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Immunosurveillance in clinical cancer management

Running title: Anticancer immunity

Guido Kroemer MD PhD¹, Timothy A. Chan MD PhD², Alexander M. M. Eggermont MD PhD³ and Lorenzo Galluzzi PhD⁴

¹Centre de Recherche des Cordeliers, Equipe Labellisée par la Ligue Contre le Cancer, Inserm U1138, Université Paris Cité, Sorbonne Université, Institut Universitaire de France, Paris, France; Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Center, Villejuif, France; Institut du Cancer Paris Carpem, Department of Biology, Hôpital Européen Georges Pompidou, AP-HP, Paris, France.

²Department of Radiation Oncology, Taussig Cancer Center, Cleveland Clinic, Cleveland, OH, USA; Center for Immunotherapy and Precision Immuno-Oncology, Cleveland Clinic, Cleveland, OH, USA; National Center for Regenerative Medicine, Cleveland, OH, USA; Case Comprehensive Cancer Center, Cleveland, OH, USA.

³University Medical Center Utrecht & Princess Maxima Center, Utrecht, the Netherlands; Comprehensive Cancer Center München, Technical University München & Ludwig Maximilian University, München, Germany.

⁴Department of Radiation Oncology, Weill Cornell Medical College, New York, NY, USA; Sandra and Edward Meyer Cancer Center, New York, NY, USA; Caryl and Israel Englander Institute for Precision Medicine, New York, NY, USA.

Corresponding authors: Guido Kroemer, Centre de Recherche des Cordeliers, 15 rue de l'Ecole de Médecine, 75006 Paris, France; Tel: +33(6)7906-7743; e-mail: kroemer@orange.fr; Lorenzo Galluzzi, Department of Radiation Oncology, Weill Cornell Medical College, 1300 York Avenue, New York, NY 10065, USA; Tel: +1(646)962-2095; e-mail: log3001@med.cornell.edu

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was on the 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. GK's brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. TAC is a co-founder of and holds equity in Gritstone Oncology; holds equity in An2H; acknowledges grant funding from An2H, AstraZeneca, Bristol Myers Squibb, Eisai, Illumina and Pfizer; has served as an advisor for An2H, AstraZeneca, Bristol Myers Squibb, Eisai, Illumina and MedImmune; and holds ownership of intellectual property on using tumour mutational burden to predict immunotherapy response, which has been licensed to PGDx. AMME has received consulting/advisory honoraria from Atreca, Agenus, BioInvent, BioNTech, Brenus, CatalYm, Galecto, GenOway, Immunocore, IO Biotech, IQVIA, ISA Pharmaceuticals, Merck&Co, MSD, Pierre Fabre, Sairopa, Scorpion Pharmaceuticals, Sellas, SkylineDX, TigaTX and Trained Therapeutics, honoraria for IDMC from Boehringer Ingelheim, IQVIA, Merck AG and Pfizer, speaker honoraria from BMS and Merck&Co/MSD, and equities from IO Biotech, Sairopa and SkylineDX. LG 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, and holds Promontory stock options. The remaining authors declare no competing interests. The funders had no role in the design of the study; in the writing of the manuscript, or in the decision to publish the results.

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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 employing such combinations, which are referred to as “chemoimmunotherapy”, as well as combinations of multiple ICIs, the latter of which - however - are generally associated with severe side effects as compared to 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, we critically discuss the importance of immunosurveillance in modern clinical cancer management.

Keywords: cancer immunotherapy; chemotherapy; immune checkpoint blockade; radiation therapy; targeted therapy; tumor-infiltrating lymphocytes.

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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 a central stage in modern oncology and they have been licensed for a wide range of solid and hematological malignancies ¹¹.

According to the three ‘E’s model of immunity-cancer co-evolution ¹², malignant and immune cells interact with each other in three discrete steps – Elimination, Equilibrium and Escape (**Fig. 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 due to local and systemic immune control. In this setting, cancer cells that acquire the ability of avoiding immune recognition or weakening immune effectors become 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}.

