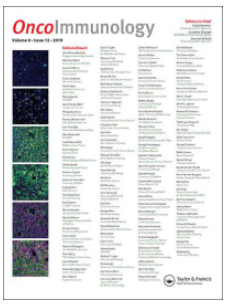

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REVIEW

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Trial watch: chemotherapy-induced immunogenic cell death in oncology

Jenny Sprooten[a], Raquel S. Laureano[a], Isaure Vanmeerbeek[a], Jannes Govaerts[a], Stefan Naulaerts[a], Daniel M. Borras[a], Lisa Kinget[b], Jitka Fucíková[c,d], Radek Špíšek[c,d], Lenka Palová Jelínková[c,d], Oliver Kepp[e,f], Guido Kroemer[e,f,g], Dmitri V. Krysko[h,i], An Coosemans[j], Rianne D.W. Vaes[k], Dirk De Ruysscher[k,l], Steven De Vleeschouwer[m,n,o], Els Wauters[p], Evelien Smits[q,r], Sabine Tejpar[s,t], Benoit Beuselinck[b], Sigrid Hatse[b], Hans Wildiers[b], Paul M. Clement[b], Peter Vandenabeele[t,u], Laurence Zitvogel[v], and Abhishek D. Garg[a]

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ABSTRACT

Immunogenic cell death (ICD) refers to an immunologically distinct process of regulated cell death that activates, rather than suppresses, innate and adaptive immune responses. Such responses culminate into T cell-driven immunity against antigens derived from dying cancer cells. The potency of ICD is dependent on the immunogenicity of dying cells as defined by the antigenicity of these cells and their ability to expose immunostimulatory molecules like damage-associated molecular patterns (DAMPs) and cytokines like type I interferons (IFNs). Moreover, it is crucial that the host's immune system can adequately detect the antigenicity and adjuvanticity of these dying cells. Over the years, several well-known chemotherapies have been validated as potent ICD inducers, including (but not limited to) anthracyclines, paclitaxels, and oxaliplatin. Such ICD-inducing chemotherapeutic drugs can serve as important combinatorial partners for anti-cancer immunotherapies against highly immuno-resistant tumors. In this Trial Watch, we describe current trends in the preclinical and clinical integration of ICD-inducing chemotherapy in the existing immuno-oncological paradigms.

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Introduction

It has been two decades since the concept of apoptosis being solely immunologically quiet and hence unable to activate the immune system has been overthrown. A large number of studies have substantiated an immunogenic variant of regulated cell death (RCD) programs like apoptosis, called immunogenic cell death (ICD)[1–4]. Since then, this concept of ICD has been extended to other RCDs, a term that refers to cell death programs that have a known intricate signaling cascade, such as necroptosis, pyroptosis, or ferroptosis[5–15].

The most well-known form is Apoptosis. Apoptosis is morphologically defined by the shrinking of cells, fragmentation of the DNA, and blebbing of the cell membrane. In contrast, necroptosis, pyroptosis, and ferroptosis are regulated forms of molecularly defined necrosis. They resemble accidental necrosis in terms of its final morphology (e.g., organelle swelling, plasma membrane rupture, cell lysis, and leakage of intracellular components) but utilize a distinct molecular machinery.

Nevertheless, some degree of caution is required with the ICD-like profile subscribed to some recently discovered RCD pathways, since a full consensus on their immunological impact is still pending[16,17]. For instance, ferroptosis, a pathway first described in 2012[18], has been shown to be

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immuno-modulatory in multiple disease models[19–22] including cancer[13,22–27]. Depending on the temporal stage of ferroptosis (i.e., early vs. late), differences in modulating experimental anti-tumor immunity have been reported[13]. However, several immunosuppressive mechanisms have also been associated with ferroptosis such as formation of lipid bodies[28], oxidized phospholipids (oxPLs)[29–33] formation, and cyclo-oxygenase 2 (MT-CO2; also known as COX2)[34,35] activation[36]. Some of the immunosuppressive mechanisms relevant for anti-tumor immunity[5] were also attributed to ferroptotic tumor-associated neutrophils resulting even in enhanced tumor growth[37]. Clinical and immuno-oncology implications of such findings are still pending.

Owing to a lot of research studies published over the last few decades, the molecular and cellular mechanisms behind ICD have been largely deciphered. Organelle and cellular stress, most particularly endoplasmic reticulum (ER) stress induced by reactive oxygen species (ROS) production, is an essential early trigger for the initiation of ICD[38–42]. Sequentially, ICD enables a time- and space-dependent organized exposure as well as release of damage-associated patterns (DAMPs) or alarmins from dying cancer cells. The main DAMPs associated with ICD include calreticulin exposure on the cell membrane[43–49], heat-shock proteins (HSPs), exposure on the cell membrane and/or passively released[50,51], passively released high-mobility group box 1 (HMGB1)[52–56], surface exposure of annexin A1 (ANXA1)[57–60], and adenosine triphosphate (ATP), which can be actively or passively released[44,61,62]. The binding of these DAMPs to their cognate pattern recognition-receptors (PRRs), present on antigen-presenting cells such as dendritic cells (DCs), eventually leads to the activation of both the innate and the adaptive immune system via a series of cytokine and chemokine networks[5,63–66]. Dying cancer cells undergoing ICD can autonomously release cytokines as well as induce cytokine production from neighboring immune or stromal cells[67–72]. Additionally, ICD can also cause the secretion of immunostimulatory and chemotactic cytokines[73–75] including, but not limited to, type I interferons (IFNs)[76–80] and chemokine (C-X-C) ligand 9 and 10 (CXCL9/10)[73,81,82]. In the correct context, ICD can also facilitate T cell expansion in a manner that leads to diversification of TCR repertoire,[83–91] which can help regress distant (metastatic) tumor lesions via abscopal effect-like immune responses[92–96]. This abscopal effect is driven by DAMPs (*i.e.*, adjuvanticity) and tumor-associated antigen (TAA) (*i.e.*, antigenicity),[97–99] thereby highlighting the importance of ICD[100–102]. The ability of ICD to initiate an immune response is highly dependent on antigenicity and adjuvanticity[103–105]. Without antigens, ICD can only induce an antigen-irrelevant inflammatory response without engagement of the adaptive immune system[106]. Conversely, the presentation of antigens to T cells with poor adjuvanticity actively promotes tolerance[107–110].

In general, ICD inducers can be broadly divided into two groups depending on how they initiate ER stress-related pathways relevant for DAMP mobilization[111–114]. ER stress will lead to unfolded protein response (UPR) activation, leading to an upregulation of pathways including PERK – eukaryotic initiation factor 2 (eIF2a)[79]. Downstream, this will cause lower amounts of IkB and more activation of nuclear factor-kB (NF-kB)[115]. The first group includes therapies that induce ICD without directly inducing ER stress. Such type I ICD inducers include radiotherapy as well as chemotherapies like paclitaxel, oxaliplatin, and anthracyclines[61,116–120]. The second group, i.e., type II ICD inducers, includes treatment modalities that induce ICD by specifically targeting the ER to induce ER stress-driven cell death, e.g., photodynamic therapy (PDT) or oncolytic viruses[121–124]. Comprehensively, ICD inducers can be part of different treatment classes including not only microbial and chemical but also physical treatments such as irradiation and high hydrostatic pressure (HHP)[57].

Importantly, there is little correlation between the specific chemical features of an anti-cancer therapy and their ability to induce ICD. For example, while cisplatin and oxaliplatin are both platinum-based chemotherapies and induce cell death via DNA adduct-formation, yet only oxaliplatin treatment results in ICD[125–128]. Over the years, at least two pre-clinical criteria have been established to classify an anti-cancer therapy as a potential ICD inducer[129,130]. First criterion is that a therapy should be able to induce tumor regression in an immuno-competent, but not immuno-deficient, mouse setting[131–133]. Secondly, the cancer cells treated with an ICD inducer should serve as an anti-cancer vaccine in a prophylactic setting[5,134–139]. To rephrase, when tumor-naïve mice are injected with cancer cells undergoing ICD upon exposure to the anti-cancer drug, subsequent challenging with live cancer cells of the same type should not result in the formation of a tumor at the vaccination and challenging site. It is important to keep in mind that these approaches of classifying ICD inducers may have clinical translational issues, since they only allow exploration in a mouse setting. For this reason, in addition to these *in vivo* mice experiments, *in vitro* or *ex vivo* settings can also be utilized to assess the immunogenic potency of dying cancer cells treated with a potential ICD inducer[57,140]. Here, the presence of aforementioned ICD-associated DAMPs can serve as a surrogate marker to confirm ICD *in vitro* or *ex vivo* [141–144]. Additionally, culturing the dying cancer cells with innate immune cells, such as DCs, to assess ICD-relevant DC functions, is also possible. Phenotypic markers like phagocytic activity[145–149], DC activation markers[150–154] (CD86 and major histocompatibility complex (CIITA, also known as MHC) Class II molecules) or the secretion of cytokines like interleukin 1 beta (IL-1β)[155–157], interleukin 6 (IL-6)[158–161], interleukin 12 (IL-12)[162,163], and tumor necrosis factor (TNF)[164–167], and the ability of DCs to activate T cell proliferation and functional activation[168–172] are examples of possible features to assess.

Multiple chemotherapeutics, commonly used in the clinic, have been identified as ICD inducers. The most commonly used chemotherapies with ICD potential are anthracyclines (including doxorubicin, epirubicin, mitoxantrone, and idarubicin), cyclophosphamide, oxaliplatin, paclitaxel, docetaxel, 5-fluorouracil, and targeted therapies like bortezomib[126,173–182]. In fact, there is concrete evidence supporting the beneficial effects of ICD in cancer patients. For instance, patients with tumors displaying markers of ER stress (like tribbles pseudokinase 3 (TRB3) and DNA damage inducible transcript 3 (DDIT3; also known as CHOP)[183–188] or ICD-associated DAMPs, such as calreticulin or HMGB1, have a better prognosis[189–197]. These findings support the pursuit for an

ideal ICD-inducing treatment regimen[40]. It is important to note that most clinical trials do not choose for specific chemotherapeutics based on their ability to induce ICD. Instead, they are based on their ability to induce tumor response and disease control, without specific knowledge about their potential to induce ICD[198,199]. In some cases, these design-related decisions can be counterproductive for immune-mediated tumor control, thereby limiting the clinical benefit for cancer patients[200–203]. Besides chemotherapeutics, there are multiple other treatment options that can induce ICD. Herein, radiation-based modalities are particularly proficient at inducing ICD and associated abscopal effect-like responses[204–209]. Additionally, some upcoming immunotherapies like oncolytic viruses also operate via ICD induction[210–214].

In this Trial Watch edition, we will be focusing on the most recent preclinical and clinical advances around ICD induction by anti-cancer chemotherapy.

Preclinical advances

Since the publication of the previous Trial Watch dealing with chemotherapeutic ICD inducers, several novel preclinical studies on this topic have been published[215]. Here, we highlight the ones that are of particular importance and/or capture the general trends in this field.

Some papers further contributed to our mechanistic understanding of ICD. Mandula et al. (H. Lee Moffitt Cancer center, Tampa, USA.) established the role of protein kinase R-like reticulum kinase (EIF2AK3; also known as PERK), a well-known ER stress sensor, in mediating ICD via a new RCD subroutine, i.e., paraptosis. They found that PERK inhibition resulted in an increased T cell activation followed by a reduction in tumor growth via type I IFN responses. These findings encourage the use of PERK-targeting therapies for cancer immunotherapy[216]. Furthermore, Hayashi et al. (Cedars-Sinai Medical Center, Los Angeles, CA, USA) reported that although gemcitabine stimulates the release of immunostimulatory DAMPs, it also triggers prostaglandin E_2 (PGE_2) release, which counteracts ICD-relevant immune responses. However, when they combined gemcitabine and PGE_2 blockade, an effective DC and T cell activation was induced, which led to tumor regression[36]. Oresta et al. (Humanitas Clinical and Research Center-IRCCS, Rozzano, Italy) found that mitochondrial metabolic reprogramming is important for ICD occurrence[217]. This is accompanied by an increased oxidative phosphorylation. Moreover, tumors with low amounts of complex 1 of the respiratory chain expression had a higher chance of recurrence after chemotherapy. Lucarini et al. (Bambino Gesù Children's Hospital, Rome, Italy) investigated the combination strategy of mitoxantrone and anti-transforming growth factor beta (TGFB1) with programmed cell death-1 (PD-1, also known as *PDCD1*) blockade in neuroblastoma mouse models. They found that the low dose of mitoxantrone by itself was already able to increase IFNγ and granzyme B (GZMB) in $CD8^+$ T cells, which were further increased upon combination with anti-TGFβ and anti-PD-1 blockades[218]. Several papers also revealed a novel connection between anti-cancer agents and the ICD pathway[125]. Humea et al. (Centre de Recherche des Cordeliers, Université de Paris, Paris, France) reported about the induction of immunogenic cell stress and ICD via dactinomycin[219], an inhibitor of DNA and RNA transcription[220]. Marin et al. (Barcelona institute of Science and Technology, Barcelona, Spain) found that senescent cells have a greater immunologic potential that could initiate $CD8^+$ T cell responses. These senescent cells are able to release alarmins and PRR agonists and increase MHCI exposure. Even more so, immunization with these cancer cells caused protection superior to the standard ICD inducers[221].

Several papers also focused on increasing tumor-directed drug delivery while decreasing toxicity using nanoparticles[222]. For example, Zhou et al. (Department of Pharmaceutics, China Pharmaceutical University, Nanjing, China) published that direct delivery of therapeutic proteins, including RNase A, PD-1 antibodies, and photothermal agents, via hydrogels forming membrane pores, increased lactate dehydrogenase (LDHA), HMGB1, and ATP release in multiple murine cancer models[223]. In due course, the intratumoral hydrogel injections resulted in more $CD8^+$ T cell tumor infiltration and a lower tumor growth compared to the saline treated tumors. Another example is the study by Yang et al. (Wuhan University, Wuhan, China). They focused on decreasing the toxicity of small-molecule inhibitors by creating a prodrug nanomicelle that integrates both a phosphoinositide 3-kinase (PIK3CG; also known as PI3K)/mammalian target of rapamycin (mTOR) inhibitor and a cyclin-dependent kinase (CDK) inhibitor, flavopiridol. With this treatment, they were able to decrease tumor growth via the induction of ICD accompanied by HMGB1 and Gasdermin E (GSDME) release as well as ATP secretion in a breast cancer cell line[224]. Song et al. (Shanghai Jiaotong University, Shanghai, China) created a porphyrin-cisplatin conjugate (NP@Pt-1) that can be triggered by light[225]. NP@Pt-1 treatment resulted in an increased ROS production leading to ATP and HMGB1 in murine colon cancer cells release compared to untreated cells. Additionally, NP@Pt-1 treatment resulted in a decreased tumor growth compared to PBS-treated tumors.

Besides nanoparticles, other innovative strategies have been implemented to optimize ICD inducing treatment regimes. Tatarova et al. (OHSU Center for Spatial Systems Biomedicine, Portland, USA) developed a microdevice that could assist with microtargeting-specific regions of the tumor. This implantable chip is able to contain 18 different treatments that can be released in separate regions[226]. Zawilska et al. (Univeristy of Wroclaw, Wroclaw, Poland) developed a liposomal docetaxel therapy that could overcome the problems of toxicity and poor pharmacokinetics. They saw that the cell growth decreased using their treatment compared to docetaxel alone. Additionally, the half life of docetaxel was significantly increased when liposomal-pegylated[227].

A series of studies are also trying to use ICD and its markers as a biomarker modality[175]. Use of an ICD-associated genetic signature is one of the approaches proposed to exploit ICD as a predicting marker for patient outcome. In high-grade glioma (HGG), such a signature was able to predict responsiveness to immune checkpoint blocker (ICB) therapy including anti-PD -1 and anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA4)[160]. This signature, composed of *FOXP3*, *IL6 LY96*,

MYD88, and *PDIA3*, was able to distinguish patients with increased immune modulation and immune escape and high expression of human leukocyte antigen (HLA)-related genes. On top of that, multiple papers have reported that even microRNAs linked to ICD-relevant DAMPs are able to predict treatment outcome[228]. Several microRNAs relevant for modulating expression of calreticulin, e.g., miR-27a-3p[229,230], or HMGB1[231–234] have been characterized.

Finally, optimizing the detection of ICD in response to chemotherapy has also been investigated further since the last Trial Watch publication[235]. Zhang et al. (Chonnam National University Medical School, Hwasun, Korea) engineered calreticulin-targeting monobodies to detect ICD more accurately[236]. Via this method, they were able to detect surface expression in multiple cancer cell lines and in mice treated with ICD inducers. Similar to this, Kim et al. (Gyeongsang National University, Jinju, Korea) created a synthetic ^{18}F-labeled peptide that specifically binds calreticulin[237]. Via this method, they were able to detect calreticulin surface exposure in mouse colon cancer tumors via a small-animal positron emission tomography (PET) scan. This staining was visible in tumors treated with multiple ICD inducers including doxorubicin, oxaliplatin, and radiation.

