Trial Watch: Immunogenic cell death inducers for anticancer chemotherapy

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Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; DAMP, damage-associated molecular pattern; EGFR, epidermal growth factor receptor; EOX, epirubicin plus oxaliplatin plus capecitabine; ER, endoplasmic reticulum; FDA, Food and Drug Administration; FOLFIRINOX, folinic acid plus 5-fluorouracil plus oxaliplatin; GM-CSF, granulocyte-macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; ICD, immunogenic cell death; mAb, monoclonal antibody; MM, multiple myeloma; NHL, non-Hodgkin’s lymphoma; NSCLC, non-small cell lung carcinoma; TACE, transcatheter arterial chemoembolization; XELOX, capecitabine plus oxaliplatin.

Introduction

Ten years ago, we were the first to introduce the term “immunogenic cell death” (ICD) to indicate a functionally peculiar type of apoptosis that — in immunocompetent hosts — can elicit an immune response against dead cell-associated antigens in the absence of any adjuvant.1,2 Indeed, the subcutaneous inoculation of cancer cells succumbing to doxorubicin (an anthracycline approved by regulatory agencies for the treatment of several tumors, see below) in vitro was sufficient to protect syngeneic mice against a re-challenge with malignant cells of the same type, but not with cancer cells of distinct origin.2 Subsequent studies by us and others identified various mechanisms that underlie not only the ability of a specific stimulus to trigger bona fide ICD as opposed to a non-immunogenic instance of apoptosis, but also the capacity of the host to detect ICD and hence mount a therapeutically relevant immune response against dying cells.1,3,6

Schematically, ICD itself relies on the coordinated emission of a series of damage-associated molecular patterns (DAMPs),7,12 including the exposure of endoplasmic reticulum (ER) chaperones on the cell surface, the secretion of ATP and the release of the non-histone chromatin-binding protein high mobility group box 1 (HMGB1),13-20 and immunostimulatory cytokines, such as type I interferons.21 When emitted in the correct spatiotemporal pattern,22-24 such DAMPs recruit antigen-presenting cells, including dendritic cells, to the site of ICD and activate them to

The term “immunogenic cell death” (ICD) is now employed to indicate a functionally peculiar form of apoptosis that is sufficient for immunocompetent hosts to mount an adaptive immune response against dead cell-associated antigens. Several drugs have been ascribed with the ability to provoke ICD when employed as standalone therapeutic interventions. These include various chemotherapeutics routinely employed in the clinic (e.g., doxorubicin, epirubicin, idarubicin, mitoxantrone, bleomycin, bortezomib, cyclophosphamide and oxaliplatin) as well as some anticancer agents that are still under preclinical or clinical development (e.g., some microtubular inhibitors of the epothilone family). In addition, a few drugs are able to convert otherwise non-immunogenic instances of cell death into bona fide ICD, and may therefore be employed as chemotherapeutic adjuvants within combinatorial regimens. This is the case of cardiac glycosides, like digoxin and digitoxin, and zoledronic acid. Here, we discuss recent developments on anticancer chemotherapy based on ICD inducers.

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Engulf dead cell-associated antigens, process and present them to CD4+ and CD8+ T lymphocytes in the context of co-stimulatory signals, resulting in the priming of a robust, antigen-specific immune response. In line with this notion, the ability of cancer cells undergoing ICD to elicit a protective immune response upon inoculation to syngeneic mice is abrogated: (1) when the molecular pathways underlying the emission of the abovementioned DAMPs are pharmacologically or genetically inhibited in malignant cells,13,32,33 as well as (2) in mice affected by relatively generalized forms or immunodeficiency or lacking specific components of the DAMP-sensing machinery, such as Toll-like receptor 4 (Tlr4) or type I interferon (α and β) receptor 1 (Ifnar1). A more detailed description of these signal transduction pathways and cellular circuitries goes beyond the scope of this Trial Watch and can be found in several recent reviews.1,3,4

Importantly, some – but not all – cell death inducers are capable of eliciting ICD,36 and this property cannot be anticipated by structural or functional considerations.3,36-38 Indeed, while cisplatin and oxaliplatin both exert cytostatic/cytotoxic effects as they induce inter- and intra-strand DNA adducts,39-42 only the latter triggers bona fide ICD as it provokes a pre-mortem ER stress response.43,44 Thus, although assays for the detection of surrogate ICD markers are available,45 the gold standard approach for determining whether a cytotoxic intervention provokes bona fide ICD still relies on vaccination experiments involving murine cancer cells and syngeneic, immunocompetent mice.3 In addition, the ability of a specific stimulus to induce ICD can be inferred by testing its antineoplastic effects on tumors established in immunocompetent versus immunodeficient hosts.3 However, this approach cannot replace vaccination experiments as several therapeutic agents mediate optimal antineoplastic effects in immunocompetent hosts only as they have an off-target immunostimulatory activity but do not induce ICD.46-48