The three 'E's 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 papilloma virus (HPV) 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 employed 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 to achieve 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 fact that successful cancer treatments, including chemotherapeutics, radiation therapy and some targeted agents operate (at least partially) via the immune system. Moreover, we will 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

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

Colorectal cancer (CRC) infiltration by CD8⁺ T lymphocytes was reported as a positive prognostic factor in 2005²⁴. This led to the development of a standardized test measuring the density of CD3⁺ and CD8⁺ T lymphocytes within and at its invasive margin using immunohistochemistry (IHC) on formaldehyde-fixed paraffin-embedded tissue sections and digital pathology, referred to as “Immunoscore”²⁵. The Immunoscore has been clinically validated for its association with time to recurrence in patients with CRC independent from patient age, sex, tumor stage, lymph node status, microsatellite instability, and other prognostic factors²⁶. Attempts are now underway to extend the use of the Immunoscore to cancer types other than CRC²⁷. Indeed, the density, composition and functionality of the tumor immune infiltrate (which includes not only CD8⁺ T lymphocytes but also other T cell populations, B cells, NK cells as well as multiple distinct myeloid cell types)^{7, 8} is relevant not only for immunotherapy, but (at least in some tumor types) also for chemotherapy. For instance, CD8⁺ 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 infiltrate³⁰⁻³². 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 RNAseq data³³, will prevail. Irrespective of this open question, it appears that the

spatial organization of intratumoral immune cells, for example in so-called “tertiary lymphoid organs” that can be found in the microenvironment of some tumors, plays an important role in immunosurveillance, at least in tumors with a detectable tumor infiltrate ⁸.

The expression levels of the PD-1 ligand PD-L1 in the TME can predict the sensitivity of individual patients with a variety of cancers to ICIs targeting PD-1 or PD-L1, 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 usage, either as a tumor proportion score (TPS), which is the percentage of cancer cells that express PD-L1 as identified by IHC, or as a combined positive score (CPS), which is the percentage of PD-L1⁺ cells within the tumor, including malignant, lymphoid and myeloid cells ³⁵. Depending on the specific malignancy, FDA approval for ICIs targeting PD-1 or PD-L1 has been restricted to cancers with a TPS or CPS higher than 1 or 10%, as determined by companion diagnostic tests (reviewed in Ref. 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 fact that multiple therapeutic agents including conventional chemotherapeutic, radiotherapy 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 non-synonymous 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 US 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/megabase (mut/Mb) 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) that is associated with the instability of specific DNA regions called microsatellites ⁴⁰. Accordingly, tumors with a molecular diagnosis of defective MMR (dMMR) or elevated 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 (FMs). Based on a recent pan cancer analysis, FMs 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 non-small 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 utilize 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 (NLR, which remains one of the strongest negative

prognostic markers for patients with cancer) ⁴⁷. While a refined immunomonitoring is not routinely performed in the clinical practice, lab tests enabling NLR 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 (ctDNA), can also be measured by a variety of 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 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 in Ref. ⁵³. Whether these observations will lead to the approval of biomarkers for routine clinical usage 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 cancer to respond to ICIs.

Moreover, not only the Immunoscore and more refined tumor-centric methods evaluating the cancer-immunity dialogue are under development, but also there is the prospect to extract information on the state of immunosurveillance from the blood and feces (**Table 1**).

Immune effects of diverse treatment modalities

Nearly two decades after pioneering preclinical work linking the efficacy of anthracyclines to the immune system ⁵⁴, it is clear that the activity of various commonly employed anticancer agents relies, at least partially, on the (re)activation of immunosurveillance ⁵⁵⁻⁵⁷. Multiple anticancer treatments in common use have been shown 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 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 exert multipronged immunostimulatory effects in the TME ⁶⁵ but also operates on malignant cells to elicit the secretion of T lymphocytes 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” (ISR), 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.

Besides 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 homo- or heterozygous patterns (~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, a number of inheritable traits such as germline variants in genes encoding innate immune sensors that drive type I IFN production during ICD like interferon induced with helicase C domain 1 (IFIH1, best known as MDA5) and stimulator of interferon 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 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 2 α (eIF2 α), which occurs during the ISR, in cancer cells or the exposure of CALR on their surface⁶², 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 on 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 as 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 vasculature⁸⁸. 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 activity⁹⁰. On the contrary, the vascular endothelial growth factor A (VEGFA) blocker bevacizumab as well as multiple tyrosine kinase inhibitors commonly employed in the management of 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 protocols⁸⁶.

