ONCOIMMUNOLOGY
2022, VOL. 11, NO. 1, e2096363 (19 pages)
https://doi.org/10.1080/2162402X.2022.2096363

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REVIEW

Trial watch: Dendritic cell (DC)-based immunotherapy for cancer

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ABSTRACT

Dendritic cell (DC)-based vaccination for cancer treatment has seen considerable development over recent decades. However, this field is currently in a state of flux toward niche-applications, owing to recent paradigm-shifts in immuno-oncology mobilized by T cell-targeting immunotherapies. DC vaccines are typically generated using autologous (patient-derived) DCs exposed to tumor-associated or -specific antigens (TAAs or TSAs), in the presence of immunostimulatory molecules to induce DC maturation, followed by reinfusion into patients. Accordingly, DC vaccines can induce TAA/TSA-specific $CD8^+$/$CD4^+$ T cell responses. Yet, DC vaccination still shows suboptimal anti-tumor efficacy in the clinic. Extensive efforts are ongoing to improve the immunogenicity and efficacy of DC vaccines, often by employing combinatorial chemo-immunotherapy regimens. In this Trial Watch, we summarize the recent preclinical and clinical developments in this field and discuss the ongoing trends and future perspectives of DC-based immunotherapy for oncological indications.

ARTICLE HISTORY
Received 28 June 2022
Accepted 28 June 2022

KEYWORDS
Dendritic cells; DAMPs; TAAs; antigen cross-presentation; T cell priming; immune checkpoint blockers; tumor-infiltrating lymphocytes; clinical trial

Introduction

The identification of dendritic cells (DCs) for the first time in 1973 by Ralph Steinman, who was eventually awarded a Nobel Prize for this ground-breaking discovery in 2011, laid the foundation for the field of DC immunology in health and disease.[1,2] Since then, extensive research has been done to understand the functionality and ontology, as well as interface with $CD4^+$/$CD8^+$ T cells and, in recent decades, to understand how to harness their immunological potential for anti-cancer immunotherapy.

DCs are professional antigen-presenting cells (APCs), largely regarded as a crucial link between innate and adaptive immune compartments.[3–6] DCs specialize in antigen presentation. They are not only able to present extracellular antigens on major histocompatibility complex (MHC) class II molecules to $CD4^+$ T helper (T_H) cells but also to present extracellular antigens on MHC class I molecules to $CD8^+$ T cells.[7] This phenomenon is known as cross-presentation and is crucial for efficacious anti-tumor immune responses.[7]

DCs are a ubiquitous and highly heterogeneous group of myeloid cells, being present all over the body, and being involved in a variety of immunological functions. Due to this heterogeneity, DC classification into well-defined biological subsets based on their phenotype, ontogeny, and functions has been continuously refined and updated as advances in high-dimensional flow cytometry and single-cell transcriptomics technologies have together accelerated the knowledge garnered on DC subsets' highly specialized features and functions.[8–11] Accordingly, the classification criteria have moved from the classical functional and location-based, toward classifying DCs based on lineage and ontogeny thereby resulting in three major subsets of DCs: two types of 'classical' or 'conventional' DCs (cDCs) i.e., type 1 cDC (cDC1) as well as type 2 cDC (cDC2), and plasmacytoid DC (pDC)[12–16]. Whereas it has historically been believed that DCs arise from monocytes, cDCs or pDCs are now well established to be fully distinct, lineage-wise, from monocyte-derived DCs (moDCs).[10,17,18] Herein, while cDC1 and cDC2 arise from

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the same common DC progenitor (CDP), the ontogeny of pDCs is still in debate, with recent studies suggesting a lymphoid origin for this subset.[19–21]

Human cDC1s can be identified using various highly specific cell surface markers, such as: cell adhesion molecule 1 (CADM1), thrombomodulin (THBD, also known as CD141), C-type lectin domain containing 9A (CLEC9A), as well as X-C motif chemokine receptor 1 (XCR1), which can also be used to identify cDC1 in mouse.[14,17,22–24] Defining the cDC2 subset is more complex due to the high heterogeneity and variability in surface marker expression both in humans and mice, leading to the subdivision of this subset into further clusters, distinguished based on CD5 expression: $CD5^+$ cDC2 (DC2) and $CD5^-$ cDC2 (DC3).[12,14] Of note, it remains unclear whether DC3 arise from CDPs.[9,14] While other cDC2 subsets have been proposed, namely DC4 ($CD1C^-CD141^-$) and DC5 ($AXL^+SIGLEC6^+$),[12] their classification within the myeloid population and functional characterization still requires further studies.

The DC subsets also exhibit functional heterogeneity, with each subset specializing in distinct and assorted overlapping immunological functions, which also vary based on location.[6] cDC1 specialize in the activation of $CD8^+$ T cells through cross-presentation and responses to intracellular pathogens.[25–28] cDC1s play a crucial role in anti-tumor immunity, being the only APCs that can efficiently prime tumor-specific $CD8^+$ T cells.[28–31] In addition, cDC1s are major producers of IFN-λ, which has been contextually described to skew T cell responses toward a T_H1 bias.[32,33] In both mice and humans, cDC1 are indispensable for attracting $CD8^+$ T cells into tumors such that, the abundance of cDC1 in the tumor microenvironment (TME) is positively correlated with patient survival.[25,34] cDC2s' main function is considered to be the presentation of exogenous antigens (e.g., from extracellular pathogens) to different $CD4^+$ T_H subsets, although this subset is as functionally heterogeneous as it is ontogenetically.[35,36] In comparison to cDC1s, knowledge on cDC2s' functions in anti-tumor responses is only starting to build up recently. It is emerging that cDC2s perform a non-redundant role in mobilizing both $CD8^+$T cell responses and $CD4^+$ T_H cell priming.[9,35,37,38] Moreover, unlike cDC1s, cDC2s can secrete high levels of interleukin-12 (IL-12),[39–41] which is crucial for T and natural killer (NK) cell expansion and survival.[41–43] pDCs excel at type I interferon (IFN) responses, mounting stronger type I IFN responses than any other DC subsets, and being the major producers of IFN-α.[44–47] Yet, high frequencies of pDCs in the tumor associate with poor prognosis in multiple human cancer types, likely due to frequent impairment of type I IFN production in the TME, leading to immunosuppression.[9,48–54]