Finalized clinical studies

All finalized clinical studies published after the previous Trial Watch (June 2019) were gathered using PubMed (http://www.ncbi.nlm.nih.gov/pubmed) with the following search string taking into account to most established ICD inducers (cancer OR tumor OR tumor OR neoplasm) AND (oxaliplatin OR cyclophosphamide OR bortezomib OR doxorubicin OR epirubicin OR idarubicin OR mitoxantrone OR paclitaxel) AND ("danger signal" OR "damage associated molecular pattern" OR "immunogenic cell death" OR "immunogenic cancer cell death" OR immunogenic OR immunogenicity), together with the clinical trial filter. Additionally, articles were filtered manually based on relevance as well as on the presence of measurements of immunological parameters. On November 15, 2022, this query with PubMed resulted in 268 published clinical trial studies. From these papers, 67 studies were investigating immune responses using biomarkers. Of note, many studies reported the blood cell counts of patients during treatment. This kind of publication was not considered for this Trial Watch, since such counts are not valid ICD biomarkers. In this section, we will give a general overview of these published clinical studies (Figure 1) and highlight a few of them.

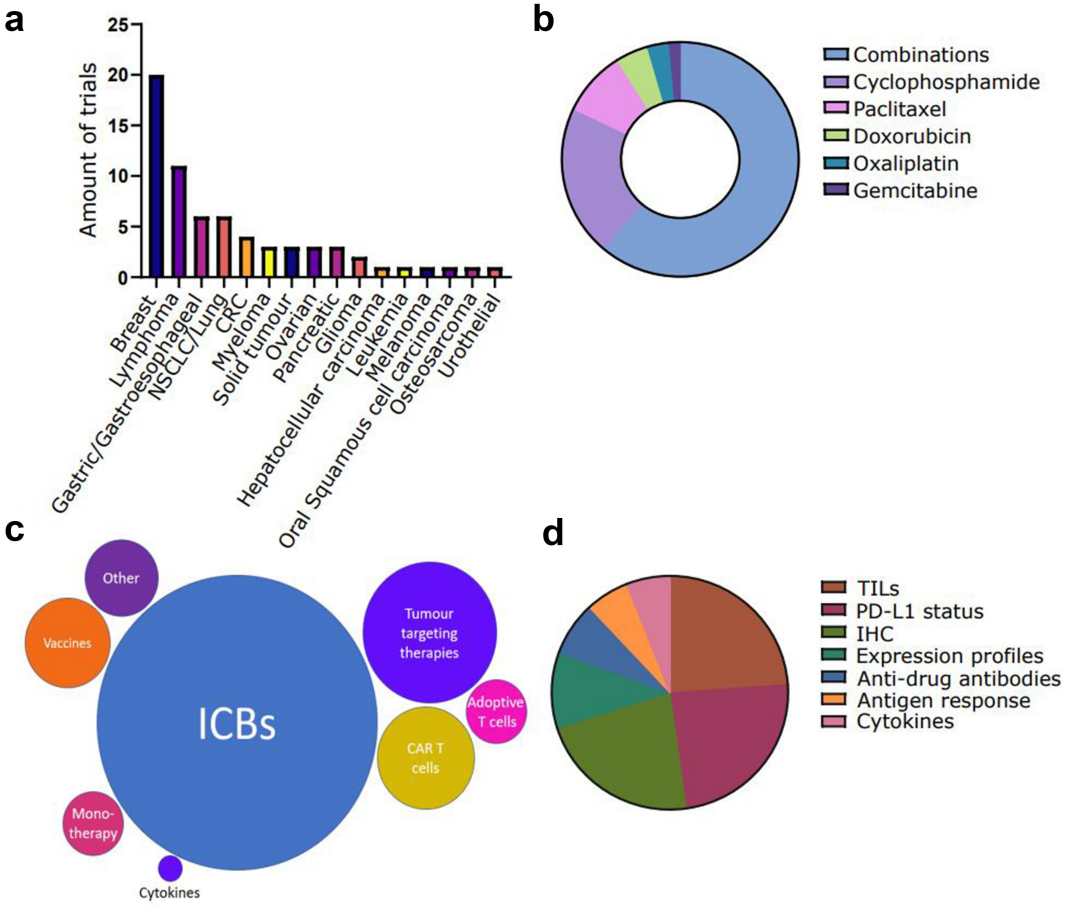

Figure 1. Recently published clinical studies testing immunogenic cell death (ICD)-inducing chemotherapy in oncology that investigate the immunogenic response. Clinical studies were classified on: (a) cancer type, (b) ICD-inducing drug, (c) combinatorial immunotherapy. (d) immunomonitoring approach, CAR, chimeric antigen receptor; CRC, colorectal carcinoma; ICB, immune checkpoint blocker; IHC, immunohistochemistry; PD-L1, programmed death-ligand; TIL, tumor-infiltrating lymphocyte.

Among these studies, we found that there were 15 individual cancer types investigated. A large portion (29.9%) of the studies focused on breast cancer (Figure 1A)[238–241]. Page et al. (Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, Oregon) reported on the efficiency of cyclophosphamide in combination with a cytokine cocktail including TNF, IL-2, IL-1, IFN-γ, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (CSF2; also known as GM-CSF), and granulocyte colony stimulating factor (CSF3; also known as G-CSF) with the product name IRX-2 in breast cancer. In this phase 1b study, they demonstrated that after treatment there was a higher T-cell activation profile, based on GZMB, GZMA, IFNG, membrane cofactor protein-4 (CD46; also known as MCP-4), S100, CD184, CC-motif chemokine ligand 21 (CCL21) and perforin-1 (ZNF395; also known as PRF-1) compared to the baseline. Additionally, they found a cyclophosphamide-associated peripheral T-regulatory (Treg) cell depletion[242]. However, upregulation of the immune-checkpoint ligand, programmed cell death ligand 1 (PD-L1, also known as CD274), assessed by immunohistochemistry (IHC) was also seen in these patients after treatment. Additionally, there were 3 "basket trials" (4.5% of all included published trials), consisting of multiple solid tumor types[243–245]. Haas et al. (University of Pennsylvania, Philadelphia, PA, USA) analyzed the effects of cyclophosphamide, with and without chimeric antigen receptor (CAR) T cells specific for mesothelin (meso), a protein highly expressed by many cancers[246–249]. They found that patients pre-treated with cyclophosphamide increased the initial CAR T cell expansion but did not alter the persistence at day 28[244]. Although both treatment arms were well tolerated, patients showed limited clinical benefit.

Most of the studies included into this Trial Watch, i.e., 41 out of 67, investigated the effect of co-treatment with more than one ICD inducer (Figure 1B). Chemotherapeutic regimes based on paclitaxel, together with other ICD inducers, were very prevalent in the published clinical trials. This was most likely because paclitaxel is regularly applied as part of a multi-modal chemotherapeutic regimen, especially against breast cancer and ovarian cancer[241,250–252]. In this sense, an immunotherapy-relevant example includes the KEYNOTE-355 trial, where the investigators tested paclitaxel or gemcitabine in combination with carboplatin and pembrolizumab, an anti-PD-1 ICB, in triple-negative breast cancer[253]. They found that the addition of pembrolizumab resulted in a significant increase in patient overall survival (OS) compared to chemotherapy alone. It is important to note that the combination of ICD inducers together with ICBs is very prevalent (Figure 1C). In general, most studies find that the addition of ICBs increases the overall response rate (ORR) compared to chemotherapy alone[254–256]. Tumor-targeting passive immunotherapies, such as trastuzumab (anti-human epidermal growth factor receptor 2 (ERBB2; also known as HER2)), are also repeatedly combined with ICD inducers. Similarly, CAR T cells are often combined with ICD inducers like fludarabine and cyclophosphamide[257–260]. The latter is not *per se* to promote an immune activation but rather to eliminate the circulating lymphocyte population.

Lastly, another parameter that we assessed in this Trial Watch was the measurement of immune response parameters. In the above studies, the most frequently used immune biomarkers were tumor infiltrating lymphocytes (TILs) analysis and the PD-L1 detection (Figure 1D)[239,261–263]. For instance, a phase II study for breast cancer investigating the addition of durvalumab, a monoclonal anti-PD-1 antibody, together with anthracycline-taxane-based neoadjuvant therapy included a broad biomarker analysis. The authors found that paclitaxel was able to increase the TILs in both treatments' arms (with and without durvalumab). Additionally, they found that both arms showed a higher pathological complete response (pCR) rate in the PD-L1-positive tumors compared to PD-L1^{low} tumors[264]. Finally, they concluded that durvalumab together with anthracycline-/taxane-based neoadjuvant chemotherapy (NACT) was the most optimal treatment regime for increased pCR rates. Additionally, more advanced molecular analysis such as RNA sequencing was also often used as biomarker discovery[242,265,266]. For instance, Pusztai et al. (Yale Cancer Center, New Haven, CT, USA) found while investigating paclitaxel in combination with durvalumab and the poly-ADP ribose polymerase (PARP) inhibitor olaparib in breast cancer that their dendritic cell signature had a positive correlation with pCR in the treatment arm[267]. Additionally, they found that their mast cell signature correlated negatively with pCR. However, they did not find any correlation between their T cell signatures and pCR in their clinical trial.

Altogether, these results highlight the promising perspectives and clinical trends in ICD research.

Ongoing clinical studies

In parallel, we also assessed the ClinicalTrials.gov database (http://www.clinicaltrials.gov/) for all the ongoing or active clinical trials using oxaliplatin, cyclophosphamide, bortezomib, doxorubicin, epirubicin, idarubicin, mitoxantrone, or paclitaxel in combination with cancer immunotherapy. With a relevant search string, we found not less than 84 clinical studies that matched the following criteria: (1) they involved at least one ICD-inducing chemotherapeutic agent and (2) they were initiated after June 2019 (when the latest Trial Watch on this topic was published).

In this context, multiple cancer types are being studied (Tables 1 and 2). Like the finalized studies described above, the ongoing clinical trials are predominately focused on breast cancer. This is a trend that has been seen over multiple Trial Watch publications[215,268]. In contrast to the published clinical trials, recently enlisted clinical studies also have a considerable percentage focusing on hematopoietic cancer types such as lymphoma, leukemia, and multiple myeloma (Table 1). Most likely, this is due to a high increase in CAR T cell studies, a treatment that has been approved for these cancer types in combination with specific chemotherapies that can also induce ICD[86]. For instance, a single arm clinical study with the aim of observing the tolerance and safety of Fludarabine in combination with CAR natural killer (NK)-CD19 cells in acute lymphoblastic leukemia (NCT05563545). Furthermore, clustering of several different solid tumor types in the same study is also something that is often noticed in these ongoing trials.

Table 1. Contemporary clinical studies assessing the therapeutic and immunological characteristics of chemotherapeutics.

Cancer type	ICD inducer	Phase	Status	Combination	Trial number
Breast cancer	Cyclophosphamide	I	Recruiting	Combined with DPX-Survivac, Letrozole, XRT	NCT04895761
		II	Recruiting	Combined with Anthracyclines and P2Et	NCT05007444
CRC	Oxaliplatin	I/II	Active, not recruiting	Combined with Leucovorin, 5-FU and Bevacizumab	NCT04068610
		II	Recruiting	Combined with Nivolumab	NCT05504252
				Combined with Capecitabine, Bevacizumab and Pembrolizumab	NCT04262687
				Combined with Atezolizumab, Bevacizumab and Capecitabine	NCT04659382
	FOLFOX		Withdrawn	Combined with Durvalumab and Oleclumab or Monalizumab	NCT04145193
Gastric cancer	Oxaliplatin	II	Recruiting	Combined with 5-FU, Capecitabine, Durvalumab, Trastuzumab, Cisplatin and Pembrolizumab	NCT04379596
Gastric or Gastroesophageal cancer		III	Recruiting	Combined with AK104 and Capecitabine	NCT05008783
Leukemia	Cyclophosphamide	I	Nyet recruiting	Combined with Fludarabine and CD19/22 targeting T cells	NCT05223686
			Recruiting	Combined with Fludarabine and Cl-135 CAR-T cells	NCT05266950
				Combined with Fludarabine and CAR-NK CD19 cells	NCT05563545
				Combined with Fludarabine and pCAR-19B cells	NCT04888442
			Completed	Combined with Fludarabine and pCAR-19B cells	NCT04888468
		II	Recruiting	Combined with Fludarabine and CNCT19 cells	NCT04684147
				Combined with Fludarabine and pCAR-19B cells	NCT05334823
Leukemia and Lymphoma	Cyclophosphamide	I	Terminated	Combined with Fludarabine and RPM CD19-mbIL 15-CAR-T cells	NCT04844086
Lymphoma		I	Recruiting	Combined with Fludarabine and CB-010	NCT04637763
				Combined with Fludarabine and LCAR-AIO cells	NCT05318963
		I/II	Recruiting	Combined with Fludarabine and CRC01	NCT04836507
				Combined with Fludarabine and allogenic CD19-car T cells	NCT05554939
	Cyclophosphamide and doxorubicin	I/II	Recruiting	Combined with Rituximab and Doxorubicin	NCT04663347
	Oxaliplatin	II	Recruiting	Combined with Lacutamab and Gemcitabine	NCT04984837
Multiple myeloma	Bortozomib	I	Recruiting	Combined with REGN5458, Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone	NCT05137054
	Cyclophosphamide	I	Recruiting	Combined with ALLO-715/647, Fludarabine and Nirogacestat	NCT04093596
			Rnrolling by invitation	Combined with Fludarabine and – 29 CAR-T cells	NCT04861480
		II	Recruiting	Combined with Fludarabine and BCMA targeting t cells	NCT05594797
Myeloid malignancies	Mitoxantrone	II	Recruiting	Combined with Magrolimab, Etoposide and Cytarabine	NCT04778410
NSCLC	Oxaliplatin	I/II	Recruiting	Combined with Nivolumab and Ipilimumab	NCT04043195
Ovarian cancer	Doxorubicin	I	Recruiting	Combined with SL-172154	NCT05483933
	Cyclophosphamide	I	Recruiting	Combined with Fludarabine and CAR T cells	NCT05225363
Pancreatic cancer	FOLFIRINOX	I/II	Recruiting	Combined with Mitazalimab	NCT04888312
Rectal cancer	Oxaliplatin	II	Recruiting	Combined with Tislelizumab and Capecitabine	NCT05420584
				Combined with Capecitabine and anti-PD1	NCT05307198
Sarcoma	Doxorubicin	I/II	Not yet recruiting	Combined with YH001 and Envafolimab	NCT05448820
Solid tumor	Cyclophosphamide	I	Recruiting	Combined with neoantigen peptide vaccine, Pembrolizumab and Sargramostim	NCT05269381
			Terminated	Combined with GEN-011, IL2 and Fludarabine	NCT04596033
	Oxaliplatin	I	Recruiting	Combined with HB002.1T and Capecitabine	NCT04802980
	Oxaliplatin or Paclitaxel	I/II	Recruiting	Combined with AK104/AK117, Cisplatin, 5FU	NCT05235542

5-FU, 5-fluorouracil; CAR-NK cells, Car natural killer cells; CAR, chimeric antigen receptor; CRC, colorectal cancer; PD-1, programmed death-1; TIL, tumor-infiltrating lymphocyte; NSCLC, non-small cell lung carcinoma.

Most of the clinical trials selected for this Trial Watch analysis applied paclitaxel, cyclophosphamide, oxaliplatin, and doxorubicin, not only as a monotherapy but also in combination with other anti-cancer treatments. The most prevalent ICD inducer is paclitaxel as shown in Table 2. However, only a small percentage of the studies assesses ICD as the main study objective. Most of the time, studies include treatment arms of the ICD inducer with and without combinatorial therapies. In general, ICD inducers are mostly combined with (1) other cell death inducers including other chemotherapeutics, such as carboplatin, or radiation therapy; (2) ICBs targeting molecules such as anti-PD-1 or anti-PD-L1 antibodies; (3) tumor-targeting passive immunotherapies such as agents against epidermal growth factor receptor (EGFR) and HER2; (4) T cells that are adoptively transferred or T cells expressing engineered TAA-specific transgenic TCRs; (5) cytokines that further stimulate the immune responses including not only interferon alpha (IFNA) but also mixtures like IRX-2 (IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12, TNF, and IFNγ). These trends are very similar to the previous Trial Watch[215] as well as the published clinical trials that we summarized above.

In these selected clinical trials, there are multiple immunological assessment methodologies that were examined with the aim of acquiring a predictive marker for treatment response as or assessing the immune response during treatment. This includes T cell analysis, either via IHC, e.g., to estimate the quantity and phenotypes of tumor-infiltrating T cells or via flow cytometry, e.g., for detailed profiling of the peripheral blood immune cell subsets. For example, clinical trial NCT05033769 is going to assess KI-67 on peripheral T cells. Additionally, in some ongoing clinical trials, such as NCT04868708, PD-L1 expression of the

Table 2. Contemporary clinical studies assessing the therapeutic and immunological characteristics of paclitaxel.

