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REVIEW

Trial watch: chemotherapy-induced immunogenic cell death in immuno-oncology

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ABSTRACT

The term 'immunogenic cell death' (ICD) denotes an immunologically unique type of regulated cell death that enables, rather than suppresses, T cell-driven immune responses that are specific for antigens derived from the dying cells. The ability of ICD to elicit adaptive immunity heavily relies on the immunogenicity of dying cells, implying that such cells must encode and present antigens not covered by central tolerance (antigenicity), and deliver immunostimulatory molecules such as damage-associated molecular patterns and cytokines (adjuvanticity). Moreover, the host immune system must be equipped to detect the antigenicity and adjuvanticity of dying cells. As cancer (but not normal) cells express several antigens not covered by central tolerance, they can be driven into ICD by some therapeutic agents, including (but not limited to) chemotherapeutics of the anthracycline family, oxaliplatin and bortezomib, as well as radiation therapy. In this Trial Watch, we describe current trends in the preclinical and clinical development of ICD-eliciting chemotherapy as partner for immunotherapy, with a focus on trials assessing efficacy in the context of immunomonitoring.

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Introduction

It has been more than a decade since the concept of boosting the immunogenic potential of cancer cells by eliciting an immunogenic variant of regulated cell death (RCD), *i.e.* immunogenic cell death (ICD), has been proposed.[1–9] A substantial number of subsequent studies have shed light on the intricate molecular and cellular mechanisms that underlie the ability of cancer cells to undergo (and the host immune system to detect) ICD.[8,10–21] Based on a series of fundamental studies, preclinical validations and clinical biomarker assessments[22-24] ICD can be defined as a functionally unique RCD subtype that is sufficient for the elicitation of adaptive immunity specifically directed toward antigens derived from cell "corpses".[4,9,12,15,21,25–36] It is now well acknowledged that, upon antigenic priming coupled to the emission of damage-associated molecular patterns (DAMPs) and immunostimulatory cytokines,[8,9,12,15,19–21,27-29,31,36–50] cancer cells undergoing ICD effectively enable the expansion of (mostly preexisting but possibly also *de novo*) T cells specific for tumor-associated antigens (TAAs) and/or tumor-specific antigens (TSAs; also known as tumor neoantigens, TNAs).[4,12,15,21,51–57] Nevertheless, based on currently available evidence, it is safe to assume that although ICD-elicited antigen-specific T cell clones might be "rich" in terms of TCR diversity (*i.e.* overall amount of T cells with unique antigen-reactive TCRs),[58–63] their "evenness" (*i.e.* uniform distribution of unique TCR-possessing T cells) might be limited due to various constrains specific to oncological contexts.[56,64–67] Such constraints include: (1) the heterogeneous expression of TAAs and TSAs within the same tumor and/or across primary tumors and their metastatic lesions;[68–76] (2) the differential 'editing' of T cells bearing TAA-directed TCRs by central (*e.g.* thymic) or peripheral (*e.g.* tissue) tolerance;[77–86] (3) the relatively limited avidity of TAA-specific (and sometimes also TSA-specific) TCRs;[87–96] and (4) the ability of cancer cells to compromise cellular fitness and/or effector functions of T cells, hence driving 'exhaustion' or 'anergy'.[97–109]

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Two main criteria should be met for any treatment modality to be classified as a *bona fide* ICD inducer.[20,110] First, ICD-eliciting agents must exhibit superior therapeutic efficacy when employed against mouse tumors growing in immunocompetent, syngeneic (as compared to immunodeficient) hosts.[19,111–113] Second, cancer cells undergoing ICD must provide tumor-naïve, syngeneic hosts with immune-mediated prophylactic protection against a subsequent challenge with living cancer cells of the same (but not different) type.[4,12,19,114–119] Here, it is important to note that the first approach, while relatively straightforward, cannot be employed to discriminate ICD inducers (*i.e.* agents that kill cancer cells in an immunogenic manner) from immunostimulatory chemotherapies (*i.e.* agents that boost immune functions by acting on the host immune system).[16,120–131] An additional experimental approach to detect ICD, which can be used only for localized treatments such as radiation therapy (RT) or intra-tumoral drug delivery, consist in assessing the response of non-treated rodent tumors that have been established contra-laterally to treated lesions (so-called "abscopal response") in immunocompetent, syngeneic hosts.[132–134] Some ICD inducers are indeed potent at eliciting adaptive anticancer immunity even in the presence of the immunosuppressive circuitries that are established by developing tumors, and not only in tumor-naïve settings.[110,135–146]

In addition to these *in vivo* experiments, which obligatorily rely on rodent cancer cells established in immunocompetent, syngeneic hosts, some *in vitro* or *ex vivo* proxy methods are available to estimate the immunogenic potential of dying cancer cells (as long as all appropriate positive and negative controls are thoroughly evaluated).[12,19,77,147–150] The main advantage of these methods is that they can be employed for both rodent and human cancer cells. In this context, cancer cells potentially undergoing ICD can be examined for the release or exposure of ICD-associated DAMPs (see below),[12,15,21,149,151–153] and/or co-cultured with myeloid cells such as dendritic cells (DCs)[21,119,154–156] which are ultimately assessed for: (1) phagocytic activity,[157–165] (2) surface activation markers (*e.g.* CD80, CD83, CD86, CD83, CD40 and/or MHC Class II molecules),[166] (3) secretory activity, with specific reference to interleukin 1 beta (IL1B), IL6, IL12 and tumor necrosis factor (TNF),[167–172] and (4) T-cell cross-priming.[173–181]

Of note, performing these *ex vivo* experiments with human cells generally involves allogeneic settings, since DCs or T cells derived from healthy individuals are typically not HLA-matched to human cancer cell lines.[156,182–190] Thus, proper controls are needed for ruling out allogeneic graft-*versus*-host immune reactions as confounding factors.[191] Moreover, *ex vivo* experiments cannot substitute for vaccination or abscopal tests *in vivo*, as some compounds are capable of eliciting all the hallmarks of ICD when administered to cancer cells, and yet those cells are unable to initiate anticancer immunity.[192–199] Thus, these assays are most suited for screening purposes, which require validation in syngeneic murine models (for rodent cancer cells), or humanized mice models capable of sustaining human myeloid and lymphoid cells (for human cancer cells, especially in the setting of patient-derived xenografts).[12,21,117,119,149,200–203]