In the absence of pathophysiological stimuli, both tissue-resident and circulating DCs exist in an immature or steady-state and are essential for immunosurveillance.[55–57] Immature DCs (iDCs) are essential to maintain tolerance to self-antigens in the periphery, having the ability to suppress or even facilitate clonal deletion of self-reactive T cells, and to promote the expansion of $CD4^+CD25^+FOXP3^+$ regulatory T cells (T_{REG}).[55,58–62] In this state, these iDCs exhibit (1) proficient uptake of extracellular material, coupled with secretion of homeostatic cytokines and chemokines, (2) retention of MHC class II molecules in late endosomes, (3) expression of various chemokine receptors, which enable rapid chemotaxis of iDCs to inflammation sites, and (4) minimal to negligible expression of co-stimulatory molecules, such as CD80, CD83, CD86, CD70, CD40, and tumor necrosis factor (ligand) superfamily member 4 (TNFSF4, also known as OX40L).[56,63]

When iDCs encounter (potentially antigenic) inflammation accompanied by microbial stimuli – e.g., pathogen-associated molecular patterns (PAMPs)[64–67] – or endogenous stimuli – e.g., damage-associated molecular patterns (DAMPs)[68–73] – they enter a complex developmental program known as maturation.[74,75] Mature DCs (mDCs) are phenotypically and functionally distinct from iDCs in various aspects, of which the most significant are as follows: (1) decreased phagocytic activity, (2) increased expression of co-stimulatory ligands and increased exposure of MHC molecules (both class I and II) on the cell surface, (3) altered expression of chemokine receptors, in particular chemokine (C-C motif) receptor 7 (CCR7), which is involved in homing to, and retention in the lymph nodes, and (4) abundant secretion of pro-inflammatory cytokines such as IL-12, IL-6, IL-1β, and chemokines such as C-X-C motif chemokine ligand 9, 10, and 11 (CXCL10, CXCL10, and CXCL11).[76–85] These modifications enable mDCs to efficiently co-stimulate and prime T cells in the lymph nodes.

DCs play a key role in anti-tumor immunity by properly priming $CD8^+$ T cells against tumor-associated or specific antigens (TAAs or TSAs), a process which is often impaired by immunosuppressive TME.[5,7,9,86–90] DCs' potent antigen presentation and T cell activation ability have made them an important player in anticancer vaccination strategies.[91–95] Classically, DC vaccines in clinical studies are created by *ex vivo* differentiation of DCs from autologous monocytes obtained from patients with apheresis, followed by exposure to TAAs/TSAs, in the presence of maturation-inducing agents or cocktails, and finally are reinfused back into the same patient.[92,96–99] Although this approach has shown some success in inducing TAA/TSA-specific immune responses in patients,[91–94] the therapeutic efficacy of DC-based vaccines in clinical studies is still limited due to the robust immunosuppressive mechanisms within the TME.[92,100–102] Additionally, while the use of moDCs for the creation of DC vaccines is highly prevalent, due to various practical reasons, mounting evidence suggests that the use of cDCs might be worth exploring, as these subsets might be superior to moDCs in their T cell stimulatory capability.[94,96,103,104] The possibility of using naturally occurring DC subsets – such as cDCs, Langerhans cells (LCs) and pDCs – as DC vaccines is being explored in clinical settings with promising early results, although protocols for the isolation or *in vitro* differentiation of these cells still need to be optimized.[105–111] Nevertheless, future clinical testing of cDC/pDC-based anticancer vaccines will answer a crucial question, i.e., is the historically low efficacy of moDC-based vaccines due to their supposedly inferior T cell-stimulatory capacity (largely suggested based on murine rather than human data), or due to other as-yet-unknown DC vaccines-specific resistance pathways.

In recent decades, the field of therapeutic DC vaccination has seen vast progress, with various strategies being explored in both preclinical and clinical settings. Broadly, DC vaccines can be classified into different groups based on the TAA/TSA delivery approach or the manipulation imposed on DCs prior to administration.[92,112] These include (1) DCs not pulsed with TAA/TSAs, either unstimulated or stimulated with different agents (e.g., immunostimulatory cytokines or PAMP/DAMPs such as toll-like receptor (TLR) agonists);[41,113–118] (2) DCs pulsed with TAA/TSAs *ex vivo*, which can be from different sources: tumor lysates, whole tumor mRNA (both of which provide a wide array of TAA/TSAs), specific TAA/TSA-based peptides or TAA/TSA-coding mRNAs (generally consisting of one or a limited amount of TAA/TSAs)[119–136] and (3) DCs transfected with viral or biochemical genetic vectors encoding TAA/TSAs or immunostimulatory factors.[136–138] Alternative DC-based therapy strategies include delivery of TAA/TSAs to DCs *in vivo*[139–144] and intra-tumoral administration of immunomodulatory molecules to stimulate DCs *in situ*;[145] as well as exosomes derived from DCs.[146–148]

As observed within our previous Trial Watch,[149] the most common therapeutic approach to DC vaccines remains the pulsing of DCs with TAAs (as peptides or tumor lysate) stimulated with maturation-inducing cocktails. This can be achieved *ex vivo* by various methods, including but not limited to (1) co-incubation of DCs with tumor lysate,[119,121,123,124,150,151] (2) co-incubation of DCs with recombinant TAAs or TAA-derived peptides,[126–128] (3) transfection of DCs with TAA-encoding plasmids or mRNA,[132,133,152–154] or (4) fusion of DCs with tumor cells.[155–159] Alternatively, DCs can be appropriated for therapeutic use by *in vivo* or *in situ* stimulation, through methods such as direct TAA delivery via immunoliposomes targeting DCs, genetic vectors targeting DCs, fusions of TAAs with monoclonal antibodies or other molecules (e.g., carbohydrates and polypeptides) targeting 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)).[139–144,160–162] Despite the significant amount of preclinical and clinical progress in the field, to date sipuleucel-T (sold commercially as Provenge®) remains the only tumor-targeting DC-based therapy being approved by the US Food and Drug Administration (FDA) in 2010, for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (i.e. hormone refractory) prostate cancer.[163,164] The marketing authorization for sipuleucel-T has since been withdrawn from the European Union. However, it is worth mentioning that sipuleucel-T was not a pure DC-based preparation but rather a mixture of various immune cells (peripheral-blood mononuclear cells), which could have been one of the reasons behind its disappointing performance.

