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Trial Watch

Chemotherapy with immunogenic cell death inducers

Erika Vacchelli[1,2,3,4,†], Fernando Aranda[1,2,3,4,†], Alexander Eggermont[1], Jérôme Galon[5,6,7,8], Catherine Sautès-Fridman[6,7,9], Isabelle Cremer[6,7,9], Laurence Zitvogel[1,10], Guido Kroemer[2,4,5,11,12,‡,*], and Lorenzo Galluzzi[1,4,5,‡,*]

[1]Gustave Roussy; Villejuif, France; [2]INSERM, U848; Villejuif, France; [3]Université Paris-Sud/Paris XI; Paris, France; [4]Equipe 11 labellisée par la Ligue Nationale contre le Cancer, Centre de Recherche des Cordeliers; Paris, France; [5]Université Paris Descartes/Paris V; Sorbonne Paris Cité; Paris, France; [6]Université Pierre et Marie Curie/Paris VI; Paris, France; [7]INSERM, UMRS1138; Paris, France; [8]Laboratory of Integrative Cancer Immunology; Centre de Recherche des Cordeliers; Paris, France; [9]Equipe 13, Centre de Recherche des Cordeliers; Paris, France; [10]INSERM, U1015; CICBT507; Villejuif, France; [11]Pôle de Biologie, Hôpital Européen Georges Pompidou; AP-HP; Paris, France; [12]Metabolomics and Cell Biology Platforms, Gustave Roussy; Villejuif, France

[†]These authors contributed equally to this work.
[‡]These authors share senior co-authorship.

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Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ASCT, allogeneic stem cell transplantation; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CRT, calreticulin; DC, dendritic cell; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HMGB1, high mobility group box 1; ICC, intrahepatic cholangiocellular carcinoma; ICD, immunogenic cell death; IL, interleukin; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; NK, natural killer; NSCLC, non-small cell lung carcinoma; TACE, transcatheter arterial chemoembolization

Accumulating evidence suggests that the clinical efficacy of selected anticancer drugs, including conventional chemotherapeutics as well as targeted anticancer agents, originates (at least in part) from their ability to elicit a novel or reinstate a pre-existing tumor-specific immune response. One of the mechanisms whereby chemotherapy can provoke the immune system to recognize and destroy malignant cells is commonly known as immunogenic cell death (ICD). Cancer cells succumbing to ICD are de facto converted into an anticancer vaccine and as such elicit an adaptive immune response. Several common chemotherapeutics share the ability of triggering ICD, as demonstrated in vaccination experiments relying on immunocompetent mice and syngeneic cancer cells. A large number of ongoing clinical trials involve such ICD inducers, often (but not always) as they are part of the gold standard therapeutic approach against specific neoplasms. In this Trial Watch, we summarize the latest advances on the use of cyclophosphamide, doxorubicin, epirubicin, oxaliplatin, and mitoxantrone in cancer patients, discussing high-impact studies that have been published during the last 13 months as well as clinical trials that have been initiated in the same period to assess the antineoplastic profile of these immunogenic drugs as off-label therapeutic interventions.

Correspondence to: Lorenzo Galluzzi; Email: deadoc@vodafone.it;
Guido Kroemer; Email: kroemer@orange.fr
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Introduction

Cancer is no longer considered as a purely cell-intrinsic disease, for several reasons. First, it has become clear that the development of both solid and hematological neoplasms critically relies upon an intimate crosstalk with non-malignant components of the tumor microenvironment, including endothelial, stromal, as well as immune cells.[1-3] Second, the notion that cancer would constitute a self entity and hence go completely unnoticed by the immune system has now been abandoned.[4-6] Research over the past two decades has indeed demonstrated that the immune system not only interacts with (and attempts to control) developing neoplasms,[4] but also (1) removes damaged and stressed cells, which are generally more prone to become malignant than their healthy counterparts (a process known as anticancer immunosurveillance);[7,8] and (2) plays a critical role in the response of various malignancies to therapy.[9-11] Both these facets of the complex interaction between (pre)neoplastic and non-malignant compartments of the tumor microenvironment have rapidly attracted interest as potential targets for the development of novel anticancer therapies, and some of these strategies have already entered the clinical practice.[2,12-14] For instance, the monoclonal antibody bevacizumab, which is currently employed in patients with colorectal, lung, and renal carcinoma,[15,16] is specific for the vascular endothelial growth factor (VEGF), hence operating as an inhibitor of angiogenesis.[17,18] Along similar lines, ipilimumab, which has been approved by the US Food and Drug Administration (FDA) for the treatment of unresectable or metastatic melanoma in 2011,[19-21] inhibits the immunosuppressive receptor cytotoxic T lymphocyte-associated protein 4 (CTLA4), thereby exerting robust immunostimulatory effects.[22,23]

Importantly, besides mediating the antineoplastic effects of a variety of active and passive immunotherapeutic interventions,[24,25] the immune system appears to play a critical role in the response of several tumors to conventional therapeutic regimens as well as to targeted anticancer agents.[10,11] In support of this notion, high levels of tumor-infiltrating $CD8^+$ T cells, alone or combined with limited amounts of intratumoral $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs), have been associated with improved disease outcome upon therapy in patients affected by a variety of solid neoplasms, including (but not limited to) breast carcinoma.[8,26,27] In addition, an ever increasing amount of preclinical data indicates that the efficacy of multiple anticancer agents and several forms of radiotherapy depends, at least in part, on an intact immune system.[28-32]