The release or exposure of ICD-associated DAMPs is regulated by multiple processes that occur in dying cancer cells,[204,205] but the ultimate immunological success of ICD also relies on the capacity of the host to recognize DAMPs and generate robust TSA/TAA-targeting adaptive immunity.[1,12,36,193,206–213] Chemotherapy-driven ICD is typically associated with: (1) surface exposure of calreticulin (CALR), which mediates pro-phagocytic effects,[205,214–216] (2) active or passive release of ATP, which operates as a short-range 'find me' signal and inflammasome activator;[217–221] (3) passive release of the non-histone chromatin-binding protein high-mobility group box 1 (HMGB1), which operates as an agonist of Toll-like receptor 4 (TLR4) and Advanced glycosylation end-product specific receptor (AGER);[57,222,223] (4) active or passive release of annexin A1 (ANXA1), a formyl peptide receptor 1 (FPR1) agonist;[155] (5) active secretion of immunostimulatory and chemotactic cytokines, including type I interferon (IFN), C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 1 (CXCL1) and CXCL10;[5,24,224–231] and (6) passive release of nucleic acids, which can engage TLR3, TLR7/8 and/or TLR9.[231–233]

These danger signals have been robustly associated with ICD induced by anthracyclines (*i.e.* idarubicin, epirubicin, doxorubicin, and mitoxantrone), but some minor, context-dependent variations exist for ICD elicited by cyclophosphamide and bortezomib.[234] Moreover, ICD driven by other cellular stressors including RT, photodynamic therapy, extracorporeal photochemotherapy and oncolytic virotherapy is not necessarily associated with the emission of the same DAMPs, cytokines and chemokines.[12,235–238] Altogether and in combination with an increased microenvironmental availability of TAAs or TSAs, ICD-associated DAMPs pave the way to: (1) abundant recruitment of antigen-presenting cells (APCs) or their precursors (as in the case of ATP, CCL2, CXCL1, ANXA1) and/or T cells (as in the case of CXCL10) to the tumor microenvironment; (2) efficient phagocytic uptake of dead/dying cancer cells and fragment thereof in the context of immunostimulatory signaling (as in the case of CALR); and, (3) potent functional activation of APCs (as in the case of ATP, HMGB1 and nucleic acids).[12,24,57,113,119,224,237] Ultimately, APCs engulfing TAAs or TSAs and receiving these immunostimulatory cues acquire an extraordinary ability to cross-present TAA- or TSA-derived epitopes to $CD4^+$ and/or $CD8^+$ T cells in the context of co-stimulation, which enables TAA/TSA-targeting immunity.[239–244]

In multiple oncological settings, cancer cells capable of undergoing ICD in response to microenvironmental or therapeutic stress are subjected to increased immunological pressure,[245] resulting in the selection of poorly immunogenic tumor variants displaying: (1) reduced antigenicity (due to TAA/TSA loss or defects in MHC Class I exposure);[246–253] (2) genetic or epigenetic annihilation of the intracellular stress pathways that support the emission of ICD-associated DAMPs, cytokines or chemokines;[254] and/or (3) direct genetic or epigenetic silencing of specific DAMPs (*e.g.* CALR) or type I IFN.[57,119,214,221,224,231,255] Alongside general immunological defects, there can also exist disruption in the detection of DAMPs that are normally emitted by cancer cells undergoing ICD.[256] Such conditions include: (1) a prominent immunological tolerance determined by the specific anatomical location

of the tumor (as in the case of the brain, mucosal surfaces and other immunologically privileged sites);[129,257–259] (2) an abundant and persistent release of immunosuppressive cytokines such as IL10;[260–264] (3) a robust production of factors that favor immune exclusion, such as transforming growth factor beta 1 (TGFB1);[265–270] (4) abundant tumor infiltration by immunosuppressive immune cells like myeloid-derived suppressor cells (MDSCs);[271–281] (5) elevated expression of co-inhibitory receptors, such as programmed cell death 1 (PDCD1, best known as PD-1) and hepatitis A virus cellular receptor 2 (HAVCR2, best known as TIM-3);[271–273,282-284] (6) lymphoid T cell depletion as a consequence of vascular exclusion;[77,79,279,285–287] and (7) cancer cell resistance to RCD driven by immune effector cells.[271,285,288]

Not surprisingly, only a few chemotherapeutic agents can cause the immunogenic demise of cancer cells.[12,21,130] Moreover, there is no clear structure-function relationship to assist the prediction of ICD inducers. Thus, even though cisplatin and oxaliplatin exhibit considerable structural overlap and share *modus operandi* as for their capacity to elicit ICD,[289] the latter but not the former drives *bona fide* ICD.[290] Similar observations apply to the DNA alkylating agents, melphalan (which is unable to cause ICD) and cyclophosphamide (a *bona fide* ICD inducer).[291] The differential ability of cisplatin (or melphalan) and oxaliplatin (or cyclophosplamide) to promote ICD reflects their uneven capacity to cause endoplasmic reticulum (ER) stress and hence favor the exposure of CALR and other ER chaperones on the surface of dying cells.[290–294]

Common chemotherapeutics that have been demonstrated to cause ICD include (but may not be limited to): (1) idarubicin, which is generally employed for the treatment of acute myeloid leukemia (AML);[214,295–297] (2) epirubicin, which is used in women with breast cancer;[4,214,296,297] (3) doxorubicin, which is approved for the treatment of AML, acute lymphoblastic leukemia (ALL), Wilms' tumors, breast cancer, lymphoma, gastric cancer, small cell lung carcinoma, neuroblastoma, multiple myeloma, thyroid cancer, sarcomas, ovarian cancer, and bladder cancer;[4,214,298–304] (4) mitoxantrone, which is licensed for use in patients with AML, non-Hodgkin's lymphoma (NHL), breast cancer, and prostate carcinoma;[4,214,296,297] (5) oxaliplatin, which is commonly employed in combinatorial regimens against colorectal carcinoma;[289,290,305–311] (6) bortezomib, which is approved for the clinical management of mantle cell lymphoma and multiple myeloma;[312–322] (7) cyclophosphamide, which is frequently employed in patients with AML, ALL, chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), lymphoma, multiple myeloma, ovarian cancer, breast cancer, neuroblastoma and retinoblastoma.[318,323–332] Finally, some chemotherapeutic agents can enhance the immunogenic potential of RCD to some degree, but not sufficiently to drive robust ICD, owing to a variety of limiting circumstances. This applies to taxanes (*e.g.* paclitaxel, docetaxel), bleomycin and vinca alkaloids.[15,113,333]

Of note, even though ICD is a major immunostimulatory pathway activated by the aforementioned chemotherapies (at least in preclinical settings), the same molecules can also boost anticancer immunity by, (1) targeting nonmalignant cells (*e.g.* immune cells, stromal cells, endothelial cells), and/or (2) by improving the immunogenicity of cancer cells independently of their demise (*e.g.* by activating the expression of NK cell-activatory ligands).[15,141,334–339] Finally, most immuno-oncology trials do not select chemotherapeutics based on their immunostimulatory potential (which in many cases does not manifest at clinically employed dose regimens), but rather based on their use a standard-of-care for selected indications. At least in some cases, such a design precludes the activation of clinically meaningful anticancer immune responses and hence limits the clinical benefit of combinatorial regimens.

