Trial watch: Dendritic cell-based anticancer immunotherapy

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ABSTRACT
Dendritic cell (DC)-based vaccines against cancer have been extensively developed over the past two decades. Typically DC-based cancer immunotherapy entails loading patient-derived DCs with an appropriate source of tumor-associated antigens (TAAs) and efficient DC stimulation through a so-called “maturation cocktail” (typically a combination of pro-inflammatory cytokines and Toll-like receptor agonists), followed by DC re-introduction into patients. DC vaccines have been documented to (re)activate tumor-specific T cells in both preclinical and clinical settings. There is considerable clinical interest in combining DC-based anticancer vaccines with T cell-targeting immunotherapies. This reflects the established capacity of DC-based vaccines to generate a pool of TAA-specific effector T cells and facilitate their infiltration into the tumor bed. In this Trial Watch, we survey the latest trends in the preclinical and clinical development of DC-based anticancer therapeutics. We also highlight how the emergence of immune checkpoint blockers and adoptive T-cell transfer-based approaches has modified the clinical niche for DC-based vaccines within the wide cancer immunotherapy landscape.

ABBREVIATIONS:
ACT, adoptive T-cell transfer; APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte; DAMP, damage-associated molecular pattern; DC, dendritic cell; ICB, immune checkpoint blocker; iDC, immature DC; IFN, interferon; IL, interleukin; MAMP, microbe-associated molecular pattern; mDC, mature DC; MRC1, mannose receptor C type 1; MUC1, mucin 1; pDC, plasmacytoid DC; TAA, tumor-associated antigen; TIL, tumor-infiltrating lymphocyte; TLR, Toll-like receptor; Treg, regulatory T cell; WT1, Wilms tumor 1

Introduction
Dendritic cells (DCs) are one of the major antigen-presenting cells (APCs) of the innate immune system. Due to their proficiency at antigen presentation, including the capacity to cross-present antigens (i.e., presenting extracellular antigens on MHC class I molecules), DCs engage a decisive spot at the interface between innate and adaptive immunity. DCs were first discovered in 1973 by Ralph Steinman, who was later awarded a Nobel Prize for this achievement.1-4 DCs are named as such due to their peculiar, tree-like morphology (“Dendron” is the Greek word for “tree”).5-7 Since their discovery nearly three decades ago, a considerable number of studies have focused on the unique phenotypic and functional characteristics of DCs.8

DCs are a relatively ubiquitous population of myeloid cells (which differentiate from common myeloid bone marrow progenitors) exhibiting heterogeneity at various levels, including morphology, ontogeny and immunological features.9 This heterogeneity is the basis for the classification of DCs into various subsets. DC subsets tend to specialize in specific immunological functions: (1) processing and presenting antigens (e.g., murine CD8α+ DCs and their human counterparts, CD141+ DCs, are particularly efficient at antigen cross-presentation),10-17 (2) specifically interfacing with selected cells from the adaptive immune system (e.g., CD14+ dermal DCs or epidermal Langerhans cells preferentially facilitate humoral or CD8+ T-cell responses, respectively)18-20 and (3) mediating specific interferon (IFN) responses (e.g., plasmacytoid DCs (pDCs) tend to react to microbial stimuli by secreting high amounts of type I IFNs).21-24

In absence of pathophysiological insults, circulating or tissue-resident DCs tend to exist in a perpetual immature state. Immature DCs (iDCs) are highly effective elicitors of immunological...
tolerance, typically due to their capacity to facilitate the suppression or clonal deletion of auto-reactive T cells as well as the clonal expansion of immunosuppressive CD4⁺CD25⁺FOXP3⁺ regulatory T cells (Tregs). 25-28 This immature state is connoted by (1) continuous engulfment of extracellular material coupled to the secretion of limited amounts of cytokines or chemokines, (2) retention of MHC class II molecules within late endosomes, (3) expression of some assorted chemokine receptors and (4) negligible expression of co-stimulatory ligands like CD86, CD40, CD83, CD70, CD80 and tumor necrosis factor (ligand) superfamily, member 4 (TNFSF4, also known as OX40L) on the cell surface. 29,30

However, several microbial (e.g., microbe-associated molecular patterns (MAMPs)) or endogenous (e.g., damage-associated molecular patterns (DAMPs)) cues can drive iDCs into maturation. 33-37 Mature DCs (mDCs) exhibit little-to-null phagocytic activity and efficiently home toward a nearby lymph node for antigen presentation to T cells rather than ensuring continuous phagocytic clearance (the latter function is mainly executed by local macrophages or neutrophils). 7,29,38 Generally, mDCs are characterized by increased expression of antigen-bound MHC class II molecules and co-stimulatory molecules (e.g., CD80, CD40, CD83, CD70, CD86 and OX40L) on the cell surface, upregulation of chemokine (C–C motif) receptor 7 (CCR7) and abundant secretion of immunostimulatory cytokines and inflammatory chemokines. 7,27,29,39-41 These molecules are used by mDCs to co-stimulate T cells during antigen presentation. 42-45

