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Trial watch: anticancer vaccination with dendritic cells

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ABSTRACT

Dendritic cells (DCs) are critical players at the intersection of innate and adaptive immunity, making them ideal candidates for anticancer vaccine development. DC-based immunotherapies typically involve isolating patient-derived DCs, pulsing them with tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs), and utilizing maturation cocktails to ensure their effective activation. These matured DCs are then reinfused to elicit tumor-specific T-cell responses. While this approach has demonstrated the ability to generate potent immune responses, its clinical efficacy has been limited due to the immunosuppressive tumor microenvironment. Recent efforts have focused on enhancing the immunogenicity of DC-based vaccines, particularly through combination therapies with T cell-targeting immunotherapies. This Trial Watch summarizes recent advances in DC-based cancer treatments, including the development of new preclinical and clinical strategies, and discusses the future potential of DC-based vaccines in the evolving landscape of immuno-oncology.

Introduction

Dendritic cells (DCs) are pivotal at the interface of innate and adaptive immunity, positioning them as prime targets for anticancer vaccine research.[1,2] In 1973, Ralph Steinman first identified DCs[3] and was awarded the Nobel Prize in 2011 for this groundbreaking discovery.[4] Steinman's pioneering research significantly advanced our understanding of the innate immune system.[5,6] These cells, which were named after the Greek term "dendron" because of their 'tree-like' shape, are now recognized as professional antigen-presenting cells (APCs).[3,5,7-11] Indeed, DCs are highly specialized in antigen presentation,[12,13] a process that is vital for initiating and regulating immune responses.[14] They are capable of presenting extracellular antigens on major histocompatibility complex (MHC) class II molecules to CD4$^+$ T helper (T$_H$)[15] cells and intracellular antigens on MHC class I molecules to CD8$^+$ cytotoxic T lymphocytes (CTLs). In addition, DCs have the ability to present extracellular antigens on major histocompatibility complex (MHC) class I, through a process known as cross-presentation.[12,13,16-18] This ability to cross-present is particularly crucial for eliciting efficacious antitumor immune responses, highlighting the importance of DCs in cancer immunotherapy.[19-21]

The field of DC research has expanded significantly since Steinman's discovery, with extensive studies focusing on the functionality and interactions of DCs with CD4$^+$ and CD8$^+$

T cells,[22-25] This research has been propelled by advances in high-dimensional flow cytometry, single-cell transcriptomics, in vivo imaging, and sophisticated in vivo transgenics. These technologies have significantly refined the classification of dendritic cells (DCs) into distinct biological subsets, defined by their phenotype, ontogeny, and function.[22,26-30] These subsets include two types of 'classical' or 'conventional' DCs: type 1 cDC (cDC1)[31,32] and type 2 cDC (cDC2), as well as plasmacytoid DCs (pDCs)[33-38] Nowadays it is well known that cDCs and pDCs are completely distinct from monocyte-derived DCs (moDCs) in terms of lineage, whereas for a long time, it was traditionally believed that DCs originated from monocytes.[2,34,39,40] While cDC1 and cDC2 share a common DC progenitor, the developmental origins of pDCs[41] remain a subject of debate.[29,42-45]

Each subset of DCs exhibits unique functional specializations, contributing to their distinct roles in immune responses during health and disease. The pDCs are renowned for their robust type I interferon (IFN) responses, in particular the production of IFN-α,[42-44,46-49] However, their presence in tumors is often associated with poor prognosis due to impaired type I IFN production in the tumor microenvironment (TME), leading to immunosuppression.[49,50] The cDC1s are particularly proficient in activating CD8$^+$ T cells through cross-

presentation and are essential for antitumor immunity, being the only canonical DCs capable of effectively prime tumor-specific CD8^{+} T cells.[29,51–56] They also produce interferon-λ, thereby manipulating T cell responses toward a helper T cell phenotype.[57] Their abundance in the TME frequently correlates with prolonged patient survival.[58,59] Conversely, cDC2s are primarily involved in presenting exogenous antigens to various CD4^{+} T helper cell subsets[60,61] and can secrete high levels of interleukin-12 (IL-12),[62,63] which is critical for the expansion and survival of T and natural killer (NK) cells.[64,65]

In homeostatic conditions, both tissue-resident (found in the tissues where they are seeded) and circulating (found in peripheral blood) DCs exist in an immature state, which is crucial for immunosurveillance and maintaining tolerance to self-antigens,[66-68] Immature DCs (iDCs) excel at taking-up extracellular material and promoting the expansion of regulatory T cells (Treg) if DCs encounter self-antigens, thereby preventing autoimmunity,[69–73] Upon encountering activating, foreign, and/or non-self stimuli, iDCs undergo maturation,[74–82] which is characterized by decreased antigen uptake, increased expression of co-stimulatory molecules, and enhanced cytokine secretion, enabling them to efficiently prime T cells in lymph nodes.[69,73]