So far, only a few stimuli have been ascribed with the ability to trigger ICD, encompassing both chemical and physical agents.3,36 Interestingly, such bona fide ICD inducers include various anticancer chemotherapeutics that have been successfully employed in the clinic for several years (Table 1), like (1) doxorubicin, an anthracycline approved by the US Food and Drug Administration (FDA) for the treatment of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), breast carcinoma, gastric cancer, lymphoma, multiple myeloma (MM), neuroblastoma, ovarian carcinoma, small cell lung carcinoma, soft tissue and bone sarcomas, thyroid carcinoma, transitional cell bladder carcinoma and Wilms’ tumor;4,49 (2) epirubicin, an anthracycline licensed for use in breast carcinoma patients;4,49 (3) idarubicin, an anthracycline currently employed for the treatment of AML;19,49 (4) mitoxantrone, an anthrancenedione licensed for use in individuals with AML, breast carcinoma, non-Hodgkin’s lymphoma (NHL) and prostate carcinoma;2,49 (5) bleomycin, a glycopeptide antibiotic commonly employed as a palliative treatment for Hodgkin’s lymphoma, NHL, penile cancer, testicular cancer, and squamous carcinomas of the head and neck, cervix and vulva;50 (6) bortezomib, a proteasomal inhibitor approved for use in subjects with MM and mantle cell lymphoma;17,51,52 (7) cyclophosphamide, an alkylating agent nowadays employed for the treatment of ALL, AML, chronic lymphocytic leukemia, breast carcinoma, chronic myeloid leukemia (CML), lymphoma, MM, mycosis fungoides, neuroblastoma, ovarian carcinoma and retinoblastoma;53 and (8) oxaliplatin, a platinum derivative approved for use in combination with 5-fluorouracil and folinic acid for the therapy of advanced colorectal carcinoma.40,44,54 Moreover, at least in some cell types, ICD can be provoked by patupilone, an experimental microtubular inhibitor of the epothilone family,55-57 and by 7A7, a monoclonal antibody (mAb) targeting the murine epidermal growth factor receptor (EGFR).58,59 However, for the reasons mentioned above, FDA-approved epothilones (i.e., ixabepilone, which is licensed for the treatment of breast carcinoma)60 and EGFR-targeting mAbs (i.e., cetuximab and panitumumab, which are currently employed for the treatment of head and neck cancer and colorectal carcinoma)61-63 may not share this ability with patupilone and 7A7, respectively. Finally, it should be noted that some FDA-approved agents such as digoxin and digitoxin (which are licensed for the treatment of various cardiac disorders),64 as well as zoledronic acid (which is commonly employed for the treatment of MM or hypercalcemia and bone lesions of oncological origin),65 are very efficient at boosting the immunogenicity of otherwise non-immunogenic instances of cell death, although they are unable to elicit ICD per se.66-69 These agents may be particularly relevant for the development of combinatorial chemotherapeutic regimens that actively engage the host immune system against malignant cells.

In the context of our monthly series,70-72 this Trial Watch discusses recent developments on anticancer chemotherapy with ICD inducers. In line with this notion, irradiation and photodynamic therapy, 2 additional interventions that trigger bona fide ICD and are commonly employed for the treatment of several neoplasms,73-82 will not be considered further here.