Owing to their significant contribution to antigen processing and presentation as well as to immunomodulation of T-cell functions, DCs have a strong impact on oncogenesis, tumor progression and response to anticancer therapy. 46-50 This crucial role of DCs has been documented in a plethora of preclinical tumor models (e.g., through vaccination, antibody-dependent depletion or genetic ablation) as well as in several clinical studies (e.g., by correlating intra-tumoral DC levels with disease outcome in various cohorts of cancer patients). 46-49,51-54 An established tumor usually strives to limit antigen availability to DCs and to enforce immunosuppression to disrupt the generation of antigen-specific T-cell responses. 8,55-59 This is one of the reasons underlying the emergence of DC-based vaccines for cancer immunotherapy. Indeed, DCs can be obtained from the monocytes of a cancer patient, loaded with an appropriate source of tumor-associated antigens (TAAs) ex vivo, matured in a proper manner ex vivo, and infused back into the patient. At least theoretically, this provides cancer patients with a pool of autologous DCs capable of priming tumor-targeting cytotoxic T lymphocytes (CTLs). 46,47,60-62

In the past few decades, significant experimental and clinical resources have been devoted to the development of anticancer DC-based vaccines. 46,47,60,63 Various types of DC-based vaccines have been generated so far, which can be classified depending on the protocol for loading DCs with TAAs or for the biochemical manipulation of DCs. 54,63 These include (but are not limited to) (1) unstimulated DCs or DCs exposed to specific maturation cocktails (consisting of various immunostimulatory cytokines and toll-like receptor (TLR) agonists), 66-70 (2) DCs exposed ex vivo to tumor-cell lysates or other preparations enriched in one or more TAAs; 71-121 (3) direct delivery of TAAs to DCs in vivo; 122-134 (4) in situ anticancer vaccination by intra-tumoral administration of immunomodulatory molecules to activate local DCs 135 and (5) exosomes derived from DCs. 136-141 However, the DC-based vaccine most commonly used so far involves the loading of DCs with a source of TAAs followed by their stimulation with defined maturation cocktails. 142,143 Ex vivo, DC loading with TAAs is typically accomplished by (1) co-culturing iDCs with either autologous or allogeneic tumor-cell lysates 71,80,144-146 or recombiant TAAs; 81,88,147 (2) transfecting DCs with vectors or RNAs coding for TAA(s), or even bulk RNA derived from tumor cells; 41,89,113,148-152 and (3) creating fusions between DCs and incapacitated malignant cells (also known as “dendritomes”). 114-121 Alternatively, TAAs can be specifically conveyed to DCs in vivo by (1) fusing them to monoclonal antibodies, polypeptides or carbohydrates that specifically target DC-specific receptors (e.g., mannose receptor, C type 1 (MRC1), CD209 (also known as DC-SIGN), and lymphocyte antigen 75 (LY75, also known as DEC-205)). 122-128,136,131,133,153 or DC-associated glycolipids (e.g., glycosphingolipid globotriaosylceramide (Gb3)); 154,155 (2) encapsulating them in immunoliposomes that target DCs, 156-158 or (3) encoding them in vectors targeting DCs. 159,162 In the latter case, to overcome the tolerogenic activity of iDCs, 123,124 strategies aiming to target DCs in vivo also need to simultaneously integrate DC-activating stimuli such as TLR agonists and/or pro-inflammatory cytokines. 163 The concept of targeting TAAs to DCs in vivo has recently been harnessed for the development of CDX1401 (Celldex Therapeutics, USA), a DC-based vaccine consisting of a fully human anti-DEC205 monoclonal antibody (3G9) fused to the human TAA cancer/testis antigen 1B (CTAG1B; also known as NY-ESO-1). 164 In an early phase clinical trial, cancer patients receiving CDX1401 in combination with TLR3 and TLR7/8 agonists experienced efficient generation of NY-ESO-1-directed T-cell and humoral responses. 164

Another strategy of DC-based vaccination that has begun to receive attention involves specific naturally occurring DC subsets, which can be isolated via high-performance antibody-coated magnetic beads. 165,166 Accumulating clinical evidence demonstrates that DC-based vaccines consisting of pDC or CD1c⁺ DCs loaded with TAA-derived peptides achieve promising efficacy in melanoma patients. 165,166 In fact, CD1c⁺ DC-based vaccines induced long-term progression-free survival (1–3 y) in ~28% of treated melanoma patients. 166 Last but not least, while most of DC-based vaccines are administered to cancer patients in a curative setting, DC-based vaccines have recently been used also as neoadjuvant treatment. 167 Breast cancer patients exhibiting overexpression of Erb-B2 receptor tyrosine kinase 2 (ERBB2; also known as HER2) are often susceptible to disease recurrence. In this setting, DC-based vaccine pulsed with HER2-derived MHC class I and II-binding peptides is being applied before surgical resection of the tumor. 167 While clinical trials based on this strategy are ongoing (e.g., NCT02063724), preliminary evidence suggests that this vaccine efficiently induces HER2-targeting immunity and decreases the burden of residual HER2high tumor cells in breast cancer patients. 167