Given their pivotal role in antigen presentation and T cell activation, DCs have become central to anticancer vaccination strategies,[83–90] Classically, in clinical studies, DC vaccines are generated by differentiating DCs ex vivo from patients' autologous monocytes, followed by exposing these DCs to tumor-associated or specific antigens (TAAs or TSAs)[91,92] and maturation-inducing agents. These DC vaccines are then reinfused back into the patients.[1,88,93–103] Although the precise relationship of such moDCs to the canonical DC lineages is not entirely clear, such cells become particularly prevalent under inflammatory conditions.[104,105,106] They are potent stimulators of CD4^{+} T cells and cross-present antigens and activate CD8^{+} T cells.[95,106] Despite some success in triggering antitumor immune responses, the therapeutic impact of DC-based vaccines in clinical trials has been constrained, largely due to the potent immunosuppressive mechanisms within the TME.[94,107–111]

Although moDCs are commonly used for vaccine development due to practical advantages, increasing evidence indicates that cDCs may have superior T cell stimulatory capabilities.[95,97,112,113] Consequently, there is growing interest in exploring naturally occurring DC subsets, such as cDCs, Langerhans cells (LCs) – cells that originate from the bone marrow and then migrate into the epithelium to perform the function of antigen recognition and presentation[114,115−] and pDCs, in the context of DC vaccines. Early clinical trials show promising results, but further validation of the protocols for isolating or differentiating these cells in vitro is still needed.[31,115–120]

To determine whether the historically low efficacy of moDC-based vaccines stems from their potentially less effective T cell stimulation or other unknown resistance mechanisms specific to DC vaccines, future clinical trials involving cDC- and pDC-based anticancer vaccines will be critical[121–125] Additionally, significant advancements have been made in the field of therapeutic DC vaccination, with a range of sophisticated strategies now being tested in preclinical and clinical trials. These strategies encompass the ex vivo loading of DCs with TAAs/TSAs, genetic modification of DCs to express TAAs or TSAs, and in vivo activation using various agents such as immunostimulatory cytokines or molecules like pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) that interact with toll-like receptors (TLRs).[123,126–129]

In defiance of considerable progress, sipuleucel-T (Provenge®), a therapy integrating DCs (amongst other immune cells) for treating asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer, remains the only FDA-approved DC-integrating therapy for the last 14 years. Indeed, sipuleucel-T is not a pure DC preparation but a mixture of various immune cells, which could have contributed to its mixed clinical performance.[130–134]

Despite the challenges, numerous ongoing clinical studies are exploring DC vaccination as a cancer treatment, with many investigating multimodal therapeutic approaches that combine DC vaccines with immune checkpoint blockers (ICBs) and adoptive T cell transfer (ACT),[135–141] These innovative combinations offer promising prospects for enhancing DC-based cancer immunotherapy.[142] This Trial Watch outlines the latest advances in preclinical and clinical research on DC vaccines, highlighting their potential as a powerful anticancer approach.

Recent preclinical developments

Numerous preclinical studies have been published since our last Trial Watch article on DC vaccination for cancer treatment in July 2022.[143] We have chosen a few key publications to highlight the main trends in the field (presented in no order).

Vedunova et al. (National Research Lobachevsky State University of Nizhny Novgorod, Nizhny Novgorod, Russia) reported the efficacy and molecular mechanism of glioma cell-loaded DC vaccines going through immunogenic cell death (ICD) induced by photosensitizer-based photodynamic therapy (PS-PDT). Herein, the transcriptional program induced in the DC vaccine following incubation with glioma cells undergoing ICD involved a T_H17-like footprint. Accordingly, in an orthotopic mouse model, the efficacy of ICD-based DC vaccine was dependent on retinoic acid receptor-related orphan receptor-(ROR)γt. Interestingly, analysis of the transcriptome of the ICD-based DC vaccine highlighted a predictive four-gene signature (CFH, GALNT3, SMC4, and VAV3) that was related to a better overall survival (OS) in glioma patients.[144]

Adamik et al. (Parker Institute for Cancer Immunotherapy, San Francisco, USA) analyzed the transcriptomic and immuno-metabolic profiles of the DC vaccines from 35 subjects enrolled in a trial with late-stage melanoma patients. DC vaccines demonstrated alterations in multiple immune and metabolic pathways, a functional decrease in oxygen consumption rate (OCR)/oxidative phosphorylation (OXPHOS), and an increase in extracellular acidification rate (ECAR)/glycolysis. By using a technique called single-cell energetic metabolism by profiling translation inhibition (SCENITH), they showed that metabolic skewing and increased glycolysis in DC vaccines impacted OS in melanoma patients. Moreover, single-cell

metabolic regulome profiling showed that the lactate transporter MCT1 (monocarboxylate transporter-1) was increased in melanoma patients' DCs as compared to healthy donors. In line with this, an increase in glucose uptake and lactate secretion was observed, the latter being described as an immune-inhibitory molecule in many immune-related processes.[145] This suggested that culture conditions that more tightly control metabolic pathways of monocytic cells might be necessary to create more effective DC vaccines capable of inducing efficacious antitumor T cell responses.[146]

