cell death*, are particularly useful in combination with ICIs. Modern oncology regimens are increasingly using such combinations, which are referred to as *chemoimmunotherapy*, as well as combinations of multiple ICIs. However, the latter are generally associated with severe side effects compared with single-agent ICIs. Of note, the success of these combinatorial strategies against locally advanced or metastatic cancers is now spurring successful attempts to move them past the postoperative (adjuvant) setting to the preoperative (neoadjuvant) setting, even for patients with operable cancers. Here, the authors critically discuss the importance of immunosurveillance in modern clinical cancer management.

Cancer; LabEx Immuno-Oncology; Cancer Research ASPIRE Award from the Mark Foundation; US Food and Drug Administration

KEYWORDS
cancer immunotherapy, chemotherapy, immune checkpoint blockade, radiation therapy, targeted therapy, tumor-infiltrating lymphocytes

INTRODUCTION

Until the beginning of the 21st century, cancer was largely viewed as a purely cell-intrinsic disease of genetic or epigenetic origin, implying that personalized treatment strategies were mostly focused on dissecting malignant cell features.[1] However, cancer is a systemic disease that involves a progressive derailment of immunological, metabolic, neuroendocrine, and potentially microbial features, hence affecting the entire bodywide ecosystem.[2,3] This notion has been particularly well documented at the level of the cancer-immunity dialogue.

The development of cancer is normally repressed by the immune system, a process referred to as *immunosurveillance*.[4] Thus, for tumors to develop into a clinically manifest disease, transformed cells must avoid or actively subvert the anticancer immune response.[5,6] For this reason, markers of immunity against malignant cells, such as the presence of T lymphocytes in the tumor microenvironment (TME) as well as genetic signatures of T-cell activation, have a major prognostic impact and—at least in some tumor types—actually predict therapeutic responses to a variety of anticancer treatments, including immunotherapy with immune checkpoint inhibitors (ICIs).[7–9] ICIs have indeed been designed to activate T lymphocytes by interrupting inhibitory signals delivered by various receptors, including programmed cell death 1 (PD-1), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and lymphocyte-activation gene 3 (LAG-3), among others.[10] ICIs now occupy central stage in modern oncology, and they have been licensed for a wide range of solid and hematological malignancies.[11]

According to the *three Es* model of immunity-cancer coevolution,[12] malignant and immune cells interact with each other in three discrete steps—*elimination*, *equilibrium*, and *escape* (Figure 1). In the first, subclinical phase, nascent cancer cells are efficiently eliminated by the immune system, a process that often involves innate immune cells, such as macrophages and natural killer (NK) cells,[13,14] as well as effectors of acquired immune responses, in particular T lymphocytes but likely also B cells (which produce antibodies).[15,16] In the second, often indolent phase, cancer and immune cells reach a precarious equilibrium in which, within a smoldering lesion, cancer cells can locally proliferate but neoplastic masses do not expand or metastasize because of local and systemic immune control. In this setting, cancer cells that acquire the ability to avoid immune recognition or that weaken immune effectors selectively expand within the tumor.[1] In the third phase, malignant cells fully escape from immune control to a point at which they become clinically detectable and become able to infiltrate adjacent tissues and ultimately generate distant metastases.[17,18]

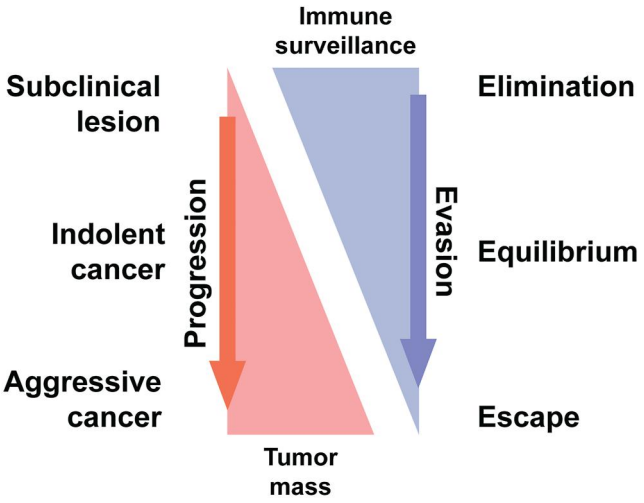

FIGURE 1 Principles of cancer immunosurveillance. According to the *three Es* model of immunity-cancer coevolution, malignant cells are initially eliminated by the host immune system but eventually acquire additional alterations that enable, first, a phase of equilibrium in which cancer cells proliferate locally but global disease burden remains under immune control and, finally, overt immune escape coupled with disease progression.

The *three Es* are also reflected in the means by which we intervene against cancer. Elimination may be achieved by prophylactic immunization,[19] as exemplified by the ability of human papillomavirus vaccination to protect against cervical carcinoma.[20] At least theoretically, cancer-preventive immune responses may also be elicited by vaccines targeting tissue-specific autoantigens expressed by stressed and (pre-)malignant cells.[21,22] In a fraction of patients, ICIs used alone or combined with other treatments can also achieve the complete elimination of malignant cells (and hence cure patients).[10] However, once cancers progress or spread (the *escape* phase), the probability of achieving durable or at least clinically relevant responses to any treatment diminishes.[17] That said, even locally invasive and metastatic cancers may respond to ICIs, demonstrating the possibility to reverse the natural progression of the disease and reestablish equilibrium.[23]

Here, we review prognostic and predictive biomarkers related to anticancer immunosurveillance and emphasize the finding that successful cancer treatments, including chemotherapeutics, radiation therapy (RT), and some targeted agents, operate (at least partially) through the immune system. Moreover, we summarize the state-of-the-art of immunotherapy, alone or in combination with other treatment modalities, placing special emphasis on preoperative treatment in the context of operable disease.

IMMUNOLOGICAL BIOMARKERS

Although immunological biomarkers with universal prognostic or predictive value are exceptions (see below), several immunological parameters have been linked to disease outcome or sensitivity to therapy in specific tumor types.

Colorectal cancer (CRC) infiltration by CD8-positive T lymphocytes was reported as a positive prognostic factor in 2005.[24] This led to the development of a standardized test measuring the density of CD3-positive and CD8-positive T lymphocytes within the tumor and at its invasive margin using immunohistochemistry on formaldehyde-fixed, paraffin-embedded tissue sections and digital pathology, referred to as the *Immunoscore*.[25] The Immunoscore has been clinically validated for its association with the time to recurrence in patients with CRC independent from patient age, sex, tumor stage, lymph node status, microsatellite instability, and other prognostic factors.[26] Attempts are now underway to extend the use of the Immunoscore to cancer types other than CRC.[27] Indeed, the density, composition, and functionality of the tumor immune infiltrate (which includes not only CD8-positive T lymphocytes but also other T-cell populations, B cells, NK cells, as well as multiple, distinct myeloid cell types)[7,8] are relevant not only for immunotherapy but (at least in some tumor types) also for chemotherapy. For instance, CD8-positive T-cell infiltration in diagnostic biopsies has been associated with improved sensitivity to preoperative chemotherapy in aggressive variants of breast cancer.[28,29]

Technological progress, including spatially resolved, single-cell transcriptomics, alone or combined with high-dimensional, multiplexed immunofluorescence analyses, is facilitating an ever more refined characterization of the tumor immune infiltrate.[30–32] It remains to be seen whether such advanced technologies coupled to artificial intelligence will enable the routine clinical testing of patient samples or whether methods that are simpler to automatize, such as the inference of intratumoral immune function from bulk RNA sequencing data,[33] will prevail. Irrespective of this open question, it appears that the spatial organization of intratumoral immune cells, for example, in *tertiary lymphoid organs* that can be found in the microenvironment of some tumors, plays in important role in immunosurveillance, at least in tumors with a detectable tumor infiltrate.[8]

The expression levels of PD-1 ligand 1 (PD-L1) in the TME can predict the sensitivity of individual patients with various cancers to ICIs targeting PD-1 or PD-L1, either alone or combined with ICIs targeting CTLA-4.[34] Distinct thresholds have been proposed to harness PD-L1 expression as a predictive biomarker for ICI use, either as a *tumor proportion score*, which is the percentage of cancer cells that express PD-L1, as identified by immunohistochemistry, or as a *combined positive score*, which is the percentage of PD-L1–positive cells within the tumor, including malignant, lymphoid, and myeloid cells.[35] Depending on the specific malignancy, US Food and Drug Administration (FDA) approval for ICIs targeting PD-1 or PD-L1 has been restricted to cancers with a tumor proportion score or a combined positive score >1 or 10%, as determined by companion diagnostic tests (for a review, see Twomey and Zhang[36]). That said, the clinical utility of PD-L1 as a predictive biomarker for ICI responsiveness varies greatly between cancer types and treatment settings.[37] At least in part, this may be explained by the finding that multiple therapeutic agents, including conventional chemotherapeutics, RT, and immunotherapy, have been shown to increase PD-L1 expression beyond baseline levels, which are typically assessed before treatment.

Tumor mutational burden (TMB), which reflects the number of nonsynonymous mutations in the genome of tumor cells, is yet another parameter that predicts immunotherapy responses in patients with cancer and has been prospectively validated as a potential pan-cancer biomarker.[34,38] In line with this notion, the FDA granted a tissue-agnostic approval to pembrolizumab, an ICI targeting PD-1, for unresectable or metastatic cancers with high TMB, currently defined as ≥10 mutations per megabase.[39] A high TMB is likely to increase the generation of novel antigenic epitopes by cancer cells (commonly referred to as *tumor neoantigens*), which render them immunogenic. At least in some cancers, such a propensity to accumulate mutations is driven by defects in a specific mechanism of DNA repair called mismatch repair (MMR), which is associated with the instability of specific DNA regions called microsatellites.[40] Accordingly, tumors with a molecular diagnosis of defective MMR (dMMR) or elevated (high) microsatellite instability (MSI-H) are exquisitely sensitive to ICIs,[41] which resulted in the FDA approval of pembrolizumab for use in patients with dMMR/MSI-H cancers irrespective of tissue of origin.[42] That said, TMB testing does not account for the immunological alterations imposed by genetic defects other than single nucleotide mutations, such as indels and frameshift mutations. Based on a recent pan-cancer analysis, frameshift mutations may indeed predict ICI sensitivity in patients with solid tumors bearing a low TMB.[43] Hence, the current approach to measure tumor immunogenicity based on genetic alterations in cancer cells has substantial room for improvement.