In this Trial Watch, we review the latest preclinical and clinical progress in the development of DC vaccines for oncological indications. Immune checkpoint blockers (ICBs) and adoptive T-cell transfer (ACT) remain at the forefront of the cancer immunotherapy field,[165–168] yet the number of ongoing clinical studies investigating the safety and efficacy of DC vaccination for cancer treatment remains high, many of which are now focusing on multimodal therapeutic regimens combining these different approaches.

Recent preclinical developments

Since the publication of our last Trial Watch on DC vaccination for oncological treatment (February 2019),[149] there has been an abundance of preclinical research published on this topic, most making use of murine models of cancer. Within this, we have selected several publications of particular interest to represent the larger trends within the field (ordered in a random manner).

Zhou et al. (University of Texas MD Anderson Cancer Center, Houston, TX, USA) found that $CD103^+$ cDC1-based vaccines were relatively superior to moDC-based vaccines in eliciting artificial OVA antigen-directed T cell responses, and resulted in complete regression of all osteosarcoma murine tumors after cytotoxic T-lymphocyte associated protein 4 (CTLA4) checkpoint blockade.[169] Zhu et al. (The First Hospital of Jilin University, Changchun, China) found that while a DC vaccine comprised of glioma lysate and CpG oligodeoxynucleotides (CpG) increased survival and tumor regression, it also upregulated programmed cell death 1 (PD1, also known as PDCD1) and programmed cell death ligand 1 (PDL1, also known as CD274) on effector T cells, DCs and glioma tissue in mice.[170] Accordingly, they found that combining the DC vaccine with anti-PDL1 antibodies had a synergistic effect and decreased T_{REG}s in the brain.[170] Ashour et al. (University of Würzburg, Würzburg, Germany) showed that injected moDCs can direct T cell priming and activation of endogenous DCs but not T_H type 1 (T_H1) polarization, which is instead mediated by IL-12 produced from lymph-node resident cDC1s.[171] Hodge et al. (University of South Carolina School of Medicine, Columbia, SC, USA), demonstrated that inducing overexpression of microRNA 155 (miR-155) enhanced the anti-tumor activity of DC vaccines against breast cancer, culminating in an increase in effector T cells, a suppression of tumor growth, and a decrease in lung metastasis.[172] Park et al. (Konkuk University, Chungju, South Korea) identified 40S ribosomal protein S3 (RSP3) as a TLR4 ligand and as a potential adjuvant for DC vaccines, inducing activation and maturation of DCs. RSP3-treated DCs facilitated tumor prevention and regression as well as increased IFN-γ producing $CD8^+$ T cells.[173] Similarly, Jang et al. (Konkuk University, Chungju, South Korea) identified another TLR4 ligand, 60S acidic ribosomal protein P2 (RPLP2), which improved DC immunogenicity, and these RPLP2-treated DC vaccines synergized with PD1 and PD-L1 blockade.[174] Dastmalchi et al. (University of Florida, Gainesville, FL, USA) demonstrated that sarcosine (intermediate in the metabolism of choline to glycine) improved DC vaccine migration to the lymph node and spleen after intradermal administration, and improved tumor control. CXCR2 blockade removed the effect of sarcosine on DC migration and consequently abrogated the survival benefit of this DC vaccine.[175] Liu et al. (Jiangxi University of Technology, Nanchang, China), showed that silencing indoleamine 2,3-dioxygenase 2 (IDO2) in DCs improved their immunogenicity, leading to enhanced cytotoxic T cell activity and decreased Tregs within the tumors post-vaccination, as well as suppression of tumor growth.[176] Previously, Endo et al. (Hokkaido University, Sapporo, Japan) had obtained similar results for increased antitumor

effect of DC vaccines by silencing of indoleamine 2,3-dioxygenase 1 (IDO1) in DCs through administration of a siRNA via a nanodevice.[177]

In a murine leukemia model, Stroopinsky at al. (Harvard Medical School) demonstrated that a DC/acute myeloid leukemia cell (AML) fusion vaccine, which had previously shown good results in a phase I/II trial,[178] synergizes with ICBs (i.e., anti-PD1, anti-hepatitis A virus cellular receptor 2 (HAVCR2, best known as TIM3), and anti- repulsive guidance molecule BMP co-receptor b (RGMb)) to induce durable leukemia-specific immunity.[179] Shi et al. (Guangxi Medical University, Guangxi, China) reported that a PD1-specific nanobody synergizes with DC/tumor-cell fusion vaccines in multiple tumor types.[180] Lau et al. (Erasmus Medical Center, Rotterdam, The Netherlands) showed that mesothelioma-lysate loaded DCs slowed tumor growth prophylactically, but in established disease only improved survival when combined with an agonistic CD40 antibody, which also induced lower expression of immune-inhibitory receptors on $CD8^+$ T cells.[181] Oba et al. (Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA) showed the immunotherapy potential of induced pluripotent stem cells-derived DCs and combined them with radiotherapy to overcome anti-PDL1 therapy resistance in non-immunogenic tumors.[182] Lapenta et al. (Istituto Superiore di Sanità, Rome, Italy) found that combining an IFNα-stimulated DC vaccine with lenalidomide leads to improved therapeutic effect in lymphoma-bearing mice.[183] El-Ashmawy et al. (Tanta University, Tanta, Egypt) used DC vaccination to target cancer stem cells and found that the DC vaccine loaded with tumor lysate significantly reduced the percentage of $CD166^+$cancer stem cells when compared to cisplatin and reversed the tumorigenic effect of Benzo(a)Pyrene in the mouse lung.[184] Gou et al. (University of Colorado, Anschutz Medical Campus, Aurora, Colorado) screened kinase inhibitors and found that MK2206, DNA-dependent protein kinase inhibitor NU7441 and mitogen-activated protein kinase kinase enzyme (MEK) inhibitor trametinib showed the best ability to improve DC immunogenicity. This combination also improved the anti-tumor activity of a glioblastoma (GBM) DC vaccine called IC107.[185]

The above selected studies represent only a fraction of an array of such preclinical studies on DC vaccination in the published literature. This indicates significant interest in optimizing and enabling anticancer DC vaccines.