**Update on the Development of ICD-Inducing Chemotherapeutics**

**Completed clinical trials.** On 2015, Jan 6th querying PubMed with the string “cancer AND (patients OR trial) AND (doxorubicin OR epirubicin OR idarubicin OR mitoxantrone OR bortezomib OR bleomycin OR cyclophosphamide OR oxaliplatin)” returned 48,701 entries, some 2,000 of which were published since the submission of our latest Trial Watch dealing with ICD-inducing chemotherapeutics (January 2014).33 This figure obviously covers a number of preclinical research papers, review articles and editorials that is difficult to quantify with precision. Moreover, in a significant fraction of the clinical articles included in this figure, doxorubicin, epirubicin, idarubicin, mitoxantrone, bortezomib, bleomycin, cyclophosphamide and oxaliplatin are employed as part of standard chemotherapeutic regimens, in on-label indications (source [http://www.ncbi.nlm.nih.gov/pubmed]). Among the clinical studies testing the safety and efficacy of ICD-inducing chemotherapeutics employed as
off-label indications, we would like to highlight the works of: (1) Butts and collaborators (Cross Cancer Institute; Edmonton, Canada), who reported that the therapeutic activity of a tumor-targeting vaccine administered to non-small cell lung carcinoma (NSCLC) patients previously receiving cyclophosphamide-based chemotherapy may be influenced by the administration schedule (<i>vs.</i> sequential <i>vs.</i> concurrent) of the latter; (2) Roulstone and colleagues (The Institute of Cancer Research; London, UK), who demonstrated that the pre-administration of high-dose cyclophosphamide to individuals with solid tumors is unable to prevent the development of humoral, neutralizing immunity against oncolytic reoviruses; (3) Bazzola and co-authors (Azienda Istituti Ospitalieri di Cremona; Cremona, Italy), who tested metronomic cyclophosphamide combined with letrozole (a non-steroidal aromatase inhibitor) and sorafenib (a multi-targeted kinase inhibitor) in primary breast cancer patients, with promising results; (4) Lutz et al. (The Sidney Kimmel Cancer Center; Baltimore, MD, US), who demonstrated that low-dose cyclophosphamide converts the tolerogenic microenvironment of pancreatic adenocarcinoma into an immunogenic one, boosting the clinical activity of an irradiated, granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting, allogeneic vaccine; (5) Zheng and collaborators (Johns Hopkins University School of Medicine; Baltimore, MD, US), who – along similar lines – proved the capacity of low-dose cyclophosphamide to support the therapeutic activity of a vaccine composed of irradiated, allogeneic human colorectal cancer cells and GM-CSF-producing bystander cells; (6) Hong and colleagues (University of Ulsan College of Medicine; Seoul, South Korea), who reported that, as compared to adjuvant folic acid and 5-fluorouracil, adjuvant FOLFOX (folic acid plus 5-fluorouracil plus oxaliplatin) is associated with an improved disease-free survival among patients with locally advanced rectal cancer after preoperative chemoradiotherapy and total mesorectal excision; (7) Noh and co-workers (Yonsei University College of Medicine; Seoul, South Korea) and Yamada et al. (National Cancer Center Hospital; Tokyo, Japan), who demonstrated the clinical efficacy of oxaliplatin in combination with capecitabine or S-1, respectively, in patients with gastric carcinoma; (8) Oettle and collaborators (Charité Universitätsmedizin; Berlin, Germany) and O’Reilly and colleagues (Memorial Sloan-Kettering Cancer Center, New York, NY, US), who provided evidence in support of the therapeutic activity of oxaliplatin as part of neoadjuvant chemotherapeutic regimens for patients with refractory or chemotherapy-naïve pancreatic carcinoma; (9) Straus and co-authors (Memorial Sloan-Kettering Cancer Center, New York, NY, US), who reported that the administration of liposomal doxorubicin to subjects with cutaneous T-cell lymphoma is associated with an objective responses rate that is among the highest ever reported for similar patient cohorts, while the subsequent application of bexarotene (a retinoid) has negligible effects on response rate and duration.

**Preclinical and translational advances.** Within the abundant preclinical literature that has been published during the last 13 months on ICD-inducing chemotherapeutics, we found of particular interest the works of: (1) Pallach and colleagues (Massachusetts Institute of Technology; Cambridge, MA, US), who demonstrated that cyclophosphamide induces an acute secretory phenotype in malignant cells, stimulating the release of various immunostimulatory cytokines that promotes a macrophage-driven, tumor-targeting innate immune response; (2) Tavora and collaborators (Barts Cancer Institute; London, UK), who showed that the inhibition of protein tyrosine kinase 2 (PTK2, also known as FAK) in the endothelial tumor...
compartment sensitizes cancer cells to doxorubicin-based chemotherapy; 110 (3) Cottini and co-authors (Harvard Medical School; Boston, MA, US), who mechanistically involved the Hippo co-activator Yes-associated protein 1 (YAP1) in the response of hematological tumor targets to DNA-damaging agents, including doxorubicin; 112, 115 (4) Ichikawa et al. (Northwestern University School of Medicine; Chicago, Illinois, US) and Liu and colleagues (Harvard Medical School; Boston, MA, US), who demonstrated that the accumulation of iron within mitochondria and consequent alterations in the activity of enzymes of the Krebs’ cycle contribute to the cardiotoxicity of doxorubicin; 119, 120 (5) Vaud and co-authors (Gustave Roussy Cancer Campus; Villejuif, France) and lida and collaborators (National Cancer Institute; Frederick, MD, US), who proved that specific changes in the gut microbiota induced by cyclophosphamide and oxaliplatin are responsible for their full-blowen therapeutic activity as they favor the elicitation of anticancer immune responses; 125-127 (6) Morton et al. (Massachusetts Institute of Technology; Cambridge, MA, US), who developed a nanoparticle-based chemotherapy delivery system that allows for the finely controlled release of up to 2 drugs, a vehicle that may be particular relevant for promoting ICD; 128 (7) Sistigu and co-authors (Gustave Roussy Cancer Campus; Villejuif, France), who demonstrated that the release of type I interferons from dying cancer cells is required for the host immune system to perceive such event as immunogenic and mount an adaptive immune response against dead cell-associated antigens; 21 and Triulzi and collaborators (Fondazione IRCCS Istituto Nazionale dei Tumori; Milan, Italy), who identified a role for serpin peptidase inhibitor, clade B (ovalbumin), member 5 (SERPINB5, best known as maspin) in the establishment of a collagen-enriched tumor microenvironment contributing to the resistance of breast carcinomas to doxorubicin.