In general, the efficacy of DC-based vaccination is influenced by various factors including the amount of functional
activation that can be achieved, the nature and source of TAAs, the immunological fitness of the host, the type of DC receptors engaged and the specific DC-subset that was targeted.\(^{168-172}\) Moreover, the presence of some cytokines like interleukin 12 (IL-12) can also be decisive for patients administered with DC-based vaccines to achieve clinical responses. Thus, the combinatorial administration of IL-12 or CD40 and TLR ligands (which stimulate IL-12 secretion) is generally encouraged.\(^{173,174}\) It is important to mention that only one cellular therapy involving DCs (but not restricted to them) is presently licensed for use in humans, namely, sipuleucel-T (branded as Provenge\(^\circ\)). Since 2010, sipuleucel-T has been approved for the treatment of asymptomatic or minimally-symptomatic metastatic castration-resistant prostate cancer.\(^{175-178}\) The company manufacturing Provenge\(^\circ\), however, filed for bankruptcy a few years later, and has now been acquired by a multinational specialty pharmaceutical company, casting doubts on the actual cost-effectiveness of their lead product.

In this Trial Watch, we recapitulate the latest developments in the field of DC-based cancer immunotherapy, discussing the results of major preclinical and clinical studies published recently, and ongoing clinical trials relative to the publication of our previous Trial Watch on this topic. Moreover, we analyze the broad impact of cancer immunotherapies including immune checkpoint blockers (ICBs),\(^{179,180}\) and adoptive T-cell transfer (ACT)\(^{181,182}\) on the field of DC-based vaccines.\(^{183,184}\) Indeed, ongoing clinical trials are identifying a niche for DC-based vaccines in a cancer immunotherapy landscape dominated by ICBs and ACT.

**Recent preclinical developments**

A number of interesting preclinical studies dealing with DC-based anticancer immunotherapy have been published in the last 2.5 y (September 2014 to February 2017, i.e., the approximate period since the publication of the latest Trial Watch on this topic). While summarizing all of these studies here is not possible, we found the following ones to be of particular interest and, in some cases, largely representing the general trends in this field (not mentioned in any particular order): (1) Mitchell et al. documented that pre-conditioning the intended site for DC-based vaccination with the tetanus/diphtheria toxoid (acting as a "recall antigen") significantly improves the lymph node-homing of DCs thereby inducing (CCL3-dependent) anti-glioblastoma immunity following DC-based vaccination in mice and patients;\(^{185}\) (2) Carreno et al. reported that a DC-based vaccine boosts (naturally-occurring) neoantigen-specific anti-melanoma immunity (comprising an increase in diversity and clonality of neoantigen-specific T cells) associated with de novo emergence of MHC class I-restricted neoantigens;\(^{186}\) (3) Garg et al. found that next-generation DC-based vaccines relying on immunogenic cell death (ICD) elicited by hypericin-dependent photodynamic therapy (Hyp-PDT) in glioma cells induce potent anti-glioblastoma immunity in an orthotopic murine model (both in prophylactic and curative settings, alone or in combination with chemotherapy), accompanied by a shift from a Treg-dominated intracranial immune contexture to a Th1/Th17/CTLs-dominated one;\(^{187}\) (4) Ohshio et al. observed that targeting immunosuppressive cancer-associated fibroblasts with an anti-fibrotic agent, tranilast, in combination with DC-based vaccination drastically improves (CTL- and NK-cell-driven) antitumor immunity against subcutaneously transplanted lymphomas, lung carcinomas and melanomas;\(^{188}\) (5) Xiang et al. documented that ovalbumin-loaded upconversion nanoparticles (i.e., nanoparticles exhibiting photon upconversion, a process wherein two or more photons of low energy are absorbed and converted into a single emitted photon of higher energy) can be used for antigen loading and maturation of DCs, which can also be tracked in vivo (via luminescence imaging), so that these DCs eventually drive potent ovalbumin-specific immunity;\(^{189}\) (6) Carmi et al. discovered that DC-based vaccines relying on tumor cells coated with naturally occurring tumor-binding IgG antibodies or DC-based vaccines administered in combination with allogeneic IgG antibodies (two strategies aimed at facilitating allogeneic tumor rejection) elicit strong antitumor immunity in mouse models of (autologous or autochthonous) melanoma as well as breast, pancreatic and lung carcinoma;\(^{190}\) (7) Vandenberk et al. reported that DC-based vaccines relying on irradiated, freeze/thawed (F/T) glioma cells induce significant anti-glioblastoma immunity, driven (at least in part) by CTL responses elicited by oxidation-associated molecular patterns (OAMPs);\(^{191}\) (8) Lu et al. observed that a DC-based vaccine generated with a cancer stem cell (CSC)-lyste administered in combination with localized radiotherapy induce potent antitumor immunity driven (at least in part) by B cell-dependent humoral responses and a significant shift in the "chemokine" of the tumor;\(^{192}\) (9) Jung et al. discovered that using *Mycobacterium tuberculosis* heat shock protein X (HspX) as an adjuvant for DC-based vaccines facilitates Th1/CTL-driven antitumor immunity;\(^{193}\) (10) Willemen et al. reported that electroporating DCs with an IFN-\(\alpha\)-coding mRNA significantly enhances their ability to drive TAA-specific CTLs and antitumor NK-cell responses;\(^{194}\) and (11) Martin et al. discovered that ansamitocin P3, a microtubule depolymerizing agent, enhances DC activation thereby making DC-based vaccines potent inducers of antigen-specific T cells, especially in combination with ICBs targeting programmed cell death 1 (PDCD1, also known as PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA4).\(^{195}\)