In sum, most if not all cancer therapeutics affect immunosurveillance either indirectly, by stressing and killing cancer cells in an immunogenic fashion, or directly, via 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 due to 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 antigens⁹⁵ to methods that involve (at least some facets of) synthetic biology such as genetically engineered viruses⁹⁶ and chimeric antigen receptor (CAR) T cells⁹⁷, which we will not discuss in this review (**Table 2**). ICIs have revolutionized oncology over the past decade due to 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 2018⁹⁹. Specifically, ICIs are monoclonal antibodies targeting molecules that normally suppress T lymphocytes and NK cells to prevent excessive (auto)immune responses¹¹. 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, while these molecules share similarities in their immunoregulatory function, they differ in expression pattern and mechanisms of action¹⁰.

PD-1 is expressed on activated T, B and NK cells, while its ligands PD-L1 and PD-L2 are expressed on cancer cells and multiple myeloid cell types⁹⁸. 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, renal cell carcinoma (RCC), mesothelioma, and Hodgkin lymphoma^{10,98}. Hence, they have been approved for many clinical indications, though their use is often predicated on a biomarker, such as PD-L1 expression, a high TMB or a dMMR/MSI-H status⁴².

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 activation¹⁰. CTLA-4 is targeted by ipilimumab, the first FDA-approved ICI that has shown efficacy as a monotherapy against melanoma¹⁰⁰, 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, tremelimumab¹⁰¹. 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 settings¹⁰².

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 receptors¹⁰³. The LAG-3 blocker relatlimab has recently been approved by the US FDA for the treatment of unresectable or metastatic melanoma in combination with nivolumab¹⁰⁴. 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 Ig and ITIM domains (TIGIT)¹⁰⁶, as well as immunotherapeutics that would activate stimulatory T cell receptors¹⁰⁷. 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 immunostimulation¹⁰⁸. 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 encephalitis¹⁰⁹. 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 non-specific immunosuppression with high-dose glucocorticoids may interfere with both ICI toxicity and efficacy¹¹¹. Thus, 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 pro-inflammatory molecule interleukin-6 (IL-6)¹¹². At this point, the side effects of ICIs are so well managed that even patients with pre-existing autoimmune conditions can be safely treated¹¹³. Neutralization of another pro-inflammatory factor, namely tumor necrosis factor (TNF) has also been shown to limit ICI-driven irAEs but not ICI efficacy in preclinical tumor models¹¹⁴, but this possibility awaits clinical validation¹¹⁵. If confirmed, such a decoupling effect on toxicity and efficacy could considerably improve the clinical management of oncological patients 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 responses¹¹⁶. This has been dramatically achieved in patients with melanoma and RCC treated with PD-1 inhibitors alone or combined with ipilimumab^{117,118}, as well as in patients with NSCLC receiving 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) and definitive cures beyond anecdotal cases in such indications, due to the short follow-up²³.

Contemporary research is focusing on the distinction between primary (innate) resistance and secondary (acquired) ICI resistance¹²⁰. 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 melanoma patients 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 duration¹²⁰. 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, (3) actively exclude T lymphocytes from the TME or directly suppress their activation¹²⁰. 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 towards an inactive, so-called “exhausted”, state¹²². Attempts are on the way to tackle both primary and secondary resistance against ICIs by means of combination therapies, as discussed in the next section.

Combinatorial strategies for the restoration of immunosurveillance

Numerous combinatorial regimens involving ICIs and agents with non-overlapping mode of actions 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 with 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 with metastatic breast cancer treated with doxorubicin were found to obtain superior clinical benefit from subsequent nivolumab administration compared to other induction therapies with 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 with metastatic breast cancer as compared to placebo ¹²⁸. Two randomized phase 3 clinical trials for patients with unresectable gastric and gastro-esophageal 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 as compared to 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. Subsequent trials confirmed clinical benefits when atezolizumab is combined with oxaliplatin-based chemotherapy plus in patients with advanced CRC ¹³², and when durvalumab plus tremelimumab are added to it in patients with NSCLC ¹³³. Durvalumab has been shown to improve overall survival in patients with NSCLC previously treated with chemotherapy plus RT as an induction therapy as

compared to 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 suggest 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 towards 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 fact 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 employed 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 out of 20 patients), including four (20%) complete responses, to subsequent PD-1 blockade ¹⁴³. This observation suggests that “resetting” the systemic ecosystem that dictate the immune tonus through microbial manipulations may improve the therapeutic utility of ICIs.