Cancer type	ICD inducer	Phase	Status	Combination	Trial number
Breast cancer	Nab-Paclitaxel	II/III	Not yet recruiting	Combined with EOC202	NCT05322720
	Nab-Paclitaxel	II	recruiting	Combined with SG001	NCT05068141
		II/III	Not yet recruiting	Combined with B013	NCT05555706
	Paclitaxel	I	Not yet recruiting	Combined with Eftilagimob alpha	NCT04252768
		I	Recruiting	Combined with Durvalumab and Trastuzumab Deruxtecan	NCT04556773
		I/II	Recruiting	Combined with Trastuzumab Deruxtecan	NCT04538742
		II	Recruiting	Combined with DC vaccines and Trastuzumab and Pertuzumab	NCT05325632
		III	Recruiting	Combined with Capecitabine and Trastuzumab Deruxtecan	NCT04494425
		III	Recruiting	Combined with Dato-DXd, Carboplatin, Capecitabine and Eribulin Mesylate	NCT05374512
	Eribulin and Paclitaxel	IV	Recruiting		NCT05033769
Cervical cancer	Paclitaxel	I	Active, not recruiting	Combined with M7824, Carboplatin, Bevacizumab and Cisplatin	NCT04551950
		II	Active, not recruiting	Combined with AK104, Bevacizumab, Cisplatin or Carboplatin	NCT04868708
		II/III	Recruiting	Combined with QL1604 and Cisplatin or Carboplatin	NCT04864782
		III	Recruiting	Combined with AK104 and Carboplatin, Cisplatin, Bevacizumab	NCT04982237
Endometrial neoplasm	Paclitaxel	III	Recruiting	Combined with Olaparib, Durvalumab and Carboplatin	NCT04269200
Gastric cancer	Paclitaxel	II	Recruiting	Combined with IMU-131 and Pembrolizumab	NCT05311176
Gastric or Gastroesophageal cancer	Paclitaxel	II/III	Not yet recruiting	Combined with QL1604	NCT04435652
		III	Recruiting	Combined with Trastuzumab Deruxtecan and Ramucirumab	NCT04704934
Head and neck squamous carcinoma	Paclitaxel	I	Recruiting	Combined with SCT-I10A, SCT200 and Docetaxel	NCT05552807
Melanoma and Pancreatic cancer	Nab-Paclitaxel	II	Recruiting	Combined with YH003, Toripalimab and Gemcitabine	NCT05031494
Nasopharyngeal carcinoma	Paclitaxel	I	aAtive, not recruiting	Combined with SHR-1316 and Carboplatin, Gemcitabine and Cisplatin	NCT04282070
NSCLC	Nab-Paclitaxel	III	Not yet recruiting	Combined with Sintilimab, Carboplatin, Cisplatin, Pemetrexed, Docetaxel and Gemcitabine	NCT05116462
	Paclitaxel	I/II	Active, not recruiting	Combined with AK104 and carboplatin	NCT04647344
		II	Recruiting	Combined with Carboplatin	NCT04832854
		III	Recruiting	Combined with SHR-1316 and Carboplatin	NCT04316364
		III	Terminated	Combined with carboplatin and Bevacizumab or PF-06439535	NCT04325698
		III	Unknown	Combined TRS003, Bevacizumab and Carboplatin	NCT04416035
		III	Completed	Combined with Bp102 or Avastin and Carboplatin	NCT05169801
		III	Recruiting	Combined with SIBP04, Avastin and Carboplatin	NCT05318443
		III	Recruiting	Combined with Cisplatin, Carboplatin, Etoposide, Pemetrexed and Ociperlimab or Tislelizumab or Durvalumab	NCT04866017
Ovarian cancer	Paclitaxel	I/II	Recruiting	Combined with TILs, interferon and Carboplatin	NCT04072263
	Paclitaxel or Doxorubicin	III	Recruiting	Combined with BD0801	NCT04908787
	Paclitaxel and Doxorubicin	III	Active, not recruiting	Combined with Mirvetuximab Soravtansine and Topotecan	NCT04209855
Pancreatic cancer	Nab-Paclitaxel	I	Recruiting	Combined with AB680, Zimberelimab and Gemcitabine	NCT04104672
		I	Active, not recruiting	Combined with Canakinumab, Spartalizumab and Gemcitabine	NCT04581343
		II	Recruiting	Combined with NIS793, Spartalizumab and Gemcitabine	NCT04390763
Solid tumor	Nab-Paclitaxel	I/II	Recruiting	Combined with DF1001 and Nicolumab	NCT04143711
		I/II	Active, not recruiting	Combined with YH003, Toripalimab and Gemcitabine	NCT04481009
		I/II	Recruiting	Combined with LYT-200, anti-PD1 and Gemcitabine	NCT04666688
		II	Recruiting	Combined with camrelizumab and famitinib	NCT05214976
		II	Recruiting	Combined with AZD0171, Durvalumab and Gemcitabine	NCT04999969
	Paclitaxel	I	Not yet recruiting	Combined with KM257	NCT05320874
		II	Recruiting	Combined with adoptive T cells	NCT05144698
		II	Recruiting	Combined with Navicixizumab	NCT05453825
	Paclitaxel or Oxaliplatin	I	Recruiting	Combined with Ociperlimab, Tislelizumab, Carboplatin, Cisplatin, 5-FU and Capecitabine	NCT04047862
		I/II	Recruiting	Combined with AK104/AK117, Cisplatin, 5FU	NCT05235542

5-FU, 5-fluorouracil; TIL, tumor-infiltrating lymphocyte; NSCLC, non-small cell lung carcinoma.

tumor tissue samples is being determined by IHC. In addition, in this clinical trial they will also investigate the development of anti-drug antibodies over 30 days after the last treatment. This latter practice is being performed in many other clinical trials (e.g., NCT04282070, NCT04093596, and NCT04888312). Another biomarker being utilized is antigen-specific immunogenicity especially in CAR T cell or adoptive T cell clinical trials (e.g.,

NCT04596033). Evaluating the presence of specific or several cytokines is also prioritized in some clinical trials. For example, NCT04895761 aims to assess the IFNγ in breast cancer patients treated with cyclophosphamide or radiotherapy in combination with a neoadjuvant aromatase inhibitor. In each treatment arm, an ELISPOT will be performed in PBMCs. Lastly, multiple ongoing clinical studies are evaluating immunological markers on a larger scale via omics technologies. Omics approaches like RNA sequencing are creating many variables that can give functional patterns associated with T cell status shifting after chemotherapy. So far, a long list of ways to create some sort of immunological output is being practiced in these clinical trials. Yet, there are still many clinical trials that are not planning on assessing any markers for immune response (e.g., NCT04637763, NCT05504252).

Conclusion

Currently, various chemotherapeutics linked to ICD are approved worldwide for use as anti-cancer treatment in patients with multiple cancer subtypes. Approval of most of these chemotherapies was largely preceded by preclinical investigations with tumor xenografts[269–272] in immunodeficient mice and therefore these were often translated to the clinic without any validation for immunemodulation[273–275]. Therefore, most of these chemotherapies are currently utilized at doses and treatment schedules that are meant to achieve tumor reduction via maximal tolerable dose[276–279] rather than a balance between short-term (tumor reduction) and long-term (anti-cancer immunity) effects. In this sense, overcoming some common side effects of chemotherapies that can also counteract ICD, i.e., neutropenia,[280–284] lymphopenia[285–289] and intestinal mucositis[290–292], should be prioritized via more tumor-targeted delivery of chemotherapies through nanoparticles or other controlled delivery methods[293,294].

The 'first generation' of anti-cancer immunotherapy has nearly passed. Despite the stunning success of immuno-oncology drugs through a broad spectrum of distinct malignant diseases, it turned out that a large majority of patients do not respond to currently approved immunotherapies, or if they do, responses are mostly transient. Currently, the field of immuno-oncology aims to tackle these immunotherapy-resistant contexts via multi-modal anti-cancer therapies integrating anti-cancer agents, falling into different treatment modalities (radiotherapy, chemotherapy, targeted therapy, and immunotherapy). However, systematically designed as well as multi-arm comparative clinical studies coupled with proper immune biomarkers aimed at identifying correct dosing and treatment scheduling/ordering are pending. Such studies are crucial to maximize the immune-activation relevant synergism between active immunotherapies and ICD-inducing chemotherapies. Simultaneously, pre-selection of patients via specific biomarkers is also necessary to tailor these multi-modal immunotherapies to specific patient subgroups rather than giving it in a nonspecific fashion thereby contributing to socio-economic healthcare burden.

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References

1. Ahmed A, Tait SWG. Targeting immunogenic cell death in cancer. Mol Oncol. 2020;14:2994–3006.
2. Troitskaya OS, Novak DD, Richter VA, Koval OA. Immunogenic cell death in cancer therapy. Acta Naturae. 2022;14:40–53. doi:10.32607/actanaturae.11523.
3. Fumet J-D, Limagne E, Thibaudin M, Ghiringhelli F. Immunogenic cell death and elimination of immunosuppressive cells: a double-edged sword of chemotherapy. Cancers (Basel). 2020;12:12. doi:10.3390/cancers12092637.
4. Galluzzi L, Vitale I, Warren S, Adjemian S, Agostinis P, Martinez AB, Chan TA, Coukos G, Demaria S, Deutsch E, et al. Consensus guidelines for the definition, detection and interpretation of immunogenic cell death. J ImmunoTher Cancer. 2020;8.
5. Wiernicki B, Maschalidi S, Pinney J, Adjemian S, Vanden Berghe T, Ravichandran KS, Vandenabeele P. Cancer cells dying from ferroptosis impede dendritic cell-mediated anti-tumor

immunity. Nat Commun. 2022;13:3676. doi:10.1038/s41467-022-31218-2.
6. Zi M, Xingyu C, Yang C, Xiaodong S, Shixian L, Shicheng W. Improved antitumor immunity of chemotherapy in OSCC treatment by Gasdermin-E mediated pyroptosis. Apoptosis. 2022;28:348–361. doi:10.1007/s10495-022-01792-3.
7. Oltean T, Lippens L, Lemeire K, De Tender C, Vuylsteke M, Denys H, Vandecasteele K, Vandenabeele P, Adjemian S. Association of cell death markers with tumor immune cell infiltrates after chemo-radiation in cervical cancer. Front Oncol. 2022;12:892813. doi:10.3389/fonc.2022.892813.
8. Mishchenko T, Balalaeva I, Gorokhova A, Vedunova M, Krysko DV. Which cell death modality wins the contest for photodynamic therapy of cancer? Cell Death Disease. 2022;13:455. doi:10.1038/s41419-022-04851-4.
9. Santofimia-Castaño P, Iovanna J. Combating pancreatic cancer chemoresistance by triggering multiple cell death pathways. Pancreatology. 2021;21:522–529. doi:10.1016/j.pan.2021.01.010.
10. Wang M, Wu M, Liu X, Shao S, Huang J, Liu B, Liang T. Pyroptosis remodeling tumor microenvironment to enhance pancreatic cancer immunotherapy driven by membrane anchoring photosensitizer. Adv Sci (Weinh). 2022;9:e2202914. doi:10.1002/advs.202202914.
11. Aaes TL, Kaczmarek A, Delvaeye T, De Craene B, De Koker S, Heyndrickx L, Delrue I, Taminau J, Wiernicki B, De Groote P, et al. Vaccination with necroptotic cancer cells induces efficient anti-tumor immunity. Cell Rep. 2016;15:274–287. doi:10.1016/j.celrep.2016.03.037.
12. Sprooten J, De Wijngaert P, Vanmeerbeerk I, Martin S, Vangheluwe P, Schlenner S, Krysko DV, Parys JB, Bultynck G, Vandenabeele P, et al. Necroptosis in immuno-oncology and cancer immunotherapy. Cells. 2020;9:1823. doi:10.3390/cells9081823.
13. Efimova I, Catanzaro E, Van der Meeren L, Turubanova VD, Hammad H, Mishchenko TA, Vedunova MV, Fimognari C, Bachert C, Coppieters F, et al. Vaccination with early ferroptotic cancer cells induces efficient antitumor immunity. J ImmunoTher Cancer. 2020;8:e001369. doi:10.1136/jitc-2020-001369.
14. Bedoui S, Herold MJ, Strasser A. Emerging connectivity of programmed cell death pathways and its physiological implications. Nat Rev Mol Cell Biol. 2020;21:678–695. doi:10.1038/s41580-020-0270-8.
15. Weinlich R, Oberst A, Beere HM, Green DR. Necroptosis in development, inflammation and disease. Nat Rev Mol Cell Biol. 2017;18:127–136. doi:10.1038/nrm.2016.149.
16. Kepp O, Kroemer G. Is ferroptosis immunogenic? The devil is in the details! Oncoimmunology. 2022;11:2127273. doi:10.1080/2162402X.2022.2127273.
17. Liu J, Dai E, Kang R, Kroemer G, Tang D. The dark side of ferroptosis in pancreatic cancer. Oncoimmunology. 2021;10:1868691. doi:10.1080/2162402X.2020.1868691.
18. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149:1060–1072.
19. Li J-Y, Yao Y-M, Y-P T. Ferroptosis: a trigger of proinflammatory state progression to immunogenicity in necroinflammatory disease. Front Immunol. 2021;12:701163. doi:10.3389/fimmu.2021.701163.
20. Demuynck R, Efimova I, Naessens F, Krysko DV. Immunogenic ferroptosis and where to find it? J ImmunoTher Cancer. 2021;9:e003430. doi:10.1136/jitc-2021-003430.
21. Li Y, Feng D, Wang Z, Zhao Y, Sun R, Tian D, Liu D, Zhang F, Ning S, Yao J, et al. Ischemia-induced ACSL4 activation contributes to ferroptosis-mediated tissue injury in intestinal ischemia/reperfusion. Cell Death Differ. 2019;26:2284–2299. doi:10.1038/s41418-019-0299-4.
22. Ye F, Chai W, Xie M, Yang M, Yu Y, Cao L, Yang L. HMGB1 regulates erastin-induced ferroptosis via RAS-JNK/p38 signaling in HL-60/NRASQ61L cells. Am J Cancer Res. 2019;9:730–739.
23. Dai E, Han L, Liu J, Xie Y, Kroemer G, Klionsky DJ, Zeh HJ, Kang R, Wang J, Tang D. Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization via release and uptake of oncogenic KRAS protein. Autophagy. 2020;16:2069–2083. doi:10.1080/15548627.2020.1714209.
24. Jeong SD, Jung B-K, Lee D, Ha J, Chang H-G, Lee J, Lee S, Yun C-O, Kim Y-C. Enhanced immunogenic cell death by apoptosis/ferroptosis hybrid pathway potentiates PD-L1 blockade cancerimmunotherapy. ACS Biomater Sci Eng. 2022;8:5188–5198. doi:10.1021/acsbiomaterials.2c00950.
25. Tang X, Liu J, Yao S, Zheng J, Gong X, Xiao B. Ferulic acid alleviates alveolar epithelial barrier dysfunction in sepsis-induced acute lung injury by activating the Nrf2/HO-1 pathway and inhibiting ferroptosis. Pharm Biol. 2022;60:2286–2294. doi:10.1080/13880209.2022.2147549.
26. He L, Wang B, Wang X, Liu Y, Song X, Zhang Y, Li X, Yang H. Uncover diagnostic immunity/hypoxia/ferroptosis/epithelial mesenchymal transformation-related CCR5. CD86, CD8A, ITGAM, And PTPRC In Kidney Transplantation Patients With Allograft Rejection. Ren Fail. 2022;44:1850–1865. doi:10.1080/0886022X.2022.2141648.
27. Giuliani KTK, Grivei A, Nag P, Wang X, Rist M, Kildey K, Law B, Ng MS, Wilkinson R, Ungerer J, et al. Hypoxic human proximal tubular epithelial cells undergo ferroptosis and elicit an NLRP3 inflammasome response in CD1c+ dendritic cells. Cell Death Disease. 2022;13:739. doi:10.1038/s41419-022-05191-z.
28. Veglia F, Tyurin VA, Mohammadyani D, Blasi M, Duperret EK, Donthireddy L, Hashimoto A, Kapralov A, Amoscato A, Angelini R, et al. Lipid bodies containing oxidatively truncated lipids block antigen cross-presentation by dendritic cells in cancer. Nat Commun. 2017;8:2122. doi:10.1038/s41467-017-02186-9.
29. Klöditz K, Fadeel B. Three cell deaths and a funeral: macrophage clearance of cells undergoing distinct modes of cell death. Cell Death Discov. 2019;5:65. doi:10.1038/s41420-019-0146-x.
30. Ramakrishnan R, Tyurin VA, Veglia F, Condamine T, Amoscato A, Mohammadyani D, Johnson JJ, Zhang LM, Klein-Seetharaman J, Celis E, et al. Oxidized lipids block antigen cross-presentation by dendritic cells in cancer. J Immunol. 2014;192:2920–2931. doi:10.4049/jimmunol.1302801.
31. Ugolini A, Tyurin VA, Tyurina YY, Tcyganov EN, Donthireddy L, Kagan VE, Gabrilovich DI, Veglia F. Polymorphonuclear myeloid-derived suppressor cells limit antigen cross-presentation by dendritic cells in cancer. JCI Insight. 2020;5. doi:10.1172/jci.insight.138581.
32. Wiernicki B, Dubois H, Tyurina YY, Hassannia B, Bayir H, Kagan VE, Vandenabeele P, Wullaert A, Vanden Berghe T. Excessive phospholipid peroxidation distinguishes ferroptosis from other cell death modes including pyroptosis. Cell Death Disease. 2020;11:922. doi:10.1038/s41419-020-03118-0.
33. Yan B, Ai Y, Sun Q, Ma Y, Cao Y, Wang J, Zhang Z, Wang X. Membrane damage during ferroptosis is caused by oxidation of phospholipids catalyzed by the oxidoreductases POR and CYB5R1. Mol Cell. 2021;81:355–369.e10. doi:10.1016/j.molcel.2020.11.024.
34. Xu Y, Liu Y, Li K, Yuan D, Yang S, Zhou L, Zhao Y, Miao S, Lv C, Zhao J. COX-2/PGE2 pathway inhibits the ferroptosis induced by cerebral ischemia reperfusion. Mol Neurobiol. 2022;59:1619–1631. doi:10.1007/s12035-021-02706-1.
35. Li Y, Wang J, Chen S, Wu P, Xu S, Wang C, Shi H, Bihl J. MiR-137 boosts the neuroprotective effect of endothelial progenitor cell-derived exosomes in oxyhemoglobin-treated SH-SY5Y cells partially via COX2/PGE2 pathway. Stem Cell Res Ther. 2020;11:330. doi:10.1186/s13287-020-01836-y.
36. Hayashi K, Nikolos F, Lee YC, Jain A, Tsouko E, Gao H, Kasabyan A, Leung HE, Osipov A, Jung SY, et al. Tipping the immunostimulatory and inhibitory DAMP balance to harness immunogenic cell death. Nat Commun. 2020;11:6299. doi:10.1038/s41467-020-19970-9.
37. Kim R, Hashimoto A, Markosyan N, Tyurin VA, Tyurina YY, Kar G, Fu S, Sehgal M, Garcia-Gerique L, Kossenkov A, et al.