Completed clinical studies

We identified 25 peer-reviewed research papers or clinical studies published since the release of our previous Trial Watch on this topic (February 2019),[149] until December 2021, that reported the safety and efficacy data of clinical trials investigating therapeutic application of DC-based vaccines for treating oncological indications.

These published studies reported results of trials spanning 13 different cancer types, of which the most common were melanoma,[186–189] followed by GBM/glioma,[190–192] prostate cancer,[193,194] ovarian cancer,[195,196] and pancreatic cancer[197,198] (Figure 1). Relative to our previous report in 2019[149], while the aforementioned tumor types remain well represented, yet we do see a shift from clinical studies focusing on 'basket trials' consisting of multiple tumor types, toward specific trials focusing on a particular oncological indication; such that, only two studies enrolled patients with multiple solid tumors,[199,200] while another study focused on peritoneal metastases derived from multiple primary malignancies.[201]

Most of these studies reported the results of clinical trials evaluating autologous DCs pulsed with TAAs or TAA-derived peptides,[188,190,191,193,196–199,202,203] TAA-coding RNAs,[189,194,204–206] and autologous cancer cell lysates[187,192,195,201,207] (Figure 1). This is in line with the ongoing trends in the field, as reported in our previous Trial Watch (February 2019).[149] Additionally, two publications reported on the safety and efficacy of TAA-coding adenovirus transfected DC vaccines.[186,208] Finally, there were two studies reporting on autologous DCs alone (i.e. without TAAs)[200,209] and another (Phase I) study that evaluated the safety of an allogenic DC vaccine, ilixadencel, which uses unloaded moDCs sourced from healthy donors stimulated by a cocktail of activation factors.[210,211]

Within the studies focused on specific TAAs, the most common targets were melanoma antigen family (MAGE) peptides – MAGE-A1[190], MAGE-A3,[188,205] MAGE-A6,[186] and MAGE-C2,[193,205] followed by glycoprotein 100 (gp100)[188–190,205] and tyrosinase[186,188,189,205] (Figure 1). These antigens are classically known as cancer-germline antigens (MAGE family) and melanocyte differentiation antigens[212] and, with the exception of one study targeting gp100 in GBM, and one study targeting MAGE-C2 in prostate cancer patients,[190,193] they were used exclusively in trials involving melanoma patients. The choice of specific antigens for DC pulsing differs significantly from our previous Trial Watch;[149] however, the general trend remains, i.e.,, the vast majority of studies target common TAAs. Two studies deviated from this by investigating DC vaccines loaded with personalized neoantigens.[197,199]

In the above studies, DC vaccination was either assessed as a single adjuvant therapy[187,193,194,196,203,205,206,210] (generally following surgery or standard-of-care), or in combination with various conventional anticancer therapies, most often chemotherapeutics[189,192,195,197–199,207,208] and other standard-of-care regimens[191,202,204] (Figure 1). Other trials combined DC vaccination with specific immunotherapeutic agents such as ICBs (primarily, anti-PD1 or anti-CTLA4 antibodies) or immunomodulatory monoclonal antibodies (e.g., anti-CD20)[188,197,199,200,209] (Figure 1).

It is noteworthy that most of the above publications reported results of Phase I or I/II studies (out of 25 studies, 9 were Phase I, 4 were Phase I/II and 11 were Phase II, and only 1 Phase III trial), evaluating the safety and potential adverse effects of DC vaccination regimens. Of note, in line with our previous Trial Watch[149] as well as available literature, DC vaccines were well tolerated, with studies reporting mostly only mild-to-moderate adverse effects (grade 1–2) such as flu-like symptoms, fatigue, and rashes in a small subset of patients. Only one Phase II study reported a significant number of severe adverse effects (36% grade 3–4); however, this is likely to be attributed to the use of ipilimumab (anti-CTLA4 ICB), as this same vaccine had been previously shown to be safe when applied as a single agent.[188,213,214]