It appears plausible that analyzing several of the aforementioned biomarkers (i.e., tumor immune infiltrate, PD-L1 expression, TMB, other mutations) in an integrated manner will yield prognostic and predictive insights that are more accurate than those obtained from each of these parameters in isolation. Indeed, when combined with the measurement of PD-L1 expression, the Immunoscore helps to predict the sensitivity of patients with nonsmall cell lung carcinoma (NSCLC) to ICIs targeting the interaction between PD-1 and PD-L1.[44]

For people with advanced or metastatic disease, an intrinsic disadvantage of tumor-centric biomarkers is that measurements require tissue (e.g., biopsies or operative specimens), limiting their usefulness for longitudinal follow-up. For this reason, attempts to use blood-borne cells have been of interest.[45,46] One of these approaches, referred to as *immunomonitoring* has been proposed as a way to measure disease status along with the general state of the immune system, which, for example, is compromised in the context of a high neutrophil/lymphocyte ratio (which remains one of the strongest negative prognostic markers for patients with cancer).[47]

Although refined immunomonitoring is not routinely performed in clinical practice, laboratory tests enabling neutrophil/lymphocyte ratio assessments are standard clinical practice for hospitalized patients.[47] Blood-borne antibodies and other soluble factors that may inform on the sensitivity of patients with cancer to ICIs, such as cytokines, chemokines, and circulating tumor DNA, can also be measured by various technologies,[48–50] but their actual prognostic and/or predictive value remains to be formally addressed.

Analyzing the microbial populations that colonize the intestine, the so-called *intestinal microbiota*, may also provide biomarkers that predict the outcome of immunotherapy. For example, reports on specific cohorts of patients with NSCLC demonstrate that a high abundance of *Akkermansia muciniphila* in the stools, as well as a low abundance of *Enterocloster* species, correlate with a favorable clinical outcome upon treatment with ICIs specific for PD-1 or PD-L1.[51,52] Of note, the detrimental effect of *Enterocloster spp.* on immunotherapy outcome correlates with the downregulation of soluble mucosal vascular addressin cell adhesion molecule 1 (MADCAM1) in the plasma, which is a poor prognostic biomarker in patients with NSCLC.[52] Several other observations delineating the impact of the intestinal microbiome on anticancer immunosurveillance are critically reviewed by Simpson et al.[53] Whether these observations will lead to the approval of biomarkers for routine clinical use in select cancers, however, remains to be determined.

In sum, several FDA-approved tests are available to evaluate PD-L1 expression, TMB, and MSI/MMR status for predicting the likelihood of individual patients with some cancers to respond to ICIs. Moreover, not only are the Immunoscore and more refined tumor-centric methods evaluating the cancer-immunity dialogue under development, but there is also the prospect of extracting information on the state of immunosurveillance from the blood and feces (Table 1).

IMMUNE EFFECTS OF DIVERSE TREATMENT MODALITIES

Nearly 2 decades after pioneering preclinical work linking the efficacy of anthracyclines to the immune system,[54] it is clear that the activity of various commonly used anticancer agents relies, at least partially, on the (re)activation of immunosurveillance.[55–57] Multiple anticancer treatments in common use have been shown to kill cancer cells by a mechanism that activates tumor-specific immune responses, or *immunogenic cell death* (ICD).[58]

The ability of cancer cell death to drive immunity depends on the ability of dying cells to emit immunostimulatory signals, referred to as *damage-associated molecular patterns* (DAMPs).[59] ICD-relevant DAMPs include (but may not be limited to): (1) adenosine triphosphate (ATP), which attracts myeloid cells, including dendritic cell (DC) precursors, to the TME and activates them upon binding to purinergic receptors[60]; (2) annexin A1 (ANXA1), a protein that leaks from dying cells and attracts DCs to their immediate vicinity through an action on formyl peptide receptor 1 (FPR1)[61]; (3) surface-exposed calreticulin (CALR),[62] which enables the phagocytosis of dying cells or corpses thereof by DCs[63] and facilitates the killing of stressed (cancer) cells by NK cells[14]; (4) high mobility group box 1 (HMGB1), a

TABLE 1 Prognostic and predictive immune-relevant biomarkers in oncology.

Biomarker	Indication(s)	Treatment	FDA-approved	Notes
CD3+ and/or CD8+ T-cell infiltration	Multiple solid tumors	N/A	No	Independent prognostic value in patients with a variety of solid malignancies
dMMR status	Agnostic	PD-1 inhibition	Yes	Likely linked with increased generation of tumor-associated antigens
Gut microbiota	Multiple solid tumors	PD-1 or PD-L1 inhibition	No	Assess status of the bodywide ecosystem that influences tumor progression
Immunoscore	Colorectal cancer	Immunotherapy	No[a]	Refined spatial assessment of tumor infiltration by various immune cells
MSI-H status	Agnostic	PD-1 inhibition	Yes	Likely linked with increased generation of tumor-associated antigens
NLR	Multiple solid tumors	Various	Yes	Strong indicator of impending disease progression in a variety of settings
PD-L1 expression	Agnostic	PD-1 or PD-L1 inhibition	Yes	Identifies potential activation of the PD-1 signaling axis in immune cells
TMB	Agnostic	PD-1 inhibition	Yes	Likely linked with increased generation of tumor-associated antigens

Abbreviations: +, positive; dMMR, defective mismatch repair; FDA, US Food and Drug Administration; MSI-H, microsatellite instability high; N/A, not applicable; NLR, neutrophil-to-lymphocyte ratio; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; TMB, tumor mutational burden.

[a]But routinely used and reimbursed by some health providers.

nuclear protein that, once released by dying cells, promotes DC maturation through Toll-like receptor 4 (TLR4) signaling[64]; and (5) type I interferon (IFN), a cytokine that not only exerts multipronged immunostimulatory effects in the TME[65] but also operates on malignant cells to elicit the secretion of T-lymphocyte attractants.[66] Importantly, the emission of many of these DAMPs originates from stress responses that (at least initially) attempt to prevent cancer cell death, including autophagy (a catabolic pathway involved in the preservation of bioenergetic homeostasis in stressed cells),[67] which is important for optimal ATP release,[68] the so-called *integrated stress response*, which underlies CALR exposure,[69] and cytosolic or endosomal nucleic acid sensing, which drives type I IFN secretion.[70] Conversely, the mechanisms underlying the release of ANXA1 and HGMB1 remain to be dissected.[71] Moreover, some stress-responsive pathways modulate DAMP emission in a context-dependent manner, such as autophagy, which is critical for ATP release driven by chemotherapy[68] but restricts type I IFN emission driven by RT.[72]

In addition to being elicited by therapy, ICD may also occur when malignant cells succumb to endogenous stress, perhaps explaining why a loss-of-function polymorphism (rs867228) in *FPR1* (allelic frequency, 20%) is associated with early onset oncogenesis across multiple malignancies.[73] For example, women who inherit rs867228 in homozygous or heterozygous patterns (approximately 34% of the population) manifest luminal B breast cancer 6 years earlier than women lacking rs867228, supporting the theory that deficient immunosurveillance promotes mammary carcinogenesis.[74] Along similar lines, several inheritable traits, such as germline variants in genes encoding innate immune sensors that drive type I IFN production during ICD like IFN induced with helicase C domain 1 (IFIH1; best known as MDA5) and stimulator of IFN response cGAMP interactor 1 (STING1), have been shown to influence the immunological landscape of various cancers[75] and hence, at least theoretically, their sensitivity to ICIs.[76]

As many cancers progress, malignant cells evolve to acquire the ability to limit DAMP emission during cell death.[58] Specifically, developing tumors become capable of: (1) actively degrading extracellular ATP upon expression of extracellular ectonucleotidases,[60] (2) sequestering CALR in the cytoplasm[77] or shedding CALR fragments that saturate CALR receptors on DCs,[78] (3) losing HMGB1 expression,[79] and (4) suppressing type I IFN signaling, either because of autophagy hyperactivation[80] or because of reduced expression of the nucleic acid sensors that elicit type I IFN responses or the signal transducers thereof.[81] Further corroborating the impact of immunosurveillance in clinical cancer management, all of these alterations have been associated with negative prognostic or predictive value in patients with a wide panel of cancers.[82] Conversely, signs of ICD, including the phosphorylation of eukaryotic initiation factor 2α (eIF2α), which occurs during the integrated stress response in cancer cells or the exposure of CALR on their surface,[62] as well as a surge in soluble DAMPs in the circulation after therapy,[83,84] have been correlated with improved disease outcome in cohorts of patients with various cancer types. Hence, an improved knowledge of ICD mechanisms may lead to the discovery of novel predictive biomarkers.

Conventional chemotherapeutics, targeted anticancer agents, and RT (especially when used according to standard fractionation schedules and delivered to conventional target volumes) can mediate robust immunosuppressive effects secondary to lymphodepletion and myelosuppression, especially when used at doses approximating the maximum tolerated dose.[85,86] In addition, they can mediate immunostimulatory effects, either by depleting immunosuppressive cell subsets (such a regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages) or—more rarely—by directly activating innate immune effectors or T lymphocytes[56,87] as well as by altering the tumor vasculature.[88] For instance, the folate pathway inhibitor pemetrexed (which is now approved in combination with carboplatin and pembrolizumab as first-line intervention for advanced NSCLC)[89] has been shown to directly alter the bioenergetic metabolism of T cells in support of their anticancer activity.[90] Conversely, the vascular endothelial growth factor A (VEGFA) blocker bevacizumab as well as multiple tyrosine kinase inhibitors commonly used in the management of renal cell carcinoma (RCC) appear to restore (at least partially) anticancer immunosurveillance by normalizing the tumor vasculature and hence enable tumor infiltration by T lymphocytes.[91,92] Developing novel therapeutic regimens that safely and efficiently combine classical chemotherapeutics and RT with ICIs may require, at least in some settings, an attentive reconsideration of standard treatment protocols.[86]

In sum, most, if not all, cancer therapeutics affect immunosurveillance either indirectly, by stressing and killing cancer cells in an immunogenic fashion, or directly, through effects on immune cells (Figure 2). This has considerable implications for the development of novel anticancer therapies, which are systematically evaluated for their effects on the immune system. Indeed, some antineoplastics recently approved for use in humans, such as the targeted anticancer agent crizotinib, have been selected because of their capacity to induce ICD,[93,94] further blurring the traditional separation of *classical* cancer therapies and immunotherapies.