**Completed clinical trials**

In the last 2.5 y (September 2014 to February 2017), 43 peer-reviewed publications have documented the outcome of various clinical trials evaluating DC-based vaccines as therapeutic anticancer interventions. These publications were acquired from PubMed (http://www.ncbi.nlm.nih.gov/pubmed), by using the following search string: “[cancer OR tumor OR tumor] AND ([DC OR dendritic OR "dendritic cells" OR "dendritic cell"] AND (vaccine OR vaccination OR infusion OR injection OR immunotherapy)).” The initial list was manually curated to ensure relevance for this Trial Watch.

More than half of these studies (Fig. 1) involved autologous DCs exposed to autologous tumor-derived RNA,\(^{196}\) tumor-cell lysates,\(^{197,203}\) autologous tumor stem cell lysates,\(^{204}\) self-renewing and proliferating autologous tumor cells,\(^{205}\) allogeneic cancer cell line lysates,\(^{206-208}\) TAAs or TAA-derived peptides\(^{209-218}\) or a combination thereof.\(^{219}\) Most clinical studies based on the latter approach preferred
melanoma-associated differentiation antigens including pre-melanosome protein (PMEL; also known as gp100), antigens belonging to the melanoma antigen gene (MAGE) family, tyrosinase (TYR) and Melan-A (MLANA; also known as MART1) (Fig. 1). In addition, a few trials tested autologous DCs manipulated by electroporation or (viral) transfection with TAA-coding mRNA (Fig. 1). Finally, a few studies preferred to use “unpulsed” autologous (matured ex vivo) DCs, administered in combination with cytokine-induced killer cells (CIKs), chemotherapy and/or radiotherapy. Other approaches included the use of autologous dendritomas, allogeneic peripheral blood mononuclear cells matured ex vivo into DCs, or autologous unpulsed DCs combined with ACT.

Regarding the distribution across different cancer types (Fig. 1), patients harboring melanoma were most commonly enrolled in these trials, followed by patients with prostate cancer, glioma or glioblastoma (GBM), hepatocellular carcinoma, non-small cell lung carcinoma (NSCLC), renal cell carcinoma (RCC), esophageal carcinoma, and pancreatic ductal adenocarcinoma, among others. Of note, only two trials included a wide range of advanced solid tumors refractory to previous treatments.

Most of these publications documented DC-based vaccines to elicit immune responses (generally in combination with standard-of-care therapies) achieving disease stabilization in most cases and partial or complete responses at a comparatively
lower frequency. In several instances, DC-based vaccines have been administered in combination with conventional immunostimulatory agents including cytokines (e.g., IL-2, colony stimulating factor 2 (CSF2; also known as GM-CSF), IFN-α/β, IFNγ or IFNβ),{199,205,221,224,227} the tetanus toxoid,{185} or TLR agonists.{211} Interestingly, a few clinical studies also tested DC-based vaccines in combination with ACT and ICBs.{198,230,235} The combination of a DC-based vaccine with ipilimumab (an anti-CTLA4 ICB currently approved for the treatment of melanoma patients) achieved a promising overall response rate of 38% (eight patients with complete responses and seven with partial responses) and a 6-mo disease control rate of 51%.{235} Similarly, among eight Stage IV melanoma patients treated with DC-based vaccination followed by tumor-infiltrating lymphocyte (TIL)-based ACT, one patient achieved complete remission and two others achieved stable disease (although in this case the study size prevented from drawing robust conclusions).{198} Interestingly, a Phase III trial demonstrated that unpulsed DCs in combination with adoptively transferred autologous activated CTLs derived from patient lymph nodes (delivered in combination with platinum-based chemotherapy) significantly improved long-term survival in NSCLC patients when compared with chemotherapy alone.{230}

Many of these studies also brought into focus various predictive biomarkers of clinical responses to DC-based vaccination. For instance, an increased overlap in the TCR repertoire of TILs and blood-borne T cells correlated with improved responses to DC-based vaccination and overall survival in glioma patients.{202} Conversely, a T-cell polarization skewed toward an immunosuppressive Th2 phenotype was found to reduce the therapeutic efficacy of DC-CIK co-administration in NSCLC patients.{207} Finally, increased plasma levels of pro-inflammatory cytokines like IL-6 and IL-8 negatively correlated with overall survival following DC-based vaccination in pancreatic ductal adenocarcinoma patients.{236}

Collectively, these studies highlight that DC-based vaccines are well-tolerated by cancer patients, with mild flu-like symptoms and local irritation at the injection site being the most common side effects, and can elicit antitumor immune response of therapeutic value.