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, as compared to patients that 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)¹⁴⁴. 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. Lastly, the chronic effects of various immunotherapies will have to be addressed. How to reduce long-term (1-2 years long) treatments must be explored. The current “revolution” of neoadjuvant immunotherapy indicates that a triple effect can be achieved: more cures, shorter treatments, less surgery.

From adjuvant to neoadjuvant schedules

A major shift in therapeutic approach is now emerging with respect to the timing of ICI administration to patients with resectable cancers¹⁴⁵. 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 neo-adjuvant (chemo)immunotherapy is administered before surgery across multiple tumor types. This appears logical from a mechanistic perspective as 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 has initially been reported in patients with cutaneous melanoma. Specifically, patients with Stage III melanoma treated with neoadjuvant nivolumab (at standard dose) plus low-dose ipilimumab exhibited the expansion of pre-existing tumor-specific T cells after only 2 cycles of immunotherapy and in the context of minimal irAEs^{146, 147}. Notably, up to 70% of these patients experienced a pathologic complete response (pCR, 100% tumor necrosis) or near-pathologic complete response (npCR, >90% tumor necrosis) that was associated with a significantly low relapse rate (<5%)^{147, 148}. These pioneering observations promoted the establishment of the Neoadjuvant Melanoma Immunotherapy Consortium (NIMC), with the objective to define clinical protocols for limiting treatment cycles, minimizing surgery, and reducing/omitting unnecessary adjuvant therapy in patients with melanoma responding to ICIs¹⁴⁹. Pooled analyses by NIMC documented that patients with melanoma achieving pCRs on neoadjuvant ICIs have a much lower probability to relapse than patients receiving BRAF/MEK inhibitors¹⁵⁰. A subsequent clinical trial enrolling 99 patients with macroscopic, Stage III melanoma receiving 2 cycles of neoadjuvant nivolumab plus low-dose ipilimumab yielded 60% pCR or npCR in index lymph nodes, with excellent

local control and relapse-free survival in the absence of therapeutic node dissection and adjuvant therapy ¹⁵¹. Moreover, a randomized, Phase 2 clinical trial enrolling patients with Stage III melanoma revealed that it is feasible to administer the first 3 (out of 18) cycles of pembrolizumab neoadjuvantly, resulting in improved event-free survival (EFS) rate as compared to immediate lymph node dissection ¹⁵². 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 with advanced melanoma by neoadjuvant immunotherapy as best medical practice ^{153, 154}.

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 ¹⁵⁵. 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 pCR rate and overall survival ¹⁵⁶. Similarly, patients bearing resectable NSCLC exhibited a better outcome after neoadjuvant chemoimmunotherapy (pembrolizumab or nivolumab plus cisplatin-based chemotherapy) followed by post-surgical immunotherapy than with neoadjuvant chemotherapy alone, with a higher percentage of major pathologic responses and improved EFS ^{157, 158}.

Meta-analyses suggest that neoadjuvant immunotherapy plus chemotherapy may also be useful for the treatment of stage II-III muscle invasive bladder cancer (MIBC) ¹⁵⁹, and locally advanced esophageal carcinoma ¹⁶⁰. In one trial, neoadjuvant pembrolizumab improved EFS in 155 patients with MIBC enrolled in a prospective clinical study ¹⁶¹. Similarly, neoadjuvant combined immunotherapy (nivolumab plus ipilimumab) yielded pathological responses in >50% of patients with gastric or gastric-esophageal junction cancers with a dMMR/MSI-H status ¹⁶². In this trial, 10% of study

volunteers did not undergo surgery because of endoscopic biopsy-proven pCRs ¹⁶². 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- 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 ^{163, 164}. Perhaps the most significant results have been achieved in patients with advanced dMMR/MSI-H CRC, in which dual neoadjuvant nivolumab plus ipilimumab results in 100% major pathologic responses (including 69% pCRs) with no relapses at 13 months follow-up ¹⁶⁵. Similarly, neoadjuvant PD-1 blockage resulted in 100% of pCRs in 12 consecutive patients with locally advanced dMMR-MSI-H rectal cancers, with no relapses at a minimal follow-up of 12 months ¹⁶⁶.