Sprooten et al.. (KU Leuven, Leuven, Belgium) used multi-omics analyses to find that clinical DC vaccines do not simply move from an immature state to functionally mature state after relevant clinical preparation steps, as widely expected based on previous data. Instead, the DC vaccines develop into three patient-dependent developmental trajectories i.e., a type I IFN response[HIGH] T1 trajectory, which associated with efficacious *in situ* antigen-specific responses and prolonged patient survival. This contrasted with the other T2 (macrophage-like state) or T3 (mature regulatory/mreg DC-like state) trajectories, both of which correlated to weak *in situ* antigen-specific reactions and a shorter patient survival. However, contrary to the above expectations, pre-clinical version of DC vaccines following the T1 differentiation trajectory induced an unprecedented negative feedback loop that resulted in CD8+ T cell-suppressive programmed death-ligand 1 positive (PD-L1+) macrophages. This was evident in both preclinical settings and glioblastoma (GBM) patients (in an ongoing Phase II clinical trial). More specifically, they observed that DC vaccines, counter to expectations, created a unique niche of PD-L1+ lymph node-associated macrophages (LAMs) as well as tumor-associated macrophages (TAMs) across lymph nodes and tumors, respectively. These LAMs and TAMs killed CD8+ T cells via TNF-related apoptosis-inducing ligand (TRAIL) signaling in both these anatomical locations thereby inhibiting these DC vaccine's ability to activate anticancer T cells. Accordingly, they showed that combining PD-L1 blockade (but not blockade of other immune-checkpoints) with DC vaccination achieved significant tumor regression by depleting PD-L1+TAMs/LAMs, suppressing myeloid inflammation, and de-inhibiting effector/stem-like memory T cells. Accordingly, they proposed a mandatory multimodal immunotherapy combined with DC vaccines exhibiting a type I IFN response[HIGH] state, to robustly overcome T cell-depleted tumors.[147]

Han et al. (University of Illinois at Urbana-Champaign, USA) to enable targeted modulation of adoptively transferred DCs for developing improved DC vaccines reported an easy metabolic labeling approach. Labeling with metabolic glycan showed a reduction of the membrane mobility of DCs, thereby activating DCs and improving their ability to present antigens and to subsequently prime T cells. Furthermore, the cell-surface chemical tags introduced via this labeling method also enabled *in vivo* conjugation of cytokines onto adoptively transferred DCs, which additionally enhanced cytotoxic T lymphocytes (CTL) response and antitumor efficacy.[148]

Basirjafar et al. (School of Medicine, Rafsanjan University of Medical Sciences, Iran) used a murine breast cancer model to access the effects of leptin and/or lipopolysaccharide (LPS)-treated DC vaccines on multiple T cell-related immunological markers. Leptin/LPS-treated DC vaccines showed more efficacy in inhibiting breast cancer development and preventing metastasis. Increasing immune responses against tumor induced by leptin/LPS-treated DC vaccines was linked to a significant increase in the frequencies of splenic CTLs and T$_H$1 cells, an increased production of IFNγ and IL-12, a significant increase in T-box transcription factor TBX21 (best known as T-bet) and granzyme expression as well as a concomitant decrease in tumor growth factor beta (TGF-β) and forkhead box protein P3 (FOXP3) expression.[149]

Chan et al. (University of Guelph, Canada) demonstrated the quick hiring of neutrophils to the draining lymph nodes of DC-vaccinated mice, a process that occurred together by an increased number of IFN-γ-producing NK cells expressing the degranulation marker CD107a. In line with this, the reduced numbers of NK cells in draining lymph nodes as compared to the controls arose from the decrease in neutrophils in DC-immunized mice. Notably, the authors also showed that DC vaccines induced IFNγ− and TNF-producing CD8+ T cells that expressed CD107a, and were not impacted by neutrophils depletion, suggesting that neutrophil-mediated antitumor immunity induced by DC vaccines might be targeted to enhance vaccination efficacy.[150]

Because cancer vaccines based on peripheral blood monocytes or bone marrow treated with granulocyte-macrophage colony-stimulating factor (GM-CSF) i.e., GMDCs, were shown to depend on the transfer of antigens from the DC vaccine to the host cDC1, Ferris et al. (Washington University in St. Louis, Missouri) evaluated whether cDC1 are superior to GMDC-based vaccines. For this, they compared antitumor responses induced by GMDCs and cDC1s in mice with a deleted enhancer located at +32 kb of the interferon regulatory factor 8 (*Irf8*) transcriptional start site (Irf8 +32$^{-/-}$ mice), which leads to a lack of endogenous cDC1s in these mice and are incapable of rejecting immunogenic fibrosarcoma. Both GMDCs and cDC1s could cross-present cell-associated antigens to CD8+ T cells *in vitro*. Still, tumor injection of GMDCs in Irf8 +32$^{-/-}$ mice failed to trigger antitumor immunity, aligned with the reported dependence on host cDC1. On the other hand, tumor injection of cDC1 into Irf8 +32$^{-/-}$ mice induced their migration to the draining lymph node, as well as CD8+ T cell activation and tumor rejection. This tumor rejection did not require antigen loading on cDC1, showing that *in vivo* acquisition of the antigen by cDC1 leads to antitumor responses.[151]

Silva et al.. (Oncology Research Institute (IPON), Federal University of Triângulo Mineiro (UFTM), Brazil) evaluated the behavior of the adhesion molecules, intercellular adhesion molecule (ICAM)-1 and ICAM-2, in DC-based immunotherapy. For this, tumor and lymph nodes of Balb/c mice were analyzed 7 and 14 days after therapy. This showed that ICAM-2 was associated with a reduction in tumor volume. This suggested that the DC vaccine enhances the immune system and that ICAM-2 might serve as a marker for high immunogenicity.[152]