Schematically, anticancer chemotherapeutics (as well as radiotherapy) can activate tumor-targeting immune responses that potentially eradicate the residual (chemo- or radioresistant) disease, hence leading to long-term clinical remissions, via 4, non-mutually exclusive mechanisms: (1) by directly stimulating the effector functions of innate or adaptive immune cells; (2) by inhibiting the immunosuppressive circuitries set in place by malignant cells to allow for tumor progression; (3) by enhancing the antigenicity of living cancer cells, their immunogenicity, or their susceptibility to immune effector mechanisms; or (4) by stimulating a peculiar type of apoptosis that results in the elicitation of adaptive immune responses against dead cell-associated antigens.[10,11,33-36] The cellular and molecular circuitries involved in the capacity of selected chemotherapeutics to directly modulate the activity of immune cells and/or to increase the antigenicity of neoplastic cells, their immunogenicity or propensity to succumb to immune effectors have been reviewed elsewhere.[10,11,34]

Immunogenic cell death (ICD) obligatorily relies on the emission of a spatiotemporally defined combination of signals by dying cells.[35-39] Such damage-associated molecular patterns (DAMPs) include (but presumably are not limited to): (1) the pre-apoptotic exposure of the endoplasmic reticulum chaperone calreticulin (CRT) to the outer leaflet of the plasma membrane; (2) the active secretion of ATP, which mainly occurs in the blebbing phase of the apoptotic program; and (3) the post-mortem release of the non-histone chromatin-binding protein high mobility group box 1 (HMGB1).[35,36,40] Altogether and in the correct order, these signals promote the uptake of apoptotic corpses by antigen-presenting cells including dendritic cells (DCs), the processing and presentation of dead cell-associated antigens, and the elicitation of an adaptive, interleukin (IL)-1β-, IL-17-, and interferon γ (IFNγ)-dependent immune response against such antigens.[35,36,40] A precise description of the molecular and cellular mechanisms that underlie the immunogenicity of cell death largely exceeds the scope of this Trial Watch and can be found elsewhere.[35,36,40]

Importantly, although measuring CRT exposure, ATP secretion, and HMGB1 release can be useful to identify ICD-inducing agents,[41,42] vaccination experiments constitute the gold standard approach to characterize immunogenic instances of cell death.[33,36] In this setting, immunocompetent mice are vaccinated with syngeneic cancer cells that are dying in response to a putative ICD inducer, and—one week later—challenged with living cancer cells of the same type. If a majority of these mice does not develop tumors, the malignant cells injected as a vaccine were indeed succumbing to ICD.[36] So far, only a few clinically relevant agents have been shown to trigger bona fide ICD.[43] These agents include (1) cyclophosphamide, an alkylating agent nowadays employed for the treatment of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), breast carcinoma, chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), lymphoma, multiple myeloma (MM), mycosis fungoides, neuroblastoma, ovarian carcinoma, and retinoblastoma;[44] (2) doxorubicin, an anthracycline currently approved by the FDA for use in patients with ALL, AML, breast carcinoma, gastric cancer, lymphoma, MM, neuroblastoma, ovarian carcinoma, small cell lung carcinoma (SCLC), soft tissue and bone sarcomas, thyroid carcinoma, transitional cell bladder carcinoma, and Wilms' tumor;[45,46] (3) epirubicin, an anthracycline commonly employed for the treatment of breast carcinoma;[45,46] (4) idarubicin, an anthracycline licensed by the FDA for use in AML;[46,47] (5) mitoxantrone, an anthracenedione nowadays used in the clinic for the therapy of multiple sclerosis as well as acute leukemia, breast carcinoma, non-Hodgkin lymphoma (NHL), and prostate cancer;[45,46] (6) oxaliplatin, a platinum-containing drug licensed for use in combination with 5-fluorouracil and folinic acid in patients with advanced colorectal carcinoma;[48-50] and (7) patupilone (also known as epothilone B or EPO906) a microtubular inhibitor that has not yet been approved for use in humans.[8,51] Indeed, although clinically employed agents including various microtubular inhibitors other than epothilones (e.g., paclitaxel) and cardiac glycosides (e.g., digoxin, digitoxin) are very efficient at converting non-immunogenic instances of cell death into immunogenic ones, they are unable to trigger ICD as standalone interventions.[8,41,42]

Along the lines of our Trial Watch series,[52,53] here we discuss recent discoveries related to the use of ICD inducers in cancer patients, presenting high-impact studies that have been published during the last 13 mo. In addition, we summarize the clinical trials that have been initiated in the same period to assess the antineoplastic profile of these immunogenic drugs as off-label therapeutic interventions.

Update on Clinical Reports

As cyclophosphamide, doxorubicin, epirubicin, idarubicin, mitoxantrone, oxaliplatin, and patupilone are all approved by the FDA or other international regulatory agencies for the treatment of specific malignancies, the safety concerns related to the use of these molecules in cancer patients are limited.[54] This translates into a huge number of clinical trials investigating the possibility that ICD inducers might exert robust antineoplastic effects as off-label therapeutic interventions. During the last 13 mo, the results of no less than 44 studies assessing the efficacy of ICD inducers in (partially or completely) off-label clinical settings have been published in peer-reviewed scientific journals (source http://www.ncbi.nlm.nih.gov/pubmed) (**Table 1**).