In conclusion, neoadjuvant ICIs targeting PD-1 alone or together with CTLA-4 or LAG-3 blockers and/or chemotherapy has generated considerable progress across a range of different malignancies, as illustrated by high rates of profound pathological 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 radiotherapy 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 chemotherapy¹⁶⁷. 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 employed so to minimize local and systemic immunosuppression^{86, 168}. 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 administered¹⁶⁹. 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, as it appears that major clinic-biological 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 responses³. 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.

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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*	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. dMMR, defective mismatch repair; 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. *but routinely employed and reimbursed by some health providers.

Table 2. Overview over FDA-approved immunotherapies

Immunotherapy	Indication(s)*	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 direct immunostimulants.	Systemic administration often associated with moderate to severe adverse events, which overall limits clinical applicability.
ICD inducers	Various	Conventional chemotherapeutics, RT 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	mAbs 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 reeducate lymphocytes against the tumor and reinfused.	One single agent (sipuleucel T) currently approved for use in patients with prostate cancer. Scarcely employed in the clinical practice.
Tumor-targeting mAbs	Breast cancer Colorectal cancer Lung cancer Lymphoma	Besides inhibiting malignant cells, some tumor-targeting mAbs 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; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; mAb, monoclonal antibody; PRR, pattern recognition receptor; RCC, renal cell carcinoma. *most common.

Figures and Legends to Figures

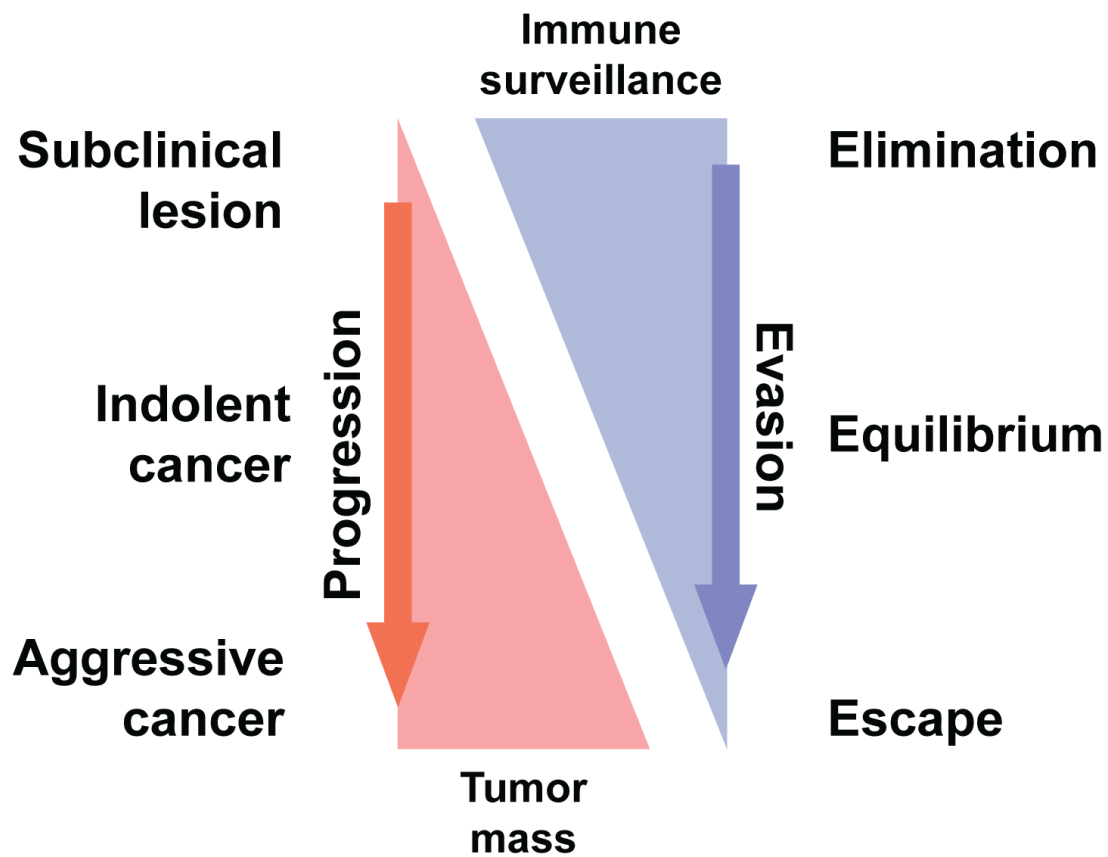


Figure 1 *Figure 1.*

Principles of cancer immunosurveillance. According to the three 'E's model of immunity-cancer co-evolution, 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 remain under immune control, and finally overt immune escape coupled with disease progression.