Sultan et al.. (Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO, USA) discovered that the efficacy of therapeutic peptide

vaccines targeting tumor-specific neoantigens is strongly influenced by the dosage of the MHC-II neoantigens included in the vaccine. To achieve this, Sultan and his team used vaccines with MHC-I neoantigens and different doses of tumor-derived MHC-II neoantigens and observed that while low doses of MHC-II-restricted peptides promoted tumor rejection, high doses inhibited rejection in tumor-bearing mice. Inhibitory cells induced by the high-dosage vaccines were identified as type 1 regulatory T (Tr1) cells (identified as FOXP3-negative, IL-10-producing inhibitory cells).[153] These tumor-specific Tr1 cells suppressed tumor rejection driven by anti-PD1 therapy, or adoptively transferred tumor-specific effector T cells. Mechanistically, Tr1 cells selectively targeted and killed cDC1s, resulting in reduced cDC1 numbers within the tumors. Overall, these findings demonstrate that Tr1 cells have a role in suppressing antitumor responses and thus impeding immune control of cancer.[154]

The studies selected above represent a small portion of the numerous preclinical studies on DC vaccines found in the published literature. This shows a significant interest in optimizing and advancing anticancer DC vaccines.

Completed clinical trials

Since the publication of our previous Trial Watch on this subject (July 2022),[143] we have identified 26 new clinical trials that investigated the safety and efficacy of DC-based therapeutic interventions in cancer patients, which have been published in the peer-reviewed scientific literature in the past 2 years (source http://www.ncbi.nlm.nih.gov/pubmed).

The findings from these published studies incorporate trials conducted across 11 distinct types of cancers, of which the most common were melanoma,[120,155-158] followed by prostate cancer,[159-162] GBM,[163-165] multiple myeloma,[166,167] lung cancer[168,169] and ovarian cancer[170,171] (Figure 1). Compared to our previous Trial Watch,[143] the new clinical trials targeted mainly the same cancer types as in the years before.

Most of the studies reviewed here present findings from clinical trials assessing autologous moDCs loaded with TAAs/TSAs or TAA-derived peptides,[120,155,157,161,166,172-175] TAA/TSAs-coding RNAs,[162,166,176] and autologous/allogenic cancer cell lysates[156,158,159,163,165,168,177,178] (Figure 1). This is in line with our previous report of July 2022[143]. Additionally, one publication reported the use of cDC2 and pDC[120] instead of moDCs, and another study used immature DCs in combination with ICBs such as anti-programmed cell death-1 (PDCD1, best known as PD-1) and anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antibodies.[160]

In contrast to our previous Trial Watch,[143] the use of individual antigens for DC pulsing has reduced substantially, such that most of the recently published studies focused on a range or mixture of TAAs (Figure 1). However, the TAAs targeted in some of these reports are in line with the general trend also reported previously, i.e., they target common TAAs, such as melanoma antigen family (MAGE) antigens,[166] Epstein–Barr virus (EBV) antigens,[173] WT1 transcription factor (WT1) antigen,[166] or baculoviral IAP repeat containing 5 (Survivin) antigen.[175]

In the studies mentioned above, DC vaccines were evaluated either as a single agent therapy[161,164-166,170,173,178] (usually after surgery) or in conjunction with conventional anticancer treatments, predominantly chemotherapeutics[159,168,169,171,175,177] and other standard-of-care (SOC) regimens[157,162,163,176] (Figure 1). Besides conventional treatments, other trials combined DC vaccines with immunotherapeutic agents such as ICBs (mainly anti-PD1 and anti-CTLA4 antibodies) or immunomodulatory factors such as GM-CSF.[155,156,158,167,172,174,179]

The majority of these publications were on Phase I or II studies, including 9 Phase I studies, 8 Phase II studies, 5 Phase I/II studies followed by only 4 Phase III studies. Existing literature, and in line with our previous reports on the subject, indicates that DC vaccines were generally well tolerated, with the majority of studies reporting only mild-to-moderate adverse effects (grade 1–2) such as fatigue, fever, and influenza-like symptoms. However, two studies reported a significant number of severe adverse events (grade 3–4): (I) a Phase I study[174] where 57.9% of the patients had grade 3 or 4 treatment-related effects, and (II) a Phase I/II study[175] where all patients had at least one adverse event of grade 3 or higher, although these effects were associated with the adjuvant chemotherapy (carboplatin/paclitaxel) rather than the DC vaccines. Overall, in these trials, DC vaccination showed promising immunological changes, demonstrated by (but not limited to) the increased antigen-specific T or B cell activity and/or the tumor infiltration of lymphocytes.