IMMUNE CHECKPOINT INHIBITORS

There are multiple techniques to mobilize the immune system against malignant cells, ranging from vaccines against tumor antigens[95] to methods that involve (at least some facets of) synthetic biology, such as genetically engineered viruses[96] and chimeric antigen receptor T cells,[97] which we do not discuss in this review (Table 2). ICIs have revolutionized oncology over the past decade because of their capacity to reinstate anticancer immunosurveillance in an antigen-agnostic fashion.[10,98] These immunotherapeutics were initially developed by James Allison and Tasuku Honjo, who shared the Nobel Prize in Physiology or Medicine in recognition of their discovery in 2018.[99] Specifically, ICIs are monoclonal antibodies targeting molecules that normally suppress T lymphocytes and NK cells to prevent excessive (auto)immune responses.[11] ICIs currently approved for use in multiple oncological indications are directed against PD-1 and its ligand PD-L1, CTLA-4, and LAG-3. Of note, although these molecules

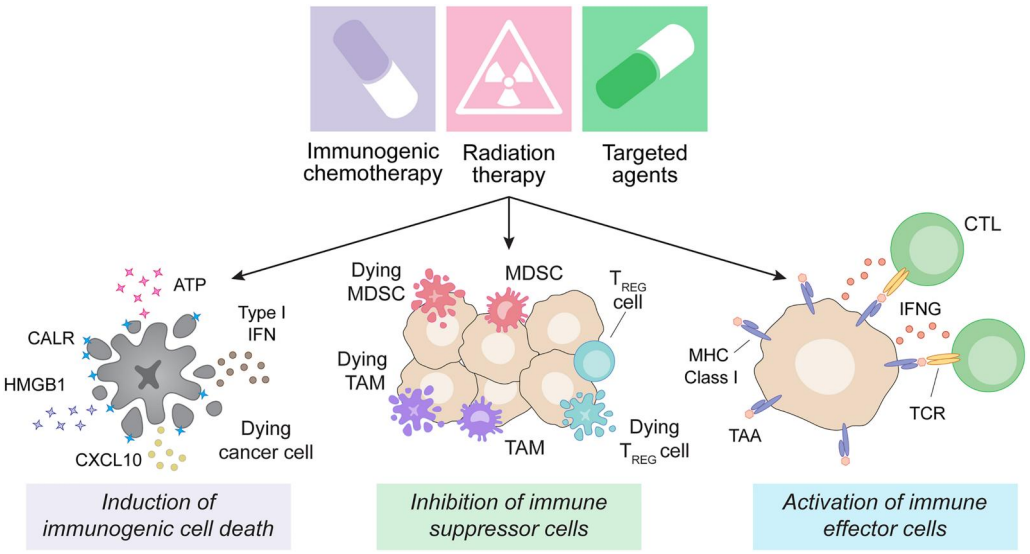

FIGURE 2 Beneficial immune effects of chemotherapy, radiation therapy, and targeted anticancer agents. Several clinically employed anticancer treatments, including classical chemotherapeutics, at least in some cases focal radiation therapy, and select targeted anticancer agents, can mediate beneficial immune effects through three general mechanisms: (1) by inducing immunogenic cell death (ICD) in cancer cells, which is associated with the emission of numerous immunostimulatory signals; (2) by inhibiting or depleting immunosuppressive cell populations, including regulatory T (T_{REG}) cells, a large fraction of tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs); or (3) by promoting the activation of immune effector cells, such as cytotoxic T lymphocytes (CTLs), which recognize malignant cells that present specific tumor-associated antigens (TAAs) on MHC class I molecules through their T-cell receptor (TCR) and respond to them by producing effector molecules, such as interferon gamma (IFNG). ATP, adenosine triphosphate; CALR, calreticulin; CXCL10, C-X-C motif chemokine ligand 10; HMGB1, high mobility group box 1; IFN, interferon; MHC, major histocompatibility complex.

share similarities in their immunoregulatory function, they differ in expression pattern and mechanisms of action.[10]

PD-1 is expressed on activated T cells, B cells, and NK cells, whereas its ligands PD-L1 and PD-L2 are expressed on cancer cells and multiple myeloid cell types.[98] Upon ligand binding, PD-1 transmits robust inhibitory signals, which can be prevented with monoclonal antibodies targeting PD-1 (e.g., nivolumab and pembrolizumab) or PD-L1 (e.g., atezolizumab, avelumab, and durvalumab).[98] PD-1 and PD-L1 inhibitors are effective against several tumors, including melanoma, bladder cancer, cervical carcinoma, cholangiocarcinoma, endometrial cancer, esophageal cancer, head and neck carcinoma, hepatocellular carcinoma, NSCLC, RCC, mesothelioma, and Hodgkin lymphoma.[10,98] Hence, they have been approved for many clinical indications, although their use is often predicated on a biomarker, such as PD-L1 expression, a high TMB, or a dMMR/MSI-H status.[42]

CTLA-4 is expressed on the surface of activated T cells, where it mediates immunosuppressive effects by outcompeting another T-cell receptor, namely, CD28, for binding to activatory molecules expressed by DCs (i.e., CD80 and CD86). This results in suppressed CD28 signaling, which inhibits T-cell activation.[10] CTLA-4 is targeted by ipilimumab, the first FDA-approved ICI that has shown efficacy as a monotherapy against melanoma,[100] but is mostly used in combination with other ICIs targeting the PD-1/PD-L1 interaction.[10,98] The same applies to the second FDA-approved ICI targeting CTLA-4: tremelimumab.[101] Indeed, CTLA-4 blockers fail to exhibit single-agent efficacy against most malignancies yet increase the response rate to PD-1/PD-L1 blockers in multiple clinical settings.[102]

LAG-3, which is expressed on activated T cells, regulatory T cells, and NK cells (often together with PD-1), is also engaged by DC receptors.[103] The LAG-3 blocker relatlimab has recently been approved by the FDA for the treatment of unresectable or metastatic melanoma in combination with nivolumab.[104] Research is underway to explore additional targets for ICIs, such as T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3)[105] and T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT),[106] as well as immunotherapeutics that would activate stimulatory T-cell receptors.[107] Targeting these proteins in combination with existing ICIs might further enhance response rate or duration at least in some oncological settings.

ICIs restore immunosurveillance by removing the breaks on anticancer T-cell responses, hence differing from other, more direct strategies of immunostimulation.[108] In line with this notion, ICIs often induce immune-related adverse events (irAEs) as part of their mechanism of action, and indeed the manifestation of such irAEs generally correlates with efficacy.[109,110] Common irAEs elicited by ICIs include dermatological manifestations (rash, pruritus), gastrointestinal disturbances (colitis, diarrhea), endocrine dysfunction (thyroiditis, hypophysitis), and (more rarely) hepatitis, pneumonitis, myocarditis, pancreatitis, and encephalitis.[109] The prompt recognition and effective management of these irAEs, which require specific guidelines and multidisciplinary collaborations, are essential to mitigate potential complications and ensure patient safety. Importantly, it appears that nonspecific immunosuppression with high-dose glucocorticoids may interfere with both ICI toxicity and efficacy.[111] Thus

TABLE 2 Overview over US Food and Drug Administration-approved immunotherapies.

Immunotherapy	Indication(s)[a]	Rationale	Notes
CAR T cells	Leukemia Lymphoma	Genetically modified, patient-derived lymphocytes are endowed with tumor-recognizing capacity and reinfused.	Associated with a high overall response rate in both pediatric and adult patients; currently subject of intense research to address secondary resistance, which occurs in a fraction of patients
Cytokines	Melanoma RCC	Recombinant type I interferon or recombinant interleukin-2 are infused intravenously as a direct immunostimulant.	Systemic administration often associated with moderate-to-severe adverse events, which overall limit clinical applicability
ICD inducers	Various	Conventional chemotherapeutics, radiotherapy, and some targeted anticancer agents kill cancer cells in an immunogenic manner.	Not developed as immunotherapeutics, but a posteriori demonstrated to engage innate and adaptive immune effectors against cancer
ICIs	Various	MoAbs specific for inhibitory receptors expressed by various lymphocyte populations unleash anticancer immunity.	Active in 15%–25% of patients with a diverse array of cancers; currently subject of intense research to address primary and secondary resistance and to identify reliable predictive biomarkers
Oncolytic viruses	Melanoma	Tumor-specific viruses optionally engineered to exert additional immunostimulatory effects elicit ICD.	Not developed as immunotherapeutics, but a posteriori demonstrated to engage innate and adaptive immune effectors against cancer
Prophylactic vaccines	Cervical carcinoma	HPV-targeting vaccination prevents the establishment of cervical tumors by ensuring a continuous elimination phase.	Technically not directed to cancer cells but to HPV-infected, premalignant cells to establish prophylactic antiviral and anticancer immunity
PRR agonists	Actinic keratosis Basal cell carcinoma	PRR activation results in the local secretion of immunostimulatory factors.	One single agent (imiquimod) currently approved for topical use in a limited number of (pre)oncological indications involving the skin
Therapeutic vaccines	Prostate cancer	Genetically modified, patient-derived myeloid cells are endowed with the capacity to re-educate lymphocytes against the tumor and are reinfused.	One single agent (sipuleucel T) currently approved for use in patients with prostate cancer; scarcely used in clinical practice
Tumor-targeting MoAbs	Breast cancer Colorectal cancer Lung cancer Lymphoma	In addition to inhibiting malignant cells, some tumor-targeting MoAbs engage effector mechanisms of innate immunity.	Not developed as immunotherapeutics, but a posteriori demonstrated to engage a panel of innate immune effectors against cancer

Abbreviations: CAR, chimeric antigen receptor; HPV, human papillomavirus; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; MoAbs, monoclonal antibodies; PRR, pattern-recognition receptor; RCC, renal cell carcinoma.

[a]Most common.

attempts are underway to develop more specific interventions that dampen the toxicity of ICIs without affecting efficacy. Promising clinical results have been obtained in this sense with tocilizumab, a monoclonal antibody that neutralizes the proinflammatory molecule interleukin-6.[112] At this point, the side effects of ICIs are so well managed that even patients with preexisting autoimmune conditions can be safely treated.[113] Neutralization of another proinflammatory factor, namely, tumor necrosis factor, has also been shown to limit ICI-driven irAEs but not ICI efficacy in preclinical tumor models,[114] but this possibility awaits clinical validation.[115] If confirmed, such a decoupling effect on toxicity and efficacy could considerably improve the clinical management of patients with cancer in the long term.

The initial perspective of immunotherapy with ICIs was to *raise the tail* of the graphical curves that illustrate progression-free and overall survival, reflecting durable, sometimes decade-long responses.[116] This has been dramatically achieved in patients with melanoma and RCC who received PD-1 inhibitors alone or combined with ipilimumab,[117,118] as well as in patients with NSCLC who received chemotherapy plus pembrolizumab or nivolumab.[89,119] Although the percentage of patients suffering from other cancers that respond to ICIs can be sizeable (usually 15%–25% of patients), it is still too early to claim long-term benefits (e.g., >10 years) or definitive cures beyond anecdotal cases in such indications because of the short follow-up.[23]

Contemporary research is focusing on the distinction between primary (innate) resistance and secondary (acquired) ICI resistance.[120] In the former setting, the goal is to provide treatment with ICIs only to patients who are predicted to respond by a clinical or molecular biomarker or to subvert the initial mechanism of resistance. In the latter scenario, the goal is instead to provide a

salvage therapy, as exemplified by dual CTLA-4 and PD-1 blockade (which can be administered to patients with melanoma that have progressed on PD-1 or PD-L1 blockade alone),[121] or to preemptively avoid escape mechanisms that abolish immunosurveillance and hence to prolong response duration.[120] Common acquired alterations that enable such an escape include the selection and consequent surge of cancer cell clones that (1) are poorly visible to immune cells, (2) are increasingly resistant to the cytotoxic effectors produced by T lymphocytes, and (3) actively exclude T lymphocytes from the TME or directly suppress their activation.[120] Moreover, tumor-infiltrating T lymphocytes chronically exposed to their targets (as in the case of established tumors that are resistant to ICIs) tend to evolve toward an inactive, so-called *exhausted* state.[122] Attempts are on the way to tackle both primary and secondary resistance against ICIs by means of combination therapies, as discussed in the section below.