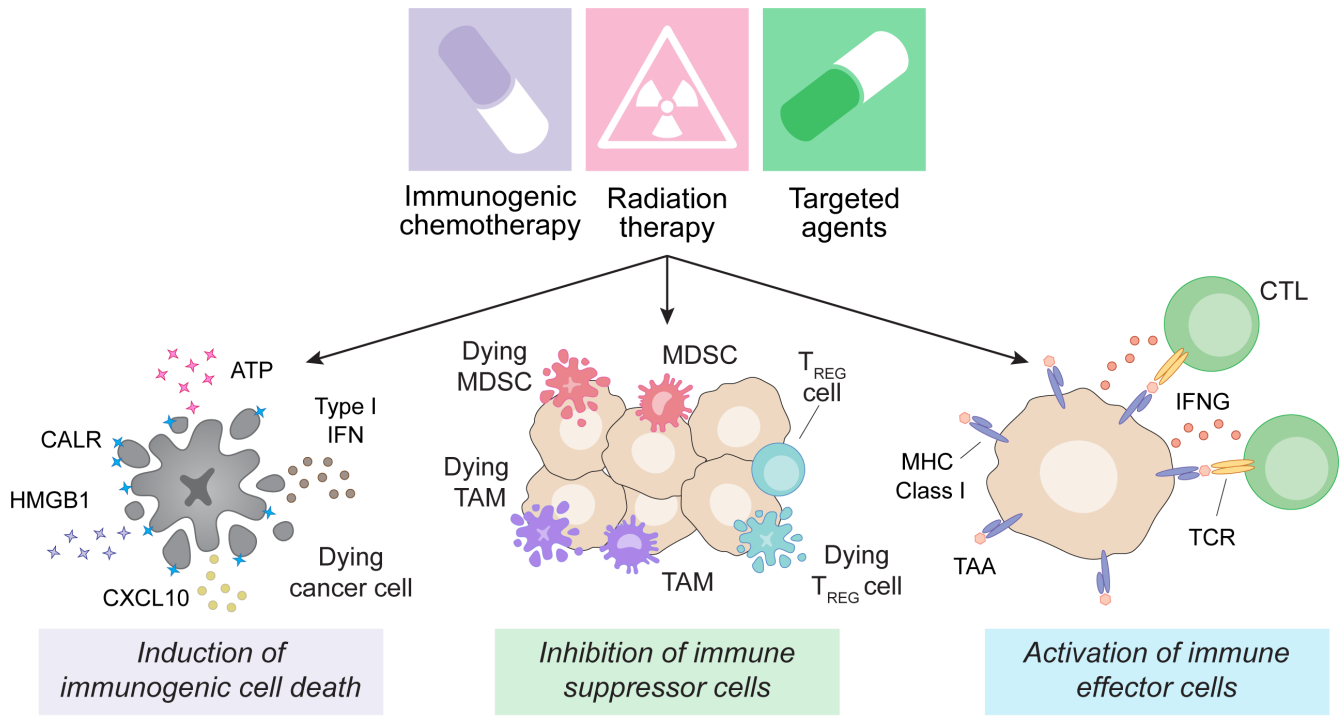


Figure 2

Figure 2. Beneficial immune effects of chemotherapy, radiation therapy and targeted anticancer agents. A number of 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 via 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, which recognize malignant cells presenting specific tumor-associated antigens (TAAs) on MHC class I molecules via their T cell receptor (TCR), and respond to them by producing effector molecules such as interferon gamma (IFNG). Abbreviations: CALR, calreticulin, CXCL10, C-X-C motif chemokine ligand 10; HMGB1, high mobility group box 1; IFN, interferon.