Recently initiated clinical trials. Since the submission of our latest Trial Watch dealing with this topic (January 2014), 33 no less than 374 clinical studies involving ICD-inducing chemotherapeutics have been initiated (doxorubicin = 75 studies; epirubicin = 23 studies; idarubicin = 18 studies; mitoxantrone = 14 studies; bleomycin = 8 studies; bortezomib = 25 studies; cyclophosphamide = 128 studies; oxaliplatin = 83 studies). In the vast majority of these trials (250 studies), however, ICD inducers are employed as on-label therapeutic interventions, most often as (part of) the gold standard chemotherapeutic regimen given to the control arm of the study. These studies will not be discussed further here. In addition, no less than 125 clinical trials have recently been initiated to test the therapeutic profile of doxorubicin (14 studies), epirubicin (8 studies), idarubicin (3 studies), mitoxantrone (4 studies), bleomycin (2 studies), bortezomib (7 studies), cyclophosphamide (34 studies), and oxaliplatin (53 studies) employed as off-label chemotherapeutic interventions (source http://clinicaltrial.gov/).

In particular, doxorubicin is being tested in subjects with breast carcinoma, receive the drug in pegylated liposomal formulation combined with carboplatin, a cisplatin derivative approved for the treatment of NSCLC and ovarian carcinoma, and paclitaxel, a microtubular inhibitor often employed in women with breast carcinoma (NCT02315196); (2) hepatocellular carcinoma (HCC), most often in the context of transcatheter arterial chemoembolization (TACE) (NCT02038296; NCT02070419; NCT02112656; NCT02125396; NCT02141906; NCT02147301; NCT02149771; NCT02182687; NCT02240771); (3) hepatic metastases from other solid tumors, again in liposomal formulation (NCT02181075); (4) melanoma, who receive doxorubicin as a standalone therapeutic intervention (NCT02094872); (5) MM, in the context of a multimodal chemoinmunotherapeutic regimen involving the immunomodulatory drug talidomide (NCT02128230); and (6) peritoneal carcinomatosis, who are treated with doxorubicin plus cisplatin as pressurized intraperitoneal aerosol chemotherapy (NCT02320448). The therapeutic profile of epirubicin is being evaluated in patients with bladder carcinoma, who receive epirubicin as a standalone intravesical chemotherapeutic (NCT02214602); (2) gastric or gastroesophageal carcinoma, invariably as part of the so-called EOX regimen (epirubicin plus oxaliplatin plus capecitabine) (NCT02128243; NCT02177552; NCT02158988); (3) HCC, in the context of TACE (NCT02220088); (4) MM, as part of induction or tumor-reduction chemotherapy followed by stem cell mobilization and consolidation chemotherapy (NCT02288741); and (5) soft tissue sarcoma, who receive epirubicin in combination with conventional chemotherapeutics of trabectedin, a macrophage-repolarizing agent (NCT02050919; NCT02066675). The clinical activity of idarubicin is being assessed in individuals with (1) CML, who receive idarubicin plus cladribine and cytarabine (2 inhibitors of nucleotide metabolism currently approved for the treatment of various forms of leukemia) (NCT02115295); (2) myelodysplastic syndrome, in the context of cytarabine-based chemotherapy and donor lymphocyte infusion (NCT02046122); and (3) HCC, who receive idarubicin in the form of drug-loaded microbeads (NCT02185768). Mitoxantrone is being tested in patients with: (1) ALL, in the context of combinatorial chemo-therapeutic regimen (NCT02101853; NCT02303821); (2) lymphoma, who are treated with mitoxantrone as a single agent (NCT02131688); and (3) various solid tumors, who also receive mitoxantrone as standalone therapeutic intervention (NCT02043756). The clinical activity of bleomycin is being investigated in subjects with: (1) HCC, in the context of electrochemotherapy (NCT02291133); and (2) non-seminomatous malignant germ cell tumors, who receive bleomycin in combination with cisplatin-based chemotherapy (NCT02104986). The efficacy of bortezomib is being assessed in individuals with (1) various hematological malignancies, who often receive bortezomib as part of multimodal chemo- or immunotherapeutic regimens (NCT02037256; NCT02112916; NCT02208037; NCT02312102); (2) neuroblastoma, who are treated with bortezomib plus difluoromethylornithine (a hitherto experimental inhibitor of polyamine biosynthesis) (NCT02139397); and (3) various solid tumors, who receive bortezomib as standalone therapeutic agent or combined with standard chemotherapy (NCT02211755; NCT02220049) (Table 2).
The efficacy of cyclophosphamide as an off-label therapeutic intervention is being evaluated in subjects with: (1) colorectal carcinoma, often in the context of capecitabine-based chemotherapy \(^{150,151}\) (NCT02271464; NCT02280694; NCT02298946); (2) medulloblastoma, who often are treated with cyclophosphamide plus a chemotherapeutic regimen based on cisplatin \(^{150,151}\) (NCT02271464; NCT02298946); (3) melanoma, to whom cyclophosphamide is administered as part of a lymphodepleting treatment followed by adoptive cell transfer \(^{152-154}\) (NCT02062359; NCT02111863; NCT02278887); NSCLC, as part of various chemotherapeutic regimens \(^{150,151}\) (NCT02049151; NCT02117024; NCT02133196; NCT022187367); (4) soft tissue sarcoma, as part of multimodality chemoimmunotherapy \(^{150,151}\) (NCT02059850; NCT02234050; NCT02306161); as well as breast carcinoma \(^{150,151}\) (NCT02276300), gastric carcinoma \(^{150,151}\) (NCT02276300; NCT02317471), ependymoma \(^{150,151}\) (NCT02265770), osteosarcoma \(^{150,151}\) (NCT02273583), pancreatic carcinoma \(^{150,151}\) (NCT02243371), prostate carcinoma \(^{150,151}\) (NCT02234921), testicular cancer \(^{150,151}\) (NCT02161692), germ cell tumors \(^{150,151}\) (NCT02161692), rhabdoid malignancies \(^{150,151}\) (NCT02114229), and various other solid tumors \(^{150,151}\) (NCT02054104; NCT02070406; NCT02096614; NCT02181075; NCT02111863; NCT02278887).