COMBINATORIAL STRATEGIES FOR THE RESTORATION OF IMMUNOSURVEILLANCE

Numerous combinatorial regimens involving ICIs and agents with nonoverlapping modes of action have been tested clinically, with variable results.[123] Such combinations have been developed following two conceptually different approaches: either ICIs combined with another treatment modality that has proven anticancer activity on its own or ICIs administered together with another treatment aimed at limiting primary or secondary resistance but displaying no intrinsic anticancer activity.

Preclinical studies have consistently pointed to treatments that induce immunogenic cell stress and death as preferred combinatorial partners for ICIs.[124,125] In support of this notion, patients who had metastatic breast cancer treated with doxorubicin were found to obtain superior clinical benefit from subsequent nivolumab administration compared with other induction therapies using cisplatin, cyclophosphamide, or RT,[126] although immunological patient features at baseline may have been unbalanced.[127] In other studies, atezolizumab was indeed found to significantly improve the efficacy of induction low-dose cyclophosphamide and pegylated doxorubicin in patients who had metastatic breast cancer compared with placebo.[128] Two randomized phase 3 clinical trials for patients with unresectable gastric and gastroesophageal junction carcinoma showed that oxaliplatin-based (but not cisplatin-based) chemotherapy (together with capecitabine or 5-fluorouracil plus leucovorin) favorably interacted with PD-1 blockers and was associated with improved overall survival compared with chemotherapy alone.[125,129,130] A subsequent meta-analysis supported the notion that oxaliplatin-based chemotherapy is superior to cisplatin-based regimens in combination with PD-1 blockers.[131] Additional trials confirmed clinical benefits when atezolizumab was combined with oxaliplatin-based chemotherapy in patients with advanced CRC[132] and when durvalumab plus tremelimumab were combined with it in patients with NSCLC.[133] Durvalumab has been shown to improve overall survival in patients with NSCLC who were previously treated with chemotherapy plus RT as induction therapy compared with placebo,[134] suggesting that RT can also induce immunological benefits that can be amplified with ICIs (at least in some tumors). Accumulating evidence from early phase clinical trials suggests that ICD-inducing oncolytic viruses may also represent promising combinatorial partners for ICIs in patients with melanoma and glioblastoma,[135,136] but results from larger studies are awaited. In summary, various ICD-inducing strategies appear to cooperate with ICIs toward superior disease control in patients with a wide range of tumors.

Despite these results, caution is important. For example, the addition of ICIs to RT does not necessarily improve patient outcomes,[137–139] potentially reflecting the notion that modern RT approaches were developed in an immune system-agnostic manner (see above).[86] Similar considerations apply to other FDA-approved treatments, including sorafenib (which is indicated for hepatocellular carcinoma), cabozantinib (which is used for RCC), as well as BRAF and MEK inhibitors combined (which are used for melanoma), all of which do not appear to interact favorably with ICIs,[140–142] despite preclinical data pointing to at least some immunogenicity.[56] The precise reasons underlying such a lack of cooperativity remain to be elucidated.

The use of agents with no anticancer activity to address ICI resistance is still the subject of clinical studies. One study has reported that secondary resistance to ICIs in patients with metastatic melanoma may be overcome by fecal microbial transplantation, yielding an objective response rate of 65% (in 13 of 20 patients), including four (20%) complete responses, to subsequent PD-1 blockade.[143] This observation suggests that *resetting* the systemic ecosystem that dictates the immune tonus through microbial manipulations may improve the therapeutic utility of ICIs.

FROM ADJUVANT TO NEOADJUVANT SCHEDULES

A major shift in therapeutic approach is now emerging with respect to the timing of ICI administration to patients who have resectable cancers.[144] Specifically, the classical approach to first surgically remove resectable lesions and/or regional lymph nodes, followed by postoperative (adjuvant) therapy, is gradually giving room to treatment schedules in which neoadjuvant (chemo)immunotherapy is administered before surgery across multiple tumor types. This appears logical from a mechanistic perspective because it may be easier to restore immunosurveillance in the presence of the tumor (which often hosts an ongoing immune response) and its lymphoid system (in which T lymphocytes are educated to recognize tumor-associated antigens) rather than in their absence.

The clinical utility of neoadjuvant treatments was initially reported in patients with cutaneous melanoma. Specifically, patients with stage III melanoma who received neoadjuvant nivolumab (at standard dose) plus low-dose ipilimumab exhibited the expansion of preexisting tumor-specific T cells after only two cycles of

immunotherapy and in the context of minimal irAEs.[145,146] Notably, up to 70% of these patients experienced a pathologic complete response (pCR; 100% tumor necrosis) or a near pCR (npCR; >90% tumor necrosis) that was associated with a significantly low relapse rate (<5%).[146,147] These pioneering observations promoted the establishment of the Neoadjuvant Melanoma Immunotherapy Consortium, with the objective of defining clinical protocols for limiting treatment cycles, minimizing surgery, and reducing/omitting unnecessary adjuvant therapy in patients with melanoma responding to ICIs.[148] Pooled analyses by the Neoadjuvant Melanoma Immunotherapy Consortium documented that patients with melanoma achieving pCRs on neoadjuvant ICIs have a much lower probability of relapse than patients receiving BRAF/MEK inhibitors.[149] A subsequent clinical trial enrolling 99 patients with macroscopic, stage III melanoma who received two cycles of neoadjuvant nivolumab plus low-dose ipilimumab yielded a 60% rate of pCRs or npCRs in index lymph nodes, with excellent local control and relapse-free survival in the absence of therapeutic node dissection and adjuvant therapy.[150] Moreover, a randomized, phase 2 clinical trial enrolling patients with stage III melanoma revealed that it is feasible to administer the first three of 18 cycles of pembrolizumab neoadjuvantly, resulting in improved event-free survival (EFS) rate compared with immediate lymph node dissection.[151] Another study suggests that relatlimab can be used to replace low-dose ipilimumab in this setting to further reduce moderate-to-severe irAEs.[104] These findings further support the recommendation to treat patients who have advanced melanoma with neoadjuvant immunotherapy as best medical practice.[152,153]

Such a recommendation appears to remain valid for patients with tumors other than melanoma. For instance, in patients with stage II–IV, locally advanced, cutaneous squamous cell cancers of the head and neck area, neoadjuvant PD-1 blockage resulted in pCRs or npCRs in two thirds of individuals, avoiding or at least minimizing mutilating surgery.[154] Similarly, in a randomized, phase 2 clinical trial enrolling 358 patients with NSCLC, neoadjuvant chemoimmunotherapy (nivolumab plus platinum-based chemotherapy) was superior to chemotherapy only with respect to the pCR rate and overall survival.[155] Similarly, patients who had resectable NSCLC exhibited a better outcome after neoadjuvant chemoimmunotherapy (pembrolizumab or nivolumab plus cisplatin-based chemotherapy) followed by postsurgical immunotherapy versus neoadjuvant chemotherapy alone, with a higher percentage of major pathologic responses and improved EFS.[156,157]

Meta-analyses suggest that neoadjuvant immunotherapy plus chemotherapy may also be useful for the treatment of stage II–III muscle-invasive bladder cancer[158] and locally advanced esophageal carcinoma.[159] In one trial, neoadjuvant pembrolizumab improved EFS in 155 patients who had muscle-invasive bladder cancer enrolled in a prospective clinical study.[160] Similarly, neoadjuvant combined immunotherapy (nivolumab plus ipilimumab) yielded pathologic responses in >50% of patients who had gastric or gastric-esophageal junction cancers with dMMR/MSI-H status.[161] In that trial, 10% of study volunteers did not undergo surgery because of endoscopic biopsy-proven pCRs.[161] For women with triple-negative breast cancer, neoadjuvant chemoimmunotherapy has been approved by regulatory agencies based on a clinical study demonstrating that pembrolizumab plus carboplatin-based and paclitaxel-based chemotherapy followed by pembrolizumab plus cyclophosphamide and an anthracycline was more efficient than a similar regimen in which pembrolizumab was replaced by placebo to elicit pCRs and improve EFS.[162,163] Perhaps the most significant results, however, have been achieved in patients with advanced dMMR/MSI-H CRC, in which dual neoadjuvant nivolumab plus ipilimumab resulted in 100% major pathologic responses (including 69% pCRs) with no relapses at a follow-up of 13 months.[164] Similarly, neoadjuvant PD-1 blockage resulted in 100% of pCRs in 12 consecutive patients who had locally advanced, dMMR/MSI-H rectal cancers, with no relapses at a minimal follow-up of 12 months.[165]

In conclusion, neoadjuvant ICIs targeting PD-1 alone or together with CTLA-4 or LAG-3 blockers and/or chemotherapy have generated considerable progress across a range of different malignancies, as illustrated by high rates of profound pathologic responses, reduced access to surgery, and shorter treatment courses. As a perspective, the future therapy of certain cancers, including melanoma and dMMR/MSI-H tumors affecting the gastrointestinal tract, may rely on neoadjuvant ICIs as a sole intervention, thus sparing tumor resection to the patients.

CONCLUSIONS AND PERSPECTIVES

Cancer immunosurveillance has revolutionized clinical oncology and will continue to do so in the future. We are now recognizing that conventional chemotherapeutics and, to some extent, RT and targeted anticancer agents mediate long-term effects through the reinstatement of immunosurveillance. This underscores the importance of studying intratumoral and systemic signs of anticancer immune responses as biomarkers to predict, monitor, and personalize treatments.

Treatment modalities other than immunotherapy can be advantageously combined with ICIs if they have a positive effect on immunosurveillance, as abundantly documented for ICD-inducing chemotherapy.[166] Similarly, at least some targeted anticancer agents as well as focal RT and locally delivered oncolytic therapies may also constitute promising combinatorial partners for ICIs, at least when used so to minimize local and systemic immunosuppression.[86,167] Hence the rational design and testing (including preclinical development) of novel combinatorial treatments for cancer should attentively consider local and systemic immune effects.

One major challenge for the development of future of immunosurveillance-centered cancer therapies resides in the choice of which immunotherapy—notably which FDA-approved or hitherto investigational ICIs—should be combined among each other or with other treatment modalities, and in which order such treatments should be administered.[168] At this point, however, there appears to be a strong rationale in favor of neoadjuvant (chemo)immunotherapy, in which tumor-associated immune responses can be driven into the most efficient phase of immunosurveillance (elimination), which durably

controls disease progression and significantly reduces the need for adjuvant therapies, in some cases even eliminating the need for surgery. Additional challenges for the field deal with the exploration of the bodywide ecosystem because it appears that major clinic-biologic parameters (such as age, body mass index, systemic metabolism, inflammation, comorbidities, past or current infections, the microbiota, and comedications) have a profound impact on cancer immunosurveillance and consequently on therapeutic responses.[3] It appears indeed plausible that a holistic approach considering the entire spatiotemporal context of cancers beyond the local TME will yield invaluable insights for the therapeutically effective restoration of immunosurveillance.