Table 1. Recently published clinical trials investigating the therapeutic profile of ICD inducers employed as off-label interventions.*

Drug	Indication(s)	Phase	Note	Ref.
Cyclophosphamide	Colorectal carcinoma	I	Combined with imatinib and bevacizumab	62
	Melanoma	II/III	Combined with low-dose IL-2	56
	NSCLC	III	Combined with MUC1-specific vaccine	57
	T-cell prolymphocytic leukemia	II	Combined with fludarabine, mitoxantrone and alemtuzumab	55
	Solid tumors	I	Combined with low-dose IL-2 and imatinib	58,59
			Combined with sorafenib and bevacizumab	60
		Ib	Combined with an IL-2-based immunocytokine	61
Doxorubicin	Hepatocellular carcinoma	III	As a single agent	63
	Osteosarcoma	II	Combined with ifosfamide, cisplatin and methotrexate	64
	Prostate cancer	II	Combined with androgen-deprivation therapy and ketoconazole	65
	Urothelial tract cancer	II	Combined with ifosfamide, gemcitabine and cisplatin	67
		II	In its pegylated liposomal form	66
	Solid tumors	I	Combined with oxaliplatin	68
Epirubicin	Gastresophageal carcinoma	I	Combined with bortezomib, carboplatin and capecitabine	70
		III	Combined with oxaliplatin, capecitabine and panitumumab	69
	Transitional bladder carcinoma	II	Combined with methotrexate, paclitaxel and carboplatin	71
Oxaliplatin	Biliary tract and pancreatic carcinoma	I	Combined with sorafenib and capecitabine	92
	Breast carcinoma	II	Combined with docetaxel	75
		II	Combined with capecitabine	74
	Chronic lymphocytic leukemia	I/II	Combined with fludarabine, cytarabine and rituximab	72
	Gallbladder cancer	II	Combined with gemcitabine	94
	Gastric carcinoma Gastresophageal carcinoma	I	Combined with docetaxel and vandetanib	90
		I	Combined with docetaxel and capecitabine	88
		I	Combined with sunitinib and capecitabine	86
		I	Combined with S-1 and irinotecan	82
		I/II	Combined with radiotherapy and docetaxel	84
		I/II	Combined with docetaxel and capecitabine	81
		II	Combined with capecitabine and bevacizumab	80
		II	Combined with docetaxel	87
		II	Combined with docetaxel and capecitabine	89
		II	Combined with docetaxel and S-1	83
		II	Combined with S-1	79
		II	Combined with sorafenib	85
	Germ cell tumors	II	Combined with bevacizumab	73
	Nasopharyngeal carcinoma	III	Combined with radiotherapy	78
	NSCLC	II	Combined with docetaxel	77
		II	Combined docetaxel and bevacizumab	76
	Ovarian carcinoma	II	Combined with gemcitabine	95
		II	Combined with topotecan	96
	Pancreatic carcinoma	I	Combined with gemcitabine, erlotinib and radiation therapy	91
		II	Combined with gemcitabine and radiation therapy	93
	Transitional bladder carcinoma	II	Combined with gemcitabine	97
	Solid tumors	I	Combined with docetaxel	98
		II	Combined with gemcitabine	99

Abbreviations: ICD, immunogenic cell death; IL-2, interleukin-2; MUC1, mucin 1; NSCLC, non-small cell lung carcinoma. *between 2012, December 1st and the day of submission.

In particular, cyclophosphamide has been tested as a possible alternative to standard therapeutic approaches in patients affected by (1) T-cell promyelocytic leukemia, as part of an induction chemotherapeutic cocktail including fludarabine and mitoxantrone;[55] (2) melanoma, according to a metronomic schedule in combination with low-dose IL-2;[56] (3) non-small cell lung carcinoma (NSCLC), as part of a therapeutic regimen encompassing a mucin 1-targeting vaccine;[57] or (4) various solid tumors, including colorectal carcinoma, in combination with low-dose IL-2 and/or tyrosine kinase receptor inhibitors such as sorafenib and imatinib.[58-62] Altogether, the results of these studies suggest that metronomic cyclophosphamide can be safely combined with conventional chemotherapeutic as well as with targeted anticancer agents and often results in immunological responses that may be therapeutically significant, at least in some patients.

The possibility that doxorubicin might promote therapeutic responses in off-label clinical settings has recently been investigated in individuals with (1) hepatocellular carcinoma (HCC), as a standalone palliative regimen compared with 5-fluorouracil, folinic acid, and oxaliplatin;[63] (2) non-metastatic osteosarcoma, in combination with high-dose ifosfamide (an alkylating mustard with a broad antineoplastic activity), cisplatin, and high-dose methotrexate;[64] (3) advanced prostate cancer, in the context of androgen deprivation therapy;[65] (4) tumors of the urothelial tract, either in its pegylated form as a single agent or combined with cisplatin, ifosfamide, and gemcitabine (a nucleoside analog licensed for the treatment of pancreatic cancer, NSCLC, breast carcinoma, and ovarian cancer);[66,67] as well as (5) in pediatric patients affected by relapsed or refractory extracranial non-hematopoietic solid tumors, in the context of oxaliplatin-based chemotherapy.[68] Conversely, epirubicin has been investigated as a potential alternative to standard therapeutic protocols in subjects bearing (1) advanced gastresophageal tumors, in combination with conventional cytotoxic agents and/or panitumumab, an FDA-approved monoclonal antibody specific for the epidermal growth factor receptor (EGFR);[69,70] or (2) transitional bladder carcinoma, as a second-line intervention for individuals who failed cisplatin- and gemcitabine-based first-line chemotherapy.[71] These anthracycline-based chemotherapeutic cocktails were generally well tolerated, but often failed to ameliorate disease outcome as compared with gold-standard therapeutic interventions.