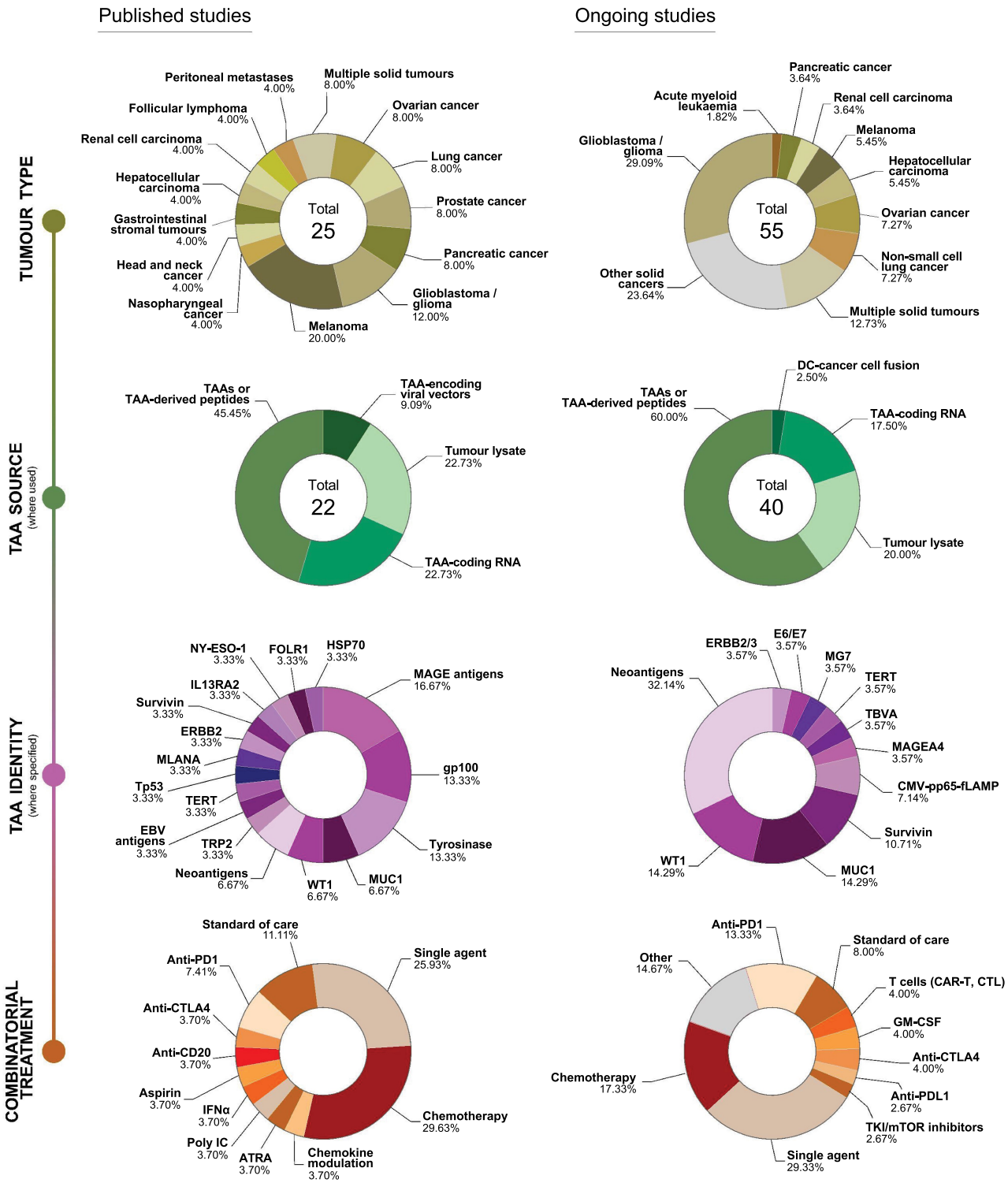

Figure 1. Overview of current strategies of dendritic cell vaccination for cancer therapy. ATRA, all-trans retinoic acid; CAR, chimeric antigen receptor; CMV-pp65, cytomegalovirus 65 kDa phosphoprotein; CTL, cytotoxic T lymphocyte; CTLA4, cytotoxic T-lymphocyte associated protein 4; DC, dendritic cell; ERBB, erb-b2 receptor tyrosine kinase; EBV, Epstein-Barr virus; fLAMP, full-length lysosome-associated membrane protein; FOLR1, folate receptor alpha; GM-CSF, granulocyte-macrophage colony-stimulating factor; gp100, glycoprotein 100; HSP70, 70 kDa heat shock protein; IFN, interferon; IL, interleukin; IL13RA2, interleukin 13 receptor subunit alpha 2; MAGE, melanoma-associated antigen; MLANA, melan-A; mTOR, mammalian target of rapamycin; MUC1, mucin 1, cell surface associated; NY-ESO-1 (official name: CTAG1B), cancer/testis antigen 1B; PD1, programmed death ligand 1; PDL1, programmed cell death 1 ligand 1; TAA, tumor-associated antigen; TBVA, tumor blood vessel antigens; TERT, telomerase reverse transcriptase; TKI, tyrosine kinase inhibitor; Tp53, tumor protein p53; TRP2, tyrosinase related protein 2; WT1, WT1 transcription factor.

DC vaccine-induced immunogenicity in patients, as measured by increased antigen-specific T- or B-cell activity and/or lymphocyte tumor infiltration (among other parameters), was consistently observed. Of note, one study reported the results of a Phase III trial which enrolled 462 newly diagnosed renal cell carcinoma patients, and evaluated the combination of a DC vaccine pulsed with tumor RNA (Rocapuldencel-T) together with sunitinib (standard of care option at the time of the trial), compared to sunitinib alone.[204] The study found that Rocapuldencel-T did not improve overall survival (OS), with an OS in the combination group of 27.7 months and 32.4 months in the sunitinib group, although the magnitude of the DC vaccine-driven immune response did correlate with OS.[204] Most studies reported clinically relevant immune responses to DC vaccines, with two studies being worthy of note: a phase II trial which tested the efficacy and safety of a DC vaccine, ICT-107 (autologous DCs pulsed with six synthetic peptide epitopes targeting GBM TAAs), in 124 newly diagnosed GBM patients, found significant improvement in progression-free survival (PFS) in the ICT-107 group by 2.2 months, with OS also showing a (albeit non-significant) increase of 2 months;[190] and a phase IIb study in melanoma patients evaluating the tumor lysate, particle-loaded, DC (TLPLDC) vaccine, an autologous DC vaccine loaded with yeast cell wall particles containing tumor lysate, which showed an increased 24-month disease free survival (DFS) rate in per-treatment analysis in the TLPLDC-treated group (62.9% versus 34.8% in the control arm).[187]

Altogether, the results of these studies convey the highly relevant clinical therapeutic potential of DC vaccination, while simultaneously indicating that there remains ample room for improvement in terms of proper patient pre-selection, cancer-type tailoring, and antigen-level personalization options.

Ongoing clinical trials

This Trial Watch covers trials 'first posted' in the period between February 2019 and December 2021, during which 55 clinical trials evaluating the dose, safety, and efficacy of DC-based vaccines against cancer were registered at http://www.clinicaltrials.gov/. The details of these trials are summarized in Table 1.