| Indication(s)                  | Phase | Status           | Notes                                                                                     | Ref.          |
|-------------------------------|-------|------------------|-------------------------------------------------------------------------------------------|---------------|
| Breast carcinoma              | I     | Recruiting       | Combined with GM-CSF, a peptide-based anticancer vaccine and imiquimod                    | NCT02276300  |
| Gastric carcinoma             |       |                  |                                            |               |
| Colorectal carcinoma          | I     | Recruiting       | Combined with a checkpoint blocker and RT                                                 | NCT02298946  |
| Colorectal carcinoma          | II    | Recruiting       | As metronomic regimen combined with bevacizumab, capecitabine and FOLFOXIRI               | NCT02271464  |
| Colorectal carcinoma          |       | Not yet recruiting| Combined with capecitabine, celecoxib and methotrexate                                   | NCT02280694  |
| Ependymoma                    | II/III| Not yet recruiting| Combined with conventional chemotherapy and RT                                           | NCT02265770  |
| Gastric carcinoma             | I/I   | Recruiting       | Combined with a HSP-based vaccine, oxaliplatin and S-1                                    | NCT02317471  |
| Germ cell tumors              | II    | Completed        | Combined with cisplatin, etoposide and bleomycin ± carboplatin                            | NCT02161692  |
| Testicular cancer             | II    | Recruiting       | Combined with a HSP-based vaccine, oxaliplatin and S-1                                    | NCT02212574  |
| Medulloblastoma               | II/III| Recruiting       | Combined with conventional chemotherapy and RT                                           | NCT02066220  |
| Melanoma                      | II    | Recruiting       | As part of a conditioning regimen followed by adoptive cell transfer-based immunotherapy| NCT02062359  |
| NSCLC                         | II    | Recruiting       | As metronomic regimen combined with a cancer cell-based vaccine                           | NCT02117024  |
|                              | III   | Active, not recruiting | Combined with a conditioning regimen followed by adoptive cell transfer-based immunotherapy | NCT02133196  |
|                              |       | Not yet recruiting| Combined with conventional chemotherapy and RT                                           | NCT02049151  |
| Germ cell tumors              |       |                  |                                            |               |
| Osteosarcoma                  | II    | Recruiting       | Combined with methotrexate                                                                | NCT02273583  |
| Pancreatic carcinoma          | II    | Recruiting       | Combined with multimodal immunotherapy                                                   | NCT02243371  |
| Prostate cancer               | I     | Recruiting       | Combined with imiquimod and a peptide-based anticancer vaccine                           | NCT02234921  |
| Rhabdoid tumors               | II    | Recruiting       | Combined with a conditioning regimen followed by adoptive cell transfer-based immunotherapy | NCT02114229  |
| Soft tissue sarcoma           | I     | Recruiting       | As part of a conditioning regimen followed by adoptive cell transfer-based immunotherapy | NCT02059850  |
| Solid tumors                  | I     | Not yet recruiting| Combined with multimodal immunotherapy                                                   | NCT02306161  |
| Solid tumors                  |       |                  |                                            |               |
| Solid tumors                  |       | Not yet recruiting| Combined with GD2-specific CAR-expressing T cells                                         | NCT02159716  |
| Solid tumors                  | I/II  | Not yet recruiting| Combined with GM-CSF and TAA-pulsed DCs                                                  | NCT02223312  |
|                              |       |                  | Combined with GD2-specific CAR-expressing T cells                                         | NCT02224599  |
|                              |       | Recruiting       | As metronomic chemotherapy combined with celecoxib and followed by lysate-based vaccine  | NCT02054104  |
|                              |       |                  | Combined with GD2-specific CAR-expressing T cells                                         | NCT02054104  |
|                              |       |                  | Combined with GD2-specific CAR-expressing T cells                                         | NCT02054104  |
|                              |       |                  | Combined with GD2-specific CAR-expressing T cells                                         | NCT02054104  |