During the last 13 mo, the clinical profile of oxaliplatin as an off label therapeutic intervention has been assessed in patients with (1) aggressive relapsed or refractory CLL, as part of a chemotherapeutic regimen involving fludarabine, cytarabine (a nucleoside analog approved for the treatment of various hematological malignancies), and rituximab (a CD20-targeting monoclonal antibody currently employed against CLL and NHL);[72] (2) refractory germ cell tumors, in combination with bevacizumab;[73] (3) breast carcinoma, combined with capecitabine (the precursor of 5-fluorouracil) or docetaxel (a microtubular inhibitor of the taxane family currently employed against various carcinomas);[74,75] (4) NSCLC, as part of a docetaxel-based chemotherapy;[76,77] (5) advanced nasopharyngeal carcinoma, coupled to radiation therapy;[78] (6) gastric or gastresophageal carcinoma, most frequently in the context of a chemotherapeutic cocktail involving docetaxel, capecitabine, or S-1 (an oral fluoropyrimidine currently approved for the treatment of gastric cancer);[79-90] (7) pancreatic, gallbladder, or biliary tract tumors, often in combination with gemcitabine-based chemotherapy;[91-94] (8) ovarian or bladder carcinoma, combined with conventional (often gemcitabine-based) therapeutic interventions;[95-97] or (9) various solid tumors, again in combination with cytotoxic chemotherapy.[98,99] Taken together, the results of these clinical trials, most of which were Phase I or II studies, indicate that oxaliplatin exerts promising antineoplastic effects in patients affected by several tumors other than colorectal carcinoma. Large, randomized Phase III trials will have to evaluate the true clinical profile of oxaliplatin in these settings.

During the last 13 mo, several publications have provided novel insights into the signaling pathways that underlie ICD and its translational relevance. For instance, we have dissected the molecular cascades whereby autophagy is responsible for the secretion of ATP in the course of ICD,[100,101] and demonstrated that both ATP and chemokine (C-C motif) ligand 2 (CCL2),[102-104] but not tumor necrosis factor α (TNFα),[105] are responsible for the therapeutically relevant accumulation of inflammatory DC-like cells within neoplastic lesions treated with ICD inducers. In addition, we and others have demonstrated a critical role for the gut microbiota in the therapeutic activity of cyclophosphamide and other immunostimulatory regimens.[106,107] The group headed by Patrizia Agostinis showed that in some circumstances autophagy may inhibit, rather than promote, ICD,[108] and that the signaling cascades elicited by hypericin-based photodynamic therapy (another bona fide ICD inducer) are amplified by selected members of the Bcl-2 protein family,[108] including phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1, best known as NOXA) but not BCL2-like 11 (BCL2L11, best known as BIM).[109] The reasons why in some cases autophagy is critically required for ICD while in others appears to inhibit it remain unclear, but may relate to differences in the experimental models employed. Indeed, also the molecular cascades that underlie the pre-apoptotic exposure of calreticulin in response to anthracycline and hypericin-based photodynamic therapy overlap to a large extent, but not entirely.[110] Of note, recent data ascribe to the circulating levels of various ICD-associated molecules, including HMGB1 and one of its receptors, advanced glycosylation end product-specific receptor (AGER, best known as RAGE), prognostic or predictive relevance in patients with breast, pancreatic, or colorectal carcinoma.[111-113] Additional studies are required to fully understand the prognostic or predictive potential of circulating ICD markers.

Update on Clinical Trials Testing Immunogenic Cell Death Inducers

When this Trial Watch was being redacted (December 2013), official sources listed no less than 255 clinical trials launched after 2012, December 1st to evaluate the therapeutic profile of bona fide ICD inducers in cancer patients (source

Table 2. Clinical trials recently launched to assess the therapeutic profile of cyclophosphamide employed as off-label intervention.*