In this edition of the Trial Watch series, we discuss recent preclinical and clinical developments on ICD induction by anticancer chemotherapeutics in the context of immuno-oncology. Of note, other inducers of ICD including RT,[225,340–344] oncolytic virotherapy,[345] high hydrostatic pressure,[12,15,346] photodynamic therapy and extracorporeal photochemotherapy[119,215,236,237,347] will not be discussed herein.

Recent preclinical advances

Since the publication of the latest Trial Watch dealing with ICD elicited by chemotherapy (September 2017),[20] several preclinical studies on this topic have been published in peer-reviewed scientific journals. Amongst these studies, we found the following ones to be of particular (representative) importance.

As compared to past decade (which was dominated by fundamental studies aimed at elucidating the molecular and cellular mechanisms underlying ICD and its detection)[20] the majority of the studies published in the last 2 years had a translational approach, largely reflecting the trend of immuno-oncology at large.[348,349] That said, at least a few studies provided fresh insights into the fundamentals of ICD. For instance, Bezu et al. (Center de Recherche des Cordeliers, Paris, France) observed that prototypical ICD inducers such as anthracyclines cause the phosphorylation of eukaryotic translation initiation factor 2A (EIF2A, best known as eIF2α) without consistently triggering other manifestations of ER stress, and that EIF2A phosphorylation strongly correlates with surface CALR exposure, *de facto* constituting a pathognomonic marker of ICD.[350] Lecciso and colleagues (University of Bologna, Bologna, Italy) documented that the release of extracellular ATP from daunorubicin-treated AML cells can elicit immunosuppressive (rather than immunostimulatory) effects within the tumor microenvironment by favoring the persistence of the regulatory T (T_{REG}) cells,[351] which can be distinguished by increased expression of PD-1, and tolerogenic DCs, which can be identified by increased indoleamine 2,3-dioxygenase 1 (IDO1) and ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1, best known as CD39) expression.[352] These studies highlight the need for better understanding the 'plasticity' associated with ICD-linked danger signaling especially in the context of resistance to immunotherapy.[353,354]

On the translational side, several preclinical studies reported the generation of nanoparticles or other nanoformulations for the improved delivery of ICD-inducing chemotherapies.[355]

Mastria et al. (Duke University, Durham, NC, USA) documented that a nanoparticle preparation of doxorubicin, *i.e.* chimeric polypeptide doxorubicin, efficiently enhances anticancer immunity as it favors tumor infiltration by T cells (including CD8+ T cells) and limits primary tumor growth as well as metastatic spread.[356] Yang and collaborators (National Institutes of Health, Bethesda, MD, USA) observed that an integrated polymersomal nanoformulation (consisting of a chimeric, cross-linked polymersome encapsulating doxorubicin and a photosensitizer that can be activated via photodynamic therapy) drives *in situ*, DC-dependent anticancer vaccination, hence retarding the progression of mouse MC38 colorectal tumors.[357] Lu and colleagues (University of California, Los Angeles, CA, USA) conjugated an IDO1 inhibitor (indoximod)[205] to oxaliplatin-bearing nanovesicles, and demonstrated that this nano-enabled approach (delivered through vaccination, intravenous or intratumoral injection) induces potent anticancer immunity in an orthotopic pancreatic ductal adenocarcinoma (PDAC) mouse model.[358] Huang et al. (Hainan Medical College, Haikou, China) developed a system for the ultrasound-controlled release of doxorubicin by liposome-microbubble complexes, resulting in superior ICD induction in lung (LL/2) and colorectal cancer (CT26) syngeneic murine models.[205] Finally, Liu and collaborators (University of North Carolina at Chapel Hill, Chapel Hill, NC, USA) achieved the targeted delivery of mitoxantrone and celastrol (a triterpenoid) via a tumor microenvironment-responsive nanocarrier, hence efficiently causing ICD-dependent therapeutic effects *in vivo* that halted cancer progression, and repressed metastatic spread.[359]

Beyond these nanotechnology-oriented studies, most of the other translational studies on ICD-inducing chemotherapies published over the past 2 years focused on combining ICD induction with immunotherapy or targeted anticancer agents, in keeping with current clinical trends.[360] D'Amico et al. (University of Basel, Basel, Switzerland) found that an antibody specific for Erb-B2 receptor tyrosine kinase 2 (ERBB2, also known as HER2) conjugated to an anthracycline derivate exerts potent anticancer effects that depend on cytotoxic T cells in a ERBB2-expressing syngeneic breast cancer model resistant to standard anti-ERBB2 therapy, and that this therapeutic effect can be further enhanced by PD-1 blockage.[205] Fend and collaborators (Gustave Roussy Cancer Campus, Villejuif, France) reported that an engineered oncolytic vaccinia virus, VV_{WR}-$TK^{-}RR^{-}$Fcu1, can mediate ICD-dependent therapeutic effects (as documented by type I IFN signaling, increased $CD8^{+}$ T cell infiltration, and improved ratio of effector $CD4^{+}$ T cells to T_{REG} cells in the tumor microenvironment) that can be potentiated by ICD-inducing chemotherapeutics or immune checkpoint blockers (ICBs).[361] Camilio and colleagues (Oslo University Hospital, Oslo, Norway) documented that combining the oncolytic peptide LTX-315 with doxorubicin elicits anticancer immune responses that limit tumor growth along with increased infiltration of $CD4^{+}$ and $CD8^{+}$ T cells.[362] Groza et al. (University of Vienna, Vienna, Austria) combined "bacterial ghosts" (*i.e.* empty envelopes of Gram-negative bacteria) with oxaliplatin to elicit therapeutically relevant T cell responses against CT26 mouse colorectal tumors coupled to the establishment of long-term immunological memory.[363] Gao and collaborators (University of Science and Technology of China, Hefei, China) found that, as compared to the either agent delivered as standalone therapy, the co-administration of doxorubicin and a small molecule IDO1 inhibitor (NLG919) profoundly inhibits the growth of 4T1 mouse mammary tumors *in vivo*.[364] Gebremeskel and colleagues (Beatrice Hunter Cancer Research Institute, Halifax, Nova Scotia, Canada) combined cyclophosphamide, gemcitabine and α-galactosylceramide (α-GalCer)-loaded DCs (which potently activate NKT cells), achieving disease eradication and long-term immunological protection in mice bearing 4T1 tumors, as demonstrated by their ability to reject a subsequent challenge with the same cancer cells.[365] Nam et al. (Korea University, Seoul, Republic of South Korea) employed ICD-inducing chemotherapy, as they boosted the phagocytic activity of APCs by blocking rho-associated coiled-coil containing protein kinase 1 (ROCK1), to activate effectual anti-tumor immunity (distinguished by improved T cell priming by DCs), causing considerable inhibition of tumor growth in multiple mouse models.[200] Combes and coauthors (Université de Montpellier, Montpellier, France) found that the resistance of colorectal cancer cells to oxaliplatin can be circumvented by inhibition of ATR serine/threonine kinase (ATR), resulting in robust therapeutic effects that largely depend on immune effectors.[366] Finally, Truxova et al. (Sotio, Prague, Czech Republic) demonstrated that AML patients whose blasts naturally expose CALR on the plasma membrane experience a survival advantage that is associated with improved NK cell functions downstream of superior type I IFN secretion and IL15 trans-presentation by myeloid cells.[205,216]