**Ongoing clinical trials**

When this Trial Watch was being redacted (February 2017), official sources listed no less than 72 clinical trials initiated after 1st of September, 2014 to be evaluating anticancer DC-based vaccines in the ClinicalTrials.gov database (http://www.clinicaltrials.gov/). These were retrieved by using the following search string: “(cancer OR tumor OR tumor) AND (((DC OR dendritic OR “dendritic cells” OR “dendritic cell”) AND (vaccine OR vaccination OR infusion OR injection)).” The initial list was manually curated to ensure relevance for this Trial Watch. The specific details of the different short-listed clinical trials are elaborated in the Table 1.

The majority of these studies involved autologous DCs exposed to autologous tumor-derived RNA, tumor-cell lysates and TAAs or TAA-derived peptides (Fig. 1 and Table 1). The rest consisted of either autologous DCs loaded with autologous tumor stem cell lysates, autologous DCs (virally) transfected with TAAs-coding mRNA, or autologous dendritomas, among others (Table 1). Most clinical studies focusing on TAAs or TAA-derived peptides selected following antigens: mucin 1 (MUC1), baculo viral IAP repeating containing 5 (BIRC5; also known as survivin), HER2, NY-ESO-1 and Wilms Tumor 1 (WT1) (Fig. 1 and Table 1). Also, several ongoing clinical trials relied on loading a complex mixture of TAAs or TAA-derived peptides onto the autologous DCs for vaccine production (Table 1). Regarding trial distribution across cancer types, patients harboring glioma or GBM were the most commonly enrolled, followed by patients with lung cancer, melanoma, liver cancer and gastric cancer, among others (Fig. 1 and Table 1). Of note, there is no ongoing Phase III clinical trial administering DC-based vaccines.

Most ongoing clinical trials are testing the administration of DC-based vaccines in combination with standard-of-care chemo- or radiotherapy (including known ICD inducers) (Table 1).{35,237,238} However, several chemotherapies that are unable to promote ICD are also being combined with DC-based vaccination, wherein cisplatin is the preferred option (Table 1).{35} Furthermore, combinatorial regimens included targeted therapies such as the broad spectrum receptor tyrosine kinase inhibitor sunitinib, the CD25-targeting antibody basiliximab, the CD20-targeted antibody rituximab and HER2-targeted antibodies like trastuzumab and pertuzumab. Interestingly, a few studies are testing DC-based vaccines in combination with anti-inflammatory drugs (e.g., celecoxib). It will be interesting to see whether such drugs increase or decrease the efficacy of DC-based vaccination.

Finally, multiple ongoing clinical trials are combining DC-based vaccines with immunostimulatory cytokines (IL-2, GM-CSF, IFN-α/β), the tetanus diphtheria toxoid, or TLR agonists (e.g., rintatolimod, hiltonol). Notably, there has been a palpable surge in the number of clinical trials combining DC-based vaccines with the tetanus diphtheria toxoid in GBM patients. Finally, several ongoing clinical trials are testing DC-based vaccines in combination with CIK cells, ICBs and ACT (Table 1).