**Abbreviations:** CAR, chimeric antigen receptor; DC, dendritic cell; EGF, epidermal growth factor; FOLFOXIRI, folinic acid plus 5-fluorouracil plus oxaliplatin plus irinotecan; GM-CSF, granulocyte macrophage colony stimulating factor; HSP, heat shock protein; n.a., not available; NSCLC, non-small cell lung carcinoma; RT, radiation therapy; TAA, tumor-associated antigen. *initiated after 2014, January 1st.*
Table 4. Clinical trials recently started to evaluate the therapeutic profile of oxaliplatin as an off-label chemotherapeutic intervention

| Indication(s)                              | Phase | Status               | Notes                                                                 | Ref.       |
|--------------------------------------------|-------|----------------------|----------------------------------------------------------------------|------------|
| Biliary tract carcinoma                    | I     | Not yet recruiting   | GEMOX regimen plus MEK inhibitor                                      | NCT02105350|
| Gallbladder carcinoma                      |       |                      |                                                                      |            |
| Breast carcinoma                           | 0     | Recruiting           | As single agent                                                      | NCT0207998 |
| Gastric cancer                             | I/I   | Completed            | FLOT regimen combined with gastrectomy ± bevacizumab                 | NCT02048540|
|                                             |       | Recruiting           | Combined with a HSP-based vaccine, cyclophosphamide and S-1          | NCT2317471 |
|                                             | II    | Completed            | XELOX regimen                                                        | NCT2071043 |
|                                             |       | Not yet recruiting   | XELOX regimen plus paclitaxel                                       | NCT02038621|
|                                             |       | Recruiting           | FOLFOX regimen combined with autologous tumor lysate-pulsed DCs and CIK cells | NCT02215837|
|                                             |       |                      | FOLFOX regimen                                                       | NCT02226380|
|                                             |       |                      | XELOX regimen plus trastuzumab                                      | NCT2250209 |
|                                             |       |                      | XELOX regimen                                                       | NCT02269904|
|                                             |       |                      | FLOT regimen                                                        | NCT2289378 |
|                                             |       |                      | SOX regimen ± radiotherapy                                           | NCT2301481 |
| III                                        | Not yet recruiting | Combined with TAS-118 |                                                                      | NCT2322593 |
|                                             |       | Recruiting           | FOLFOX or XELOX regimen                                              | NCT2114359 |
|                                             |       |                      | EOX regimen ± cisplatin and mitomycin C                              | NCT2158988 |
|                                             |       |                      | XELOX regimen plus D2 lymphadenectomy                                | NCT2240524 |
| Gastroesophageal cancer                     | I/I   | Not yet recruiting   | FOLFOX or FLOT or FOLFIIR regimen combined with tumor-targeting antibodies | NCT02213289|
|                                             |       | Recruiting           | XELOX regimen plus paclitaxel                                       | NCT02273713|
|                                             | II    | Not yet recruiting   | SOX or XELOX regimen                                                 | NCT02216149|
|                                             |       | Recruiting           | FOLFOX or PEMOX regimen                                              | NCT2296671 |
|                                             |       | Recruiting           | FOLFOX regimen combined with RT ± carboplatin and paclitaxel         | NCT2037048 |
|                                             |       |                      | EOX or FOLFOX regimen plus cisplatin and S-1                         | NCT2128243 |
|                                             |       |                      | EOX regimen                                                          | NCT2177552 |