Indication(s)	Phase	Status	Notes	Ref.
Colorectal carcinoma	I	Not yet recruiting	Combined with a cancer cell-based vaccine and a DNA methyltransferase inhibitor	NCT01966289
DSRCT	II	Recruiting	Combined with vincristine-based chemotherapy and radiation therapy	NCT01946529
Endometrial carcinoma	II	Active, not recruiting	Combined with cisplatin, doxorubicin and radiation therapy	NCT01918124
Esophageal cancer	II	Not yet recruiting	As part of non-myeloablative conditioning followed by ACT	NCT01795976
Ewing sarcoma	II	Recruiting	Combined with doxorubicin-based chemotherapy and radiation therapy	NCT01864109
Glioblastoma	II	Not yet recruiting	Combined with bevacizumab, a cell-based vaccine and GM-CSF	NCT01903330
Lung carcinoma	II	Recruiting	Combined with an autophagosome-derived vaccine and GM-CSF or imiquimod	NCT01909752
	III	Not yet recruiting	Combined with cisplatin and etoposide	NCT01947062
Medulloblastoma	II	Not yet recruiting	Combined with various conventional chemotherapeutics	NCT02017964
	II	Recruiting	Combined with conventional chemotherapy upon craniospinal irradiation	NCT01878617
Melanoma	I	Not yet recruiting	As part of non-myeloablative conditioning followed by ACT	NCT01955460
		Recruiting	As part of non-myeloablative conditioning followed by ACT	NCT01946373
	I/II	Recruiting	Combined with various conventional chemotherapeutics upon irradiation	NCT01898039
	II	Not yet recruiting	Combined with an allogeneic cell-based vaccine expressing CD137L	NCT01883323
			As part of non-myeloablative conditioning followed by ACT	NCT01995344
		Recruiting	As part of non-myeloablative conditioning followed by ACT	NCT01807182
				NCT01814046
				NCT01993719
			Combined with IL-2	NCT01833767
Myelomonocytic leukemia	II	Recruiting	As part of non-myeloablative conditioning followed by ASCT	NCT01824693
Renal cell carcinoma	I	Not yet recruiting	As part of non-myeloablative conditioning preceded by SBRT and followed by ACT	NCT01943188
Rhabdomyosarcoma	II	Recruiting	Combined with multimodal therapy	NCT01871766
Solid tumors	II	Recruiting	As part of non-myeloablative conditioning followed by haploidentical BMT	NCT01804634
			As part of non-myeloablative conditioning followed by ACT	NCT01967823
	III	Not yet recruiting	Combined with celecoxib, etoposide and thalidomide	NCT01858571
		Recruiting	Combined with standard chemotherapy ± G-CSF	NCT01987596
Waldenström's macroglobulinemia	III	Not yet recruiting	Combined with rituximab, dexamethasone ± bortezomib	NCT01788020

Abbreviations: ACT, adoptive cell transfer; ASCT, allogeneic stem cell transplantation; BMT, bone marrow transplantation; CD137L, CD137 ligand; DSRCT, desmoplastic small round cell tumor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-2, interleukin-2; SBRT; stereotactic body radiation therapy. *between 2012, December 1st and the day of submission.

http://www.clinicaltrials.gov). One hundred 53 of these studies (83 involving cyclophosphamide, 63 doxorubicin, 14 epirubicin, 6 idarubicin, 7 mitoxantrone, and 32 oxaliplatin) were performed in on-label clinical settings, and hence will not be further discussed here. In addition, during the last 13 mo, 107 clinical trials have been launched to assess the clinical activity of ICD inducers in off-label settings. Of these studies, 27 involve cyclophosphamide, 17 doxorubicin, 6 epirubicin, 7 idarubicin, and 53 oxaliplatin.

Cyclophosphamide is being tested as an off-label intervention (1) in melanoma patients, either as part of a fludarabine- and IL-2-containing, non-myeloablative conditioning regimen combined to the adoptive transfer of tumor-infiltrating lymphocytes[24,114] (NCT01807182; NCT01814046; NCT01883323; NCT01946373; NCT01955460; NCT01993719; NCT01995344), or given on a metronomic schedule in support of low-dose intravenous IL-2[58,59] (NCT01833767) or an allogeneic melanoma cell line engineered to express the immunostimulatory protein tumor necrosis factor (ligand) superfamily, member 9 (TNFSF9, best known as CD137L)[115] (NCT01898039); (2) in patients with various forms of sarcoma, combined with a vincristine-containing (radio)therapeutic regimen (NCT01864109; NCT01871766; NCT01946529); (3) in children affected by hematopoietic neoplasms, as part of a non-myeloablative conditioning regimen preceding allogeneic stem cell transplantation (ASCT) (NCT01824693), or solid tumors, in combination with other chemotherapeutics (NCT01858571; NCT01987596); (4) in medulloblastoma patients, as part of combinatorial induction or maintenance regimens (NCT01878617; NCT02017964); (5) in individuals with lung carcinoma, either at metronomic doses in support of conventional chemotherapy (NCT01947062) or in combination with a vaccine based on cancer cell-derived autophagosomes[116] (NCT01909752); and (6) in patients affected by a variety of other hematological and solid tumors, including Waldenström's macroglobulinemia (NCT01788020), glioblastoma (NCT01903330), esophageal carcinoma (NCT01795976), renal cell carcinoma (NCT01943188), endometrial carcinoma (NCT01918124), colorectal carcinoma (NCT01966289), and others (NCT01804634; NCT01967823) (**Table 2**).

The safety and therapeutic profile of doxorubicin employed as an off-label intervention are currently under investigation (1) in patients with HCC or intrahepatic cholangiocellular carcinoma (ICC), most often in the context of transcatheter arterial chemoembolization (TACE) and/or combined with sorafenib[117,118] (NCT01798134; NCT01798147; NCT01798160; NCT01840592; NCT01857726; NCT01858207; NCT01906216; NCT01966133); (2) in women with reproductive tract neoplasms, either as a standalone therapeutic intervention, be it unconjugated (NCT01849874; NCT01767155) or in the form of AEZS-108 (i.e., conjugated to gonadotropin-releasing hormone 1)[119] (NCT01767155), either combined with conventional chemotherapeutics and/or radiotherapy (NCT01918124; NCT01970722), or co-administered with trabectedin, an orphan drug[120,121] (NCT01846611); and (3) in subjects affected by retinoblastoma (NCT01783535), glioblastoma (NCT01851733), salivary gland cancer (NCT01969578), or other neoplasms (NCT01970540). In addition, epirubicin is being evaluated as an off-label therapeutic intervention against esophageal and gastric carcinomas, most often in combination with a platinum derivative[50] and 5-fluorouracil (or capecitabine)[122] (NCT01787539; NCT01870791; NCT01924819); MM, in combination with the proteasomal inhibitor bortezomib and dexamethasone[123] prior to ASCT (NCT01852799; NCT01868828); and HCC, in the context of TACE (NCT01833286). Finally, the off-label clinical potential of idarubicin is being assessed (1) in ALL patients, either as a standalone therapeutic intervention (NCT01990807), either combined with etoposide (a DNA-damaging chemical) in the context of ASCT conditioning (NCT01873807), or as part of a fludarabine- and cytarabine-containing chemotherapeutic cocktail (NCT02013167); (2) in subjects with acute promyelocytic leukemia, in combination with all-*trans* retinoic acid (NCT01987297); (3) in NHL patients, as a standalone therapeutic measure (NCT01958996); and (4) in individuals affected by myelodysplastic syndromes, combined with cytarabine-based chemotherapy (NCT01812252; NCT01831232) (**Table 3**).