Ferroptosis of tumour neutrophils causes immune suppression in cancer. Nature. 2022;612:338–346. doi:10.1038/s41586-022-05443-0.
38. Li C, Zhang Y, Yan S, Zhang G, Wei W, Qi Z, Li B. Alternol triggers immunogenic cell death via reactive oxygen species generation. Oncoimmunology. 2021;10:1952539. doi:10.1080/2162402X.2021.1952539.
39. Galluzzi L, Yamazaki T, Kroemer G. Linking cellular stress responses to systemic homeostasis. Nat Rev Mol Cell Biol. 2018;19:731–745. doi:10.1038/s41580-018-0068-0.
40. Nayagom B, Amara I, Habiballah M, Amrouche F, Beaune P, de Waziers I. Immunogenic cell death in a combined synergic gene- and immune-therapy against cancer. Oncoimmunology. 2019;8:e1667743. doi:10.1080/2162402X.2019.1667743.
41. Clemen R, Arlt K, von Woedtke T, Bekeschus S. Gas plasma protein oxidation increases immunogenicity and human antigen-presenting cell maturation and activation. Vaccines (Basel). 2022;10:10. doi:10.3390/vaccines10111814.
42. Wang J, Li J, Wu Y, Xu X, Qian X, Lei Y, Liu H, Zhang Z, Li Y. ROS-Responsive nanocomplex of Apd-L1 and cabazitaxel improves intratumor delivery and potentiates radiation-mediated antitumor immunity. Nano Lett. 2022;22:8312–8320. doi:10.1021/acs.nanolett.2c03227.
43. Panaretakis T, Kepp O, Brockmeier U, Tesniere A, Bjorklund A-C, Chapman DC, Durchschlag M, Joza N, Pierron G, van Endert P, et al. Mechanisms of pre-apoptotic calreticulin exposure in immunogenic cell death. Embo J. 2009;28:578–590. doi:10.1038/emboj.2009.1.
44. Garg AD, Krysko DV, Verfaillie T, Kaczmarek A, Ferreira GB, Marysael T, Rubio N, Firczuk M, Mathieu C, Roebroek AJM, et al. A novel pathway combining calreticulin exposure and ATP secretion in immunogenic cancer cell death. Embo J. 2012;31:1062–1079. doi:10.1038/emboj.2011.497.
45. Obeid M, Tesniere A, Ghiringhelli F, Fimia GM, Apetoh L, Perfettini J-L, Castedo M, Mignot G, Panaretakis T, Casares N, et al. Calreticulin exposure dictates the immunogenicity of cancer cell death. Nat Med. 2007;13:54–61. doi:10.1038/nm1523.
46. Giglio P, Gagliardi M, Bernardini R, Mattei M, Cotella D, Santoro C, Piacentini M, Corazzari M. Ecto-calreticulin is essential for an efficient immunogenic cell death stimulation in mouse melanoma. Genes Immun. 2019;20:509–513. doi:10.1038/s41435-018-0047-7.
47. Fucikova J, Kasikova L, Truxova I, Laco J, Skapa P, Ryska A, Spisek R. Relevance of the chaperone-like protein calreticulin for the biological behavior and clinical outcome of cancer. Immunol Lett. 2018;193:25–34. doi:10.1016/j.imlet.2017.11.006.
48. Venkateswaran K, Verma A, Bhatt AN, Shrivastava A, Manda K, Raj HG, Prasad A, Len C, Parmar VS, Dwarakanath BS. Emerging roles of calreticulin in cancer: implications for therapy. Curr Protein Pept Sci. 2018;19:344–357. doi:10.2174/1389203718666170111123253.
49. Vaes RDW, Reynders K, Sprooten J, Nevola KT, Rouschop KMA, Vooijs M, Garg AD, Lambrecht M, Hendriks LEL, Rucevic M, et al. Identification of potential prognostic and predictive immunological biomarkers in patients with stage i and stage iii non-small cell lung cancer (NSCLC): a prospective exploratory study. Cancers (Basel). 2021;13:6259. doi:10.3390/cancers13246259.
50. Xiu Z, Sun T, Yang Y, He Y, Yang S, Xue X, Yang W, Wang B. Curcumin enhanced ionizing radiation-induced immunogenic cell death in glioma cells through endoplasmic reticulum stress signaling pathways. Oxid Med Cell Longev. 2022;2022:1–17. doi:10.1155/2022/5424411.
51. Zhao L, Li D, Zhang Y, Huang Q, Zhang Z, Chen C, Xu C-F, Chu X, Zhang Y, Yang X. HSP70-promoter-driven CRISPR/Cas9 system activated by reactive oxygen species for multifaceted anticancer immune response and potentiated immunotherapy. Acs Nano. 2022;16:13821–13833. doi:10.1021/acsnano.2c01885.
52. Luo Y, Chihara Y, Fujimoto K, Sasahira T, Kuwada M, Fujiwara R, Fujii K, Ohmori H, Kuniyasu H. High mobility group box 1 released from necrotic cells enhances regrowth and metastasis of cancer cells that have survived chemotherapy. Eur J Cancer. 2013;49:741–751. doi:10.1016/j.ejca.2012.09.016.
53. Kroemer G, Kepp O. Radiochemotherapy-induced elevations of plasma HMGB1 levels predict therapeutic responses in cancer patients. Oncoimmunol. 2021;10:2005859. doi:10.1080/2162402X.2021.2005859.
54. He C, Sun S, Zhang Y, Xie F, Li S. The role of irreversible electroporation in promoting M1 macrophage polarization via regulating the HMGB1-RAGE-MAPK axis in pancreatic cancer. Oncoimmunol. 2021;10:1897295. doi:10.1080/2162402X.2021.1897295.
55. Turubanova VD, Mishchenko TA, Balalaeva IV, Efimova I, Peskova NN, Klapshina LG, Lermontova SA, Bachert C, Krysko O, Vedunova MV, et al. Novel porphyrazine-based photodynamic anti-cancer therapy induces immunogenic cell death. null. 2021;11:7205. doi:10.1038/s41598-021-86354-4.
56. Turubanova VD, Balalaeva IV, Mishchenko TA, Catanzaro E, Alzeibak R, Peskova NN, Efimova I, Bachert C, Mitroshina EV, Krysko O, et al. Immunogenic cell death induced by a new photodynamic therapy based on photosens and photodithazine. J ImmunoTher Cancer. 2019;7:350. doi:10.1186/s40425-019-0826-3.
57. Fucikova J, Kepp O, Kasikova L, Petroni G, Yamazaki T, Liu P, Zhao L, Spisek R, Kroemer G, Galluzzi L. Detection of immunogenic cell death and its relevance for cancer therapy. Cell Death Disease. 2020;11:1013. doi:10.1038/s41419-020-03221-2.
58. Arai H, Xiao Y, Loupakis F, Kawanishi N, Wang J, Battaglin F, Soni S, Zhang W, Mancao C, Salhia B, et al. Immunogenic cell death pathway polymorphisms for predicting oxaliplatin efficacy in metastatic colorectal cancer. J ImmunoTher Cancer. 2020;8:e001714. doi:10.1136/jitc-2020-001714.
59. Baracco EE, Petrazzuolo A, Kroemer G. Assessment of annexin A1 release during immunogenic cell death. Methods Enzymol. 2019;629:71–79.
60. Baracco EE, Stoll G, Van Endert P, Zitvogel L, Vacchelli E, Kroemer G. Contribution of annexin A1 to anticancer immunosurveillance. Oncoimmunology. 2019;8:e1647760. doi:10.1080/2162402X.2019.1647760.
61. Zhang J, Sun X, Zhao X, Yang C, Shi M, Zhang B, Hu H, Qiao M, Chen D, Zhao X. Combining immune checkpoint blockade with ATP-based immunogenic cell death amplifier for cancer chemo-immunotherapy. Acta Pharm Sin B. 2022;12:3694–3709. doi:10.1016/j.apsb.2022.05.008.
62. Kepp O, Bezu L, Yamazaki T, Di Virgilio F, Smyth MJ, Kroemer G, Galluzzi L. ATP and cancer immunosurveillance. Embo J. 2021;40:e108130. doi:10.15252/embj.2021108130.
63. Serrano Del Valle A, Beltrán-Visiedo M, de Poo-Rodríguez V, Jiménez-Alduán N, Azaceta G, Díez R, Martínez-Lázaro B, Izquierdo I, Palomera L, Naval J, et al. Ecto-calreticulin expression in multiple myeloma correlates with a failed anti-tumoral immune response and bad prognosis. Oncoimmunology. 2022;11:2141973. doi:10.1080/2162402X.2022.2141973.
64. Spisek R, Charalambous A, Mazumder A, Vesole DH, Jagannath S, Dhodapkar MV. Bortezomib enhances dendritic cell (DC)-mediated induction of immunity to human myeloma via exposure of cell surface heat shock protein 90 on dying tumor cells: therapeutic implications. Blood. 2007;109:4839–4845. doi:10.1182/blood-2006-10-054221.
65. Sprooten J, Vanmeerbeek I, Datsi A, Govaerts J, Borras D, Naulaerts S, Laureano R, Calvet A, Kuballa M, Sabel M, et al. A lymph node-to-tumour PD-L1+macrophage circuit antagonizes dendritic cell immunotherapy. bioRxiv. 2023. doi:10.1101/2023.03.14.532534;.
66. Pan C, Wang Y, Liu Q, Hu Y, Fu J, Xie X, Zhang S, Xi M, Wen J. Phenotypic profiling and prognostic significance of immune infiltrates in esophageal squamous cell carcinoma. Oncoimmunology. 2021;10:1883890. doi:10.1080/2162402X.2021.1883890.
67. Schafer ZT, Brugge JS. IL-6 involvement in epithelial cancers. J Clin Invest. 2007;117:3660–3663. doi:10.1172/JCI34237.