Herein, the results of the 4 Phase III studies that assessed the clinical benefits of DC-based therapy need particular attention. One Phase III trial enrolled 1182 patients with metastatic castration-resistant prostate cancer (mCRPC), and evaluated the efficacy and safety of DCVAC/PCa (DC-based vaccine where DCs prepared from the patient's monocytes were collected and subsequently exposed to a human prostate adenocarcinoma cell line (LNCaP) killed by immunogenic modality) combined with chemotherapy (docetaxel and prednisone) versus chemotherapy alone.[159] The study reported no difference in OS between the DCVAC/PCa plus chemotherapy and chemotherapy alone groups, with OS of 23.9 months and 24.3 months, respectively. Also, no differences in the secondary efficacy endpoints (radiological progression-free survival, time to prostate-specific antigen progression, or skeletal-related events) were observed. Another study evaluated the possible delayed clinical outcome caused by sipuleucel-T in men with mCRPC.[161] Two cohorts of men were included: the prospective evaluation of chronic pancreatitis for epidemiologic and translational studies (PROCEED) which is the first prospective, observational cohort study of chronic pancreatitis in the USA; and the cohort of mCRPC patients treated with sipuleucel-T at Dana-Farber Cancer Institute (DFCI). From these cohorts, men who received three infusions of sipuleucel-T and did not initiate a new therapy for more than 6 months after completion of sipuleucel-T, were included. Prostate-specific antigen (PSA) response was observed in 19.9% of patients from the PROCEED cohort and 14.3% of patients from the DFCI cohort, and with a median OS of 49 and 60 months, respectively. In this analysis of mCRPC patients treated with sipuleucel-T, using two datasets, a delayed PSA response was observed in a subset of patients,
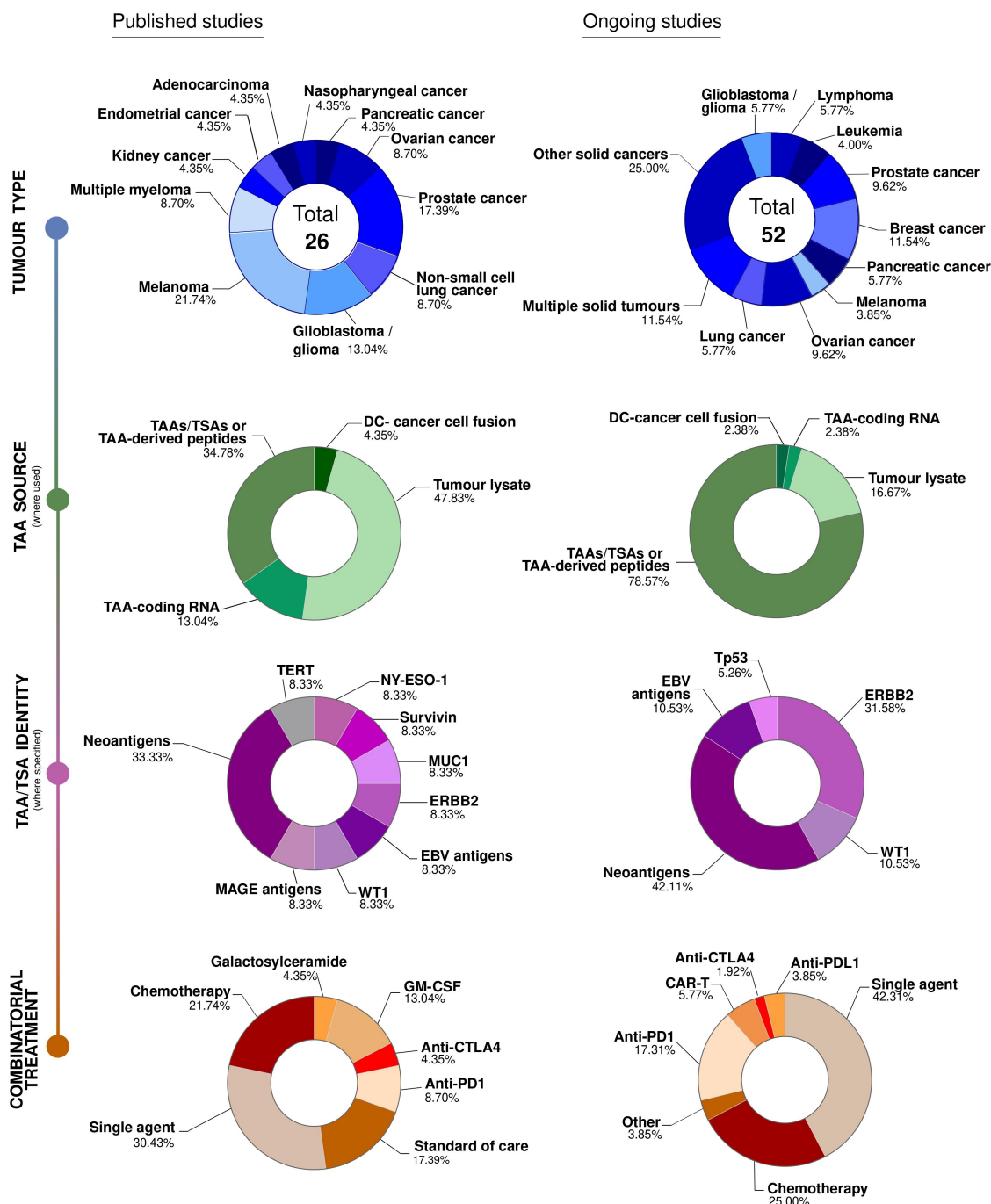
Figure 1. Overview of current strategies of dendritic cell (DC) vaccination for cancer therapy. DC, dendritic cell; MUC1, mucin 1, cell surface associated; NY-ESO-1 (official name: CTAG1B), cancer/testis antigen 1B; TAA, tumor-associated antigen; TSA, tumor-specific antigen; TERT, telomerase reverse transcriptase; WT1, WT1 transcription factor; CAR, chimeric antigen receptor; CTL, cytotoxic T lymphocyte; CTLA4, cytotoxic T-lymphocyte associated protein 4; ERBB, erb-b2 receptor tyrosine kinase; EBV, Epstein-Barr virus; GM-CSF, granulocyte-macrophage colony-stimulating factor; MAGE, melanoma-associated antigen; PD1, programmed death ligand 1; PDL1, programmed cell death 1 ligand 1; Tp53, tumor protein p53.