The safety and efficacy of oxaliplatin employed as an off-label therapeutic intervention are being assessed (1) in patients affected by gastric or esophageal carcinoma, most frequently in the context of the so-called DOX (docetaxel plus oxaliplatin plus capecitabine), EOX (epirubicin plus oxaliplatin plus capecitabine), FOLFOX (folinic acid plus 5-fluouracil plus oxaliplatin), SOX (S-1 plus oxaliplatin) or XELOX (capecitabine plus oxaliplatin) regimens (NCT01747551; NCT01748773; NCT01748851; NCT01757366; NCT01761461; NCT01769508; NCT01787539; NCT01795027; NCT01798251; NCT01815853; NCT01824459; NCT01843829; NCT01851941; NCT01870791; NCT01876927; NCT01880632; NCT01882933; NCT01889303; NCT01896531; NCT01913639; NCT01928290; NCT01928524; NCT01932580; NCT01935778; NCT01946061; NCT01962376; NCT01963702; NCT01980407); (2) in pancreatic cancer patients, near to invariably as part of the FOLFIRINOX (folinic acid plus 5-fluorouracil plus irinotecan plus oxaliplatin) regimen (NCT01760694; NCT01771146; NCT01811277; NCT01821612; NCT01821729; NCT01827553; NCT01835041; NCT01836432; NCT01867892; NCT01888978; NCT01896869; NCT01897454; NCT01905150; NCT01921751; NCT01926197; NCT01959139; NCT01964287); (3) in individuals affected by several other hematological and solid neoplasms, including extranodal natural killer (NK)/T-cell lymphoma (NCT01921790), breast carcinoma (NCT01937507), germ cell tumors (NCT01782339), HCC (NCT01775501), ICC (NCT01862315), gastrointestinal tumors (NCT01845337), malignancies of the biliary tract and gallbladder (NCT01811277; NCT01926236), and reproductive tract cancers (NCT01936974) (**Table 4**).Of note, during the

Table 3. Clinical trials recently launched to assess the therapeutic profile of FDA-approved anthracyclines employed as off-label interventions.*

Drug	Indication(s)	Phase	Status	Note	Ref.
Doxorubicin	Glioblastoma	n.a.	Not yet recruiting	Combined with magnetic resonance imaging-guided laser ablation	NCT01851733
	Hepatocellular carcinoma	n.a.	Recruiting	In the context of DEB-based TACE	NCT01798134
				In the context of TACE, alone or combined with cisplatin	NCT01857726
		II	Recruiting	Combined with sorafenib	NCT01840592
				In the context of TACE, combined with RFA	NCT01858207
		II/III	Recruiting	In the context of TACE, combined with sorafenib	NCT01906216
		III	Enrolling by invitation	In the context of TACE, combined with ethiodized oil	NCT01966133
		IV	Active, not recruiting	In the context of DEB-based TACE	NCT01798160
	Intrahepatic cholangiocellular carcinoma	IV	Recruiting	In the context of DEB-based TACE	NCT01798147
	Reproductive tract tumors	n.a.	Not yet recruiting	As PLD in combination with other chemotherapeutics	NCT01970722
		II	Active, not recruiting	Combined with cyclophosphamide, cisplatin, and radiation therapy	NCT01918124
		III	Recruiting	As single agent, unconjugated or conjugated to gonadotropin-releasing hormone 1	NCT01767155
				As single agent	NCT01849874
				As single agent or combined with dexamethasone and trabectedin	NCT01846611
	Retinoblastoma	II	Recruiting	Combined with conventional chemotherapy and plaque radiotherapy	NCT01783535
	Salivary gland cancer	II	Not yet recruiting	Combined with cisplatin	NCT01969578
	Solid tumors	I	Recruiting	Combined with lurbinectedin	NCT01970540
Epirubicin	Esophageal carcinoma Gastric carcinoma Gastresophageal carcinoma	II	Recruiting	EOX regimen combined with intravenous omega-3 fish oil	NCT01870791
		II/III	Recruiting	Combined with 5-FU and cisplatin	NCT01924819
				EOX regimen	NCT01787539
	Hepatocellular carcinoma	III	Not yet recruiting	In the context of TACE	NCT01833286
	Multiple myeloma	II	Recruiting	Combined with bortezomib, dexamethasone and autologous SCT	NCT01852799
		IV	Recruiting	Combined with bortezomib, dexamethasone and autologous SCT	NCT01868828
Idarubicin	ALL	III	Not yet recruiting	Combined with standard of care chemotherapeutic agents	NCT02013167
		IV	Recruiting	As single agent	NCT01990807
				As part of intensified conditioning followed by autologous SCT	NCT01873807
	AML MDS	II	Recruiting	Combined with cytarabine and pravastatin	NCT01831232
	APL	IV	Recruiting	Combined with all-*trans* retinoic acid	NCT01987297
	MDS	n.a.	Recruiting	Combined with cytarabine	NCT01812252
	NHL	I/II	Recruiting	As single agent	NCT01958996