|                                             |       |                      | Combined with 5-FU and RT                                            | NCT2241499 |
|                                             |       |                      | Combined with capecitabine, carboplatin, epirubicin, S-FU, paclitaxel and RT | NCT2287129 |
|                                             | II/III| Recruiting           | SOX regimen ± radiotherapy                                           | NCT2193594 |
| Gastrointestinal cancer                     | I     | Not yet recruiting   | FOLFOX regimen plus alisertib                                        | NCT2319018 |
|                                             |       | Recruiting           | FOLFOX regimen plus arginine deiminase                               | NCT2102022 |
|                                             | I/I   | Not yet recruiting   | FOLFOX regimen plus pembrolizumab                                   | NCT2268825 |
|                                             |       | Recruiting           | XELOX regimen plus gemcitabine                                      | NCT2233205 |
| Hepatocellular carcinoma                    | I     | Recruiting           | FOLFOX regimen plus ramucruban                                      | NCT2069041 |
|                                             | II    | Not yet recruiting   | SOX regimen plus sorafenib                                          | NCT2129322 |
|                                             |       | Recruiting           | PACOX regimen                                                       | NCT2089633 |
|                                             | III   | Recruiting           | Combined with doxorubicin for TACE                                   | NCT2149771 |
| Lymphoma                                   | I     | Not yet recruiting   | GEMOX regimen plus dexamethasone and G-CSF                          | NCT2181218 |
|                                             | II    | Recruiting           | GEMOX regimen plus asparaginplus RT                                 | NCT2080234 |
|                                             | III   | Recruiting           | GEMOX regimen plus asparaginplus                                     | NCT2085655 |
| Pancreatic carcinoma                        | I     | Recruiting           | FIRINOX regimen                                                     | NCT2148549 |
|                                             | I/I   | Recruiting           | XELOX regimen plus momelotinib                                      | NCT2244489 |
|                                             | II    | Not yet recruiting   | FOLFOX regimen plus paclitaxel                                      | NCT2109341 |
|                                             |       | Recruiting           | FOLFOX regimen plus RT                                               | NCT2128100 |
|                                             |       |                      | FOLFOX regimen                                                       | NCT2143219 |
|                                             |       |                      | FOLFOX regimen plus encapsulated asparaginase                       | NCT2195180 |
|                                             |       | Recruiting           | GEMOX regimen plus RT                                               | NCT2035072 |
|                                             |       |                      | FOLFIIRINOX regimen                                                  | NCT2047474 |
|                                             |       |                      | FOLFOX regimen plus abraxane                                        | NCT2080221 |
|                                             |       |                      | FOLFIIRINOX regimen plus gemcitabine and paclitaxel                  | NCT2125136 |
|                                             |       |                      | FOLFIIRINOX regimen                                                  | NCT2241551 |
|                                             |       |                      | FOLFOX regimen plus gemcitabine and RT                              | NCT2178709 |
|                                             |       |                      | FOLFOX regimen plus gemcitabine and RT                              | NCT2243358 |
|                                             | II/III| Not yet recruiting   | FOLFIIRINOX regimen plus natriumfolinate                             | NCT2173096 |
|                                             |       | Recruiting           | FOLFIIRINOX regimen plus capecitabine and RT                         | NCT2311439 |