suggesting a delayed but detectable clinical activity. On the basis of (previous) promising Phase I/II data, another Phase III trial in advanced renal cell carcinoma (RCC) further investigated the safety and efficacy of the combination therapy involving CMN001 (a DC-based immunotherapy, employing autologous DC electroporated with autologous tumor RNA) plus the SOC sunitinib.[176] In the trial, 426 patients were either treated with CMN-001 plus SOC treatment or SOC treatment alone. The study reported almost no difference in OS between the combinatorial group (27.7 months) and the SOC group

(32.4 months). The last Phase III trial covered by our current survey, focused on investigating whether adding autologous tumor lysate-loaded DC vaccine (DCVax-L) to SOC extends survival among GBM patients.[163] The study involved 232 patients with newly diagnosed GBM or recurrent GBM in the DCVax-L group and 99 patients in the SOC only group. Median OS for patients with newly diagnosed GBM treated with DCVax-L was 19.3 months vs. 16.5 in SOC only groups. For recurrent GBM patients treated with DCVax-L this median OS was 13.2 months vs.7.8 in SOC only groups. This study

demonstrated that incorporating DCVax-L with the SOC might extend survival in patients with both newly diagnosed GBM and recurrent GBM, compared to matched external controls who only received SOC. Although the results of this study require additional validation with compatible control arm.

Overall, the findings from these studies underscore the inconsistent clinical potential of DC vaccination. This suggests significant opportunities for enhancement in areas such as patient selection, tailoring for specific cancer types, personalizing antigens, and developing more targeted combinatorial strategies.

Ongoing clinical trials

This Trial Watch recorded 52 'ongoing' clinical trials registered at http://www.clinicaltrials.gov/in the period between January 2022 and February 2024, evaluating the efficacy, safety, and therapeutic profile of anticancer DC vaccination. The details of these trials are summarized in Table 1.

In these ongoing clinical trials, the most common cancer being targeted is breast cancer followed by basket trials that enroll patients with multiple solid tumors (Figure 1 and Table 1). Such basket studies cover a range of tumor types like breast cancer, ovarian cancer, prostate cancer, non-small cell lung cancer, and leukemia (Figure 1 and Table 1). Notably, although the majority of studies are Phase I or II trials, at least two advanced-phase clinical trials are evaluating DC vaccination: a Phase III study enrolling mCRPC patients (NCT06134232), and a Phase II/III trial focusing on pancreatic ductal adenocarcinoma (NCT05955157). This suggests that some DC-based therapies have progressed to a more advanced clinical development.

In most of the ongoing trials, the DC vaccines consist of autologous DCs pulsed with TAAs/TSAs, TAA-derived peptides, or tumor lysates (Figure 1 and Table 1). However, several studies are focusing on DCs pulsed with personalized TSAs or neoantigens (Table 1). Trials reporting autologous DCs pulsed with TAAs show a variety of common TAAs as targets, such as WT1, and EBV antigens as described before (Figure 1 and Table 1).

Interestingly, most of the ongoing trials administer DC-based vaccination alone, or in combination with other cancer therapies, including (but not limited to) ICBs targeting PD-1 (pembrolizumab or nivolumab), or CTLA4 (ipilimumab). Besides ICBs, chemo- and radiotherapy and other immunotherapeutic strategies such as ACT and chimeric antigen receptor (CAR) T cells are also being used (Figure 1 and Table 1). The goal of these combinations is to improve the efficacy of these DC-based vaccines.

In summary, the field of clinical DC vaccines is moving toward the use of tailored TAAs or personalized TSA approaches with the tendency to combine DC-based therapies with other forms of immunotherapy and/or chemotherapy.

Status update on clinical trials

Since our previous Trial Watch (July 2022) several clinical trials listed previously on DC-based vaccination as cancer treatment have changed status. NCT04523688, NCT04348747, NCT04093323, and NCT05127824 are now "Recruiting", after being previously listed as "Not yet recruiting". NCT04552886, NCT04837547, and NCT04147078 have changed their status from "Recruiting" to "Completed". NCT04105582 is now listed as "Completed" after having been listed as "Active not recruiting". The following trials have changed to "Active, not recruiting" from "Recruiting": NCT04487756, NCT04911621, NCT04968366, NCT03970746. NCT04078269 changed from "Unknown" to "Active, not recruiting". Additionally, several trials are now listed with "Unknown" status: NCT04085159, NCT04571632, NCT04801147, NCT04317248, NCT04335890, NCT05023928, NCT04567069, NCT03914768, NCT04115761, NCT04888611, NCT04277221, NCT03870113, NCT04082182, NCT04292769, NCT05020119, NCT04672473, NCT04476641, NCT04388033. Lastly, the following trials have terminated: NCT04614051 and NCT04615845 (difficult recruitment), NCT04963413 (terminated by mutual agreement of sponsor and institution), NCT03927222 (resource shortage), and NCT04203901 (strategic corporate decision).