Altogether, these studies demonstrate that ICD-inducing chemotherapy can initiate robust anticancer immunity, which can be further potentiated by multiple immunotherapeutic regimens currently employed in the clinic. That said some cancers display immunological alterations that prevent the activation of tumor-targeting immunity by malignant cells undergoing ICD. This constitutes a major obstacle to efficacy of ICD-inducing chemotherapy, and further preclinical studies are required for the development of efficacious combinatorial regimens.

Finalized clinical studies

Subsequent to the publication of our previous Trial Watch on ICD-inducing chemotherapeutics (September 2017),[20] various clinical studies have assessed the efficacy of *bona fide* ICD-inducing chemotherapeutics (*i.e.* doxorubicin, epirubicin, idarubicin, mitoxantrone, bortezomib, cyclophosphamide or oxaliplatin), most often in combination with immunotherapy and in the context of immunomonitoring programs. These clinical reports were identified by querying PubMed (http://www.ncbi.nlm.nih.gov/pubmed) with the string "(cancer OR tumor OR tumor OR neoplasm) AND (oxaliplatin OR cyclophosphamide OR bortezomib OR doxorubicin OR epirubicin OR idarubicin OR mitoxantrone) AND (immune OR immunogenic OR "immunogenic cell death" OR immunological)", accompanied by an article-type filter (Article types>Clinical trial) and

followed by a manual selection of articles for direct relevance to this Trial Watch.

Voorwerk et al. (The Netherlands Cancer Institute, Amsterdam, the Netherlands) treated 67 patients with metastatic triple-negative breast cancer (TNBC), with a PD-1-targeting ICB (nivolumab) in combination with various conventional cancer treatments including ICD inducers (RT, cyclophosphamide, doxorubicin) as well as a non-ICD inducer (cisplatin). In the context of this Phase II trial (TONIC), the best objective response rates (ORRs) were achieved by nivolumab plus doxorubicin (35%), which was superior to nivolumab plus cisplatin (23%).[367] In consideration of the multi-arm design of this clinical study, we interpret these data as convincing clinical evidence in favor of combining *bona fide* ICD-inducing chemotherapeutics with ICBs, at least in the context of TNBC.[367] Scurr and collaborators (Cardiff University, Cardiff, UK) reported the results of a randomized Phase I/II study enrolling 55 metastatic colorectal cancer patients. In this context, cyclophosphamide combined with a modified vaccinia virus Ankara-5T4 (MVA-5T4) elicited robust anticancer immunity (as assessed by humoral immunological markers as well as by circulating T_{REG} depletion), culminating with protracted patient survival in the absence of severe toxicities.[368] Federico and colleagues (University of Tennessee Health Science Center, Memphis, TN, USA) documented that the combination of various chemotherapeutic regimens (cyclophosphamide plus topotecan, irinotecan plus temozolomide and ifosfamide plus carboplatin plus etoposide) with a monoclonal antibody specific for ganglioside G2 (hu14.18K322A), recombinant cytokines, and adoptively transferred NK cells not only is feasible in children suffering from refractory/recurrent neuroblastoma, but also exhibits robust clinical activity, as demonstrated by an ORR of 61.5%.[369]

Bota et al. (University of California Irvine, Irvine, CA, USA) reported that combining an allogeneic/autologous vaccine (ERC1671) with recombinant colony stimulating factor 2 (CSF2, best known as GM-CSF), cyclophosphamide and bevacizumab (a monoclonal antibody specific VEGFA)[205] results in a clinically-relevant survival benefit in glioblastoma patients (12 months *vs.* 7.5 months for patients receiving bevacizumab only).[370] Kanekiyo and colleagues (Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan) combined a vaccine based on 5 HLA-A*24:02-restricted peptides with oxaliplatin in patients with colorectal cancer, finding humoral responses to multiple peptides that were associated with cytotoxic T-cell responses and/or improved overall survival (OS).[371] Geyer and collaborators (Memorial Sloan Kettering Cancer Center, New York, NY, USA) employed CD19-targeting chimeric antigen receptor (CAR) T cells in patients afflicted by residual CLL upon chemotherapy with pentostatin (is a purine analog that inhibits nucleic acid synthesis), cyclophosphamide and rituximab (a CD20-targeting monoclonal antibody).[205] This approach achieved 38% ORR, with two patients exhibiting complete responses exceeding 28 months in the absence of severe cytokine release syndromes.[372]

Other clinical studies focused on assessing biomarkers of immune activation in patients receiving ICD-inducing chemotherapeutics. Foukakis et al. (Karolinska University Hospital, Stockholm, Sweden) documented that clinical responses to anthracycline-based neoadjuvant chemotherapy amongst 109 patients with breast cancer were more frequent when tumors were characterized by a transcriptional signature that the authors named "immune module score".[373] Similarly, Kwa and collaborators (NYU Langone Medical Center, New York, NY, USA) observed that the administration of cyclophosphamide plus exemestane (an aromatase inhibitor, belonging to the class of anti-estrogens agents)[205] to women with breast cancer resulted in clinical responses that were accompanied by increases in the circulating levels of various effector T cell subsets (but limited changes in blood-borne T_{REG} cells).[374] Conversely, Werter and colleagues (VU University Medical Center, Amsterdam, The Netherlands) were unable to document (in the context of a Phase I clinical trial) any clinical benefit for patients with renal cell carcinoma receiving cyclophosphamide plus everolimus (an MTORC1 inhibitor),[205] despite successful depletion of circulating T_{REG} cells.[375] Along similar lines, Toulmonde et al. (Institut Bergonié, Bordeaux, France) found that a PD-1-targeting ICB combined with cyclophosphamide has limited clinical activity in patients with advanced soft-tissue sarcoma and gastrointestinal stromal tumor (GIST).[376] These latter findings have been attributed to the elevated degree of immunosuppression that characterize at least some subsets of soft-tissue sarcoma and GIST, which are characterized by robust infiltration by macrophages and prominent IDO1 activity.[376] Stevens and colleagues (Radboudumc, Nijmegen, The Netherlands) reported that wild-type enhancer of zeste 2 polycomb repressive complex 2 subunit (*EZH2*) status, chromosome 18 gain, and low amounts of $CD68^{+}CD163^{+}$ cells were potent predictors of therapeutic failure of multimodal, cyclophosphamide- and doxorubicin-based chemotherapy plus rituximab in patients with follicular lymphoma.[377] Finally, Aspeslagh et al. (Gustave Roussy Cancer Campus, Villejuif, France) documented, (1) that cancer patients receiving first-line ICBs against PD-1 or CD274 (best known as PD-L1) obtain limited therapeutic benefit from the subsequent administration of conventional chemotherapy (irrespective of their ability to induce ICD), and that (2) prior exposure to ICD-inducing chemotherapeutics (*e.g.* oxaliplatin, cyclophosphamide, doxorubicin, epirubicin, bortezomib) did not seem to improve the activity of ICBs administered subsequently.[378]