Future directions will be focused on an earlier use of immunotherapy combinations (triple ICI regimens, chemoimmunotherapy, and immunotherapy combined with targeted anticancer agents). Innovation *at the front door*, i.e., in the neoadjuvant setting, will become the mainstay of development in the coming 5 years for multiple tumor types that are abundantly infiltrated by T cells at baseline and hence exquisitely sensitive to ICIs in patients with an intact immune system. Thus, all drug development programs will need a neoadjuvant component to learn quickly in responsive patients compared with patients who have received various therapy lines, for whom the opportunity for a cure has been missed (e.g., once patients develop liver metastases, one is faced with profound immunosuppression, both local and systemic).[169] Moreover, the development of novel TME modulators, in particular agents that target immunosuppressive myeloid cells, is a priority to overall improve the efficacy of ICIs. Finally, the chronic effects of various immunotherapies will have to be addressed. How to reduce long-term (1–2 years) treatments must be explored. The current *revolution* of neoadjuvant immunotherapy indicates that a triple effect can be achieved: more cures, shorter treatments, less surgery.

ACKNOWLEDGMENTS

Guido Kroemer is supported by the Ligue Contre le Cancer (équipe labellisée), Agence National de la Recherche (ANR)—Projets blancs, AMMICa (Analyse Moléculaire, Modélisation et Imagerie de la Maladie Cancéruse; Grant No. US23/CNRS UMS3655), Association pour la Recherche sur le Cancer (ARC), Cancéropôle Ile-de-France, Fondation pour la Recherche Médicale (FRM), a donation by Elior, Equipex Onco-Pheno-Screen, the European Joint Programme on Rare Diseases (EJPRD), a European Research Council Advanced Investigator Award (ERC-2021-ADG, ICD-Cancer; Grant No. 101052444), European Union Horizon 2020 Projects Oncobiome, Prevalung (Grant No. 101095604), Crimson, Institut National du Cancer (INCa), Institut Universitaire de France, LabEx Immuno-Oncology (Grant/Contract No. ANR-18-IDEX-0001), a Cancer Research ASPIRE Award from the Mark Foundation, RHU Immunolife, the Seerave Foundation, SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE), and SIRIC Cancer Research and Personalized Medicine (CARPEM). This study contributes to the Initiative of Excellence (IdEx) Université de Paris project (No. ANR-18-IDEX-0001). Views and opinions expressed are those of the author(s) only and do not necessarily reflect those of the European Union, the European Research Council, or any other granting authority. Neither the European Union nor any other granting authority can be held responsible for them. Timothy A. Chan is supported by one R35 grant (Grant No. CA232097), one R01 grant (Grant No. CA205426), and one U54 grant (Grant No. CA274513) from the National Institutes of Health/National Cancer Institute (NIH/NCI). Alexander M. M. Eggermont is supported by the European Union Horizon MELCAYA (Melanoma in Children, Adolescents, and Young Adults) Program. Lorenzo Galluzzi is/has been supported (as a principal investigator [PI], unless otherwise indicated) by one R01 grant from the NIH/NCI (Grant No. CA271915), by two Breakthrough Level 2 grants from the US Department of Defense Breast Cancer Research Program (Grant No. BC180476P1 and BC210945), by a grant from the STARR Cancer Consortium (Grant No. I16-0064), by a Transformative Breast Cancer Consortium Grant from the US Department of Defense Breast Cancer Research Program (Grant No. W81XWH2120034; Formenti, PI), by a U54 grant from the NIH/NCI (Grant No. CA274291; Deasy, Formenti, and Weichselbaum, PIs), by the 2019 Laura Ziskin Prize in Translational Research (No. ZP-6177; Formenti, PI) from Stand Up to Cancer, by a Mantle Cell Lymphoma Research Initiative grant (Chen-Kiang, PI) from the Leukemia and Lymphoma Society, by a Rapid Response Grant from the Functional Genomics Initiative (New York, NY), by a pre-SPORE (pre-Specialized Programs of Research Excellence) grant (Demaria and Formenti, PIs) and a Clinical Trials Innovation Grant from the Sandra and Edward Meyer Cancer Center (New York, NY), by start-up funds from the Department of Radiation Oncology at Weill Cornell Medicine (New York, NY), by industrial collaborations with Lytix Biopharma (Oslo, Norway), Promontory (New York, NY), and Onxeo (Paris, France), as well as by donations from Promontory (New York, NY), the Luke Heller TECPR2 Foundation (Boston, MA), Sotio a.s. (Prague, Czech Republic), Lytix Biopharma (Oslo, Norway), Onxeo (Paris, France), Ricerchiamo (Brescia, Italy), and Noxopharm (Chatswood, Australia). We thank Laurence Zitvogel for critical reading. The funders had no role in the design of the study, in the writing of the article, or in the decision to publish the results.

CONFLICT OF INTEREST STATEMENT

Guido Kroemer has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Tollys, and Vascage outside the submitted work; he is on the Board of Directors of the Bristol Myers Squibb Foundation, France; is a scientific cofounder of everImmune, Osasuna Therapeutics, Samsara Therapeutics, and Therafast Bio; is on the scientific advisory boards of Hevolution, Institut Servier, and Longevity Vision Funds; and is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis, and metabolic disorders; Guido Kroemer's wife, Laurence Zitvogel, has held research contracts with GlaxoSmithKline, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi Sankyo, Pilège, Merus, Transgene, 9 Meters Biopharma, Tusk, and Roche; served on the Board of Directors of Transgene; is a cofounder of everImmune; and holds patents covering the treatment of cancer and the therapeutic manipulation of the

microbiota; in addition, Guido Kroemer's brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. Timothy A. Chan is a cofounder of and holds equity in Gritstone Oncology; holds equity in An2H; reports grant funding from An2H, AstraZeneca, Bristol Myers Squibb, Eisai, Illumina, and Pfizer outside the submitted work; has served as an advisor for An2H, AstraZeneca, Bristol Myers Squibb, Eisai, Illumina, and MedImmune outside the submitted work; and holds ownership of intellectual property on using tumor mutational burden to predict immunotherapy response, which has been licensed to PGDx. Alexander M. M. Eggermont has received consulting/advisory honoraria from Atreca, Agenus, BioInvent, BioNTech, Brenus, CatalYm, Galecto, GenOway, Immunocore, IO Biotech, IQVIA, ISA Pharmaceuticals, Merck & Company, MSD, Pierre Fabre, Sairopa, Scorpion Pharmaceuticals, Sellas, SkylineDX, TigaTX, and Trained Therapeutics; honoraria for independent data monitoring committee (IDMC) from Boehringer Ingelheim, IQVIA, Merck AG, and Pfizer; and speakers' honoraria from Bristol Myers Squibb and Merck & Company/MSD, all outside the submitted work; and has equity in IO Biotech, Sairopa, and SkylineDX. Lorenzo Galluzzi is/has been holding research contracts with Lytix Biopharma, Promontory, and Onxeo; has received consulting/advisory honoraria from Boehringer Ingelheim, AstraZeneca, OmniSEQ, Onxeo, The Longevity Labs, Inzen, Imvax, Sotio, Promontory, Noxopharm, EduCom, and the Luke Heller TECPR2 Foundation, all outside the submitted work; and holds Promontory stock options.

ORCID

Lorenzo Galluzzi https://orcid.org/0000-0003-2257-8500

REFERENCES

1. Vitale I, Shema E, Loi S, Galluzzi L. Intratumoral heterogeneity in cancer progression and response to immunotherapy. *Nat Med*. 2021;27(2):212-224. doi:10.1038/s41591-021-01233-9
2. Liu L, Shah K. The potential of the gut microbiome to reshape the cancer therapy paradigm: a review. *JAMA Oncol*. 2022;8(7):1059-1067. doi:10.1001/jamaoncol.2022.0494
3. Kroemer G, McQuade JL, Merad M, André F, Zitvogel L. Bodywide ecological interventions on cancer. *Nat Med*. 2023;29(1):59-74. doi:10.1038/s41591-022-02193-4
4. Finn OJ. A believer's overview of cancer immunosurveillance and immunotherapy. *J Immunol*. 2018;200(2):385-391. doi:10.4049/jimmunol.1701302
5. Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. *Nat Rev Immunol*. 2006;6(10):715-727. doi:10.1038/nri1936
6. Palucka AK, Coussens LM. The basis of oncoimmunology. *Cell*. 2016;164(6):1233-1247. doi:10.1016/j.cell.2016.01.049
7. Bruni D, Angell HK, Galon J. The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy. *Nat Rev Cancer*. 2020;20(11):662-680. doi:10.1038/s41568-020-0285-7
8. Fridman WH, Meylan M, Petitprez F, Sun CM, Italiano A, Sautès-Fridman C. B cells and tertiary lymphoid structures as determinants of tumour immune contexture and clinical outcome. *Nat Rev Clin Oncol*. 2022;19(7):441-457. doi:10.1038/s41571-022-00619-z
9. Ayers M, Lunceford J, Nebozhyn M, et al. IFN-gamma-related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest*. 2017;127(8):2930-2940. doi:10.1172/jci91190
10. Sharma P, Goswami S, Raychaudhuri D, et al. Immune checkpoint therapy-current perspectives and future directions. *Cell*. 2023;186(8):1652-1669. doi:10.1016/j.cell.2023.03.006
11. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science*. 2018;359(6382):1350-1355. doi:10.1126/science.aar4060
12. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science*. 2011;331(6024):1565-1570. doi:10.1126/science.1203486
13. Wattrus SJ, Smith ML, Rodrigues CP, et al. Quality assurance of hematopoietic stem cells by macrophages determines stem cell clonality. *Science*. 2022;377(6613):1413-1419. doi:10.1126/science.abo4837
14. Sen Santara S, Lee DJ, Crespo Â, et al. Publisher correction: the NK cell receptor NKp46 recognizes ecto-calreticulin on ER-stressed cells. *Nature*. 2023;618(7964):E17. doi:10.1038/s41586-023-06151-z
15. Shankaran V, Ikeda H, Bruce AT, et al. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature*. 2001;410(6832):1107-1111. doi:10.1038/35074122
16. Meylan M, Petitprez F, Becht E, et al. Tertiary lymphoid structures generate and propagate anti-tumor antibody-producing plasma cells in renal cell cancer. *Immunity*. 2022;55(3):527-541.e525. doi:10.1016/j.immuni.2022.02.001
17. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature*. 2017;541(7637):321-330. doi:10.1038/nature21349
18. Pantel K, Alix-Panabières C. Crucial roles of circulating tumor cells in the metastatic cascade and tumor immune escape: biology and clinical translation. *J Immunother Cancer*. 2022;10(12):e005615. doi:10.1136/jitc-2022-005615
19. Schiller JT, Lowy DR, Frazer IH, et al. Cancer vaccines. *Cancer Cell*. 2022;40(6):559-564. doi:10.1016/j.ccell.2022.05.015
20. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. *Lancet*. 2019;393(10167):169-182. doi:10.1016/s0140-6736(18)32470-x
21. Zitvogel L, Perreault C, Finn OJ, Kroemer G. Beneficial autoimmunity improves cancer prognosis. *Nat Rev Clin Oncol*. 2021;18(9):591-602. doi:10.1038/s41571-021-00508-x
22. Schoen RE, Boardman LA, Cruz-Correa M, et al. Randomized, double-blind, placebo-controlled trial of MUC1 peptide vaccine for prevention of recurrent colorectal adenoma. *Clin Cancer Res*. 2023;29(9):1678-1688. doi:10.1158/1078-0432.ccr-22-3168
23. Lin EP, Hsu CY, Berry L, Bunn P, Shyr Y. Analysis of cancer survival associated with immune checkpoint inhibitors after statistical adjustment: a systematic review and meta-analyses. *JAMA Netw Open*. 2022;5(8):e2227211. doi:10.1001/jamanetworkopen.2022.27211
24. Pagès F, Berger A, Camus M, et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. *N Engl J Med*. 2005;353(25):2654-2666. doi:10.1056/nejmoa051424
25. Galon J, Pages F, Marincola FM, et al. Cancer classification using the Immunoscore: a worldwide task force. *J Transl Med*. 2012;10(1):205. doi:10.1186/1479-5876-10-205
26. Pagès F, Mlecnik B, Marliot F, et al. International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. *Lancet*. 2018;391(10135):2128-2139. doi:10.1016/s0140-6736(18)30789-x
27. Angell HK, Bruni D, Barrett JC, Herbst R, Galon J. The Immunoscore: colon cancer and beyond. *Clin Cancer Res*. 2020;26(2):332-339. doi:10.1158/1078-0432.ccr-18-1851
28. Denkert C, Loibl S, Noske A, et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. *J Clin Oncol*. 2010;28(1):105-113. doi:10.1200/jco.2009.23.7370