Concluding remarks

In comparison with our previous trial watch, we observe a slight decline in the number of ongoing clinical trials (from 55 to 52) using DC vaccines for cancer therapy.[135,180] This decrease is likely due to the quick adoption of ICBs as part of the SOC for multiple cancers, along with the limited-to-poor clinical performance of DC vaccines[180–184] However, ICBs are also not effective for all cancers, and both primary as well as adaptive or acquired resistance to ICBs remain significant challenges in many cancers[185–191] As a result, DC vaccines are finding niche applications, for example, in cancers characterized by an immune-cold microenvironment (e.g., GBM) and resistance to ICBs, ACTs and/or CAR-T cells[192–199] This reflects an increasing focus on pinpointing specific tumor types where DC vaccines may be effective, particularly when combined with other therapies,[184,200–207] or when integrating the targeting of tumor-specific neoantigens[208,209,210] DC vaccines are also being explored to 'pre-prime' tumors for subsequent T cell-based therapies.[170,211,212]

Also, there seems to be a disconnection between preclinical research, which focuses on increasing the immunogenicity of DC vaccines, and the clinical unmet needs.[213] Regardless of several compositions being tested,[214–218] the clinical outcomes have not matched the preclinical promise.[219] This suggests that issues beyond DC vaccine-associated immunogenicity, such as adaptive or acquired resistance pathways might be operating in the clinical context and require urgent preclinical as well as translational investigations.[6,220–226]

Emerging technologies, such as personalized neoantigenic vaccines and multimodal combinatorial therapies, hold promise in addressing the limitations of DC vaccines by enhancing antigen specificity, boosting immunogenicity, and overcoming tumor immunosuppression.[21,134,140] By combining the precision of neoantigen targeting with the synergy of multiple therapeutic modalities, these emerging technologies have the potential to revolutionize cancer immunotherapy, enabling more robust and durable antitumor responses.[208,217,219]

Table 1. Overview of clinical trials registered on clinicaltrials.gov between January 2022 and February 2024 testing dendritic cell (dc)-based immunotherapy in cancer patients.

Strategies	Indication	Phase	Status	TAA/TSA(s)	Combinatorial treatment	Reference
Autologous DCs	Gastrointestinal Tumors	II	Not yet recruiting	n. a	Pembrolizumab, Nivolumab, Sintilimab, Toripalimab, Camrelizumab, Tislelizumab	NCT05461235
	Glioma		Recruiting	n. a	Single agent	NCT06156150
			Recruiting	n. a		NCT06043232
	Hepatocellular Carcinoma	II	Not yet recruiting	n. a	Single agent	NCT06193733
	Liver Cancer	I/II	Not yet recruiting	n. a	Single agent	NCT05622825
	Pancreas Cancer	I/II	Not yet recruiting	n. a	ICBs	NCT06172634
		II/III	Recruiting	n. a	Tegafur	NCT05955157
	Pleural Mesotheliomas	I	Not yet recruiting	n. a	Single agent	NCT05304208
	Postoperative treatment	Early I	Not yet recruiting	n. a	Oral NMN	NCT06036355
	Prostate Cancer	I	Recruiting	n. a	Prodencel	NCT05533203
	Solid Tumors	I	Recruiting	n. a	Single agent	NCT06015269
Autologous DCs loaded with tumor lysate	Melanoma	I/II	Completed	Tumour Lysate, TAAs	PROLEUKIN	NCT06152367
	NSCLC	I/II	Recruiting	Tumour Lysate	N-803	NCT05642195
	Ovarian Cancer	I/II	Recruiting	Tumour Lysate	Single agent	NCT05773859
	Pancreatic Cancer	I	Completed	Tumour Lysate	Mitazalimab	NCT05650918
	Solid Tumors	I/II	Recruiting	Tumour Lysate	Nivolumab, Entinostat	NCT05898828
		II	Recruiting	Tumour Lysate	Single agent	NCT06175221
Autologous DCs transfected or pulsed with TAA-coding RNA(s)	Angiosarcoma	I	Recruiting	Tumor-derived mRNA, tumor lysate	Paclitaxel, Filgrastim, Pegylatedinterferin alpha-2A	NCT05799612
Autologous DCs loaded with recombinant TAAs or TAA-derived peptide(s)	Breast Cancer	I/II	Recruiting	ERBB2	Trastuzumab, Pepinemab	NCT05378464
		I	Recruiting	ERBB2, ERBB3	Single agent	NCT05504707
		II	Recruiting	ERBB2	Trastazumab, Pertuzumab, Paclitaxel	NCT05325632
		I	Not yet recruiting	Neoantigens	Single agent	NCT06195618
		I	Recruiting	Neoantigens	Single agent	NCT05809752
		II	Not yet recruiting	ERBB2	Pembrolizumab	NCT05539365
	Colorectal Carcinoma	II	Not yet recruiting	Neoantigens	Pembrolizumab	NCT05518032
	ESCC	I	Unknown status	Neoantigens	Single agent	NCT05317325
	Fallopian Tube Carcinosarcoma	I/II	Recruiting	Neoantigens	Pembrolizumab	NCT05920798
	Glioma	I	Not yet recruiting	Neoantigens	Ipilimumab, Nivolumab, Poly ICLC	NCT05457959
	Head and Neck Carcinoma	I/II	Recruiting	HPV	Poly-ICLC	NCT06007092
	Hematologic Neoplasms	I	Enrolling by invitation	EBV antigens	Single agent	NCT05635591
	Leukemia	I	Withdrawn	Neoantigens	STING Dependent Activators (STAVs)	NCT05321940
	Lung Carcinoma	I	Recruiting	Neoantigens	Pembrolizumab, Durvalumab	NCT05886439
	Lymphoma	Early I	Active, not recruiting	EBV antigens	Single agent	NCT05882305
	Nasopharyngeal Cancer	I/II	Recruiting	Neoantigens	Single agent	NCT05261750
	Neoplasms	I	Withdrawn	Neoantigens	Single agent	NCT05589844
	NSCLC	I	Recruiting	Personalized neoantigens	Low dose cyclophosphamide	NCT05195619
	Ovarian Cancer	I	Unknown status	Tumor-associated antigen and patient-specific neoantigens	Single agent	NCT05270720
		I/II	Not yet recruiting	Personalized neoantigens, tumor lysate	Low dose cyclophosphamide	NCT05714306
	Pleural Mesotheliomas	I/II	Recruiting	WT-1	Atezolizumab, Platinum/Pemetrexed based chemotherapy	NCT05765084
	Prostate Cancer	III	Not yet recruiting	Neoantigens	Sipuleucel-T	NCT06134232
		II	Recruiting	Neoantigens	Testoterone cypionate	NCT06100705
		I	Recruiting	Neoantigens	Single agent	NCT05806814