Importantly, some clinical studies lent support to the notion that the failure of ICD-inducing chemotherapy does not compromise the activity of immunotherapy, at least in some settings. Thus, Overman et al. (MD Anderson Cancer Center, Houston, TX, USA) treated patients with defective mismatch repair (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer progressing on standard-of-care chemotherapeutics (including oxaliplatin) with nivolumab, observing 68.9% (51/74) patients on tumor control exceeding 12 weeks.[379]

Taken together, these studies reveal that ICD-inducing chemotherapy may provide immunological benefits to cancer patients that are accompanied by clinical activity, at least in some settings and especially in the context of immunotherapy. However, there are oncological indications in which the immunological and clinical effects of ICD-inducing

chemotherapeutics remain debatable. It will therefore be critical to identify the precise oncological indications and/or contexts in which the initiation of ICD by chemotherapy provides maximal therapeutic advantage. Current evidence points to breast carcinoma and colorectal carcinoma as putative settings in which ICD inducers can be favorably combined with immunotherapy for optimal clinical activity.

Ongoing clinical studies

When the current Trial Watch was redacted the ClinicalTrials.gov database (http://www.clinicaltrials.gov/) listed no less than 103 clinical studies that matched the following criteria: (1) they involved at least one *bona fide* ICD-inducing chemotherapeutic agent; (2) they were implemented in the context of immunomonitoring; and (3) they were initiated after July 2017 (when the latest Trial Watch on this topic was published)[20] (Figure 1, Tables 1 and 2).

In this context, multiple immunological biomarkers (including several biomarkers of ICD) are being examined (Figure 1a, Tables 1 and 2), including: (1) T-cell immunoprofiling, including assessment of T cell activation, suppression, phenotype, and exhaustion, as well as the quantification of tumor-infiltrating or circulating T cells; (2) quantification of immunosuppressive ligands (*e.g.* PD-L1) and/or their receptors (*e.g.* PD-1, TIM-3) in the tumor microenvironment; (3) assessment of humoral immune responses specific for TAAs; (4) quantification of blood-borne cytokines relevant for antitumor immunity, including (but not limited to) IL6, TNF, interferon beta 1 (IFNB1), and interferon gamma (IFNG); and (5) immunological assessment of CAR T cell number and activity (mostly in the circulation). In addition, multiple ongoing clinical studies are evaluating immunological biomarkers in an unbiased fashion by harnessing omics approaches such as bulk or single-cell RNA sequencing and multispectral immunohistochemistry. These clinical studies are expected to provide valuable information on genetic signatures or functional patterns that are associated with T cell activation and clinical activity downstream of ICD induction by chemotherapy, potentially leading to the development of prognostic or predictive biomarkers.

In line with previously documented trends,[20] breast carcinoma is one of the most common oncological indications for the use of ICD-inducing chemotherapy in combination with immunotherapy. In addition, multiple relatively nonselective "basket trials" have been initiated to test this therapeutic paradigm in cohorts of patients with various solid and hematological malignancies, including gastric and (gastro)esophageal cancer, myeloma, lymphoma, colorectal carcinoma and others (Figure 1b, Tables 1 and 2). Overall, clinical trials enrolling individuals with solid tumors are more common as compared to studies accruing patients with hematological malignancies. Although multiple reasons may underlie such an apparent discrepancy, it is tempting to speculate that overall disease incidence and responsiveness to standard-of-care treatment may play a prominent role in this scenario. Of note, ICD-inducing chemotherapeutics are being tested in subjects with hematological tumors most often in combination with CAR T cells, in order to maximize the clinical activity of the latter and/or to expand it to specific malignancies that are not particularly sensitive upfront, such as liver, lung, ovarian or prostate cancers (amongst others).[205]

Most of the clinical studies charted in this survey plan to administer cyclophosphamide, oxaliplatin, doxorubicin, epirubicin, or bortezomib, not only as archetypally on-label interventions but also as components of standard-of-care regimens (Figure 1c, Tables 1 and 2). In a limited fraction of cases, assessment of ICD induction by treatment is a primary objective of the study. Cyclophosphamide is often being used with the principal aim of inhibiting or depleting tumor-infiltrating or circulating T_{REG} cells (Table 2). Common combinatorial partners for ICD-eliciting chemotherapeutics include other (non-chemotherapeutic) ICD inducers such as RT, as well as chemotherapeutic agents that boost the immunogenic potential of cancer cells without inducing ICD,[380] such as melphalan, docetaxel or paclitaxel (Tables 1 and 2).

Moreover, in line with the contemporary immuno-oncology landscape, most oncologists are combining ICD-inducing chemotherapeutics with active or passive immunotherapy (Figure 1d, Tables 1 and 2). These generally consist of: (1) ICBs targeting PD-1, such as nivolumab, pembrolizumab, or SHR-1210; PD-L1, like atezolizumab, durvalumab, or avelumab; cytotoxic T-lymphocyte associated protein 4 (CTLA4; such as ipilimumab or tremelimumab; or killer cell lectin-like receptor C1 (KLRC1, best known as NKG2A, such as monalizumab; (2) immunostimulatory monoclonal antibodies such as CD40 agonistic antibodies; (3) tumor-targeting antibodies specific for CD38, CD20, epidermal growth factor receptor (EGFR), VEGFA, IL6, or ERBB2; (4) adoptively transferred T cells, including T cells engineered to express TAA-specific CARs; (5) immunostimulatory cytokines including GM-CSF, CSF3, IL2, IFNA or IRX-2 (a cell-free mixture of IL1B, IL2, IL6, IL8, IL10, IL12, TNF and IFNG);[205] (6) DC-based vaccines, amongst others (Figure 1d, Tables 1 and 2). These trends deviate from those we documented in the previous Trial Watch dealing with ICD-inducing chemotherapy,[20] in that ICBs[271,381,382] and CAR T cells[383-385] have substituted immunostimulatory cytokines as the most common combinatorial partner for ICD inducers. Overall, these trends mirror current expectations on the ability of various immunotherapeutic agents, notably ICBs, to achieve optimal efficacy once ICD is initiated by optimal chemotherapeutic regimens, especially in oncological indications that are poorly sensitive to either approach employed alone. Ongoing clinical studies will shed some light on this possibility, with specific reference to which precise ICD inducer should be employed in combination with which immunotherapeutic agent, for which indication and according to which schedule.