68. Showalter A, Limaye A, Oyer JL, Igarashi R, Kittipatarin C, Copik AJ, Khaled AR. Cytokines in immunogenic cell death: applications for cancer immunotherapy. Cytokine. 2017;97:123–132. doi:10.1016/j.cyto.2017.05.024.
69. De Martino M, Vanpouille-Box C. Type I interferon induces cancer stem cells-mediated chemotherapy resistance. Oncoimmunology. 2022;11:2127274. doi:10.1080/2162402X.2022.2127274.
70. Vanmeerbeek I, Govaerts J, Laureano RS, Sprooten J, Naulaerts S, Borras DM, Laoui D, Mazzone M, Van Ginderachter JA, Garg AD. The interface of tumour-associated macrophages with dying cancer cells in immuno-oncology. Cells. 2022;11(23):3890. doi:10.3390/cells11233890.
71. Murgaski A, Kiss M, Van Damme H, Kancheva D, Vanmeerbeek I, Keirsse J, Hadadi E, Brughmans J, Arnouk SM, Hamouda AEI, et al. Efficacy of CD40 agonists is mediated by distinct cdc subsets and subverted by suppressive macrophages. Cancer Res. 2022;82:3785–3801. doi:10.1158/0008-5472.CAN-22-0094.
72. Sprooten J, Coosemans A, Garg AD. A first-in-class, non-invasive, immunodynamic biomarker approach for precision immuno-oncology. Oncoimmunology. 2022;11:2024692. doi:10.1080/2162402X.2021.2024692.
73. Garg AD, Vandenberk L, Fang S, Fasche T, Van Eygen S, Maes J, Van Woensel M, Koks C, Vanthillo N, Graf N, et al. Pathogen response-like recruitment and activation of neutrophils by sterile immunogenic dying cells drives neutrophil-mediated residual cell killing. Cell Death Differ. 2017;24:832–843. doi:10.1038/cdd.2017.15.
74. Castiello L, Zevini A, Vulpis E, Muscolini M, Ferrari M, Palermo E, Peruzzi G, Krapp C, Jakobsen M, Olagnier D, et al. An optimized retinoic acid-inducible gene I agonist M8 induces immunogenic cell death markers in human cancer cells and dendritic cell activation. Cancer Immunol Immunother. 2019;68:1479–1492. doi:10.1007/s00262-019-02380-2.
75. Lau TS, Chan LKY, Man GCW, Wong CH, Lee JHS, Yim SF, Cheung TH, McNeish IA, Kwong J. Paclitaxel induces immunogenic cell death in ovarian cancer via TLR4/IKK2/SNARE-Dependent exocytosis. Cancer Immunol Res. 2020;8:1099–1111. doi:10.1158/2326-6066.CIR-19-0616.
76. Forveille S, Sauvat A, Zhang S, Zhao L, Kroemer G, Kepp O. Assessment of type I interferon responses as a feature of immunogenic cell death. Methods Cell Biol. 2022;172:135–143.
77. Sansone C, Bruno A, Piscitelli C, Baci D, Fontana A, Brunet C, Noonan DM, Albini A. Natural compounds of marine origin as inducers of immunogenic cell death (ICD): potential role for cancer interception and therapy. Cells. 2021;10:10. doi:10.3390/cells10020231.
78. Garg AD, Agostinis P. Cell death and immunity in cancer: from danger signals to mimicry of pathogen defense responses. Immunol Rev. 2017;280:126–148. doi:10.1111/imr.12574.
79. Sprooten J, Garg AD. Type I interferons and endoplasmic reticulum stress in health and disease. Int Rev Cell Mol Biol. 2020;350:63–118.
80. Sprooten J, Agostinis P, Garg AD. Type I interferons and dendritic cells in cancer immunotherapy. Int Rev Cell Mol Biol. 2019;348:217–262.
81. Klein JC, Wild CA, Lang S, Brandau S. Differential immunomodulatory activity of tumor cell death induced by cancer therapeutic toll-like receptor ligands. Cancer Immunol Immunother. 2016;65:689–700. doi:10.1007/s00262-016-1828-3.
82. Lopez-Pelaez M, Young L, Vazquez-Chantada M, Nelson N, Durant S, Wilkinson RW, Poon E, Gaspar M, Valge-Archer V, Smith P, et al. Targeting DNA damage response components induces enhanced STING-dependent type-I IFN response in ATM deficient cancer cells and drives dendritic cell activation. Oncoimmunology. 2022;11:2117321. doi:10.1080/2162402X.2022.2117321.
83. Roussot N, Ghiringhelli F, Rébé C. Tumor immunogenic cell death as a mediator of intratumor CD8 T-Cell recruitment. Cells. 2022;11(20).
84. Radogna F, Diederich M. Stress-induced cellular responses in immunogenic cell death: implications for cancer immunotherapy. Biochem Pharmacol. 2018;153:12–23.
85. Maher J, Adami AA. Antitumor immunity: easy as 1, 2, 3 with monoclonal bispecific trifunctional antibodies? Cancer Res. 2013;73:5613–5617. doi:10.1158/0008-5472.CAN-13-1852.
86. Pocaterra A, Catucci M, Mondino A. Adoptive T cell therapy of solid tumors: time to team up with immunogenic chemo/radiotherapy. Curr Opin Immunol. 2022;74:53–59. doi:10.1016/j.coi.2021.10.004.
87. Darmon A, Zhang P, Marill J, Mohamed Anesary N, Da Silva J, Paris S. Radiotherapy-activated NBTXR3 nanoparticles modulate cancer cell immunogenicity and TCR repertoire. Cancer Cell Int. 2022;22:208. doi:10.1186/s12935-022-02615-w.
88. Minute L, Teijeira A, Sanchez-Paulete AR, Ochoa MC, Alvarez M, Otano I, Etxeberrria I, Bolaños E, Azpilikueta A, Garasa S, et al. Cellular cytotoxicity is a form of immunogenic cell death. J ImmunoTher Cancer. 2020;8:8. doi:10.1136/jitc-2019-000325.
89. Malviya V, Yshii L, Junius S, Garg AD, Humblet-Baron S, Schlenner SM. Regulatory T cell stability and functional plasticity in health and disease. Immunol Cell Biol. 2022;101:112–129. doi:10.1111/imcb.12613.
90. Dillard P, Casey N, Pollmann S, Vernhoff P, Gaudernack G, Kvalheim G, Wälchli S, Inderberg EM. Targeting KRAS mutations with HLA class II-restricted TCRs for the treatment of solid tumors. Oncoimmunology. 2021;10:1936757. doi:10.1080/2162402X.2021.1936757.
91. Naulaerts S, Datsi A, Borras DM, Antoranz Martinez A, Messiaen J, Vanmeerbeek I, Sprooten J, Laureano RS, Govaerts J, Panovska D, et al. Multiomics and spatial mapping characterizes human CD8+ T cell states in cancer. Sci Transl Med. 2023;15:eadd1016. doi:10.1126/scitranslmed.add1016.
92. Luo R, Onyshchenko K, Wang L, Gaedicke S, Grosu A-L, Firat E, Niedermann G. Necroptosis-dependent immunogenicity of cisplatin: implications for enhancing the radiation-induced abscopal effect. Clin Cancer Res. 2022;29(3):667–683.
93. Bian Q, Huang L, Xu Y, Wang R, Gu Y, Yuan A, Ma X, Hu J, Rao Y, Xu D, et al. A facile low-dose photosensitizer-incorporated dissolving microneedles-based composite system for eliciting antitumor immunity and the abscopal effect. Acs Nano. 2021;15:19468–19479. doi:10.1021/acsnano.1c06225.
94. Franzese O, Torino F, Giannetti E, Cioccoloni G, Aquino A, Faraoni I, Fuggetta MP, De Vecchis L, Giuliani A, Kaina B, et al. Abscopal effect and drug-induced xenogenization: a strategic alliance in cancer treatment? Int J Mol Sci. 2021;22:22. doi:10.3390/ijms221910672.
95. Arabpour M, Paul S, Grauers Wiktorin H, Kaya M, Kiffin R, Lycke N, Hellstrand K, Martner A. An adjuvant-containing cDC1-targeted recombinant fusion vaccine conveys strong protection against murine melanoma growth and metastasis. Oncoimmunology. 2022;11:2115618. doi:10.1080/2162402X.2022.2115618.
96. Koerner J, Horvath D, Oliveri F, Li J, Basler M. Suppression of prostate cancer and amelioration of the immunosuppressive tumor microenvironment through selective immunoproteasome inhibition. Oncoimmunology. 2023;12:2156091. doi:10.1080/2162402X.2022.2156091.
97. Yasmin-Karim S, Ziberi B, Wirtz J, Bih N, Moreau M, Guthier R, Ainsworth V, Hesser J, Makrigiorgos GM, Chuong MD, et al. Boosting the abscopal effect using immunogenic biomaterials with varying radiation therapy field sizes. Int J Radiat Oncol Biol Phys. 2022;112:475–486. doi:10.1016/j.ijrobp.2021.09.010.
98. Xing D, Siva S, Hanna GG. The abscopal effect of stereotactic radiotherapy and immunotherapy: fool's gold or el dorado? Clin Oncol (R Coll Radiol. 2019;31:432–443. doi:10.1016/j.clon.2019.04.006.
99. Moreau M, Yasmin-Karim S, Kunjachan S, Sinha N, Gremse F, Kumar R, Chow KF, Ngwa W. Priming the abscopal effect using multifunctional smart radiotherapy biomaterials loaded with

immunoadjuvants. Front Oncol. 2018;8:56. doi:10.3389/fonc.2018.00056.
100. Jin C, Wang Y, Li Y, Li J, Zhou S, Yu J, Wang Z, Yu Y, Zhang H, Wang D, et al. Doxorubicin-Near infrared dye conjugate induces immunogenic cell death to enhance cancer immunotherapy. Int J Pharm. 2021;607:121027. doi:10.1016/j.ijpharm.2021.121027.
101. Zhou M, Luo C, Zhou Z, Li L, Huang Y. Improving anti-PD-L1 therapy in triple negative breast cancer by polymer-enhanced immunogenic cell death and CXCR4 blockade. J Control Release. 2021;334:248–262. doi:10.1016/j.jconrel.2021.04.029.
102. Zheng J, Sun J, Chen J, Zhu S, Chen S, Liu Y, Hao L, Wang Z, Chang S. Oxygen and oxaliplatin-loaded nanoparticles combined with photo-sonodynamic inducing enhanced immunogenic cell death in syngeneic mouse models of ovarian cancer. J Control Release. 2021;332:448–459. doi:10.1016/j.jconrel.2021.02.032.
103. Galaine J, Turco C, Vauchy C, Royer B, Mercier-Letondal P, Queiroz L, Loyon R, Mouget V, Boidot R, Laheurte C, et al. CD4 T cells target colorectal cancer antigens upregulated by oxaliplatin. Int J Cancer. 2019;145:3112–3125. doi:10.1002/ijc.32620.
104. Zhou Y, Bastian IN, Long MD, Dow M, Li W, Liu T, Ngu RK, Antonucci L, Huang JY, Phung QT, et al. Activation of NF-κB and p300/CBP potentiates cancer chemoimmunotherapy through induction of MHC-I antigen presentation. Proc Natl Acad Sci USA. 2021;118:118. doi:10.1073/pnas.2025840118.
105. Lei X, Khatri I, de Wit T, de Rink I, Nieuwland M, Kerkhoven R, van Eenennaam H, Sun C, Garg AD, Borst J, et al. CD4+ helper T cells endow cDC1 with cancer-impeding functions in the human tumor micro-environment. Nat Commun. 2023;14:217. doi:10.1038/s41467-022-35615-5.
106. Sistigu A, Yamazaki T, Vacchelli E, Chaba K, Enot DP, Adam J, Vitale I, Goubar A, Baracco EE, Remédios C, et al. Cancer cell–autonomous contribution of type I interferon signaling to the efficacy of chemotherapy. Nat Med. 2014;20:1301–1309. doi:10.1038/nm.3708.
107. Xie D, Wang Q, Wu G. Research progress in inducing immunogenic cell death of tumor cells. Front Immunol. 2022;13:1017400. doi:10.3389/fimmu.2022.1017400.
108. Kroemer G, Galassi C, Zitvogel L, Galluzzi L. Immunogenic cell stress and death. Nat Immunol. 2022;23:487–500. doi:10.1038/s41590-022-01132-2.
109. Jhunjhunwala S, Hammer C, Delamarre L. Antigen presentation in cancer: insights into tumour immunogenicity and immune evasion. Nat Rev Cancer. 2021;21:298–312. doi:10.1038/s41568-021-00339-z.
110. Vanmeerbeek I, Borras DM, Sprooten J, Bechter O, Tejpar S, Garg AD. Early memory differentiation and cell death resistance in T cells predicts melanoma response to sequential anti-CTLA4 and anti-PD1 immunotherapy. Genes Immun. 2021;22:108–119. doi:10.1038/s41435-021-00138-4.
111. Gong T, Liu L, Jiang W, Zhou R. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. Nat Rev Immunol. 2020;20:95–112. doi:10.1038/s41577-019-0215-7.
112. Fucikova J, Moserova I, Urbanova L, Bezu L, Kepp O, Cremer I, Salek C, Strnad P, Kroemer G, Galluzzi 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.
113. Rodrigues MC, Morais JAV, Ganassin R, Oliveira GRT, Costa FC, Morais AAC, Silveira AP, Silva VCM, Longo JPF, Muehlmann LA. An overview on immunogenic cell death in cancer biology and therapy. Pharmaceutics. 2022;14:14. doi:10.3390/pharmaceutics14081564.
114. Krysko DV, Garg AD, Kaczmarek A, Krysko O, Agostinis P, Vandenabeele P. Immunogenic cell death and DAMPs in cancer therapy. Nat Rev Cancer. 2012;12:860–875. doi:10.1038/nrc3380.
115. Rufo N, Garg AD, Agostinis P. The unfolded protein response in immunogenic cell death and cancer immunotherapy. Trends Cancer. 2017;3:643–658. doi:10.1016/j.trecan.2017.07.002.
116. Wang J, Zhang H, Yin X, Bian Y, Zhang J. Oxaliplatin induces immunogenic cell death in human and murine laryngeal cancer. J Oncol. 2022;2022:1–12. doi:10.1155/2022/3760766.
117. Shi M, Zhang J, Wang Y, Han Y, Zhao X, Hu H, Qiao M, Chen D. Blockage of the IDO1 pathway by charge-switchable nanoparticles amplifies immunogenic cell death for enhanced cancer immunotherapy. Acta Biomater. 2022;150:353–366. doi:10.1016/j.actbio.2022.07.022.
118. Lévesque S, Le Naour J, Pietrocola F, Paillet J, Kremer M, Castoldi F, Baracco EE, Wang Y, Vacchelli E, Stoll G, et al. A synergistic triad of chemotherapy, immune checkpoint inhibitors, and caloric restriction mimetics eradicates tumors in mice. Oncoimmunology. 2019;8:e1657375. doi:10.1080/2162402X.2019.1657375.
119. Vienot A, Pallandre J-R, Renaude E, Viot J, Bouard A, Spehner L, Kroemer M, Abdeljaoued S, van der Woning B, de Haard H, et al. Chemokine switch regulated by TGF-β1 in cancer-associated fibroblast subsets determines the efficacy of chemo-immunotherapy. Oncoimmunology. 2022;11:2144669. doi:10.1080/2162402X.2022.2144669.
120. Kim R, Kin T. Current and future therapies for immunogenic cell death and related molecules to potentially cure primary breast cancer. Cancers (Basel). 2021;13:4756. doi:10.3390/cancers13194756.
121. Chen Y, Xiong T, Zhao X, Du J, Sun W, Fan J, Peng X. Tumor cell-responsive photodynamic immunoagent for immunogenicity-enhanced orthotopic and remote tumor therapy. Adv Healthcare Mater. 2022;12:e2202085. doi:10.1002/adhm.202202085.
122. Liu X, Liu Y, Li X, Huang J, Guo X, Zhang J, Luo Z, Shi Y, Jiang M, Qin B, et al. ER-Targeting PDT converts tumors into in situ therapeutic tumor vaccines. Acs Nano. 2022;16:9240–9253. doi:10.1021/acsnano.2c01669.
123. Zeng Q, Yang J, Ji J, Wang P, Zhang L, Yan G, Wu Y, Chen Q, Liu J, Zhang G, et al. PD-L1 blockade potentiates the antitumor effects of ALA-PDT and optimizes the tumor microenvironment in cutaneous squamous cell carcinoma. Oncoimmunology. 2022;11:2061396. doi:10.1080/2162402X.2022.2061396.
124. Kudling TV, Clubb JHA, Quixabeira DCA, Santos JM, Havunen R, Kononov A, Heiniö C, Cervera-Carrascon V, Pakola S, Basnet S, et al. Local delivery of interleukin 7 with an oncolytic adenovirus activates tumor-infiltrating lymphocytes and causes tumor regression. Oncoimmunology. 2022;11:2096572. doi:10.1080/2162402X.2022.2096572.
125. Chang X, Bian M, Liu L, Yang J, Yang Z, Wang Z, Lu Y, Liu W. Induction of immunogenic cell death by novel platinum-based anticancer agents. Pharmacol Res. 2022;187:106556. doi:10.1016/j.phrs.2022.106556.
126. Nishimura J, Deguchi S, Tanaka H, Yamakoshi Y, Yoshii M, Tamura T, Toyokawa T, Lee S, Muguruma K, Ohira M. Induction of immunogenic cell death of esophageal squamous cell carcinoma by 5-fluorouracil and cisplatin. Vivo. 2021;35:743–752. doi:10.21873/invivo.12315.
127. Liu P, Chen J, Zhao L, Hollebecque A, Kepp O, Zitvogel L, Kroemer G. PD-1 blockade synergizes with oxaliplatin-based, but not cisplatin-based, chemotherapy of gastric cancer. Oncoimmunology. 2022;11:2093518. doi:10.1080/2162402X.2022.2093518.
128. Bag A, Schultz A, Bhimani S, Stringfield O, Dominguez W, Mo Q, Cen L, Adeegbe D. Coupling the immunomodulatory properties of the HDAC6 inhibitor ACY241 with Oxaliplatin promotes robust anti-tumor response in non-small cell lung cancer. Oncoimmunology. 2022;11:2042065. doi:10.1080/2162402X.2022.2042065.
129. Krackhardt AM, Anliker B, Hildebrandt M, Bachmann M, Eichmüller SB, Nettelbeck DM, Renner M, Uharek L, Willimsky G, Schmitt M, et al. Clinical translation and regulatory aspects of CAR/TCR-based adoptive cell therapies—the German cancer consortium approach. Cancer Immunol Immunother. 2018;67:513–523. doi:10.1007/s00262-018-2119-y.

130. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L, Amelio I, Andrews DW, et al. Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018. Cell Death Differ. 2018;25:486–541. doi:10.1038/s41418-017-0012-4.
131. Krysko DV, Demuynck R, Efimova I, Naessens F, Krysko O, Catanzaro E. In Vitro veritas: from 2D cultures to organ-on-a-chip models to study immunogenic cell death in the tumor microenvironment. Cells. 2022;11:11. doi:10.3390/cells11223705.
132. Sun T, Li Y, Yang Y, Liu B, Cao Y, Yang W. Enhanced radiation-induced immunogenic cell death activates chimeric antigen receptor T cells by targeting CD39 against glioblastoma. Cell Death Disease. 2022;13:875. doi:10.1038/s41419-022-05319-1.
133. Vergato C, Doshi KA, Roblyer D, Waxman DJ. Type-I interferon signaling is essential for robust metronomic chemo-immunogenic tumor regression in murine breast cancer. Cancer Res Commun. 2022;2:246–257. doi:10.1158/2767-9764.CRC-21-0148.
134. Garg AD, Vandenberk L, Koks C, Verschuere T, Boon L, Van Gool SW, Agostinis P. Dendritic cell vaccines based on immunogenic cell death elicit danger signals and T cell-driven rejection of high-grade glioma. Sci Transl Med. 2016;8:328ra27. doi:10.1126/scitranslmed.aae0105.
135. Aaes TL, Vandenabeele P. The intrinsic immunogenic properties of cancer cell lines, immunogenic cell death, and how these influence host antitumor immune responses. Cell Death Differ. 2021;28:843–860. doi:10.1038/s41418-020-00658-y.
136. Uscanga-Palomeque AC, Calvillo-Rodríguez KM, Gómez-Morales L, Lardé E, Denèfle T, Caballero-Hernández D, Merle-Béral H, Susin SA, Karoyan P, Martínez-Torres AC, et al. CD47 agonist peptide PKHB1 induces immunogenic cell death in T-cell acute lymphoblastic leukemia cells. Cancer Sci. 2019;110:256–268. doi:10.1111/cas.13885.
137. Chen J, Jin Z, Zhang S, Zhang X, Li P, Yang H, Ma Y. Arsenic trioxide elicits prophylactic and therapeutic immune responses against solid tumors by inducing necroptosis and ferroptosis. Cell Mol Immunol. 2022;20:51–64. doi:10.1038/s41423-022-00956-0.
138. Martínez-Torres AC, Calvillo-Rodríguez KM, Uscanga-Palomeque AC, Gómez-Morales L, Mendoza-Reveles R, Caballero-Hernández D, Karoyan P, Rodríguez-Padilla C. PKHB1 tumor cell lysate induces antitumor immune system stimulation and tumor regression in syngeneic mice with tumoral T lymphoblasts. J Oncol. 2019;2019:9852361. doi:10.1155/2019/9852361.
139. Fang S, Agostinis P, Salven P, Garg AD. Decoding cancer cell death-driven immune cell recruitment: an in vivo method for site-of-vaccination analyses. Methods Enzymol. 2020;636:185–207.
140. Workenhe ST, Pol J, Kroemer G. Tumor-intrinsic determinants of immunogenic cell death modalities. Oncoimmunology. 2021;10:1893466. doi:10.1080/2162402X.2021.1893466.
141. Oduro PK, Zheng X, Wei J, Yang Y, Wang Y, Zhang H, Liu E, Gao X, Du M, Wang Q. The Cgas-STING signaling in cardiovascular and metabolic diseases: future novel target option for pharmacotherapy. Acta Pharm Sin B. 2022;12:50–75. doi:10.1016/j.apsb.2021.05.011.
142. Kim EH, Wong S-W, Martinez J. Programmed necrosis and disease: we interrupt your regular programming to bring you necroinflammation. Cell Death Differ. 2019;26:25–40. doi:10.1038/s41418-018-0179-3.
143. Faiz A, Heijink IH, Vermeulen CJ, Guryev V, van den Berge M, Nawijn MC, Pouwels SD. Cigarette smoke exposure decreases CFLAR expression in the bronchial epithelium, augmenting susceptibility for lung epithelial cell death and DAMP release. null. 2018;8:12426. doi:10.1038/s41598-018-30602-7.
144. Chiang S-F, Huang K-Y, Chen W-L, Chen T-W, Ke T-W, Chao KSC. An independent predictor of poor prognosis in locally advanced rectal cancer: rs867228 in formyl peptide receptor 1 (FPR1). Oncoimmunology. 2021;10:1926074. doi:10.1080/2162402X.2021.1926074.
145. Liu P, Zhao L, Loos F, Marty C, Xie W, Martins I, Lachkar S, Qu B, Waeckel-Énée E, Plo I, et al. Immunosuppression by mutated calreticulin released from malignant cells. Mol Cell. 2020;77:748–760.e9. doi:10.1016/j.molcel.2019.11.004.
146. Brieske C, Lamprecht P, Kerstein-Staehle A. Immunogenic cell death as driver of autoimmunity in granulomatosis with polyangiitis. Front Immunol. 2022;13:1007092. doi:10.3389/fimmu.2022.1007092.
147. Novohradsky V, Pracharova J, Kasparkova J, Imberti C, Bridgewater HE, Sadler PJ, Brabec V. Induction of immunogenic cell death in cancer cells by a photoactivated platinum(IV) prodrug. Inorg Chem Front. 2020;7:4150–4159. doi:10.1039/D0QI00991A.
148. Matsusaka K, Azuma Y, Kaga Y, Uchida S, Takebayashi Y, Tsuyama T, Tada S. Distinct roles in phagocytosis of the early and late increases of cell surface calreticulin induced by oxaliplatin. Biochem Biophys Rep. 2022;29:101222. doi:10.1016/j.bbrep.2022.101222.
149. Li F, Zheng X, Wang X, Xu J, Zhang Q. Macrophage polarization synergizes with oxaliplatin in lung cancer immunotherapy via enhanced tumor cell phagocytosis. Transl Oncol. 2021;14:101202. doi:10.1016/j.tranon.2021.101202.
150. Sequeira GR, Sahores A, Dalotto-Moreno T, Perrotta RM, Pataccini G, Vanzulli SI, Polo ML, Radisky DC, Sartorius CA, Novaro V, et al. Enhanced antitumor immunity via endocrine therapy prevents mammary tumor relapse and increases immune checkpoint blockade sensitivity. Cancer Res. 2021;81:1375–1387. doi:10.1158/0008-5472.CAN-20-1441.
151. Tomić S, Petrović A, Puač N, Škoro N, Bekić M, Petrović ZL, Čolić M. Plasma-activated medium potentiates the immunogenicity of tumor cell lysates for dendritic cell-based cancer vaccines. Cancers (Basel). 2021;13:1626. doi:10.3390/cancers13071626.
152. Truxova I, Kasikova L, Salek C, Hensler M, Lysak D, Holicek P, Bilkova P, Holubova M, Chen X, Mikyskova R, et al. Calreticulin exposure on malignant blasts correlates with improved natural killer cell-mediated cytotoxicity in acute myeloid leukemia patients. Haematologica. 2020;105:1868–1878. doi:10.3324/haematol.2019.223933.
153. Laureano RS, Sprooten J, Vanmeerbeerk I, Borras DM, Govaerts J, Naulaerts S, Berneman ZN, Beuselinck B, Bol KF, Borst J, et al. Trial watch: dendritic cell (DC)-based immunotherapy for cancer. Oncoimmunology. 2022;11:2096363. doi:10.1080/2162402X.2022.2096363.
154. Hensler M, Rakova J, Kasikova L, Lanickova T, Pasulka J, Holicek P, Hraska M, Hrnciarova T, Kadlecova P, Schoenenberger A, et al. Peripheral gene signatures reveal distinct cancer patient immunotypes with therapeutic implications for autologous DC-based vaccines. Oncoimmunology. 2022;11:2101596. doi:10.1080/2162402X.2022.2101596.
155. Das S, Shapiro B, Vucic EA, Vogt S, Bar-Sagi D. Tumor cell-derived IL1β promotes desmoplasia and immune suppression in pancreatic cancer. Cancer Res. 2020;80:1088–1101. doi:10.1158/0008-5472.CAN-19-2080.
156. Tang AC, Rahavi SM, Fung S-Y, Lu HY, Yang H, Lim CJ, Reid GS, Turvey SE. Combination therapy with proteasome inhibitors and TLR agonists enhances tumour cell death and IL-1β production. Cell Death Disease. 2018;9:162. doi:10.1038/s41419-017-0194-1.
157. Petrovski G, Ayna G, Majai G, Hodrea J, Benko S, Mádi A, Fésüs L. Phagocytosis of cells dying through autophagy induces inflammasome activation and IL-1β release in human macrophages. Autophagy. 2011;7:321–330. doi:10.4161/auto.7.3.14583.
158. Tang L, Cai D, Qin M, Lu S, Hu M-H, Ruan S, Jin G, Wang Z. Oxaliplatin-based platinum(IV) prodrug bearing toll-like receptor 7 agonist for enhanced immunochemotherapy. ACS Omega. 2020;5:726–734. doi:10.1021/acsomega.9b03381.
159. Beltrán Hernández I, Angelier ML, Del Buono D'Ondes T, Di Maggio A, Yu Y, Oliveira S. The potential of nanobody-targeted photodynamic therapy to trigger immune responses. Cancers (Basel). 2020;12:12. doi:10.3390/cancers12040978.
160. Tang X, Guo D, Yang X, Chen R, Jiang Q, Zeng Z, Li Y, Li Z. Upregulated immunogenic cell-death-associated gene signature predicts reduced responsiveness to immune-checkpoint-blockade

therapy and poor prognosis in high-grade gliomas. Cells. 2022;11(22).
161. Bent EH, Millán-Barea LR, Zhuang I, Goulet DR, Fröse J, Hemann MT. Microenvironmental IL-6 inhibits anti-cancer immune responses generated by cytotoxic chemotherapy. Nat Commun. 2021;12:6218. doi:10.1038/s41467-021-26407-4.
162. Wang D, Cong J, Fu B, Zheng X, Sun R, Tian Z, Wei H. Immunogenic chemotherapy effectively inhibits KRAS-Driven lung cancer. Cancer Lett. 2020;492:31–43. doi:10.1016/j.canlet.2020.07.043.
163. Ishii K, Shimizu M, Kogo H, Negishi Y, Tamura H, Morita R, Takahashi H. A combination of check-point blockade and α-galactosylceramide elicits long-lasting suppressive effects on murine hepatoma cell growth in vivo. Immunobiology. 2020;225:151860.
164. Varga Z, Rácz E, Mázló A, Korodi M, Szabó A, Molnár T, Szöőr Á, Veréb Z, Bácsi A, Koncz G. Cytotoxic activity of human dendritic cells induces RIPK1-dependent cell death. Immunobiology. 2021;226:152032. doi:10.1016/j.imbio.2020.152032.
165. Serrano R, Lettau M, Zarobkiewicz M, Wesch D, Peters C, Kabelitz D. Stimulatory and inhibitory activity of STING ligands on tumor-reactive human gamma/delta T cells. Oncoimmunology. 2022;11:2030021. doi:10.1080/2162402X.2022.2030021.
166. Sprooten J, Vankerckhoven A, Vanmeerbeek I, Borras DM, Berckmans Y, Wouters R, Laureano RS, Baert T, Boon L, Landolfo C, et al. Peripherally-driven myeloid NFkB and IFN/ISG responses predict malignancy risk, survival, and immunotherapy regime in ovarian cancer. J ImmunoTher Cancer. 2021;9:e003609. doi:10.1136/jitc-2021-003609.
167. Leclercq G, Servera LA, Danilin S, Challier J, Steinhoff N, Bossen C, Odermatt A, Nicolini V, Umaña P, Klein C, et al. Dissecting the mechanism of cytokine release induced by T-cell engagers highlights the contribution of neutrophils. Oncoimmunology. 2022;11:2039432. doi:10.1080/2162402X.2022.2039432.
168. Ghiringhelli F, Apetoh L, Tesniere A, Aymeric L, Ma Y, Ortiz C, Vermaelen K, Panaretakis T, Mignot G, Ullrich E, et al. Activation of the NLRP3 inflammasome in dendritic cells induces IL-1β–dependent adaptive immunity against tumors. Nat Med. 2009;15:1170–1178. doi:10.1038/nm.2028.
169. Liu J, Meng Y, Li B, Wang P, Wan X, Huang W, Li R. Ferroptosis-related biotargets and network mechanisms of fucoidan against colorectal cancer: an integrated bioinformatic and experimental approach. Int J Biol Macromol. 2022;222:1522–1530. doi:10.1016/j.ijbiomac.2022.09.255.
170. Zhu C, Fang Z, Peng L, Gao F, Peng W, Song F. Curcumin suppresses the progression of colorectal cancer by improving immunogenic cell death caused by irinotecan. Chemotherapy. 2022;67:211–222. doi:10.1159/000518121.
171. Jeong H, Lee S-Y, Seo H, Kim DH, Lee D, Kim B-J. Potential of Mycobacterium tuberculosis chorismate mutase (Rv1885c) as a novel TLR4-mediated adjuvant for dendritic cell-based cancer immunotherapy. Oncoimmunology. 2022;11:2023340. doi:10.1080/2162402X.2021.2023340.
172. Pipperger L, Riepler L, Kimpel J, Siller A, Stoitzner P, Bánki Z, von Laer D. Differential infection of murine and human dendritic cell subsets by oncolytic vesicular stomatitis virus variants. Oncoimmunology. 2021;10:1959140. doi:10.1080/2162402X.2021.1959140.
173. Rébé C, Demontoux L, Pilot T, Ghiringhelli F. Platinum derivatives effects on anticancer immune response. Biomolecules. 2019;10:10. doi:10.3390/biom10010013.
174. Lamberti MJ, Montico B, Ravo M, Nigro A, Giurato G, Iorio R, Tarallo R, Weisz A, Stellato C, Steffan A, et al. Integration of miRNA: mRNA co-expression revealed crucial mechanisms modulated in immunogenic cancer cell death. Biomedicines. 2022;10:1896. doi:10.3390/biomedicines10081896.
175. Birmpilis AI, Paschalis A, Mourkakis A, Christodoulou P, Kostopoulos IV, Antimissari E, Terzoudi G, Georgakilas AG, Armpilia C, Papageorgis P, et al. Immunogenic cell death, damps and prothymosin α as a putative anticancer immune response biomarker. Cells. 2022;11:11. doi:10.3390/cells11091415.
176. Cacan E, Ozmen ZC. Regulation of Fas in response to bortezomib and epirubicin in colorectal cancer cells. J Chemother. 2020;32:193–201. doi:10.1080/1120009X.2020.1740389.
177. Jie Y, Yang X, Chen W. Pulsatilla decoction combined with 5-fluorouracil triggers immunogenic cell death in the colorectal cancer cells. Cancer Biother Radiopharm. 2021;37:945–954. doi:10.1089/cbr.2020.4369.
178. Jiang M, Zeng J, Zhao L, Zhang M, Ma J, Guan X, Zhang W. Chemotherapeutic drug-induced immunogenic cell death for nanomedicine-based cancer chemo-immunotherapy. Nanoscale. 2021;13:17218–17235. doi:10.1039/D1NR05512G.
179. Pol JG, Le Naour J, Kroemer G. FLT3LG - a biomarker reflecting clinical responses to the immunogenic cell death inducer oxaliplatin. Oncoimmunology. 2020;9:1755214. doi:10.1080/2162402X.2020.1755214.
180. Krysko DV, Kaczmarek A, Krysko O, Heyndrickx L, Woznicki J, Bogaert P, Cauwels A, Takahashi N, Magez S, Bachert C, et al. TLR-2 and TLR-9 are sensors of apoptosis in a mouse model of doxorubicin-induced acute inflammation. Cell Death Differ. 2011;18:1316–1325. doi:10.1038/cdd.2011.4.
181. Kepp O, Cerrato G, Sauvat A, Kroemer G. Nanoparticles releasing immunogenic cell death inducers upon near-infrared light exposure. Oncoimmunology. 2022;11:2131227. doi:10.1080/2162402X.2022.2131227.
182. Pol JG, Plantureux C, Pérez-Lanzón M, Kroemer G. PDIA3 as a potential bridge between immunogenic cell death and autoreactivity. Oncoimmunology. 2022;11:2130558. doi:10.1080/2162402X.2022.2130558.
183. Corazzari M, Rapino F, Ciccosanti F, Giglio P, Antonioli M, Conti B, Fimia GM, Lovat PE, Piacentini M. Oncogenic BRAF induces chronic ER stress condition resulting in increased basal autophagy and apoptotic resistance of cutaneous melanoma. Cell Death Differ. 2015;22:946–958. doi:10.1038/cdd.2014.183.
184. Wen H, Zhong Y, Yin Y, Qin K, Yang L, Li D, Yu W, Yang C, Deng Z, Hong K. A marine-derived small molecule induces immunogenic cell death against triple-negative breast cancer through ER stress-CHOP pathway. Int J Biol Sci. 2022;18:2898–2913. doi:10.7150/ijbs.70975.
185. Li X, Zheng J, Chen S, Meng F-D, Ning J, Sun S-L. Oleandrin, a cardiac glycoside, induces immunogenic cell death via the PERK/elF2α/ATF4/CHOP pathway in breast cancer. Cell Death Disease. 2021;12:314. doi:10.1038/s41419-021-03605-y.
186. Xu Q, Chen C, Lin A, Xie Y. Endoplasmic reticulum stress-mediated membrane expression of CRT/ERp57 induces immunogenic apoptosis in drug-resistant endometrial cancer cells. Oncotarget. 2017;8:58754–58764. doi:10.18632/oncotarget.17678.
187. Verfaillie T, van Vliet A, Garg AD, Dewaele M, Rubio N, Gupta S, de Witte P, Samali A, Agostinis P. Pro-apoptotic signaling induced by photo-oxidative ER stress is amplified by Noxa, not Bim. Biochem Biophys Res Commun. 2013;438:500–506. doi:10.1016/j.bbrc.2013.07.107.
188. Fang C, Weng T, Hu S, Yuan Z, Xiong H, Huang B, Cai Y, Li L, Fu X. IFN-γ-induced ER stress impairs autophagy and triggers apoptosis in lung cancer cells. Oncoimmunology. 2021;10:1962591. doi:10.1080/2162402X.2021.1962591.
189. Yadollahvandmiandoab R, Jalalizadeh M, Buosi K, Garcia-Perdomo HA, Reis LO. Immunogenic cell death role in urothelial cancer therapy. Curr Oncol. 2022;29:6700–6713. doi:10.3390/curroncol29090526.
190. Wang X, Huang H, Liu X, Li J, Wang L, Li L, Li Y, Han T. Immunogenic cell death-related classifications in breast cancer identify precise immunotherapy biomarkers and enable prognostic stratification. Front Genet. 2022;13:1052720. doi:10.3389/fgene.2022.1052720.
191. Zhang W, Liu T, Jiang L, Chen J, Li Q, Wang J. Immunogenic cell death-related gene landscape predicts the overall survival and