In these ongoing clinical trials, the most common cancer type being targeted is GBM, followed by basket trials enrolling patients with various solid tumors (Figure 1 and Table 1). Cancer type-focussed studies cover a wide variety of tumor types apart from GBM, e.g., patients with ovarian cancer, non-small cell lung cancer, hepatocellular cancer, and melanoma (Figure 1 and Table 1). While most ongoing trials are in Phase I or II, there are currently at least three (active) advanced (Phase III) clinical trials testing DC vaccines for the treatment of cancer: two of these are testing TAA-loaded DC vaccines in GBM (NCT05100641 and NCT04277221), while another trial is enrolling patients with neoplasms to treat them with a combination of DCs with cytokine-induced killer cells (CIK), known as DC-CIK (NCT04292769).

Within these ongoing studies, the most common therapeutic approach to DC vaccination consists of autologous DCs pulsed with TAAs or TAA-derived peptides, followed by tumor lysate and TAA-coding RNA (Figure 1 and Table 1). Several recent studies are focusing on TAA or TAA-derived peptide mixtures as well as personalized (or pre-defined) neoantigens (Table 1). The trials targeting common TAAs show a variety of TAAs as target, contingent on the tumor type, with the most common being WT1 transcription factor (WT1), mucin 1 cell surface associated (MUC1), survivin, and the human cytomegalovirus protein 65 kDa phosphoprotein (pp65) (Figure 1 and Table 1).

To improve immunogenicity and efficacy, DC vaccination is being combined in preclinical and clinical studies with other cancer therapies such as chemo- and radiotherapy, as well as with other immunotherapeutic strategies such as adoptive cell transfer[215] including transfer of chimeric antigen receptor (CAR) T cells,[216–222] CIK cells[223,224] and NK cells,[43,225–227] antibody-based therapy (e.g., ICB or immunostimulatory antibodies),[228,229] recombinant cytokines,[230,231] or targeted therapies (e.g., tyrosine kinase inhibitors).[232–236] While a significant portion of ongoing trials are investigating DC vaccination as a single (adjuvant) agent (generally after completion of standard of care regimens), various other anticancer therapies are also being tested in combination with the goal of improving the efficacy of these DC vaccines (Figure 1 and Table 1). Of these, a combination of ICB stands out, with PD1 being the most common immune-checkpoint being targeted therein, followed by CTLA4 and PDL1 (Figure 1 and Table 1). The majority of these used only one ICB (alone or in combination with other cancer therapies such as chemotherapy), with only two trials combining DC vaccines with two or more ICBs (Table 1). Other common combinations within ongoing studies include (1) chemotherapy, in particular cyclophosphamide, decitabine, and temozolomide, (2) granulocyte-macrophage colony-stimulating factor (GM-CSF), and (3) adoptive transfer of T cells (Figure 1 and Table 1).

In summary, the field of clinical DC vaccines is moving toward ICB-resistant tumor landscapes (e.g., GBM), with particular emphasis on TAA-tailored or personalized approaches coupled with1e combinatorial regimen designing involving chemotherapeutics or ICBs.

Status update on clinical trials

Several clinical trials listed in our previous Trial Watch on DC-based vaccination for cancer therapy have changed status since its publication (July 2019).[149] NCT03688178, NCT03546426, NCT03743298 are now "Recruiting," after being previously listed as "Not yet recruiting." NCT03450044, NCT03152565, NCT03086564, NCT03707808, which were previously listed as "Recruiting," have now been listed as "Completed." NCT03657966, NCT03615404, NCT03114631changed from "Active, not recruiting" to "Completed." The following trials have changed to "Active, not recruiting," from "Recruiting": NCT03325101, NCT03083054, NCT03387553, NCT03400917, NCT03406715, NCT03686683, NCT03697707. NCT03360708 changed from "Not yet recruiting" to "Active, not recruiting." Moreover, several trials are now currently listed with "Unknown" status (due to status not being verified in the past 2 years): NCT03085966, NCT03638765, NCT03815084, NCT03214939, NCT03410732, NCT03393416, NCT03674073,

Table 1. Overview of clinical trials registered on clinicaltrials.gov between February 2019 and December 2021 testing dendritic cell-based immunotherapy in cancer patients.

Strategy	Indication	Phase	Status	TAA/TSA(s)	Combinatorial treatment	Reference
Autologous DCs	Glioblastoma	I	Recruiting	n.a.	Single agent	NCT04552886
	Hepatocellular carcinoma	I	Recruiting	n.a.	Radiotherapy, PCV13 vaccine	NCT03942328
	Lung cancer	Ib/II	Recruiting	n.a.	Atezolizumab	NCT04487756
	Neoplasms	I/II	Recruiting	n.a.	CAR-T/CTL therapy	NCT04085159
	Ovarian cancer	III	Withdrawn	n.a.	Standard therapy	NCT03905902
		I	Recruiting	n.a.	Single agent	NCT04614051
		II	Recruiting	n.a.	Single agent	NCT04834544
	Prostate cancer	I	Recruiting	n.a.	Single agent	NCT04615845
	Solid tumors	II	Recruiting	n.a.	Avelumab, ipilimumab, pembrolizumab	NCT04571632
Autologous DCs loaded with tumor lysate	Glioblastoma	II	Not yet recruiting	Tumor lysate	Temozolomide	NCT04523688
		I/II	Recruiting	Tumor lysate	Single agent	NCT04801147
		I	Terminated	Tumor lysate	Single agent	NCT04002804
		I	Recruiting	Tumor lysate	Pembrolizumab, Poly ICLC	NCT04201873
		I/II	Recruiting	Tumor lysate	Cyclophosphamide, nivolumab, ipilimumab	NCT03879512
	Melanoma	I	Not yet recruiting	Tumor lysate	PV-001-DV (Dengue virus-1)	NCT03990493
	Pancreatic cancer	I	Recruiting	Tumor lysate, tumor RNA	Single agent	NCT04157127
	Solid tumors	II	Recruiting	Tumor lysate	IL-2	NCT04166006
Autologous DCs transfected or pulsed with TAA-coding RNA(s)	Glioblastoma	I	Recruiting	CMV-pp65-fLAMP mRNA	GM-CSF	NCT04963413
		II	Suspended	CMV-pp65-fLAMP mRNA	GM-CSF, temozolomide, tetanus-diphtheria toxoid	NCT03927222
	Glioma	I/II	Recruiting	WT1 mRNA	Temozolomide, standard therapy	NCT04911621
	Hepatocellular carcinoma	II	Recruiting	Tumor-derived mRNA	Cyclophosphamide	NCT04317248
	Melanoma	I	Active, not recruiting	Tumor-derived mRNA	Single agent	NCT04335890
	Neuroblastoma	I	Recruiting	Tumor-derived mRNA	Autologous T cells	NCT04837547
	Renal cell carcinoma	II	Recruiting	Tumor-derived mRNA	Nivolumab, ipilimumab, TKI+mTOR inhibitors	NCT04203901