**Status update on clinical trials**

The following clinical trials, enlisted in the previous edition of Trial Watch dealing with this topic,{238} have changed status since: NCT02042053 and NCT02107378 have been “Terminated,” NCT02115126 and NCT02033616, have been “Withdrawn;” NCT02063724, NCT02049489, NCT01974661, NCT02107937, NCT02107950, NCT02107404, NCT02137746, NCT01956630, NCT02129075 and, NCT01981122, were previously “Recruiting” but are now listed as “Active, Not recruiting;” NCT0183297, NCT02070406, NCT02151448, NCT01983748 and, NCT02170389, were previously “Not yet recruiting,” but are now listed as “Recruiting;” NCT01926639 and NCT02159950, have since been “Completed” (source http://www.clinicaltrials.gov). NCT02115126 and NCT02033616 have been withdrawn due to unknown reasons. NCT02107378 has been terminated due to a not-better specified decision by the trial sponsors, and NCT02042053 has been terminated because the principal investigator of the trial left the designated institute.
| Type of DC vaccine | Cancer type                          | Trial phase | Status                  | TAA(s)           | Combinatorial treatment                                                                 | Ref.       |
|--------------------|--------------------------------------|-------------|-------------------------|------------------|--------------------------------------------------------------------------------------------|------------|
| DCs transfected with adenovirus coding TAAs | Small cell lung cancer               | I/II        | Active, not recruiting  | MUC1, Survivin   | CIK cells                                                                                 | NCT02688673 |
|                   | NSCLC                                 | I/II        | Not yet recruiting      | SOCS, MUC1, Survivin | CIK cells                                                                                 | NCT02688686 |
|                   | Esophageal cancer                     | I/II        | Active, not recruiting  | MUC1, Survivin   | CIK cells                                                                                 | NCT02693236 |
|                   | Gastric cancer                        | I           | Not yet recruiting      | CEA              | CTLs                                                                                     | NCT02602249 |
|                   | Multiple myeloma                      | I           | Active, not recruiting  | Survivin         | Autologous haematopoietic cell transplantation                                           | NCT02496273 |
|                   |                                      |             |                         |                  |                                                                                            | NCT02851056 |
|                   | Allogeneic DCs (Intuvax)              | RCC         | Recruiting              | —                | Sunitinib (Nephrectomy)                                                                   | NCT02432846 |
|                   |                                      | Gastrointestinal stromal tumors | Not yet recruiting | —                | Sunitinib                                                                                 | NCT02686944 |
|                   | Autologous DCs                        | Ovarian cancer | Recruiting                | —                | Cisplatin, celecoxib, IFN, Rintatolimod                                                  | NCT02432378 |
|                   |                                      | Solid tumors | Active, not recruiting   | —                | Pemetrexed, Carboplatin                                                                   | NCT02882659 |
|                   |                                      | NSCLC with wild type-EGFR | Recruiting               | —                | Pemetrexed, Carboplatin                                                                   | NCT02669719 |
|                   |                                      | Follicular lymphoma | Recruiting                | —                | Intranodal immunotherapy (Radiation, Rituximab, GM-CSF) and Pembrolizumab                | NCT02677155 |
|                   |                                      | Colon cancer   | Not yet recruiting        | —                | Calecoxib, IFN2b, Rintatolimod                                                          | NCT02615574 |
|                   | Autologous DCs loaded with tumor cell lysate | Multiple myeloma | I/II Recruiting            | —                | Cyclophosphamide                                                                         | NCT02248402 |
|                   |                                      | RCC          | Not yet recruiting        | —                | CIKs                                                                                     | NCT02487550 |
|                   |                                      | Sarcomas or CNS tumors | Recruiting               | —                | Surgery/Chemotherapy/Radiotherapy                                                         | NCT02496520 |
|                   |                                      | Colorectal cancer | Not yet recruiting         | —                | Modified FOLFOX6 [mFOLFOX6] (Oxaliplatin, 5-Fluorouracil and Leucovorin)               | NCT02503150 |
|                   |                                      | Solid pediatric malignancies | Completed                | —                | IL-2                                                                                     | NCT02533895 |
|                   |                                      | Esophageal cancer | Recruiting                | —                | CIK cells; Prior to DC-CIK: Paclitaxel, cisplatin                                         | NCT02644863 |
|                   |                                      | Melanoma      | Recruiting                | —                | IL2                                                                                      | NCT02718391 |
|                   |                                      | Neuroblastoma | Recruiting                | —                | Standard-of-Care ICBs treatment                                                         | NCT02678741 |
|                   |                                      | GBM          | Active, not recruiting    | —                | Haematopoietic progenitor cell (HPC) transplant                                          | NCT02745756 |
|                   |                                      | GBM          | Recruiting                | —                | Temozolomide, Radiotherapy                                                              | NCT02772094 |
|                   |                                      | GBM          | Not yet recruiting         | —                | Basiliximab, Tetanus Diptheria toxin                                                     | NCT02366728 |
|                   |                                      | Colorectal cancer | Not yet recruiting         | —                | Nivolumab                                                                                 | NCT03014804 |
|                   |                                      | GBM          | Not yet recruiting         | —                |                                                                                         | NCT02820584 |
|                   |                                      | GBM          | Recruiting                | —                | Mixture of five allogeneic tumor cell lysates                                             | NCT02395679 |
|                   | Hematological malignancies            | I/II         | Recruiting                | Minor histocompatibility complex | —                                                                                      | NCT02528682 |
|                   | Acute myeloid leukemia                | I/II         | Recruiting                | —                | —                                                                                         | NCT02405338 |
|                   | Glioma and/or GBM                     | I/II         | Recruiting                | —                | —                                                                                         | NCT02465268 |
|                   | I                                      | Recruiting                | —                | GM-CSF, Tetanus Dipheria Toxoid                                                          | NCT02529072 |
|                   | II                                      | Recruiting                | —                | Nivolumab, Tetanus Dipheria Toxoid                                                        | NCT02694982 |
|                   | II                                      | Recruiting                | —                | Temozolomide, Allogeneic PBMCs, Autologous irradiated tumor cells                          | NCT02808364 |
|                   | II                                      | Recruiting                | —                | Allogeneic PBMCs, Chemo/Radiotherapy and cycles of Temozolomide treatment                 | NCT02709616 |
|                   | II                                      | Recruiting                | —                | Platinum/Pemetrexed, Cisplatin, TAs-pulsed Allogeneic PBMCs, Autologous irradiated tumor cells | NCT02649829 |
|                   | Pleural mesothelioma                   | I/II         | Recruiting                | WT1              | Allogeneic PBMCs, Chemo/Radiotherapy and cycles of Temozolomide treatment                 | NCT02808416 |