immune infiltration status of ovarian cancer. Front Genet. 2022;13:1001239. doi:10.3389/fgene.2022.1001239.
192. Han Y, Cai Q, Xie X, Gao S, Fan X. Development and validation of prognostic index based on immunogenic cell death-related genes with melanoma. Front Oncol. 2022;12:1011046. doi:10.3389/fonc.2022.1011046.
193. Cao X, Zhou X, Chen C, Wang Z, Sun Q. Identification of tumor antigens and immunogenic cell death-related subtypes for the improvement of immunotherapy of breast cancer. Front Cell Dev Biol. 2022;10:962389. doi:10.3389/fcell.2022.962389.
194. Fu J, Zhang W, Jiang T. Immunogenic cell death mediation patterns reveal novel paradigm for characterizing the immune microenvironment and immunotherapeutic responses in bladder cancer. Front Genet. 2022;13:1035484. doi:10.3389/fgene.2022.1035484.
195. Liao X, Liu H, Zhang Z, Zhang J, Zhang C, Zhao W. An immunogenic cell death-associated classification predictions are important for breast invasive carcinoma prognosis and immunotherapy. Front Genet. 2022;13:1010787. doi:10.3389/fgene.2022.1010787.
196. Ding D, Zhao Y, Su Y, Yang H, Wang X, Chen L. Prognostic value of antitumor drug targets prediction using integrated bioinformatic analysis for immunogenic cell death-related lncRNA model based on stomach adenocarcinoma characteristics and tumor immune microenvironment. Front Pharmacol. 2022;13:1022294. doi:10.3389/fphar.2022.1022294.
197. Kofla G, Radecke C, Frentsch M, Walther W, Stintzing S, Riess H, Bullinger L, Na IK. Conventional amphotericin B elicits markers of immunogenic cell death on leukemic blasts, mediates immunostimulatory effects on phagocytic cells, and synergizes with PD-L1 blockade. Oncoimmunology. 2022;11:2068109. doi:10.1080/2162402X.2022.2068109.
198. Eid M, Ostřížková L, Kunovský L, Brančíková D, Kala Z, Hlavsa J, Janeček P, Kosíková I, Blažková M, Slabý O, et al. Current view of neoadjuvant chemotherapy in primarily resectable pancreatic adenocarcinoma. Neoplasma. 2021;68:1–9. doi:10.4149/neo_2020_200408N372.
199. Iacoboni G, Zucca E, Ghielmini M, Stathis A. Methodology of clinical trials evaluating the incorporation of new drugs in the first-line treatment of patients with diffuse large B-cell lymphoma (DLBCL): a critical review. Ann Oncol. 2018;29:1120–1129. doi:10.1093/annonc/mdy113.
200. Wei D, Qi J, Hamblin MR, Wen X, Jiang X, Yang H. Near-infrared photoimmunotherapy: design and potential applications for cancer treatment and beyond. Theranostics. 2022;12:7108–7131. doi:10.7150/thno.74820.
201. Brennan L, Brouwer-Visser J, Nüesch E, Karpova M, Heller A, Gaire F, Schneider M, Gomes B, Korski K. T-Cell heterogeneity in baseline tumor samples: implications for early clinical trial design and analysis. Front Immunol. 2022;13:760763. doi:10.3389/fimmu.2022.760763.
202. Van Gool SW, Makalowski J, Fiore S, Sprenger T, Prix L, Schirrmacher V, Stuecker W. Randomized controlled immunotherapy clinical trials for GBM challenged. Cancers (Basel). 2020;13:13. doi:10.3390/cancers13010032.
203. Cho H, Kim JE, Hong YS, Kim SY, Kim J, Ryu Y-M, Kim S-Y, Kim TW. Comprehensive evaluation of the tumor immune microenvironment and its dynamic changes in patients with locally advanced rectal cancer treated with preoperative chemoradiotherapy: from the phase II ADORE study. Oncoimmunology. 2022;11:2148374. doi:10.1080/2162402X.2022.2148374.
204. Huang Z, Wang Y, Yao D, Wu J, Hu Y, Yuan A. Nanoscale coordination polymers induce immunogenic cell death by amplifying radiation therapy mediated oxidative stress. Nat Commun. 2021;12:145. doi:10.1038/s41467-020-20243-8.
205. 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;21:120–134. doi:10.1038/s41590-019-0561-4.
206. Vaes RDW, Hendriks LEL, Vooijs M, De Ruysscher D. Biomarkers of radiotherapy-induced immunogenic cell death. Cells. 2021;10:10. doi:10.3390/cells10040930.
207. Prasit KK, Ferrer-Font L, Burn OK, Anderson RJ, Compton BJ, Schmidt AJ, Mayer JU, Chen C-J, Dasyam N, Ritchie DS, et al. Intratumoural administration of an NKT cell agonist with CpG promotes NKT cell infiltration associated with an enhanced anti-tumour response and abscopal effect. Oncoimmunology. 2022;11:2081009. doi:10.1080/2162402X.2022.2081009.
208. Patel RB, Hernandez R, Carlson P, Grudzinski J, Bates AM, Jagodinsky JC, Erbe A, Marsh IR, Arthur I, Aluicio-Sarduy E, et al. Low-dose targeted radionuclide therapy renders immunologically cold tumors responsive to immune checkpoint blockade. Sci Transl Med. 2021;13. doi:10.1126/scitranslmed.abb3631.
209. Lejeune P, Cruciani V, Berg-Larsen A, Schlicker A, Mobergslien A, Bartnitzky L, Berndt S, Zitzmann-Kolbe S, Kamfenkel C, Stargard S, et al. Immunostimulatory effects of targeted thorium-227 conjugates as single agent and in combination with anti-PD-L1 therapy. J ImmunoTher Cancer. 2021;9:e002387. doi:10.1136/jitc-2021-002387.
210. Shekarian T, Sivado E, Jallas A-C, Depil S, Kielbassa J, Janoueix-Lerosey I, Hutter G, Goutagny N, Bergeron C, Viari A, et al. Repurposing rotavirus vaccines for intratumoral immunotherapy can overcome resistance to immune checkpoint blockade. Sci Transl Med. 2019;11:11. doi:10.1126/scitranslmed.aat5025.
211. Li X, Lu M, Yuan M, Ye J, Zhang W, Xu L, Wu X, Hui B, Yang Y, Wei B, et al. CXCL10-armed oncolytic adenovirus promotes tumor-infiltrating T-cell chemotaxis to enhance anti-PD-1 therapy. Oncoimmunology. 2022;11:2118210. doi:10.1080/2162402X.2022.2118210.
212. Wang Q, Ma X, Wu H, Zhao C, Chen J, Li R, Yan S, Li Y, Zhang Q, Song K, et al. Oncolytic adenovirus with MUC16-BiTE shows enhanced antitumor immune response by reversing the tumor microenvironment in PDX model of ovarian cancer. Oncoimmunology. 2022;11:2096362. doi:10.1080/2162402X.2022.2096362.
213. Tappe KA, Budida R, Stankov MV, Frenz T, Shah R, Volz A, Sutter G, Kalinke U, Behrens GMN. Immunogenic cell death of dendritic cells following modified vaccinia virus Ankara infection enhances CD8+ T cell proliferation. Eur J Immunol. 2018;48:2042–2054. doi:10.1002/eji.201847632.
214. He T, Hao Z, Lin M, Xin Z, Chen Y, Ouyang W, Yang Q, Chen X, Zhou H, Zhang W, et al. Oncolytic adenovirus promotes vascular normalization and nonclassical tertiary lymphoid structure formation through STING-mediated DC activation. Oncoimmunology. 2022;11:2093054. doi:10.1080/2162402X.2022.2093054.
215. Vanmeerbeek I, Sprooten J, De Ruysscher D, Tejpar S, Vandenberghe P, Fucikova J, Spisek R, Zitvogel L, Kroemer G, Galluzzi L, et al. Trial watch: chemotherapy-induced immunogenic cell death in immuno-oncology. Oncoimmunology. 2020;9:1703449. doi:10.1080/2162402X.2019.1703449.
216. Mandula JK, Chang S, Mohamed E, Jimenez R, Sierra-Mondragon RA, Chang DC, Obermayer AN, Moran-Segura CM, Das S, Vazquez-Martinez JA, et al. Ablation of the endoplasmic reticulum stress kinase PERK induces paraptosis and type I interferon to promote anti-tumor T cell responses. Cancer Cell. 2022;40:1145–1160.e9. doi:10.1016/j.ccell.2022.08.016.
217. Oresta B, Pozzi C, Braga D, Hurle R, Lazzeri M, Colombo P, Frego N, Erreni M, Faccani C, Elefante G, et al. Mitochondrial metabolic reprogramming controls the induction of immunogenic cell death and efficacy of chemotherapy in bladder cancer. Sci Transl Med. 2021;13. doi:10.1126/scitranslmed.aba6110.
218. Lucarini V, Melaiu O, D'Amico S, Pastorino F, Tempora P, Scarsella M, Pezzullo M, De Ninno A, D'Oria V, Cilli M, et al. Combined mitoxantrone and anti-TGFβ treatment with PD-1 blockade enhances antitumor immunity by remodelling the tumor immune landscape in neuroblastoma. J Exp Clin Cancer Res. 2022;41:326. doi:10.1186/s13046-022-02525-9.
219. Humeau J, Sauvat A, Cerrato G, Xie W, Loos F, Iannantuoni F, Bezu L, Lévesque S, Paillet J, Pol J, et al. Inhibition of transcription by dactinomycin reveals a new characteristic of immunogenic cell stress. EMBO Mol Med. 2020;12:e11622. doi:10.15252/emmm.201911622.

220. Ioele G, Chieffallo M, Occhiuzzi MA, De Luca M, Garofalo A, Ragno G, Grande F. Anticancer drugs: recent strategies to improve stability profile, pharmacokinetic and pharmacodynamic properties. Molecules. 2022;27:27. doi:10.3390/molecules27175436.
221. Marin I, Boix O, Garcia-Garijo A, Sirois I, Caballe A, Zarzuela E, Ruano I, Attolini C-O, Prats N, López-Domínguez JA, et al. Cellular senescence is immunogenic and promotes antitumor immunity. Cancer Discov. 2023;13:410–431. doi:10.1158/2159-8290.CD-22-0523.
222. Kepp O, Kroemer G. A nanoparticle-based tour de force for enhancing immunogenic cell death elicited by photodynamic therapy. Oncoimmunology. 2022;11:2098658. doi:10.1080/2162402X.2022.2098658.
223. Zhou Z, Yang R, Dong J, Di Y, Yang Y, Huang Y, Yang X, Liu W, Wang J, Liu P, et al. Pore forming–mediated intracellular protein delivery for enhanced cancer immunotherapy. Sci Adv. 2022;8:eabq4659. doi:10.1126/sciadv.abq4659.
224. Yang Q, Ma X, Xiao Y, Zhang T, Yang L, Yang S, Liang M, Wang S, Wu Z, Xu Z, et al. Engineering prodrug nanomicelles as pyroptosis inducer for codelivery of PI3K/mTOR and CDK inhibitors to enhance antitumor immunity. Acta Pharm Sin B. 2022;12:3139–3155. doi:10.1016/j.apsb.2022.02.024.
225. Song H, Cai Z, Li J, Xiao H, Qi R, Zheng M. Light triggered release of a triple action porphyrin-cisplatin conjugate evokes stronger immunogenic cell death for chemotherapy, photodynamic therapy and cancer immunotherapy. J Nanobiotechnology. 2022;20:329. doi:10.1186/s12951-022-01531-5.
226. Tatarova Z, Blumberg DC, Korkola JE, Heiser LM, Muschler JL, Schedin PJ, Ahn SW, Mills GB, Coussens LM, Jonas O, et al. A multiplex implantable microdevice assay identifies synergistic combinations of cancer immunotherapies and conventional drugs. Nat Biotechnol. 2022;40:1823–1833. doi:10.1038/s41587-022-01379-y.
227. Zawilska P, Machowska M, Wisniewski K, Grynkiewicz G, Hrynyk R, Rzepecki R, Gubernator J. Novel pegylated liposomal formulation of docetaxel with 3-n-pentadecylphenol derivative for cancer therapy. Eur J Pharm Sci. 2021;163:105838. doi:10.1016/j.ejps.2021.105838.
228. Lamberti MJ, Nigro A, Casolaro V, Rumie Vittar NB, Dal Col J. Damage-associated molecular patterns modulation by microRNA: relevance on immunogenic cell death and cancer treatment outcome. Cancers (Basel). 2021;13:2566. doi:10.3390/cancers13112566.
229. Yan X, Yu H, Liu Y, Hou J, Yang Q, Zhao Y. MiR-27a-3p functions as a tumor suppressor and regulates non-small cell lung cancer cell proliferation via targeting HOXB8. Technol Cancer Res Treat. 2019;18:1533033819861971. doi:10.1177/1533033819861971.
230. Colangelo T, Polcaro G, Ziccardi P, Muccillo L, Galgani M, Pucci B, Milone MR, Budillon A, Santopaolo M, Mazzoccoli G, et al. The miR-27a-calreticulin axis affects drug-induced immunogenic cell death in human colorectal cancer cells. Cell Death Disease. 2016;7:e2108. doi:10.1038/cddis.2016.29.
231. He S-J, Cheng J, Feng X, Yu Y, Tian L, Huang Q. The dual role and therapeutic potential of high-mobility group box 1 in cancer. Oncotarget. 2017;8:64534–64550. doi:10.18632/oncotarget.17885.
232. Son G-H, Kim Y, Lee JJ, Lee K-Y, Ham H, Song J-E, Park ST, Kim Y-H. MicroRNA-548 regulates high mobility group box 1 expression in patients with preterm birth and chorioamnionitis. null. 2019;9:19746. doi:10.1038/s41598-019-56327-9.
233. Lv X, Yao L, Nie YQ, Xu XY. MicroRNA-520a-3p suppresses non-small-cell lung carcinoma by inhibition of high mobility group box 1 (HMGB1). Eur Rev Med Pharmacol Sci. 2018;22:1700–1708. doi:10.26355/eurrev_201803_14583.
234. Yun Z, Meng F, Jiang P, Yue M, Li S. MicroRNA-548b suppresses aggressive phenotypes of hepatocellular carcinoma by directly targeting high-mobility group box 1 mRNA. Cancer Manag Res. 2019;11:5821–5834. doi:10.2147/CMAR.S198615.
235. Tatsuno K, Han P, Edelson R, Hanlon D. Detection of immunogenic cell death in tumor vaccination mouse model. Methods Mol Biol. 2021;2255:171–186.
236. Zhang Y, Thangam R, You S-H, Sultonova RD, Venu A, Min J-J, Hong Y. Engineering calreticulin-targeting monobodies to detect immunogenic cell death in cancer chemotherapy. Cancers (Basel). 2021;13:2801. doi:10.3390/cancers13112801.
237. Kim D-Y, Pyo A, Yun M, Thangam R, You S-H, Zhang Y, Jung Y-R, Nguyen D-H, Venu A, Kim HS, et al. Imaging calreticulin for early detection of immunogenic cell death during anticancer treatment. J Nucl Med. 2021;62:956–960. doi:10.2967/jnumed.120.245290.
238. Chumsri S, Serie DJ, Li Z, Pogue-Geile KL, Soyano-Muller AE, Mashadi-Hossein A, Warren S, Lou Y, Colon-Otero G, Knutson KL, et al. Effects of age and immune landscape on outcome in HER2-positive breast cancer in the NCCTG N9831 (Alliance) and NSABP B-31 (NRG) Trials. Clin Cancer Res. 2019;25:4422–4430. doi:10.1158/1078-0432.CCR-18-2206.
239. Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Henschel V, Molinero L, Chui SY, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21:44–59. doi:10.1016/S1470-2045(19)30689-8.
240. de Boo L, Cimino-Mathews A, Lubeck Y, Daletzakis A, Opdam M, Sanders J, Hooijberg E, van Rossum A, Loncova Z, Rieder D, et al. Tumour-infiltrating lymphocytes (TILs) and BRCA-like status in stage III breast cancer patients randomised to adjuvant intensified platinum-based chemotherapy versus conventional chemotherapy. Eur J Cancer. 2020;127:240–250. doi:10.1016/j.ejca.2019.12.003.
241. Emens LA, Molinero L, Loi S, Rugo HS, Schneeweiss A, Diéras V, Iwata H, Barrios CH, Nechaeva M, Nguyen-Duc A, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer: biomarker evaluation of the IMpassion130 study. J Natl Cancer Inst. 2021;113:1005–1016. doi:10.1093/jnci/djab004.
242. Page DB, Pucilowska J, Sanchez KG, Conrad VK, Conlin AK, Acheson AK, Perlewitz KS, Imatani JH, Aliabadi-Wahle S, Moxon N, et al. A phase ib study of preoperative, locoregional IRX-2 cytokine immunotherapy to prime immune responses in patients with early-stage breast cancer. Clin Cancer Res. 2020;26:1595–1605. doi:10.1158/1078-0432.CCR-19-1119.
243. Ishihara M, Kitano S, Kageyama S, Miyahara Y, Yamamoto N, Kato H, Mishima H, Hattori H, Funakoshi T, Kojima T, et al. NY-ESO-1-specific redirected T cells with endogenous TCR knockdown mediate tumor response and cytokine release syndrome. J ImmunoTher Cancer. 2022;10:e003811. doi:10.1136/jitc-2021-003811.
244. Haas AR, Tanyi JL, O'Hara MH, Gladney WL, Lacey SF, Torigian DA, Soulen MC, Tian L, McGarvey M, Nelson AM, et al. Phase I study of lentiviral-transduced chimeric antigen receptor-modified T cells recognizing mesothelin in advanced solid cancers. Mol Ther. 2019;27:1919–1929. doi:10.1016/j.ymthe.2019.07.015.
245. Somaiah N, Chawla SP, Block MS, Morris JC, Do K, Kim JW, Druta M, Sankhala KK, Hwu P, Jones RL, et al. A phase 1b study evaluating the safety, tolerability, and immunogenicity of CMB305, a lentiviral-based prime-boost vaccine regimen, in patients with locally advanced, relapsed, or metastatic cancer expressing NY-ESO-1. Oncoimmunology. 2020;9:1847846. doi:10.1080/2162402X.2020.1847846.
246. Chang K, Pastan I. Molecular cloning of mesothelin, a differentiation antigen present on mesothelium, mesotheliomas, and ovarian cancers. Proc Natl Acad Sci USA. 1996;93:136–140. doi:10.1073/pnas.93.1.136.
247. Ordóñez NG. Application of mesothelin immunostaining in tumor diagnosis. Am J Surg Pathol. 2003;27:1418–1428. doi:10.1097/00000478-200311000-00003.
248. Steinbach D, Onda M, Voigt A, Dawczynski K, Wittig S, Hassan R, Gruhn B, Pastan I. Mesothelin, a possible target for