(*Continued*)

Table 1. (Continued).

Strategy	Indication	Phase	Status	TAA/TSA(s)	Combinatorial treatment	Reference
Autologous DCs loaded with recombinant TAAs or TAA-derived peptide(s)	Acute myeloid leukemia	I	Recruiting	WT1, TERT, survivin	Single agent	NCT05000801
	Bladder cancer	II	Completed	MUC1, WT1	Standard therapy	NCT04184232
	Breast cancer	I	Active, not recruiting	Personalized neoantigens	Single agent	NCT04105582
		IIa	Not yet recruiting	ERBB2, ERBB3	Pembrolizumab	NCT04348747
	Endometrial cancer	II	Completed	MUC1, survivin	Carboplatin, paclitaxel	NCT04212377
	Esophagus cancer	I	Not yet recruiting	TAAs	Single agent	NCT05023928
	Gastric cancer	I/II	Recruiting	MG7	CTLs, sintilimab	NCT04567069
	Glioblastoma	I	Recruiting	Neoantigens	Temozolomide	NCT04968366
		I	Enrolling by invitation	Neoantigens	Cyclophosphamide, bevacizumab	NCT03914768
		II	Recruiting	TAAs	Standard therapy	NCT04115761
		II	Recruiting	TAAs	Camrelizumab	NCT04888611
		III	Recruiting	TAAs	Single agent	NCT04277221
		III	Not yet recruiting	TAAs	GM-CSF	NCT05100641
	Hepatocellular carcinoma	II	Recruiting	Neoantigens	Nivolumab	NCT04912765
	Lung cancer	I	Unknown	Neoantigens	Single agent	NCT03871205
	Melanoma	II	Not yet recruiting	TAAs	Celecoxib, IFN alfa-2b, rintatolimod	NCT04093323
	Neoplasms	I	Not yet recruiting	E6/E7	Single agent	NCT03870113
	NSCLC	I	Unknown	Personalized neoantigens	Single agent	NCT04078269
		Ia	Active, not recruiting	Neoantigens	Single agent	NCT04082182
		I/II	Recruiting	TAAs	Single agent, chemotherapy or pembrolizumab	NCT03970746
		I/II	Unknown	WT1, survivin, MAGEA4, MUC1	Single agent	NCT04199559
	Pancreatic cancer	Ib	Recruiting	Personalized neoantigens	Nivolumab, standard therapy	NCT04627246
	Renal cell carcinoma	IIa	Not yet recruiting	TBVA peptides	Cabozantinib	NCT05127824
	Solid tumors	I	Recruiting	TAAs	Single agent	NCT04147078
Autologous DC-CIK /CTL combinations	Neoplasms	III	Recruiting	n.a.	Decitabine	NCT04292769
	Solid tumors	I	Recruiting	Personalized neoantigens	Single agent	NCT05020119
		I/II	Recruiting	TAAs	Decitabine	NCT04672473
		II	Recruiting	n.a.	Single agent	NCT04476641
			Recruiting	n.a.	Chemotherapy	NCT04214717
DC-cancer cell fusion	Glioblastoma	I/II	Recruiting	n.a.	IL-12, temozolomide	NCT04388033
Allogenic DCs	Ovarian cancer	I	Recruiting	n.a.	Single agent	NCT04739527

Abbreviations: CAR, chimeric antigen receptor; CIK, cytokine-induced killer; CMV-pp65, cytomegalovirus 65 kDa phosphoprotein; CTL, cytotoxic T lymphocyte; DC, dendritic cell; ERBB, erb-b2 receptor tyrosine kinase; fLAMP, full-length lysosome-associated membrane protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MAGEA4, melanoma-associated antigen A4; mTOR, mammalian target of rapamycin; MUC1, mucin 1, cell surface associated; n.a., not applicable; NSCLC, non-small cell lung cancer; PCV13, pneumococcal conjugate vaccine 13; TAA, tumour-associated antigen; TBVA, tumour blood vessel antigen; TERT, telomerase reverse transcriptase; TKI, tyrosine kinase inhibitor; WT1, WT1 transcription factor.

NCT03282617, NCT03525652, NCT03185429, NCT03360630, NCT03190811, NCT03057340, NCT03736330, NCT03047525, NCT03815630. Lastly, the following trials have been terminated: NCT03300843 (slow accrual), NCT03735290 (decision made to not move forward to phase II), or NCT03782064 (lack of funding).