29. Kroemer G, Senovilla L, Galluzzi L, André F, Zitvogel L. Natural and therapy-induced immunosurveillance in breast cancer. *Nat Med*. 2015;21(10):1128-1138. doi:10.1038/nm.3944
30. Lu S, Stein JE, Rimm DL, et al. Comparison of biomarker modalities for predicting response to PD-1/PD-L1 checkpoint blockade: a systematic review and meta-analysis. *JAMA Oncol*. 2019;5(8):1195-1204. doi:10.1001/jamaoncol.2019.1549
31. Luca BA, Steen CB, Matusiak M, et al. Atlas of clinically distinct cell states and ecosystems across human solid tumors. *Cell*. 2021;184(21):5482-5496. doi:10.1016/j.cell.2021.09.014
32. Oliveira G, Wu CJ. Dynamics and specificities of T cells in cancer immunotherapy. *Nat Rev Cancer*. 2023;23(5):295-316. doi:10.1038/s41568-023-00560-y
33. Fasching PA, Szeto C, Denkert C, et al. Inferred immune-cell activity is an independent predictor of HER2-negative breast cancer prognosis and response to paclitaxel-based therapy in the GeparSepto trial. *Clin Cancer Res*. 2023;29(13):2456-2465. doi:10.1158/1078-0432.ccr-22-2213
34. Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. *Nat Rev Cancer*. 2019;19(3):133-150. doi:10.1038/s41568-019-0116-x
35. Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. *J Immunother Cancer*. 2019;7(1):278. doi:10.1186/s40425-019-0768-9
36. Twomey JD, Zhang B. Cancer immunotherapy update: FDA-approved checkpoint inhibitors and companion diagnostics. *AAPS J*. 2021;23(2):39. doi:10.1208/s12248-021-00574-0
37. Doroshow DB, Bhalla S, Beasley MB, et al. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat Rev Clin Oncol*. 2021;18(6):345-362. doi:10.1038/s41571-021-00473-5
38. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol*. 2020;21(10):1353-1365. doi:10.1016/s1470-2045(20)30445-9
39. Marcus L, Fashoyin-Aje LA, Donoghue M, et al. FDA approval summary: pembrolizumab for the treatment of tumor mutational burden-high solid tumors. *Clin Cancer Res*. 2021;27(17):4685-4689. doi:10.1158/1078-0432.ccr-21-0327
40. Klapp V, Alvarez-Abril B, Leuzzi G, Kroemer G, Ciccia A, Galluzzi L. The DNA damage response and inflammation in cancer. *Cancer Discov*. 2023;13(7):1521-1545. doi:10.1158/2159-8290.cd-22-1220
41. André T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383(23):2207-2218. doi:10.1056/nejmoa2017699
42. Tateo V, Marchese PV, Mollica V, Massari F, Kurzrock R, Adashek JJ. Agnostic approvals in oncology: getting the right drug to the right patient with the right genomics. *Pharmaceuticals (Basel)*. 2023;16(4):614. doi:10.3390/ph16040614
43. Florou V, Floudas CS, Maoz A, et al. Real-world pan-cancer landscape of frameshift mutations and their role in predicting responses to immune checkpoint inhibitors in cancers with low tumor mutational burden. *J Immunother Cancer*. 2023;11(8):e007440. doi:10.1136/jitc-2023-007440
44. Ghiringhelli F, Bibeau F, Greillier L, et al. Immunoscore immune checkpoint using spatial quantitative analysis of CD8 and PD-L1 markers is predictive of the efficacy of anti–PD1/PD-L1 immunotherapy in non-small cell lung cancer. *EBioMedicine*. 2023;92:104633. doi:10.1016/j.ebiom.2023.104633
45. Wang Z, Duan J, Cai S, et al. Assessment of blood tumor mutational burden as a potential biomarker for immunotherapy in patients with non-small cell lung cancer with use of a next-generation sequencing cancer gene panel. *JAMA Oncol*. 2019;5:696-702. doi:10.1001/jamaoncol.2018.7098
46. Kim H, Park S, Han KY, et al. Clonal expansion of resident memory T cells in peripheral blood of patients with non-small cell lung cancer during immune checkpoint inhibitor treatment. *J Immunother Cancer*. 2023;11(2):e005509. doi:10.1136/jitc-2022-005509
47. Wu M, Yang S, Feng X, Li C, Yu F, Dong J. Prognostic value of the postoperative neutrophil-lymphocyte ratio in solid tumors: a meta-analysis. *PLoS One*. 2021;16(4):e0250091. doi:10.1371/journal.pone.0250091
48. Loriot Y, Marabelle A, Guégan JP, et al. Plasma proteomics identifies leukemia inhibitory factor (LIF) as a novel predictive biomarker of immune-checkpoint blockade resistance. *Ann Oncol*. 2021;32(11):1381-1390. doi:10.1016/j.annonc.2021.08.1748
49. Olivera I, Sanz-Pamplona R, Bolaños E, et al. A therapeutically actionable protumoral axis of cytokines involving IL-8, TNFα, and IL-1β. *Cancer Discov*. 2022;12(9):2140-2157. doi:10.1158/2159-8290.cd-21-1115
50. Cabel L, Proudhon C, Romano E, et al. Clinical potential of circulating tumour DNA in patients receiving anticancer immunotherapy. *Nat Rev Clin Oncol*. 2018;15(10):639-650. doi:10.1038/s41571-018-0074-3
51. Derosa L, Routy B, Thomas AM, et al. Intestinal Akkermansia muciniphila predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer. *Nat Med*. 2022;28(2):315-324. doi:10.1038/s41591-021-01655-5
52. Fidelle M, Rauber C, Alves Costa Silva C, et al. A microbiota-modulated checkpoint directs immunosuppressive intestinal T cells into cancers. *Science*. 2023;380(6649):eabo2296. doi:10.1126/science.abo2296
53. Simpson RC, Shanahan ER, Scolyer RA, Long GV. Towards modulating the gut microbiota to enhance the efficacy of immune-checkpoint inhibitors. *Nat Rev Clin Oncol*. 2023;20(10):697-715. doi:10.1038/s41571-023-00803-9
54. Casares N, Pequignot MO, Tesniere A, et al. Caspase-dependent immunogenicity of doxorubicin-induced tumor cell death. *J Exp Med*. 2005;202(12):1691-1701. doi:10.1084/jem.20050915
55. Galluzzi L, Humeau J, Buqué A, Zitvogel L, Kroemer G. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. *Nat Rev Clin Oncol*. 2020;17(12):725-741. doi:10.1038/s41571-020-0413-z
56. Petroni G, Buqué A, Zitvogel L, Kroemer G, Galluzzi L. Immunomodulation by targeted anticancer agents. *Cancer Cell*. 2021;39(3):310-345. doi:10.1016/j.ccell.2020.11.009
57. Rodriguez-Ruiz ME, Vitale I, Harrington KJ, Melero I, Galluzzi L. Immunological impact of cell death signaling driven by radiation on the tumor microenvironment. *Nat Immunol*. 2020;21(2):120-134. doi:10.1038/s41590-019-0561-4
58. Kroemer G, Galassi C, Zitvogel L, Galluzzi L. Immunogenic cell stress and death. *Nat Immunol*. 2022;23(4):487-500. doi:10.1038/s41590-022-01132-2
59. Gong T, Liu L, Jiang W, Zhou R. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. *Nat Rev Immunol*. 2020;20(2):95-112. doi:10.1038/s41577-019-0215-7
60. Kepp O, Bezu L, Yamazaki T, et al. ATP and cancer immunosurveillance. *EMBO J*. 2021;40(13):e108130. doi:10.15252/embj.2021108130
61. Vacchelli E, Ma Y, Baracco EE, et al. Chemotherapy-induced antitumor immunity requires formyl peptide receptor 1. *Science*. 2015;350(6263):972-978. doi:10.1126/science.aad0779
62. Fucikova J, Spisek R, Kroemer G, Galluzzi L. Calreticulin and cancer. *Cell Res*. 2021;31(1):5-16. doi:10.1038/s41422-020-0383-9