Concluding remarks

Multiple chemotherapeutic agents that induce *bona fide* ICD are presently approved by regulatory authorities worldwide for use in patients with a wide variety of malignant disorders (encompassing hematological and solid tumors). However, these chemotherapeutics have been largely developed (preclinically) in human xenografts established in highly immunodeficient mice[205] and translated to the clinic according to ever more

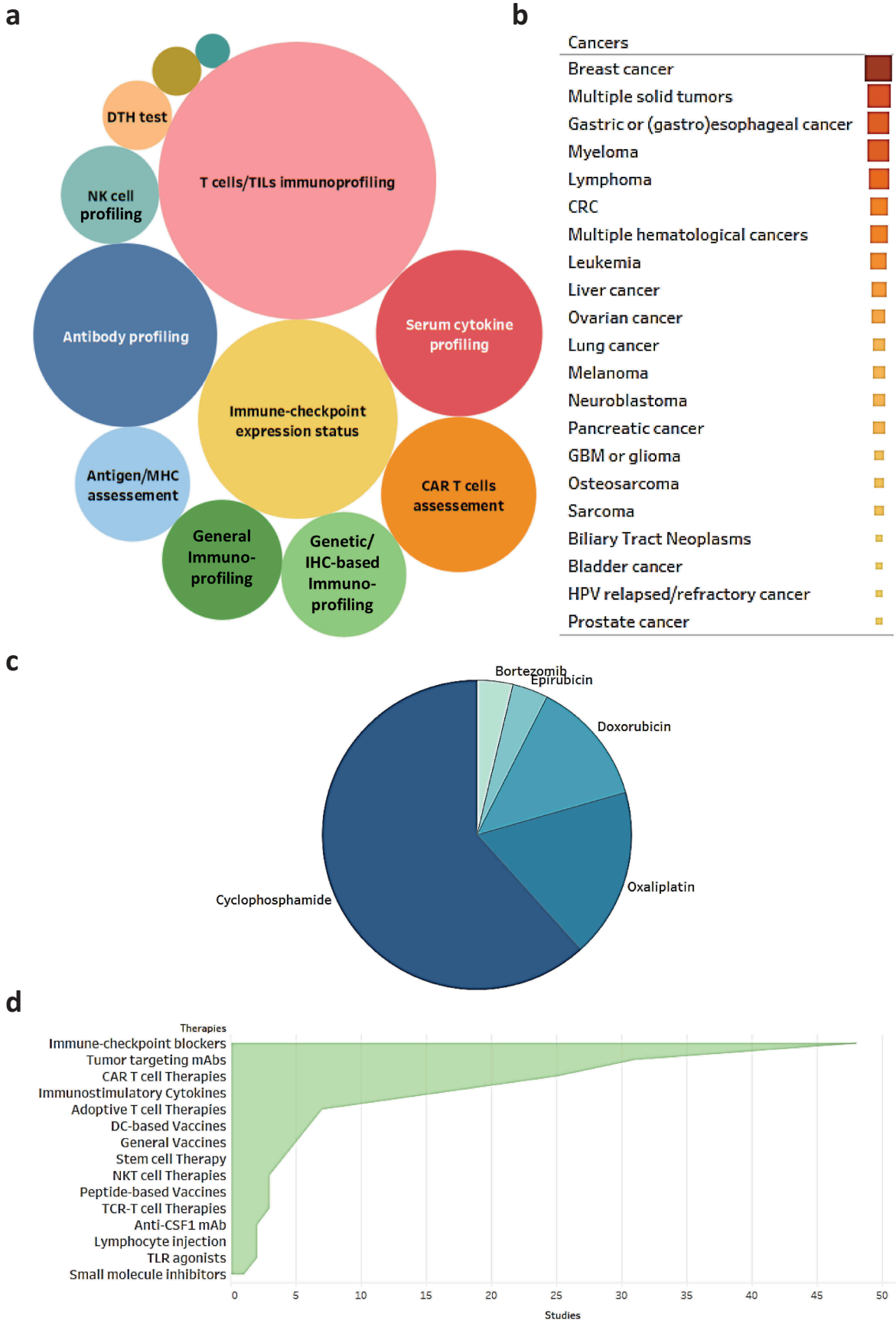

Figure 1. Current clinical studies testing immunogenic cell death (ICD)-inducing chemotherapy in combination with immunotherapy for oncological indications. Clinical studies were classified based on: (a) immunomonitoring approach, (b) indication, (c) ICD-inducing drug, and (d) combinatorial immunotherapy. CAR, chimeric antigen receptor; CRC, colorectal carcinoma; DC, dendritic cell; DTH, delayed-type hypersensitivity; GBM, glioblastoma; HPV, human papillomavirus; IHC, immunohistochemistry; NK, natural killer; NKT, natural killer T; TIL, tumor-infiltrating lymphocyte; TLR, toll-like receptor.

Table 1. Contemporary clinical studies assessing the therapeutic and immunological characteristics of ICD-inducing chemotherapies.