immunotherapy, is expressed in primary AML cells. Eur J Haematol. 2007;79:281–286. doi:10.1111/j.1600-0609.2007.00928.x.
249. Takamizawa S, Yazaki S, Kojima Y, Yoshida H, Kitadai R, Nishikawa T, Shimoi T, Sudo K, Okuma HS, Tanioka M, et al. High mesothelin expression is correlated with non-squamous cell histology and poor survival in cervical cancer: a retrospective study. Bmc Cancer. 2022;22:1215. doi:10.1186/s12885-022-10277-0.
250. Pusztai L, Yau C, Wolf DM, Han HS, Du L, Wallace AM, String-Reasor E, Boughey JC, Chien AJ, Elias AD, et al. Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: results from the adaptively randomized I-SPY2 trial. Cancer Cell. 2021;39:989–998.e5. doi:10.1016/j.ccell.2021.05.009.
251. Yin W, Wang Y, Wu Z, Ye Y, Zhou L, Xu S, Lin Y, Du Y, Yan T, Yang F, et al. Neoadjuvant trastuzumab and pyrotinib for locally advanced HER2-positive breast cancer (NeoATP): primary analysis of a phase II study. Clin Cancer Res. 2022;28:3677–3685. doi:10.1158/1078-0432.CCR-22-0446.
252. Lee J-Y, Kim B-G, Kim J-W, Lee JB, Park E, Joung J-G, Kim S, Choi CH, Kim HS. Korean Gynecologic Oncology Group (KGOG) investigators. Biomarker-guided targeted therapy in platinum-resistant ovarian cancer (AMBITION; KGOG 3045): a multicentre, open-label, five-arm, uncontrolled, umbrella trial. J Gynecol Oncol. 2022;33:e45. doi:10.3802/jgo.2022.33.e45.
253. Cortes J, Rugo HS, Cescon DW, Im S-A, Yusof MM, Gallardo C, Lipatov O, Barrios CH, Perez-Garcia J, Iwata H, et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. N Engl J Med. 2022;387:217–226.
254. Jiang Y-Z, Liu Y, Xiao Y, Hu X, Jiang L, Zuo W-J, Ma D, Ding J, Zhu X, Zou J, et al. Molecular subtyping and genomic profiling expand precision medicine in refractory metastatic triple-negative breast cancer: the FUTURE trial. Cell Res. 2021;31:178–186. doi:10.1038/s41422-020-0375-9.
255. Sang W, Wang X, Geng H, Li T, Li D, Zhang B, Zhou Y, Song X, Sun C, Yan D, et al. Anti-PD-1 therapy enhances the efficacy of CD30-directed chimeric antigen receptor T cell therapy in patients with relapsed/refractory CD30+ lymphoma. Front Immunol. 2022;13:858021. doi:10.3389/fimmu.2022.858021.
256. Ozaki Y, Tsurutani J, Mukohara T, Iwasa T, Takahashi M, Tanabe Y, Kawabata H, Masuda N, Futamura M, Minami H, et al. Safety and efficacy of nivolumab plus bevacizumab, paclitaxel for HER2-negative metastatic breast cancer: primary results and biomarker data from a phase 2 trial (WJOG9917B). Eur J Cancer. 2022;171:193–202. doi:10.1016/j.ejca.2022.05.014.
257. Blumenschein GR, Devarakonda S, Johnson M, Moreno V, Gainor J, Edelman MJ, Heymach JV, Govindan R, Bachier C, Doger de Spéville B, et al. Phase I clinical trial evaluating the safety and efficacy of ADP-A2M10 SPEAR T cells in patients with MAGE-A10+ advanced non-small cell lung cancer. J ImmunoTher Cancer. 2022;10:e003581. doi:10.1136/jitc-2021-003581.
258. Creelan BC, Wang C, Teer JK, Toloza EM, Yao J, Kim S, Landin AM, Mullinax JE, Saller JJ, Saltos AN, et al. Tumor-infiltrating lymphocyte treatment for anti-PD-1-resistant metastatic lung cancer: a phase 1 trial. Nat Med. 2021;27:1410–1418. doi:10.1038/s41591-021-01462-y.
259. Sang W, Shi M, Yang J, Cao J, Xu L, Yan D, Yao M, Liu H, Li W, Zhang B, et al. Phase II trial of co-administration of CD19- and CD20-targeted chimeric antigen receptor T cells for relapsed and refractory diffuse large B cell lymphoma. Cancer Med. 2020;9:5827–5838. doi:10.1002/cam4.3259.
260. Shah BD, Bishop MR, Oluwole OO, Logan AC, Baer MR, Donnellan WB, O'Dwyer KM, Holmes H, Arellano ML, Ghobadi A, et al. KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: zUMA-3 phase 1 results. Blood. 2021;138:11–22. doi:10.1182/blood.2020009098.
261. Wang F, Wei XL, Wang FH, Xu N, Shen L, Dai GH, Yuan XL, Chen Y, Yang SJ, Shi JH, et al. Safety, efficacy and tumor mutational burden as a biomarker of overall survival benefit in chemo-refractory gastric cancer treated with toripalimab, a PD-1 antibody in phase Ib/II clinical trial NCT02915432. Ann Oncol. 2019;30:1479–1486. doi:10.1093/annonc/mdz197.
262. Narayan P, Wahby S, Gao JJ, Amiri-Kordestani L, Ibrahim A, Bloomquist E, Tang S, Xu Y, Liu J, Fu W, et al. FDA approval summary: atezolizumab plus paclitaxel protein-bound for the treatment of patients with advanced or metastatic TNBC whose tumors express PD-L1. Clin Cancer Res. 2020;26:2284–2289. doi:10.1158/1078-0432.CCR-19-3545.
263. Smith SD, Till BG, Shadman MS, Lynch RC, Cowan AJ, Wu QV, Voutsinas J, Rasmussen HA, Blue K, Ujjani CS, et al. Pembrolizumab with R-CHOP in previously untreated diffuse large B-cell lymphoma: potential for biomarker driven therapy. Br J Haematol. 2020;189:1119–1126. doi:10.1111/bjh.16494.
264. Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmer JU, Grischke EM, Furlanetto J, Tesch H, Hanusch C, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;30:1279–1288. doi:10.1093/annonc/mdz158.
265. Kohli K, Yao L, Nowicki TS, Zhang S, Black RG, Schroeder BA, Farrar EA, Cao J, Sloan H, Stief D, et al. IL-15 mediated expansion of rare durable memory T cells following adoptive cellular therapy. J ImmunoTher Cancer. 2021;9:e002232. doi:10.1136/jitc-2020-002232.
266. Pasqualini C, Rubino J, Brard C, Cassard L, André N, Rondof W, Scoazec J-Y, Marchais A, Nebchi S, Boselli L, et al. Phase II and biomarker study of programmed cell death protein 1 inhibitor nivolumab and metronomic cyclophosphamide in paediatric relapsed/refractory solid tumours: arm G of AcSé-ESMART, a trial of the European innovative therapies for children with cancer consortium. Eur J Cancer. 2021;150:53–62. doi:10.1016/j.ejca.2021.03.032.
267. Pusztai L. The effectiveness of immune checkpoint inhibitors in the neoadjuvant and post-neoadjuvant breast cancer settings. Clin Adv Hematol Oncol. 2022;20:552–555.
268. Garg AD, More S, Rufo N, Mece O, Sassano ML, Agostinis P, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: immunogenic cell death induction by anticancer chemotherapeutics. Oncoimmunology. 2017;6:e1386829. doi:10.1080/2162402X.2017.1386829.
269. Zhao Y-Y, Lian J-X, Lan Z, Zou K-L, Wang W-M, Yu G-T. Ferroptosis promotes anti-tumor immune response by inducing immunogenic exposure in HNSCC. Oral Dis. 2021;29:933–941. doi:10.1111/odi.14077.
270. Ye T, Jiang K, Wei L, Barr MP, Xu Q, Zhang G, Ding C, Meng S, Piao H. Oncolytic Newcastle disease virus induces autophagy-dependent immunogenic cell death in lung cancer cells. Am J Cancer Res. 2018;8:1514–1527.
271. Rosato RR, Dávila-González D, Choi DS, Qian W, Chen W, Kozielski AJ, Wong H, Dave B, Chang JC. Evaluation of anti-PD-1-based therapy against triple-negative breast cancer patient-derived xenograft tumors engrafted in humanized mouse models. Breast Cancer Res. 2018;20:108. doi:10.1186/s13058-018-1037-4.
272. Pasquereau-Kotula E, Habault J, Kroemer G, Poyet J-L, Ma W-L. The anticancer peptide RT53 induces immunogenic cell death. PLos One. 2018;13:e0201220. doi:10.1371/journal.pone.0201220.
273. Nebot-Bral L, Coutzac C, Kannouche PL, Chaput N. Why is immunotherapy effective (or not) in patients with MSI/MMRD tumors? Bull Cancer. 2019;106:105–113. doi:10.1016/j.bulcan.2018.08.007.
274. Frey B, Rückert M, Deloch L, Rühle PF, Derer A, Fietkau R, Gaipl US. Immunomodulation by ionizing radiation-impact for design of radio-immunotherapies and for treatment of

inflammatory diseases. Immunol Rev. 2017;280:231–248. doi:10.1111/imr.12572.
275. Goéré D, Flament C, Rusakiewicz S, Poirier-Colame V, Kepp O, Martins I, Pesquet J, Eggermont A, Elias D, Chaput N, et al. Potent immunomodulatory effects of the trifunctional antibody catumaxomab. Cancer Res. 2013;73:4663–4673. doi:10.1158/0008-5472.CAN-12-4460.
276. Pasquiers B, Benamara S, Felices M, Nguyen L, Declèves X. Review of the existing translational pharmacokinetics modeling approaches specific to monoclonal antibodies (mAbs) to support the First-In-Human (FIH) dose selection. Int J Mol Sci. 2022;23:23. doi:10.3390/ijms232112754.
277. Kaestner SA, Sewell GJ. Chemotherapy dosing part I: scientific basis for current practice and use of body surface area. Clin Oncol (R Coll Radiol). 2007;19:23–37. doi:10.1016/j.clon.2006.10.010.
278. Martin JH, Dimmitt S. The rationale of dose-response curves in selecting cancer drug dosing. Br J Clin Pharmacol. 2019;85:2198–2204. doi:10.1111/bcp.13979.
279. Flieswasser T, Van Loenhout J, Freire Boullosa L, Van den Eynde A, De Waele J, Van Audenaerde J, Lardon F, Smits E, Pauwels P, Jacobs J. Clinically relevant chemotherapeutics have the ability to induce immunogenic cell death in non-small cell lung cancer. Cells. 2020;9:1474. doi:10.3390/cells9061474.
280. McCormick M, Richardson T, Rapkin L, Kalpatthi R. Risk factors for readmission following febrile neutropenia in pediatric oncology patients. J Pediatr Hematol Oncol. 2022;45:e496–e501. doi:10.1097/MPH.0000000000002585.
281. Xu T, Liu Y, Lu X, Liang J. Toxicity profile of combined immune checkpoint inhibitors and thoracic radiotherapy in esophageal cancer: a meta-analysis and systematic review. Front Immunol. 2022;13:1039020. doi:10.3389/fimmu.2022.1039020.
282. Panchenko AV, Tyndyk ML, Maydin MA, Baldueva IA, Artemyeva AS, Kruglov SS, Kireeva GS, Golubev AG, Belyaev AM, Anisimov VN. Melatonin administered before or after a cytotoxic drug increases mammary cancer stabilization rates in HER2/Neu mice. Chemotherapy. 2020;65:42–50. doi:10.1159/000509238.
283. Bawankar PR, Ankar R. Evidence generation of standard nursing protocol on chemotherapy-induced neutropenia among oncology nurses. Cureus. 2022;14:e31217. doi:10.7759/cureus.31217.
284. Gwak H, Lim S-T, Jeon Y-W, Park HS, Kim SH, Suh Y-J. COVID-19 prevention guidance and the incidence of febrile neutropenia in patients with breast cancer receiving TAC Chemotherapy with Prophylactic Pegfilgrastim. J Clin Med. 2022;11(23): 7053.
285. Xu Z, Yang L, Yu H, Guo L. A machine learning model for grade 4 lymphopenia prediction during pelvic radiotherapy in patients with cervical cancer. Front Oncol. 2022;12:905222. doi:10.3389/fonc.2022.905222.
286. Ni W, Xiao Z, Zhou Z, Chen D, Feng Q, Liang J, Lv J. Severe radiation-induced lymphopenia during postoperative radiotherapy or chemoradiotherapy has poor prognosis in patients with stage IIB-III after radical esophagectomy: a post hoc analysis of a randomized controlled trial. Front Oncol. 2022;12:936684. doi:10.3389/fonc.2022.936684.
287. Mayr P, Lutz M, Schmutz M, Hoeppner J, Liesche-Starnecker F, Schlegel J, Gaedcke J, Claus R. Progressive multifocal leukoencephalopathy associated with chemotherapy induced lymphocytopenia in solid tumors - case report of an underestimated complication. Front Oncol. 2022;12:905103. doi:10.3389/fonc.2022.905103.
288. Hsiehchen D, Naqash AR, Espinoza M, Von Itzstein MS, Cortellini A, Ricciuti B, Owen DH, Laharwal M, Toi Y, Burke M, et al. Association between immune-related adverse event timing and treatment outcomes. Oncoimmunology. 2022;11:2017162. doi:10.1080/2162402X.2021.2017162.
289. Yang S-H, Lu L-C, Kao H-F, Chen B-B, Kuo T-C, Kuo S-H, Tien Y-W, Bai L-Y, Cheng A-L, Yeh K-H. Negative prognostic implications of splenomegaly in nivolumab-treated advanced or recurrent pancreatic adenocarcinoma. Oncoimmunology. 2021;10:1973710. doi:10.1080/2162402X.2021.1973710.
290. Kaczmarek A, Brinkman BM, Heyndrickx L, Vandenabeele P, Krysko DV. Severity of doxorubicin-induced small intestinal mucositis is regulated by the TLR-2 and TLR-9 pathways. J Pathol. 2012;226:598–608. doi:10.1002/path.3009.
291. Dahlgren D, Sjöblom M, Hellström PM, Lennernäs H. Chemotherapeutics-induced intestinal mucositis: pathophysiology and potential treatment strategies. Front Pharmacol. 2021;12:681417. doi:10.3389/fphar.2021.681417.
292. Roberti MP, Yonekura S, Duong CPM, Picard M, Ferrere G, Tidjani Alou M, Rauber C, Iebba V, Lehmann CHK, Amon L, et al. Chemotherapy-induced ileal crypt apoptosis and the ileal microbiome shape immunosurveillance and prognosis of proximal colon cancer. Nat Med. 2020;26:919–931. doi:10.1038/s41591-020-0882-8.
293. Morano WF, Aggarwal A, Love P, Richard SD, Esquivel J, Bowne WB. Intraperitoneal immunotherapy: historical perspectives and modern therapy. Cancer Gene Ther. 2016;23:373–381. doi:10.1038/cgt.2016.49.
294. Aghanejad A, Bonab SF, Sepehri M, Haghighi FS, Tarighatnia A, Kreiter C, Nader ND, Tohidkia MR. A review on targeting tumor microenvironment: the main paradigm shift in the mAb-based immunotherapy of solid tumors. Int J Biol Macromol. 2022;207:592–610. doi:10.1016/j.ijbiomac.2022.03.057.