(Continued on next page)
| Type of DC vaccine                                      | Cancer type                  | Trial phase | Status          | TAA(s)                                      | Combinatorial treatment                                      | Ref.          |
|--------------------------------------------------------|------------------------------|-------------|-----------------|---------------------------------------------|--------------------------------------------------------------|---------------|
| Autologous DCs loaded with TAA(s) or TAA-derived peptide(s) | Prostate cancer              | II          | Recruiting      | TARP                                        | —                                                            | NCT02362451  |
|                                                        |                               | I           | Enrolling by invitation | TARP                                      | —                                                            | NCT02362464  |
|                                                        |                               | II          | Recruiting      | Whole antigens, NY-ESO-1, MUC1 PepTivator   | —                                                            | NCT0269976   |
| Breast cancer                                          | I                             | Recruiting  | Tumor blood vessel antigen | Gemcitabine                                | —                                                            | NCT02479230  |
| CML                                                    | I/II                          | Recruiting  | BCR/ABL, WT1, proteinase-3 | —                                         | —                                                            | NCT02543749  |
| Melanoma                                               | II                            | Active, not recruiting | —              | —                                           | —                                                            | NCT02574377  |
|                                                        |                              | Active      | —               | —                                           | —                                                            | NCT02993315  |
|                                                        | II                            | Recruiting  | NY-ESO-1, Melan-A/MART-1 | —                                         | —                                                            | NCT02334735  |
| Solid malignancies                                     | I/II                          | Not yet recruiting | —              | —                                           | —                                                            | NCT02705703  |
| Liver cancer                                           | I/II                          | Not yet recruiting | Sp17, Ropporn, AKAP4, PTTG1, Span-xb, HER2, HM1.24, NY-ESO-1, MAGE-1 | —                                         | —                                                            | NCT02709993  |
| Solid tumors                                           | I                             | Not yet recruiting | NY-ESO-1        | —                                           | —                                                            | NCT02775292  |
|                                                        | I/II                          | Recruiting  | —               | —                                           | —                                                            | NCT02789195  |
| RCC                                                    | I/II                          | Not yet recruiting | MAGE-3, MAGE-4, Survivin, HER2, COX-2 CTL epitopes | —                                         | —                                                            | NCT02529579  |
|                                                        | I/II                          | Terminated  | MAGE-A1, MAGE-A3, NY-ESO-1 | —                                         | —                                                            | NCT02332889  |
| HGG, medulloblastomas, CNS tumors                      | Ductal carcinoma in situ      | I/II        | Active, not recruiting | HER2                                        | Trastuzumab, Pertuzumab                                      | NCT02336984  |
| HER-2 positive cancers                                  | I                             | Temporarily not available | —              | —                                           | —                                                            | NCT02473653  |
| Pancreatic cancer                                       | I/II                          | Recruiting  | —               | —                                           | —                                                            | NCT02548169  |
|                                                        | I/II                          | Recruiting  | —               | —                                           | —                                                            | NCT02529579  |
|                                                        | I/II                          | Withdrawn   | MUC1            | —                                           | —                                                            | NCT02310971  |
|                                                        | I/II                          | Recruiting  | IDH1R132H       | —                                           | —                                                            | NCT02771301  |
| Glioma                                                 | NSCLC                         | I           | Withdrawn       | Neoantigens                                 | Cyclophosphamide                                              | NCT02419170  |
| Dendritomas                                             | Multiple myeloma              | II          | Recruiting      | —                                           | —                                                            | NCT02728102  |
|                                                        |                               |             |                 | —                                           | —                                                            |               |
| Autologous DC-CIK combinations                          | Solid tumors                  | I/II        | Recruiting      | —                                           | CIK cells, anti-PD1 immunotherapy                             | NCT02886897  |
|                                                        | Hepatocellular carcinoma      | I           | Recruiting      | —                                           | CIK cells, TACE, S-FU, Lipiodol                               | NCT02487017  |
|                                                        | Breast cancer                 | I           | Active, not recruiting | —                                         | CIKs, Capecitabine                                            | NCT02491697  |
| DC-CTL                                                  | NSCLC                         | II          | Not yet recruiting | —                                           | Gemcitabine/Cisplatin                                        | NCT02766348  |
| DCs combination with T cells targeting neoantigens or TAA | Biliary tract tumors          | I/II        | Recruiting      | —                                           | Gemcitabine                                                  | NCT02632019  |
|                                                        | Liver cancer                  | I/II        | Recruiting      | —                                           | —                                                            | NCT02873442  |
|                                                        | I/II                          | Recruiting  | —               | —                                           | —                                                            | NCT02862613  |
|                                                        | I/II                          | Recruiting  | —               | —                                           | —                                                            | NCT02632188  |
|                                                        | I/II                          | Recruiting  | —               | —                                           | —                                                            | NCT02638857  |
|                                                        | Gastric cancer                | I/II        | Recruiting      | —                                           | Cisplatin, S-FU                                              | NCT02862561  |
|                                                        | I/II                          | Recruiting  | —               | —                                           | Cisplatin, S-FU                                              | NCT02873520  |
|                                                        | Lung cancer                   | I/II        | Recruiting      | —                                           | Cisplatin, Gemcitabine                                       | NCT02862587  |
|                                                        | I/II                          | Recruiting  | —               | —                                           | Cisplatin, Gemcitabine                                       | NCT02873416  |