63. Obeid M, Tesniere A, Ghiringhelli F, et al. Calreticulin exposure dictates the immunogenicity of cancer cell death. *Nat Med*. 2007;13(1):54-61. doi:10.1038/nm1523
64. Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat Med*. 2007;13(9):1050-1059. doi:10.1038/nm1622
65. Zitvogel L, Galluzzi L, Kepp O, Smyth MJ, Kroemer G. Type I interferons in anticancer immunity. *Nat Rev Immunol*. 2015;15(7):405-414. doi:10.1038/nri3845
66. Sistigu A, Yamazaki T, Vacchelli E, et al. Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy. *Nat Med*. 2014;20(11):1301-1309. doi:10.1038/nm.3708
67. Klionsky DJ, Petroni G, Amaravadi RK, et al. Autophagy in major human diseases. *EMBO J*. 2021;40(19):e108863. doi:10.15252/embj.2021108863
68. Michaud M, Martins I, Sukkurwala AQ, et al. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. *Science*. 2011;334(6062):1573-1577. doi:10.1126/science.1208347
69. Bezu L, Sauvat A, Humeau J, et al. eIF2α phosphorylation is pathognomonic for immunogenic cell death. *Cell Death Differ*. 2018;25(8):1375-1393. doi:10.1038/s41418-017-0044-9
70. Vanpouille-Box C, Demaria S, Formenti SC, Galluzzi L. Cytosolic DNA sensing in organismal tumor control. *Cancer Cell*. 2018;34(3):361-378. doi:10.1016/j.ccell.2018.05.013
71. Tang D, Kang R, Zeh HJ, Lotze MT. The multifunctional protein HMGB1: 50 years of discovery. *Nat Rev Immunol*. 2023. doi:10.1038/s41577-023-00894-6
72. Yamazaki T, Kirchmair A, Sato A, et al. Mitochondrial DNA drives abscopal responses to radiation that are inhibited by autophagy. *Nat Immunol*. 2020;21(10):1160-1171. doi:10.1038/s41590-020-0751-0
73. Le Naour J, Liu P, Zhao L, et al. A TLR3 ligand reestablishes chemotherapeutic responses in the context of FPR1 deficiency. *Cancer Discov*. 2021;11(2):408-423. doi:10.1158/2159-8290.cd-20-0465
74. Carbonnier V, Le Naour J, Bachelot T, et al. Rs867228 in FPR1 accelerates the manifestation of luminal B breast cancer. *Oncoimmunology*. 2023;12(1):2189823. doi:10.1080/2162402x.2023.2189823
75. Sayaman RW, Saad M, Thorsson V, et al. Germline genetic contribution to the immune landscape of cancer. *Immunity*. 2021;54(2):367-386. doi:10.1016/j.immuni.2021.01.011
76. Benci JL, Xu B, Qiu Y, et al. Tumor interferon signaling regulates a multigenic resistance program to immune checkpoint blockade. *Cell*. 2016;167(6):1540-1554. doi:10.1016/j.cell.2016.11.022
77. Lin H, Kryczek I, Li S, et al. Stanniocalcin 1 is a phagocytosis checkpoint driving tumor immune resistance. *Cancer Cell*. 2021;39(4):480-493. doi:10.1016/j.ccell.2020.12.023
78. Liu P, Zhao L, Loos F, et al. Immunosuppression by mutated calreticulin released from malignant cells. *Mol Cell*. 2020;77(4):748-760. doi:10.1016/j.molcel.2019.11.004
79. Yamazaki T, Hannani D, Poirier-Colame V, et al. Defective immunogenic cell death of HMGB1-deficient tumors: compensatory therapy with TLR4 agonists. *Cell Death Differ*. 2014;21(1):69-78. doi:10.1038/cdd.2013.72
80. Galluzzi L, Pietrocola F, Bravo-San Pedro JM, et al. Autophagy in malignant transformation and cancer progression. *EMBO J*. 2015;34(7):856-880. doi:10.15252/embj.201490784
81. Bidwell BN, Slaney CY, Withana NP, et al. Silencing of Irf7 pathways in breast cancer cells promotes bone metastasis through immune escape. *Nat Med*. 2012;18(8):1224-1231. doi:10.1038/nm.2830
82. Fucikova J, Moserova I, Urbanova L, et al. Prognostic and predictive value of DAMPs and DAMP-associated processes in cancer. *Front Immunol*. 2015;6:402. doi:10.3389/fimmu.2015.00402
83. Exner R, Sachet M, Arnold T, et al. Prognostic value of HMGB1 in early breast cancer patients under neoadjuvant chemotherapy. *Cancer Med*. 2016;5(9):2350-2358. doi:10.1002/cam4.827
84. Inoue H, Tsutsumi H, Tanaka K, et al. Increased plasma levels of damage-associated molecular patterns during systemic anticancer therapy in patients with advanced lung cancer. *Transl Lung Cancer Res*. 2021;10(6):2475-2486. doi:10.21037/tlcr-21-92
85. Kuderer NM, Desai A, Lustberg MB, Lyman GH. Mitigating acute chemotherapy-associated adverse events in patients with cancer. *Nat Rev Clin Oncol*. 2022;19(11):681-697. doi:10.1038/s41571-022-00685-3
86. Galluzzi L, Aryankalayil MJ, Coleman CN, Formenti SC. Emerging evidence for adapting radiotherapy to immunotherapy. *Nat Rev Clin Oncol*. 2023;20(8):543-557. doi:10.1038/s41571-023-00782-x
87. Hauth F, Ho AY, Ferrone S, Duda DG. Radiotherapy to enhance chimeric antigen receptor T-cell therapeutic efficacy in solid tumors: a narrative review. *JAMA Oncol*. 2021;7:1051-1059. doi:10.1001/jamaoncol.2021.0168
88. Cao Y, Langer R, Ferrara N. Targeting angiogenesis in oncology, ophthalmology and beyond. *Nat Rev Drug Discov*. 2023;22(6):476-495. doi:10.1038/s41573-023-00671-z
89. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078-2092. doi:10.1056/nejmoa1801005
90. Schaer DA, Geeganage S, Amaladas N, et al. The folate pathway inhibitor pemetrexed pleiotropically enhances effects of cancer immunotherapy. *Clin Cancer Res*. 2019;25(23):7175-7188. doi:10.1158/1078-0432.ccr-19-0433
91. Huang Y, Yuan J, Righi E, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. *Proc Natl Acad Sci U S A*. 2012;109(43):17561-17566. doi:10.1073/pnas.1215397109
92. Farsaci B, Donahue RN, Coplin MA, et al. Immune consequences of decreasing tumor vasculature with antiangiogenic tyrosine kinase inhibitors in combination with therapeutic vaccines. *Cancer Immunol Res*. 2014;2(11):1090-1102. doi:10.1158/2326-6066.cir-14-0076
93. Xie W, Forveille S, Iribarren K, et al. Lurbinectedin synergizes with immune checkpoint blockade to generate anticancer immunity. *Oncoimmunology*. 2019;8(11):e1656502. doi:10.1080/2162402x.2019.1656502
94. Montes de Oca R, Alavi AS, Vitali N, et al. Belantamab mafodotin (GSK2857916) drives immunogenic cell death and immune-mediated antitumor responses in vivo. *Mol Cancer Ther*. 2021;20(10):1941-1955. doi:10.1158/1535-7163.mct-21-0035
95. Lang F, Schrörs B, Löwer M, Türeci Ö, Sahin U. Identification of neoantigens for individualized therapeutic cancer vaccines. *Nat Rev Drug Discov*. 2022;21(4):261-282. doi:10.1038/s41573-021-00387-y
96. Shalhout SZ, Miller DM, Emerick KS, Kaufman HL. Therapy with oncolytic viruses: progress and challenges. *Nat Rev Clin Oncol*. 2023;20(3):160-177. doi:10.1038/s41571-022-00719-w
97. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. *Nat Rev Clin Oncol*. 2023;20(6):359-371. doi:10.1038/s41571-023-00754-1
98. Chamoto K, Yaguchi T, Tajima M, Honjo T. Insights from a 30-year journey: function, regulation and therapeutic modulation of PD1.