Drug	Indication(s)	Phase	Status	Notes	Ref.
Bortezomib	Multiple myeloma	II	Recruiting	Combined with GSK2857916, lenalidomide and/or dexamethasone	NCT03544281
		III	Recruiting	Combined with multimodal chemotherapy and daratumumab	NCT03742297
			Recruiting	Combined with multimodal chemotherapy, bb2121 autologous CAR-T cells and daratumumab	NCT03651128
	Plasma cell myeloma	II	Recruiting	Combined with ixazomib, dexamethasone and daratumumab	NCT03763162
Doxorubicin	Bladder cancer	I/II	Recruiting	Combined with multimodal chemotherapy, durvalumab and tremelimumab	NCT03549715
	Breast cancer	I	Withdrawn	Combined with glembatumumab vedotin	NCT03473691
		II	Recruiting	Combined with ipilimumab and nivolumab	NCT03409198
			Not yet recruiting	Combined with nivolumab	NCT03815890
		III	Recruiting	Combined with multimodal chemotherapy and atezolizumab	NCT03197935
		n.s.	Recruiting	Combined with cyclophosphamide, taxol and alpha lipoic acid	NCT03908528
	Lymphoma	I	Recruiting	Combined with multimodal chemotherapy, RO7082859, obinutuzumab, rituximab and tocilizumab	NCT03467373
		II	Not yet recruiting	Combined with multimodal chemotherapy, nivolumab and rituximab	NCT03749018
	Neuroblastoma	II	Recruiting	Combined with dinutuximab, sargramostim, ASCT and EBRT	NCT03786783
	Osteosarcoma	II	Not yet recruiting	Combined with multimodal chemotherapy	NCT03390946
			Recruiting	Combined with APX005M	NCT03719430
	Ovarian cancer	II	Not yet recruiting	Combined with paclitaxel, gemcitabine, and pembrolizumab	NCT03539328
		III	Recruiting	Combined with carboplatin, niraparib and atezolizumab	NCT03598270
	Renal medullary carcinoma	II	Recruiting	Combined with multimodal chemotherapy	NCT03587662
Epirubicin	Breast cancer	II	Recruiting	Combined with nab-paclitaxel, cyclophosphamide and pembrolizumab	NCT03289819
			Recruiting	Combined with multimodal chemotherapy and pembrolizumab	NCT03515798
			Not yet recruiting	Combined with multimodal chemotherapy, trastuzumab, pertuzumab, atezolizumab and trastuzumab	NCT03894007
	Small cell lung cancer	II	Not yet recruiting	Combined with SHR-1210	NCT03755115
	Colorectal cancer	I	Recruiting	Combined with fluorouracil, leucovorin and CYAD-101	NCT03692429
		II	Recruiting	Combined with nivolumab, 5-fluorouracil and leucovorin	NCT03388190
			Active, not yet recruiting	Combined with 5-fluorouracil, cetuximab and avelumab	NCT03174405
			Recruiting	Combined with 5-fluorouracil, levoleuucovorin, bevacizumab and atezolizumab	NCT03698461
			Recruiting	Combined with surgical resection, 5-fluorouracil, leucovorin and pembrolizumab	NCT03844750
			Not yet recruiting	Combined with surgical resection, capecitabine and pembrolizumab	NCT03984578
		III	Recruiting	Combined with fluorouracil, leucovorin calcium and bevacizumab	NCT02997228
	Gastric, esophageal and/or gastroesophageal cancer	I	Recruiting	Combined with surgical resection, fluorouracil and atezolizumab	NCT03784326
		I/II	Withdrawn	Combined with surgical resection, radiation, fluorouracil and monalizumab	NCT03307941
		II	Not yet Recruiting	Combined with capecitabine	NCT03764553
		II	Recruiting	Combined with multimodal chemotherapy and atezolizumab	NCT03421288
			Recruiting	Combined with fluorouracil, leucovorin and zolbetuximab	NCT03505320
			Recruiting	Combined with fluorouracil, leucovorin, nivolumab and trastuzumab	NCT03409848
		II	Recruiting	Combined with fluorouracil, leucovorin and pembrolizumab	NCT03488667
	Gastrointestinal neoplasms	I/II	Recruiting	Combined with capecitabine and IMU-131	NCT02795988
	Lymphoma	I	Recruiting	Combined with gemcitabine, atezolizumab and rituximab	NCT03321643
		II/III	Recruiting	Combined with gemcitabine, nivolumab and rituximab	NCT03366272
	Pancreatic cancer	III	Recruiting	Combined with multimodal chemotherapy and anti-PDCD1 antibody	NCT03977272
			Recruiting	Combined with multimodal chemotherapy and anti-PDCD1 antibody	NCT03983057

ASCT, Autologous hematopoietic stem cell transplantation; CAR, chimeric antigen receptor; EBRT, external beam radiation therapy; NS, not specified.

obsolete concept of maximum tolerated dose (MTD), in the absence of any immunomonitoring.[386] Thus, ICD inducers are currently employed according to doses and treatment schedules that ensure maximal cytotoxicity in the context of limited side effects on normal tissues, but do not consider potential inputs from the host immune systems. In line with this notion, two of the most common side effects of chemotherapy are neutropenia and lymphopenia, implying that the ICD inducers employed according to current standards are toxic to immune cells and favor (at least some degree of) immunodeficiency.[119,154,387–389]