Abbreviations: 5-FU, 5-fluorouracil; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; DEB, drug-eluting bead; EOX, epirubicin + oxaliplatin + capecitabine; FDA, Food and Drug Administration; MDS, myelodysplastic syndrome; n.a, not available; NHL, non-Hodgkin's lymphoma; PLD, pegylated liposomal doxorubicin; RFA, radiofrequency ablation; SCT, stem cell transplantation; TACE, transcatheter arterial chemoembolization. *between 2012, December 1st and the day of submission.

Table 4. Clinical trials recently launched to assess the therapeutic profile of oxaliplatin employed as off-label intervention.*

Indication(s)	Phase	Status	Note	Ref.
Biliary tract cancer	III	Not yet recruiting	FOLFOX regimen	NCT01926236
Biliary tract cancer Pancreatic cancer	II	Recruiting	SOX regimen	NCT01811277
Breast carcinoma	II	Recruiting	FOLFOX regimen, administered to hepatic metastases by HAI	NCT01937507
Esophageal carcinoma Gastric carcinoma	I	Recruiting	DOS regimen	NCT01928524
	II	Active, not recruiting	XELOX regimen ± ginsenoside Rg3	NCT01757366
		Not yet recruiting	XELOX regimen combined with radiotherapy ± carboplatin and paclitaxel	NCT01843829
			FOLFIRINOX regimen ± trastuzumab	NCT01928290
			SOL regimen	NCT01980407
		Recruiting	EOX regimen combined with intravenous omega-3 fish oil	NCT01870791
			FLOT regimen	NCT01932580
			FOLFOX regimen ± aflibercept	NCT01747551
			FOLFOX regimen combined with regorafenib	NCT01913639
			DOX regimen	NCT01876927
			FOLFOX regimen ± GDC-0068	NCT01896531
			FOLFOX regimen combined radiation therapy	NCT01889303
			SOX regimen	NCT01946061
			XELOX regimen	NCT01798251
			XELOX regimen	NCT01963702
			XELOX regimen combined with radiotherapy and trastuzumab	NCT01748773
		Completed	FOLFOX regimen	NCT01851941
	II/III	Not yet recruiting	XELOX regimen	NCT01880632
		Recruiting	EOX regimen	NCT01787539
	III	Not yet recruiting	DOX or XELOX regimen	NCT01935778
			SOX regimen	NCT01824459
		Recruiting	Combined with gastrectomy and HIPEC	NCT01882933
			FOLFOX or XELOX regimen	NCT01748851
			SOX regimen	NCT01761461
			SOX regimen	NCT01795027
			XELOX regimen ± radiation therapy	NCT01815853
	IV	Recruiting	XELOX regimen ± bevacizumab	NCT01962376
Gastrointestinal cancer	II	Not yet recruiting	XELOX regimen or combined with teysuno	NCT01845337
Germ cell tumors	II	Recruiting	Combined with conventional chemotherapeutics	NCT01782339
Hepatocellular carcinoma	II	Recruiting	FOLFOX regimen combined with sorafenib	NCT01775501
Intrahepatic cholangiocellular carcinoma	II	Recruiting	GEMOX regimen combined with HAI-based chemotherapy	NCT01862315
NK/T-cell lymphoma	II	Recruiting	GemAOD regimen combined with bevacizumab	NCT01921790

Table 4. Clinical trials recently launched to assess the therapeutic profile of oxaliplatin employed as off-label intervention.* (continued)

Pancreatic cancer	n.a.	Recruiting	FOLFIRINOX regimen combined with IORT	NCT01760694
			FOLFIRINOX regimen	NCT01771146
			FOLFIRINOX regimen combined with chemoradiation and surgery	NCT01821612
	I	Recruiting	FOLFIRINOX regimen combined with 6,8-bis(benzylthio)octanoic acid	NCT01835041
	I/II	Not yet recruiting	FOLFIRINOX regimen ± PEGPH20	NCT01959139
		Recruiting	FOLFIRINOX and GEMBRAX regimens combined	NCT01964287
	II	Enrolling by invitation	FOLFIRINOX or GOFL regimen combined with chemoradiotherapy	NCT01867892
		Not yet recruiting	FOLFIRINOX regimen	NCT01896869
			FOLFIRINOX regimen combined With 3D-CRT and capecitabine	NCT01921751
			Sequential G-FLIP and G-FLIP-DM regimens combined with vitamin C	NCT01905150
		Recruiting	DOS or FOLFOX or GEMOX regimen	NCT01888978
			FOLFIRINOX regimen combined with gemcitabine and IMRT	NCT01897454
			FOLFIRINOX regimen combined with losartan and PBRT	NCT01821729
	III	Recruiting	FOLFIRINOX regimen ± SBRT	NCT01926197
			FOLFIRINOX regimen combined with chemoradiation and immunotherapy	NCT01836432
			FOLFIRINOX regimen combined with radiation therapy ± gemcitabine	NCT01827553
Reproductive tract tumors	II	Recruiting	GEMOX regimen combined with platinum based chemotherapy and bevacizumab	NCT01936974