Nat Rev Immunol. 2023;23(10):682-695. doi:10.1038/s41577-023-00867-9

99. Two win Nobel for immune regulation discoveries. *Cancer Discov*. 2018;8:1338-1339. doi:10.1158/2159-8290.CD-NB2018-127
100. Wolchok JD, Hodi FS, Weber JS, et al. Development of ipilimumab: a novel immunotherapeutic approach for the treatment of advanced melanoma. *Ann N Y Acad Sci*. 2013;129(1):1-13. doi:10.1111/nyas.12180
101. Keam SJ. Tremelimumab: first approval. *Drugs*. 2023;83(1):93-102. doi:10.1007/s40265-022-01827-8
102. Korman AJ, Garrett-Thomson SC, Lonberg N. The foundations of immune checkpoint blockade and the ipilimumab approval decennial. *Nat Rev Drug Discov*. 2022;21(7):509-528. doi:10.1038/s41573-021-00345-8
103. Nguyen LT, Ohashi PS. Clinical blockade of PD1 and LAG3—potential mechanisms of action. *Nat Rev Immunol*. 2015;15(1):45-56. doi:10.1038/nri3790
104. Amaria RN, Postow M, Burton EM, et al. Neoadjuvant relatlimab and nivolumab in resectable melanoma. *Nature*. 2022;611(7934):155-160. doi:10.1038/s41586-022-05368-8
105. Gomes de Morais AL, Cerdá S, de Miguel M. New checkpoint inhibitors on the road: targeting TIM-3 in solid tumors. *Curr Oncol Rep*. 2022;24(5):651-658. doi:10.1007/s11912-022-01218-y
106. Rousseau A, Parisi C, Barlesi F. Anti-TIGIT therapies for solid tumors: a systematic review. *ESMO Open*. 2023;8(2):101184. doi:10.1016/j.esmoop.2023.101184
107. Kraehenbuehl L, Weng CH, Eghbali S, Wolchok JD, Merghoub T. Enhancing immunotherapy in cancer by targeting emerging immunomodulatory pathways. *Nat Rev Clin Oncol*. 2022;19(1):37-50. doi:10.1038/s41571-021-00552-7
108. Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. *Nat Rev Clin Oncol*. 2022;19(4):237-253. doi:10.1038/s41571-021-00588-9
109. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin*. 2020;70(2):86-104. doi:10.3322/caac.21596
110. Ramos-Casals M, Brahmer JR, Callahan MK, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers*. 2020;6(1):38. doi:10.1038/s41572-020-0160-6
111. Kalfeist L, Galland L, Ledys F, Ghiringhelli F, Limagne E, Ladoire S. Impact of glucocorticoid use in oncology in the immunotherapy era. *Cells*. 2022;11(5):770. doi:10.3390/cells11050770
112. Fa'ak F, Buni M, Falohun A, et al. Selective immune suppression using interleukin-6 receptor inhibitors for management of immune-related adverse events. *J Immunother Cancer*. 2023;11(6):e006814. doi:10.1136/jitc-2023-006814
113. Tison A, Garaud S, Chiche L, Cornec D, Kostine M. Immune-checkpoint inhibitor use in patients with cancer and pre-existing autoimmune diseases. *Nat Rev Rheumatol*. 2022;18(11):641-656. doi:10.1038/s41584-022-00841-0
114. Perez-Ruiz E, Minute L, Otano I, et al. Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy. *Nature*. 2019;569(7756):428-432. doi:10.1038/s41586-019-1162-y
115. Chen AY, Wolchok JD, Bass AR. TNF in the era of immune checkpoint inhibitors: friend or foe? *Nat Rev Rheumatol*. 2021;17(4):213-223. doi:10.1038/s41584-021-00584-4
116. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell*. 2015;161(2):205-214. doi:10.1016/j.cell.2015.03.030
117. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34. doi:10.1056/nejmoa1504030
118. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277-1290. doi:10.1056/nejmoa1712126
119. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2040-2051. doi:10.1056/nejmoa1810865
120. Vesely MD, Zhang T, Chen L. Resistance mechanisms to anti-PD cancer immunotherapy. *Annu Rev Immunol*. 2022;40(1):45-74. doi:10.1146/annurev-immunol-070621-030155
121. VanderWalde A, Bellasea SL, Kendra KL, et al. Ipilimumab with or without nivolumab in PD-1 or PD-L1 blockade refractory metastatic melanoma: a randomized phase 2 trial. *Nat Med*. 2023;29(9):2278-2285. doi:10.1038/s41591-023-02498-y
122. Chow A, Perica K, Klebanoff CA, Wolchok JD. Clinical implications of T cell exhaustion for cancer immunotherapy. *Nat Rev Clin Oncol*. 2022;19(12):775-790. doi:10.1038/s41571-022-00689-z
123. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. *Nat Rev Drug Discov*. 2019;18(3):197-218. doi:10.1038/s41573-018-0007-y
124. Pfirschke C, Engblom C, Rickelt S, et al. Immunogenic chemotherapy sensitizes tumors to checkpoint blockade therapy. *Immunity*. 2016;44(2):343-354. doi:10.1016/j.immuni.2015.11.024
125. Liu P, Chen J, Zhao L, et al. PD-1 blockade synergizes with oxaliplatin-based, but not cisplatin-based, chemotherapy of gastric cancer. *Oncoimmunology*. 2022;11(1):2093518. doi:10.1080/2162402x.2022.2093518
126. Voorwerk L, Slagter M, Horlings HM, et al. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. *Nat Med*. 2019;25(6):920-928. doi:10.1038/s41591-019-0432-4
127. Demaria S, Romano E, Brackstone M, Formenti SC. Immune induction strategies to enhance responses to PD-1 blockade: lessons from the TONIC trial. *J Immunother Cancer*. 2019;7(1):318. doi:10.1186/s40425-019-0783-x
128. Røssevold AH, Andresen NK, Bjerre CA, et al. Atezolizumab plus anthracycline-based chemotherapy in metastatic triple-negative breast cancer: the randomized, double-blind phase 2b ALICE trial. *Nat Med*. 2022;28(12):2573-2583. doi:10.1038/s41591-022-02126-1
129. Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6(10):1571-1580. doi:10.1001/jamaoncol.2020.3370
130. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27-40. doi:10.1016/s0140-6736(21)00797-2
131. Guo X, Yang B, He L, Sun Y, Song Y, Qu X. PD-1 inhibitors plus oxaliplatin or cisplatin-based chemotherapy in first-line treatments for advanced gastric cancer: a network meta-analysis. *Front Immunol*. 2022;13:905651. doi:10.3389/fimmu.2022.905651
132. Antoniotti C, Rossini D, Pietrantonio F, et al. Upfront FOLFOXIRI plus bevacizumab with or without atezolizumab in the treatment of patients with metastatic colorectal cancer (AtezoTRIBE): a multicentre, open-label, randomised, controlled, phase 2 trial. *Lancet Oncol*. 2022;23(7):876-887. doi:10.1016/s1470-2045(22)00274-1
133. Johnson ML, Cho BC, Luft A, et al. Durvalumab with or without tremelimumab in combination with chemotherapy as first-line therapy for metastatic non-small-cell lung cancer: the phase III POSEIDON study. *J Clin Oncol*. 2023;41(6):1213-1227. doi:10.1200/jco.22.00975

134. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350. doi:10.1056/nejmoa1809697
135. Chesney JA, Puzanov I, Collichio FA, et al. Talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone for advanced melanoma: 5-year final analysis of a multicenter, randomized, open-label, phase II trial. *J Immunother Cancer*. 2023;11(5):e006270. doi:10.1136/kotc-2022-006270
136. Nassiri F, Patil V, Yefet LS, et al. Oncolytic DNX-2401 virotherapy plus pembrolizumab in recurrent glioblastoma: a phase 1/2 trial. *Nat Med*. 2023;29(6):1370-1378. doi:10.1038/s41591-023-02347-y
137. Lim M, Weller M, Idbaih A, et al. Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter. *Neuro Oncol*. 2022;24(11):1935-1949. doi:10.1093/neuonc/noac116
138. Omuro A, Brandes AA, Carpentier AF, et al. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: an international randomized phase III trial. *Neuro Oncol*. 2023;25(1):123-134. doi:10.1093/neuonc/noac099
139. Lee NY, Ferris RL, Psyrri A, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol*. 2021;22(4):450-462. doi:10.1016/s1470-2045(20)30737-3
140. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2022;23(1):77-90. doi:10.1016/s1470-2045(21)00604-5
141. Dummer R, Long GV, Robert C, et al. Randomized phase III trial evaluating spartalizumab plus dabrafenib and trametinib for BRAF V600-mutant unresectable or metastatic melanoma. *J Clin Oncol*. 2022;40(13):1428-1438. doi:10.1200/jco.21.01601
142. Pal SK, Albiges L, Tomczak P, et al. Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. *Lancet*. 2023;402(10397):185-195. doi:10.1016/s0140-6736(23)00922-4
143. Routy B, Lenehan JG, Miller WH Jr, et al. Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial. *Nat Med*. 2023;29(8):2121-2132. doi:10.1038/s41591-023-02453-x
144. Maio M, Blank C, Necchi A, et al. Neoadjuvant immunotherapy is reshaping cancer management across multiple tumour types: the future is now. *Eur J Cancer*. 2021;152:155-164. doi:10.1016/j.ejca.2021.04.035
145. Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. *Nat Med*. 2018;24(11):1655-1661. doi:10.1038/s41591-018-0198-0
146. Rozeman EA, Menzies AM, van Akkooi ACJ, et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. *Lancet Oncol*. 2019;20(7):948-960. doi:10.1016/s1470-2045(19)30151-2
147. Rozeman EA, Hoefsmit EP, Reijers ILM, et al. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. *Nat Med*. 2021;27(2):256-263. doi:10.1038/s41591-020-01211-7
148. Amaria RN, Menzies AM, Burton EM, et al. Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium. *Lancet Oncol*. 2019;20(7):e378-e389. doi:10.1016/s1470-2045(19)30332-8
149. Menzies AM, Amaria RN, Rozeman EA, et al. Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). *Nat Med*. 2021;27(2):301-309. doi:10.1038/s41591-020-01188-3
150. Reijers ILM, Menzies AM, van Akkooi ACJ, et al. Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the PRADO trial. *Nat Med*. 2022;28(6):1178-1188. doi:10.1038/s41591-022-01851-x
151. Patel SP, Othus M, Chen Y, et al. Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma. *N Engl J Med*. 2023;388(9):813-823. doi:10.1056/nejmoa2211437
152. van Akkooi ACJ, Blank C, Eggermont AMM. Neo-adjuvant immunotherapy emerges as best medical practice, and will be the new standard of care for macroscopic stage III melanoma. *Eur J Cancer*. 2023;182:38-42. doi:10.1016/j.ejca.2023.01.004
153. Garbe C, Dummer R, Amaral T, et al. Neoadjuvant immunotherapy for melanoma is now ready for clinical practice. *Nat Med*. 2023;29(6):1310-1312. doi:10.1038/s41591-023-02336-1
154. Gross ND, Miller DM, Khushalani NI, et al. Neoadjuvant cemiplimab for stage II to IV cutaneous squamous-cell carcinoma. *N Engl J Med*. 2022;387(17):1557-1568. doi:10.1056/nejmoa2209813
155. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386(21):1973-1985. doi:10.1056/nejmoa2202170
156. Wakelee H, Liberman M, Kato T, et al. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med*. 2023;389(6):491-503. doi:10.1056/nejmoa2302983
157. Provencio M, Nadal E, Gonzalez-Larriba JL, et al. Perioperative nivolumab and chemotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2023;389(6):504-513. doi:10.1056/nejmoa2215530
158. Chen H, Yang W, Xue X, Li Y, Jin Z, Ji Z. Neoadjuvant immunotherapy and chemoimmunotherapy for stage II–III muscle invasive bladder cancer. *Front Immunol*. 2022;13:986359. doi:10.3389/fimmu.2022.986359
159. Wang J, Zhang K, Liu T, et al. Efficacy and safety of neoadjuvant immunotherapy combined with chemotherapy in locally advanced esophageal cancer: a meta-analysis. *Front Oncol*. 2022;12:974684. doi:10.3389/fonc.2022.974684
160. Basile G, Bandini M, Gibb EA, et al. Neoadjuvant pembrolizumab and radical cystectomy in patients with muscle-invasive urothelial bladder cancer: 3-year median follow-up update of PURE-01 trial. *Clin Cancer Res*. 2022;28(23):5107-5114. doi:10.1158/1078-0432.ccr-22-2158
161. André T, Tougeron D, Piessen G, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: the GERCOR NEONIPIGA phase II study. *J Clin Oncol*. 2023;41(2):255-265. doi:10.1200/jco.22.00686
162. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810-821. doi:10.1056/nejmoa1910549
163. Schmid P, Cortes J, Dent R, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med*. 2022;386(6):556-567. doi:10.1056/nejmoa2112651
164. Chalabi M, Fanchi LF, Dijkstra KK, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and

MMR-deficient early-stage colon cancers. *Nat Med*. 2020;26(4):566-576. doi:10.1038/s41591-020-0805-8

165. Cercek A, Lumish M, Sinopoli J, et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. *N Engl J Med*. 2022;386(25):2363-2376. doi:10.1056/nejmoa2201445
166. Sprooten J, Laureano RS, Vanmeerbeek I, et al. Trial watch: chemotherapy-induced immunogenic cell death in oncology. *Oncoimmunology*. 2023;12(1):2219591. doi:10.1080/2162402x.2023.2219591
167. Kepp O, Marabelle A, Zitvogel L, Kroemer G. Oncolysis without viruses—inducing systemic anticancer immune responses with local therapies. *Nat Rev Clin Oncol*. 2020;17(1):49-64. doi:10.1038/s41571-019-0272-7
168. Petroni G, Galluzzi L. Impact of treatment schedule on the efficacy of cytostatic and immunostimulatory agents. *Oncoimmunology*. 2021;10(1):1889101. doi:10.1080/2162402x.2021.1889101
169. Yu J, Green MD, Li S, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat Med*. 2021;27(1):152-164. doi:10.1038/s41591-020-1131-x

How to cite this article: Kroemer G, Chan TA, Eggermont AMM, Galluzzi L. Immunosurveillance in clinical cancer management. *CA Cancer J Clin*. 2024;74(2):187-202. doi:10.3322/caac.21818