Abbreviations: S-FU, 5-fluourouracil; CEA, Carcinoembryonic antigen; CIK, cytokine-induced killer; CML, chronic myeloid leukemia; CNS, central nervous system; COX, cyclooxygenase; CTL, cytotoxic T lymphocytes; DC, dendritic cell; DLI, donor lymphocyte infusion; GBM, glioblastoma multiforme; GM-CSF, granulocyte macrophage colony-stimulating factor; GMCSF, granulocytic monocytic colony-stimulating factor; HGG, high-grade glioma; ICB, immune checkpoint blocker; IFN, interferon; IL, interleukin; IMAGE, melanoma antigen family; MLANA, melan A; MUC1, mucin 1; NSCLC, non-small cell lung cancer; NY-ESO-1, New York esophageal squamous cell carcinoma-1; PBMC, peripheral blood mononuclear cells; PD1, programmed cell death-1; PRAME, preferentially expressed antigen in melanoma; RCC, renal cell carcinoma; TAA, tumor-associated antigen; TACE, trans-cathether arterial chemoembolization; TARP, T-cell receptor γ alternate reading frame protein; TCR, T cell receptor; WT1, Wilms tumor 1.
Concluding remarks

A plethora of strategies have been developed in the past decades to exploit the anticancer activity of DCs – culminating in the paradigm of DC-based cancer immunotherapy. The studies presented in this survey show that – despite the emergence of ICBs and ACT – the field of DC-based vaccination is still vibrant (both preclinically and clinically). However, ICBs and ACT have definitely influenced the clinical application of DC-based vaccines. For instance, many clinical studies that have been published in the period between September 2014 and February 2017 were initiated before or just around the time ICBs gained clinical foothold. In these studies, DC-based vaccines were mostly administered to melanoma patients and hence were based on melanoma-associated differentiation antigens240 (Fig. 1). However, the major survival advantage provided to melanoma patients by ICBs is not responsive to DC-based vaccines. Interestingly, recombinant TAAs, TAA-derived peptides and tumor-cell lysates remain the preferred source of antigens for loading DCs for DC-based vaccines across both Phase I/II clinical trials (derived from Phase I/II clinical trials) rather than on long-term survival, also reflecting a paucity in Phase III clinical trials testing anticancer DC-based vaccines.68,184,187,241 Interestingly, recombiant TAAs, TAA-derived peptides and tumor-cell lysates remain the preferred source of antigens for loading DCs for DC-based vaccines across both published and ongoing clinical studies (Fig. 1 and Table 1). These trends illustrate that the field of DC-based vaccines is readily adapting to the shift in cancer immunotherapy.

As it stands, there is an urgent need for clinical studies demonstrating that DC-based vaccines can induce durable objective responses and improve long-term survival in cancer patients. While the field of DC-based vaccination gained momentum with the approval of sipuleucel-T for the immunotherapy of prostate cancer patients,242 the overall development of DC-based vaccines has been facing multiple obstacles. For instance, DC-based vaccines have failed to achieve more than 15% objective response rates in cancer patients.48 Moreover, most of the clinical efficacy data in this setting rely on short-term criteria (derived from Phase I/II clinical trials) rather than on long-term survival, also reflecting a paucity in Phase III clinical trials testing anticancer DC-based vaccines.46 Besides efficacy issues, the development of DC-based vaccination for clinical use has also been hampered by the relatively high financial and human resources associated with production in good manufacturing practice (GMP) facilities.47 Immunologically speaking, the relatively low avidity of TAA-specific T cells and the robust immunosuppression imposed on TILs have constituted major obstacles to the efficacy of DC-based vaccines even when vaccines could successfully generate tumor-specific, peripheral CTLs (a typical mechanistic biomarker of the immunostimulatory potency of DC-based vaccines in patients).47,243-245 At least theoretically, this latter problem could be overcome by combining DC-based vaccines with ICBs or ACT – an endeavor currently being pursued by many investigators. That said, highly reliable predictive biomarkers of the clinical efficacy of DC-based vaccines are still missing. In conclusion, there is an urgent need to reduce the costs associated with the manufacturing of DC-based vaccines and to increase the homogeneity of the process (which would enable for multi-center Phase III clinical trials). Moreover, biomarker-guided clinical trials involving highly efficacious DC-based vaccines combined with ICBs, ACT or other (immuno)therapies will have to be designed to elucidate the actual clinical potential of DC-based vaccination.

Disclosure of potential conflicts of interest

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