Concluding remarks

Based on our clinical trials survey, some decline in the number of published as well as ongoing clinical trials applying DC vaccines for anticancer therapy is noticeable.[237,238] It is reasonable to believe that the rapid establishment of ICBs as standard of care for many cancers coupled with disappointing clinical performance of DC vaccines are together responsible for this decline. However, it is also clear that ICBs cannot be used for treatment of all cancers, and primary and secondary resistance to ICB remains an unresolved issue in cancer types where ICBs are used.[239–241] In line with this, DC vaccines are starting to occupy niche applications, e.g., GBM, which has failed to respond to ICBs across a series of high-profile clinical trials.[242–244] This suggests that there is great interest in delineating specific tumor niches where DC vaccines can be applied, especially in combination with other conventional (e.g., chemotherapy) or immunotherapeutic (e.g., ICBs) anticancer therapies, where the use of DC vaccines to prime tumors for subsequent T cell-based therapies is also being explored.[245–249]

Clinical trials applying DC vaccines need to urgently demonstrate some clear survival advantages or at least reveal clear mechanisms for their failures to move the field toward actionable deliverables, like approval of DC-based vaccines by regulatory authorities or 'next-generation' clinical trials with novel designs and DC vaccine formulations striving to overcome previous failures. Completed Phase III clinical trials in the field are scarce and thus far have failed to show significant advantage achieved via DC-based vaccines in cancer patients.[204,250] The results of other advanced trials that are currently ongoing or recently finished are eagerly awaited, particularly for those cancer-types that have failed to respond to currently approved ICBs.

Based on recent trends in the field of DC vaccines, there seems to be a prevalent disconnect between preclinical focus and clinical requirements. The preclinical DC vaccine research continues to focus on increasing the immunogenicity of DC vaccines (e.g., new maturating agents). However, over the last decades several DC vaccine formulations with sufficiently wide spectrum of immunogenicity have been clinically tested without sufficiently proportional clinical success.[101,251–255] Thus, it is not clear if the lack of immunogenicity is the sole reason for clinical failure of DC vaccines or if there are also specific primary, adaptive, or acquired resistance pathways that require better attention, together with the limitations of preclinical models in accurately reflecting the clinical reality.[256–259] We believe that preclinical research needs to better address the previous clinical failures of DC vaccines and move forward in a definitive fashion to avoid redundancy. This will likely entail a shift from moDC-based vaccines to physiological DC subsets-based vaccination, among other avenues.[255,260–263] Yet, as of now the difficulty in generating cDC1/2 from patients in large amounts remains a hurdle for cDC-based DC vaccinations. Simultaneously, DC vaccine research also needs to account for challenges that are also plaguing success of ICBs in the clinic, e.g., deep immunosuppressive niches within the TME of lymphocytes-depleted solid tumors,[249,264–266] adaptive or acquired emergence of antigen-loss variant versions of cancer cells,[267–270] and the patient-to-patient immune heterogeneity (owing to immune haplotypes, archetypes, ethnicities, as well as microbiome variations).[271,272] Manufacturing and production costs associated with DC vaccines also need to be considered and reduced, possibly through higher automation, to ease overall practicability.

Finally, ICBs owe a large part of their clinical success to guided application via specific immune biomarkers like tumor mutational burden or PD-L1 positivity.[273–282] These trends have highlighted the values of biomarker-driven patient preselection for the success of anticancer immunotherapy.[283–286] However, unfortunately, there is a severe lack of robust patient pre-selection biomarkers to guide the application of DC-based vaccines, thereby setting them up for failure. This situation needs to rapidly change. Therefore, it is urgent to use multi-omics biomarker profiling technologies to comprehensively document the biomarkers most likely to predict positive patient responses to DC vaccines. This will help support the design of clinical trials focused on patient subsets selected via specific biomarkers, thereby increasing their response probability to DC vaccines.

Despite their limited success to date, DC vaccines still exhibit immense potential as a tool in cancer immunotherapy, and novel technologies and the ever-increasing knowledge of DC biology and immune resistance mechanisms in the TME will allow for the engineering of better DC vaccines, along with increased personalization. We believe that DC vaccines stand to occupy an essential niche in the sensitization and priming of tumors to overcome ICB non-responsiveness in various cancer types and patients.

Acknowledgements

Research in ADG lab is supported by Research Foundation Flanders (FWO) (Fundamental Research Grant, G0B4620N; Excellence of Science/EOS grant, 30837538, for 'DECODE' consortium), KU Leuven (C1 grant, C14/19/098, C3 grant, C3/21/037, and POR award funds, POR/16/040), Kom op Tegen Kanker (Stand Up To Cancer, the Flemish Cancer Society) (KOTK/2018/11509/1 to ADG, SDV; KOTK/2019/11955/1 to AC, ADG), VLIR-UoS (iBOF grant, iBOF/21/048, for 'MIMICRY' consortium). JS is funded by Kom op tegen Kanker (Stand up to Cancer), the Flemish Cancer Society via Emmanuel van der Schueren (EvDS) PhD fellowship (projectID: 12699). IV is supported by FWO-SB PhD Fellowship (1S06821N). DMB is supported by KU Leuven's Postdoctoral mandate grant (PDMT1/21/032). BB is supported by FWO Senior Clinical Investigator Fellowship (1801520N). LK is funded by Kom op tegen Kanker (Stand up to Cancer), the Flemish cancer society via Emmanuel van der Schueren (EvDS) PhD fellowship (projectID: 3328). JdV is supported by Health Holland grant LSHM18056-SGF. Research in ZB lab is supported by Kom op Tegen Kanker (Stand Up To Cancer, the Flemish Cancer Society) (including KotK_UA/2018/11465/1 and KotK_UZA/2018/11465/1), Stichting tegen Kanker (Foundation against Cancer) (CA/2016/753, CA/2020/1496), Research Foundation Flanders (FWO) (Applied Biomedical Research with a Primary Social Finality Grant, T00216N), Belgian National Cancer Plan, Stichting Semmy (Semmy Foundation), Olivia Hendrickx Research Fund vzw and UZA

foundation. Research in the lab of BN and ST is supported by Kom op Tegen Kanker (Stand Up To Cancer, the Flemish Cancer Society) and by the Dutch Brain Tumor Foundation.

Disclosure statement

ADG has received speaker/lecture remuneration or consultancy fees from Boehringer Ingelheim, Miltenyi Biotec or Isoplexis. AC is a contracted researcher for Oncoinvent AS and Novocure and a consultant for Sotio a.s.

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Data availability statement

All data included in this Trial Watch are publicly available at https://clinicaltrials.gov/

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