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; 5-FU, 5 fluorouracil; DOS, docetaxel + oxaliplatin + S1; DOX, docetaxel + oxaliplatin + capecitabine; EOX, epirubicin + oxaliplatin + capecitabine; FLOT, 5-FU + oxaliplatin + docetaxel; FOLFIRINOX, folinic acid + 5-FU + irinotecan + oxaliplatin; FOLFOX, folinic acid + 5-FU + oxaliplatin; G-FLIP, gemcitabine + 5FU + folinic acid + irinotecan + oxaliplatin; G-FLIP-DM, G-FLIP + docetaxel + mitomycin C; GemAOD, gemcitabine + oxaliplatin + pegaspargase + dexamethasone; GEMBRAX, albumin-bound paclitaxel + gemcitabine; GEMOX, gemcitabine + oxaliplatin; GOFL, gemcitabine + oxaliplatin, folinic acid + 5-FU; HAI, hepatic arterial infusion; HIPEC, hyperthermic intraperitoneal chemoperfusion; IMRT, intensity-modulated radiation therapy; IORT, intraoperative radiation therapy; n.a., not available; NK, natural killer; PBRT, proton beam radiation therapy; PEGPH20, pegylated recombinant human hyaluronidase; SBRT, stereotactic body radiotherapy; SOL, S-1 + oxaliplatin + leucovorin; SOX, S-1 + oxaliplatin; XELOX, capecitabine + oxaliplatin. *between 2012, December 1st and the day of submission.

last 13 mo no clinical trial has been initiated to evaluate the therapeutic profile of mitoxantrone in off-label oncological settings, and the status of only one of the studies discussed in our previous Trial Watches dealing with ICD inducers has changed since their publication.[124,125] Thus, official sources now list NCT01701375, testing mitoxantrone in combination with cytarabine and a cyclin-dependent kinase inhibitor (PD 0332991) in adults with relapsed and refractory acute leukemia or high-risk myelodysplastic syndrome, as terminated owing to sponsor withdrawal. Only 2 patients participated into this Phase I study, one of whom experienced relatively serious adverse effects including bone marrow aplasia and hyperbilirubinemia. Both these patients also suffered from less severe toxicities, including grade I-II mucositis (source http://www.clinicaltrials.gov).

Concluding Remarks

It has now become clear that several clinically successful anticancer agents share the unsuspected ability to activate, rather than inhibit, the immune system.[10,11] The molecular and cellular circuitries that underlie such an immunostimulatory activity include ICD, a particular case of apoptosis that results in the activation of an adaptive immune response specific for dead cell-associated antigens.[35,36,43] Cyclophosphamide, doxorubicin, epirubicin, idarubicin, mitoxantrone, and oxaliplatin are all currently approved by the US FDA and other international regulatory agencies for the treatment of some malignancies, and are all able to trigger ICD, as demonstrated by gold-standard vaccination experiments based on syngeneic tumor models.[35,36,43] Also patupilone belongs to the short list of bona fide ICD inducers,[8,9] but has not yet been approved for use in humans. Another epothilone, namely ixabepilone, is currently employed as a standalone therapeutic intervention in anthracycline-, taxane- and capecitabine-resistant breast carcinoma patients, or in combination with capecitabine for the treatment of anthracycline- and taxane-resistant locally advanced or metastatic breast carcinoma,[126,127] yet its ability to promote ICD remains unclear. As a matter of fact, the capacity of a given chemical to trigger the immunogenic demise of cancer cells cannot be anticipated by structural or functional considerations, as compounds that are as similar to each other as cisplatin and oxaliplatin have been shown to differ in this respect.[48,49] In line with this notion, although 7A7, a monoclonal antibody specific for murine EGFR, has been shown to trigger bona fide ICD,[128] whether clinically employed EGFR-targeting agents including panitumumab, cetuximab (2

monoclonal antibodies)[129,130] and erlotinib (a small compound that inhibits EGFR at the enzymatic level)[131,132] promote the immunogenic demise of cancer cells remains to be determined.

It is interesting to note that the abovementioned ICD inducers as well as many other currently employed anticancer agents that have an immunostimulatory activity have been identified and developed empirically, based on their ability to mediate relatively selective antineoplastic effects in vitro and in vivo, in immunodeficient mice implanted with human cancer cells.[10] Thus, the immunostimulatory potential of all these compounds has gone unnoticed for decades, in part owing to the experimental models employed until now (and still very diffuse), which were/are inapt to evaluate such a clinically relevant aspect of the pharmacology of a given agent. This also implies that many potentially efficient anticancer agents have never been fished out of large chemical libraries by standard screening procedures, or have gone lost at subsequent validation steps. We are deeply convinced that preclinical models that involve the immune system (for instance, syngeneic tumors developing in immunocompetent mice), or components thereof (for instance, cancer cells cultured in the presence of dendritic cells, macrophages, T cells, and/or NK cells),[10] and the systematic analysis of the immunological parameters that may affect the clinical response of patients to therapy (immunomonitoring)[133,134] are crucial for the discovery of next-generation chemotherapeutics, i.e., molecules that simultaneously hit cancer cells while exerting potent immunostimulatory effects. We have already bumped into some of these compounds in the past century, it is now time to go actively get the missing ones.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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