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

Indication(s)	Phase	Status	Notes	Ref.
B cell lymphoma	II	Recruiting	Combined with pembrolizumab and DPX-survivax	NCT03349450
Breast cancer	I	Withdrawn	Combined with doxorubicin and glembatumumab vedotin	NCT03473691
	I/II	Recruiting	Combined with SV-BR-GM, pembrolizumab and interferon inoculation	NCT03328026
	II	Recruiting	Combined with doxorubicin, nivolumab and ipilimumab	NCT03409198
		Not yet recruiting	Combined with multimodal chemotherapy, pertuzumab, atezolizumab, trastuzumab emtansine and surgical resection	NCT03894007
		Recruiting	Combined with epirubicin, nab-paclitaxel and pembrolizumab	NCT03289819
		Recruiting	Combined with multimodal chemotherapy and pembrolizumab	NCT03515798
	III	Recruiting	Combined with multimodal chemotherapy and atezolizumab	NCT03197935
	NA	Recruiting	Combined with doxorubicin and alpha lipoic acid	NCT03908528
Gastroesophageal cancer	I/II	Recruiting	Combined with pembrolizumab and IRX-2	NCT03918499
Glioma	I	Recruiting	Combined with fludarabine, temozolomide, TTRNA-DC vaccine with GM-CSF, TTRNA-xALT, autologous HSC and Td vaccine	NCT03396575
		Withdrawn	Combined with fludarabine, GINAKIT cells	NCT02439788
	I/II	Recruiting	Combined with surgical resection and lysate-loaded dendritic cell vaccine	NCT03879512
	II	Recruiting	Combined with multimodal chemotherapy, ASCT, EBRT, sargrasmostim, dinutuximab and aldesleukin	NCT03786783
Hematological malignancies	I	Recruiting	Combined with multimodal chemotherapy, total body irradiation and cord blood stem cells	NCT03885947
		Not yet recruiting	Combined with fludarabine and CAR-aNKT cells	NCT03774654
	I/II	Recruiting	Combined with fludarabine, ALLO-501 and ALLO-647	NCT03939026
		Withdrawn	Combined with GM-CSF and TAPA-pulsed DC vaccine	NCT02223312
		Active, not recruiting	Combined with GM-CSF and TAPA-pulsed DC vaccine	NCT02709993
	II	Recruiting	Combined with fludarabine and axicabtagene ciloleucel	NCT03761056
		Recruiting	Combined with multimodal chemotherapy, nivolumab and rituximab	NCT03749018
	n.s	Recruiting	Combined with cord blood transplantation	NCT03802773
Leukemia	I	Recruiting		NCT03241940
		Recruiting	Combined with fludarabine phosphate and CD19/CD22 CAR-T cell therapy	NCT03233854
		Not yet recruiting	Combined with fludarabine, CD19 CAR-T cells and PD-1 KO engineered T cells	NCT03298828
		Recruiting	Combined with tacrolimus, allogeneic HSC transplantation, filgrastim and total marrow irradiation	NCT03467386
		Recruiting	Combined with fludarabine and omnImmune	NCT03790072
		Recruiting	Combined with leukapheresis, fludarabine and huJCAR014	NCT03103971
		Recruiting	Combined with fludarabine and anti-CD19/CD22 CAR-T cells	NCT03919526
	I/II	Recruiting	Combined with fludarabine and KTE-X19	NCT03624036
	III	Recruiting	Combined with multimodal chemotherapy, TBRT, G-CSF and peripheral blood transplant	NCT03480360
	NA	Recruiting	Combined with multimodal chemotherapy, thymoglobuline, cyclosporine, lymphocyte injection of prophylactic donor and transfusion graft of peripheral stem cells	NCT03035422
Liver cancer	I	Recruiting	Combined with nivolumab and IRX-2	NCT03655002
		Active, not recruiting	Combined with fludarabine and GAP-T cells	NCT02932956
	I/II	Recruiting	Combined with IMA970A and CV8102	NCT03203005
		Recruiting	Combined with fludarabine and MUC-1 CAR-T cells	NCT03633773
	II/III	Recruiting	Combined with iNKT cells and human recombinant IL-2	NCT04011033
Lung cancer	I	Recruiting	Combined with radiation, G-CSF and PBMCs	NCT02579005
		Not yet recruiting	Combined with fludarabine and PD-L1 CAR-T cells	NCT03330834
Melanoma	I	Recruiting	Combined with fludarabine, IL-2, nivolumab and adoptive transfer of autologous TILs	NCT03475134
		Recruiting	Combined with fludarabine, autologous TILs, aldesleukin, nivolumab and ipilimumab	NCT03526185
Myeloid malignancies	II	Not yet recruiting	Combined with multimodal chemotherapy cyclosporine, tacrolimus and HSC transplantation	NCT03270748
Myeloma	I	Recruiting	Combined with fludarabine and SLAMF7 CAR-T therapy	NCT03710421
		Recruiting	Combined with fludarabine, gamma secretase inhibitor LY3039478, BCMA specific CAR-T cells	NCT03502577
		Recruiting	Combined with fludarabine, BCMA CART and huCAR-T19,	NCT03549442
		Recruiting	Combined with fludarabine and CAR-BCMA T cells	NCT03716856
	NA	Recruiting	Combined with fludarabine and CAR-BCMA T cells	NCT03380039
Osteosarcoma	II	Recruiting	Combined with fludarabine, fludarabine phosphate, aldesleukin and TILs	NCT03449108
Ovarian cancer	I	Recruiting	Combined with decitabine, aldesleukin, genetically engineered NY-ESO 1 specific T lymphocytes	NCT03017131
		Recruiting	Combined with fludarabine and anti-meso CAR-T cells	NCT03799913
	II	Withdrawn	Combined with anti-CSF1 mAb PD-0360324	NCT02948101
Pancreatic cancer	I	Recruiting	Combined with GVAX, pembrolizumab and IMC-CS4	NCT03153410

(*Continued*)

Table 2. (Continued).

Indication(s)	Phase	Status	Notes	Ref.
Prostate cancer	I	Recruiting	Combined with fludarabine, fludarabine phosphate and autologous anti-PSCA-CAR-T-cells	NCT03873805
Sarcoma	II	Withdrawn	Combined with pembrolizumab, GSK3377794 and fludarabine	NCT03697824
Solid and hematological malignancies	I/II	Recruiting	Combined with CAR-T cell therapy	NCT03638206
Solid malignancies	I	Withdrawn	Combined with GM-CSF and TAPA-pulsed DC vaccine	NCT02705703
		Recruiting	Combined with RT, aspirin, nivolumab and ipilimumab	NCT03728179
	I/II	Recruiting	Combined with fludarabine and PD-1 expressing mesoCAR-T cells	NCT03615313
		Active, not recruiting	Combined with imiquimod topical cream and TAPA-pulsed DC vaccine	NCT02224599
	II	Recruiting	Combined with pembrolizumab and DPX-survivax	NCT03836352

ALLO, allogeneic; ASCT, autologous hematopoietic stem cell transplantation; CAR-aNKT cells, CAR allogeneic natural killer T cells; CAR, chimeric antigen receptor; DC, dendritic cell; CSF-1, colony stimulating factor 1; EBRT, external beam radiation therapy; GAP, glypican 3; GINAKIT cells, GD2-specific CAR- and interleukin 15-expressing autologous NKT cells; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSC, hematopoietic stem cell; IL, interleukin; mAb, monoclonal antibody; Meso-CAR-T cells, mesothelin-redirected chimeric antigen receptor T cell; iNKT cells, invariant NKT cells; KO, knock-out; NA, not applicable; NS, not specified; PBMC, peripheral blood mononuclear cell; PSC, pluripotent stem cells; RT, radiotherapy; TAPA, tumor-associated peptide antigen; TBRT, total body RT; TD, Tetanus-Diphtheria; TIL, tumor-infiltrating lymphocyte; TTRNA, total tumor RNA; xALT, autologous lymphocyte transfer.

Even beyond the induction of ICD, several chemotherapeutics have been shown to elicit on-target or off-target immunostimulatory doses, especially when employed at low doses and/or according to revisited treatment protocols.[390–393] As we stand at the apex of the immunotherapy revolution, the immunomodulatory effects of traditional anticancer agents, including chemotherapy, RT and others, can no longer be ignored. Thus, preclinical studies based on immunocompetent models followed by well-designed and highly immunomonitored clinical trials[394] are urgently awaited to identify new doses and treatment schedules that enable maximal immunostimulation by chemotherapy and hence set an optimal stage for combination with ICBs and other forms of immunotherapy.

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Disclosure of potential conflicts of interest

DDR received financial assistance from Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca, Philips and Olink. He is also in the advisory board of Bristol-Myers Squibb, Celgene, Merck/Pfizer, Roche/Genentech, AstraZeneca, MSD and Seattle Genetics. DDR has been involved in advisory capacity (non-financial) with NOXXON and MOLOGEN. Other authors have no particular conflict of interests to declare with relation to this particular manuscript. LG provides remunerated consulting to Astra Zeneca, Boehringer Ingelheim, Inzen, OmniSEQ, and the Luke Heller TECPR2 Foundation, and receives research funding from Lytix, Phosplatin and Sotio.

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