**Abbreviations:** 5-FU, 5-fluorouracil; CIK, cytokine-inducer killer; DC, dendritic cell; EOX, epirubicin plus oxaliplatin plus capecitabine; FIRINOX, 5-FU plus irinotecan plus oxaliplatin; FLOT, 5-FU plus oxaliplatin plus docetaxel; FOLFIIRINOX, folinic acid plus 5-FU plus irinotecan plus oxaliplatin; FOLFOX, folinic acid plus 5-FU plus oxaliplatin; G-CSF, granulocyte colony-stimulating factor; GEMOX, gemcitabine plus oxaliplatin; HSP, heat shock protein; PACOX, pegylated human arginase plus XELOX; PEMOX, pemetrexed plus oxaliplatin; RT, radiation therapy; SOX, S-1 plus oxaliplatin; TACE, transcatheter arterial chemoembolization; XELOX, capecitabine plus oxaliplatin. *initiated after 2014, January 1st.*
The clinical profile of off-label oxaliplatin is being assessed in patients with: (1) gastric, gastroesophageal or gastrointestinal carcinomas, most often in the context of either the so-called XELOX (capecitabine plus oxaliplatin)\textsuperscript{155,156} or FOLFOX (folinic acid plus 5-fluorouracil plus oxaliplatin)\textsuperscript{157,158} regimen (NCT02038621; NCT02048540; NCT02071043; NCT02114359; NCT02158988; NCT02191566; NCT02221587; NCT02226380; NCT02240524; NCT02250209; NCT02269904; NCT02289378; NCT02301481; NCT02317471; NCT02322593; NCT0237048; NCT02128243; NCT02177552; NCT02193594; NCT02231289; NCT02216149; NCT02242149; NCT02273713; NCT02287129; NCT02296671; NCT02102022; NCT02233205; NCT02268825; NCT02319018); (2) HCC, who often receive oxaliplatin combined with other conventional chemotherapeutics or with targeted anticancer agents (NCT02069041; NCT02089633; NCT02129322; NCT02149771); (3) lymphoma, invariably in the context of the so-called GEMOX (gemcitabine plus oxaliplatin) regimen\textsuperscript{159,160} (NCT02082034; NCT02085655; NCT02181218); (4) pancreatic carcinoma, most frequently as part of the so-called FOLFIRINOX (folinic acid plus 5-fluorouracil plus irinotecan plus oxaliplatin) regimen\textsuperscript{161,162} (NCT02035072; NCT02047474; NCT020808221; NCT02109341; NCT02125136; NCT02128100; NCT02143219; NCT02148549; NCT02172976; NCT02178709; NCT02195180; NCT02241551; NCT02243358; NCT02244489; NCT02311439); (5) breast carcinoma, who receive oxaliplatin as a standalone therapeutic agent (NCT02077998); and (6) biliary tract or gallbladder carcinoma, who are treated with the GEMOX regimen plus a MEK inhibitor\textsuperscript{163} (NCT02105350) (Table 4).

Of note, the vast majority of these studies is ongoing, with a few notable exceptions. Thus, NCT02070419, a Phase II study investigating the therapeutic profile of doxorubicin-based TACE alone or combined with radiation therapy in HCC patients, has been withdrawn as the principal investigator left the institution. Moreover, NCT02038296, a Phase II trial testing epirubicin as part of induction or tumor reduction chemotherapy followed by stem cell mobilization in MM patients, have all been already completed (source http://clinicaltrials.gov/). The results of NCT02043756, which suggest that a pegylated variant of mitoxantrone is well tolerated by patients with solid tumors up to a dose of 18 mg/m\textsuperscript{2} and may exert clinical efficacy,\textsuperscript{164} and NCT02161692, which failed to meet the primary end point,\textsuperscript{165} have already been published. Conversely, to the best of our knowledge, the results of NCT02038296, NCT02048540, NCT02071043, NCT02220049, and NCT02288741 have not been released yet.

**Concluding Remarks**

As discussed above, a bunch of clinically employed chemotherapeutics are able to trigger an immunogenic variant of apoptosis that – in immunocompetent hosts – triggers an adaptive immune response against dead cell-associated antigens.\textsuperscript{3,36} Since these ICD inducers are not only approved by international regulatory agencies for use in subjects with various hematological and solid neoplasms, but also are part of consolidated therapeutic protocols, safety concerns are generally limited. Thus, these molecules are frequently included in clinical trials as (part of) the therapeutic regimen(s) administered to the control arm of the study. Moreover, FDA-approved ICD inducers are often investigated in off-label oncological indications, either as standalone therapeutic interventions or combined with other chemo-, radio- or immunotherapies. Consequently, a huge number of clinical studies involving chemical ICD inducers are initiated yearly.

Now, great efforts are being devoted to the development of combinatorial regimens relying on the co-administration of conventional or targeted anticancer agents plus one form of immunotherapy.\textsuperscript{48,166} In this setting, it is tempting to hypothesize that the clinical profile of anticancer chemotherapy based on ICD inducers may be considerably ameliorated by the concomitant administration of various immunostimulatory interventions,\textsuperscript{167} in particular checkpoint blockers such as the cytotoxic T lymphocyte-associated protein 4 (CTLA4)-targeting mAb ipilimumab and the programmed cell death 1 (PD1)-targeting mAbs pembrolizumab and nivolumab.\textsuperscript{168-171} The results of several trials that have already been launched will clarify the actual clinical value of such combinatorial immunochemotherapeutic paradigms.

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No potential conflicts of interest were disclosed.

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