ONCOIMMUNOLOGY
2023, VOL. 12, NO. 1, 2219591
https://doi.org/10.1080/2162402X.2023.2219591

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REVIEW

Trial watch: chemotherapy-induced immunogenic cell death in oncology

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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.

ARTICLE HISTORY
Received 22 December 2022
Revised 25 May 2023
Accepted 25 May 2023

KEYWORDS
CAR T cells, antigen-presenting cells; chemotherapy; danger signals; dendritic cell; immune-checkpoint blockers; immunogenic cell death; immunotherapy

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.

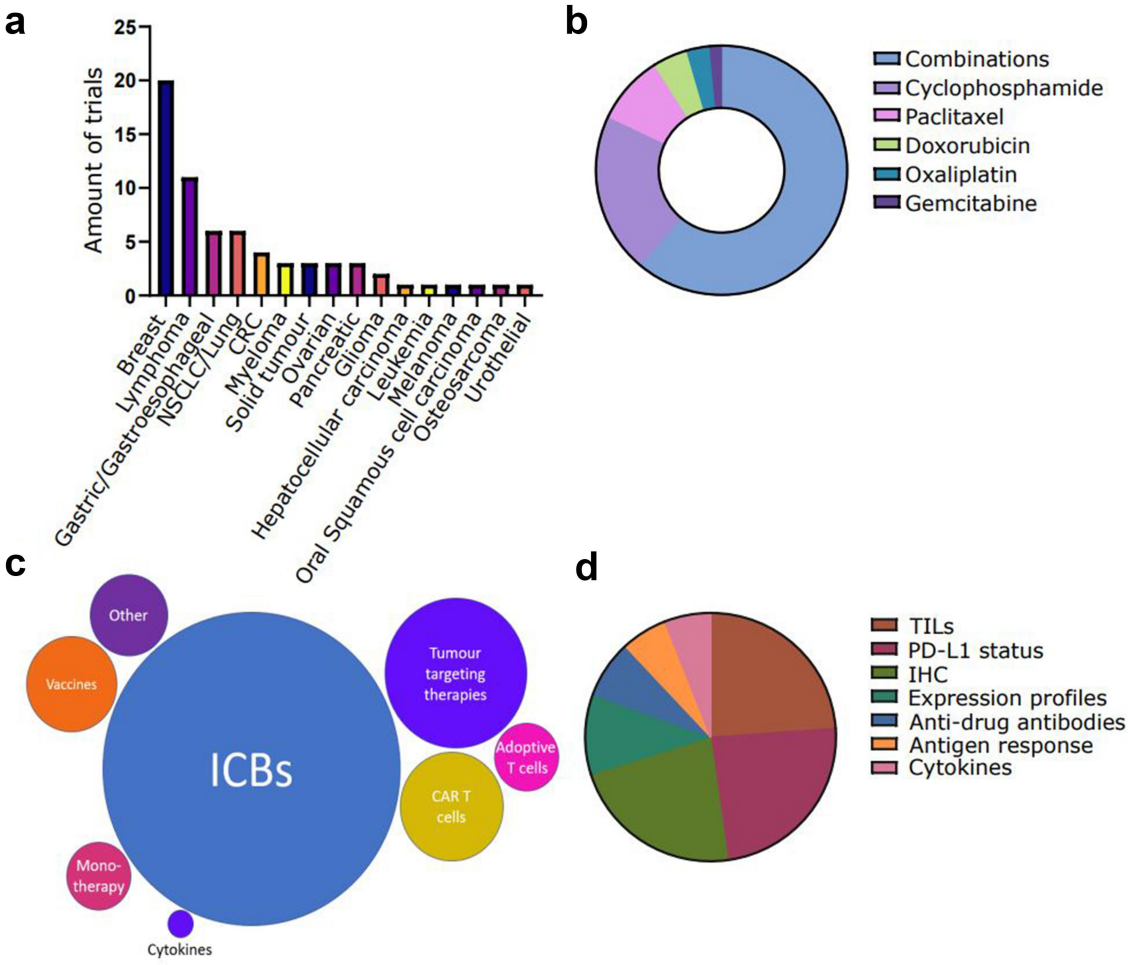

Figure 1. Recently published clinical studies testing immunogenic cell death (ICD)-inducing chemotherapy in oncology that investigate the immunogenic response. Clinical studies were classified on: (a) cancer type, (b) ICD-inducing drug, (c) combinatorial immunotherapy. (d) immunomonitoring approach, 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.

Acknowledgments

This study was supported by Research Foundation Flanders (FWO) (Fundamental Research Grant, G0B4620N to ADG; Excellence of Science/EOS grant, 30837538, for 'DECODE' consortium, for ADG), KU Leuven (C1 grant, C14/19/098; C3 grant, C3/21/037; and POR award funds, POR/16/040 to ADG), Kom op Tegen Kanker (KOTK/2018/11509/1 to ADG; and KOTK/2019/11955/1 to ADG), and VLIR-UOS (iBOF grant, iBOF/21/048, for 'MIMICRY' consortium to ADG). I. V. was supported by FWO-SB PhD Fellowship (1S06821N). J.S. was funded by Kom op tegen Kanker (Stand up to Cancer), the Flemish cancer society via Emmanuel van der Schueren (EvDS) PhD fellowship (projectID: 12699). D.M.B. was supported by KU Leuven's Postdoctoral FWO fellowship (1279223N). R.S. was supported by FWO-SB PhD Fellowship (1S44123N); E.S. was supported by the KOTK (KOTK/2019/7878); O.K. was supported by Institut National du Cancer (INCa) and the DIM ELICIT; D.V.K. was supported by FWO-Flanders (G016221N) and Excellence of Science/EOS grant, 40007488. Research in the Vandenabeele unit was supported by the FWO (research grants G.0C76.18N, G.0B71.18N, G.0B96.20N, G.0A93.22N, EOS MODEL-IDI Grant (30826052), and EOS CD-INFLADIS (40007512)), grants from the Special Research Fund UGent (Methusalem grant BOF16/MET_V/007, iBOF ATLANTIS grant 20/IBF/039), grants from the Foundation against Cancer (F/2016/865, F/2020/1505), CRIG and GIGG consortia, and VIB.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study is supported by Research Foundation Flanders (FWO) (Fundamental Research Grant, G0B4620N to ADG; Excellence of Science/EOS grant, 30837538, for 'DECODE' consortium, for ADG), KU Leuven (C1 grant, C14/19/098; C3 grant, C3/21/037; and POR award funds, POR/16/040 to ADG), Kom op Tegen Kanker (KOTK/2018/11509/1 and KOTK/2019/11955/1 to ADG) and VLIR-UOS (iBOF grant, iBOF/21/048, for 'MIMICRY' consortium to ADG and ST). IV and RSL are supported by FWO-SB PhD Fellowship (1S06821N and 1S44123N). JS is funded by Kom op tegen Kanker (Stand up to Cancer), the Flemish cancer society through the Emmanuel van der Schueren (EvDS) PhD fellowship (projectID: 12699). DMB got support from Senior Postdoctoral FWO fellowship (1279223N) and KU Leuven's Postdoctoral mandate grant (PDMT1/21/032).

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