(*Continued*)

Table 1. (Continued).

Strategies	Indication	Phase	Status	TAA/TSA(s)	Combinatorial treatment	Reference
		II	Recruiting	Personalized neoantigens	Single agent	NCT05751941
	Solid Tumors	I/II	Recruiting	WT-1	Single agent	NCT05964361
			Recruiting	Neoantigens	Single agent	NCT05749627
		I	Recruiting	Neoantigens	Levatinib, Nivolumab	NCT05767684
		I	Recruiting	Tp53	Abraxane, Cyclophosphamide, anti-PD1, Anti-CTLA4	NCT05631886
Autologous DC-CIK/CTL combinations	Leukemia	I	Recruiting	n. a	Antigen-specific T cells CART/CTL	NCT05262673
		I	Recruiting	n. a	Antigen-specific T cells CART/CTL	NCT05277753
	Lymphoma	I	Recruiting	n. a	CD19 CAR-T	NCT05585996
	Solid Tumors	I	Unknown status	TAAs	Single agent	NCT05235607

Abbreviations: CAR, chimeric antigen receptor; CTL, cytotoxic T lymphocyte; CIK, cytokine-induced killer; DC, dendritic cell; ERBB, erb-b2 receptor tyrosine kinase; n.a., not applicable; NSCLC, non-small cell lung cancer; TAA, tumor-associated antigen; TBVA, tumor blood vessel antigen; WT1, WT1 transcription factor; Tp53, tumor protein p53; ESCC, esophageal squamous cell carcinoma; EBV, Epstein-Barr virus; HPV, Human papillomavirus.

Of course, to advance the development of DC vaccines toward socio-economic impact, they must either demonstrate clear survival benefits in patients or mechanisms behind their clinical failures must be identified, to guide future improvements. The number of Phase III clinical trials for DC vaccines is limited[159,161,163,176] and has not shown significant benefits.[227] The results of other advanced trials, especially for cancers that do not respond to current ICBs, are eagerly awaited. Subsequent investigations should address the shortcomings of previous DC vaccine trials and explore alternative strategies, such as using physiological DCs instead of moDCs.[142] However, generating large quantities of certain DC subsets, like cDC1/cDC2, remains a challenge[228–231] DC vaccine research must also address challenges similar to those faced by ICBs,[219] such as immunosuppressive TME, the emergence of antigen-loss variants, and patient-to-patient immune heterogeneity or diversity.[13,91,232–234] Also, manufacturing costs must be reduced, potentially through higher automation or even using HLA-matched donors, to improve practicality. Moreover, ICBs have benefited immensely from the use of specific biomarkers[183,235–237] to guide patient pre-selection for their personalized application. But there is a severe lack of robust biomarkers for similar patient pre-selection for DC vaccines. Using multi-omics and spatial biomarker profiling to identify predictors of positive responses to DC vaccines could help design better clinical trials focused on specific patient subsets rather than all cancer or patients, thereby improving response rates as well as possibility of robust regulatory approvals.[238–240]

Finally, while success has been somewhat limited up to now, DC vaccines still possess substantial potential in the field of cancer immunotherapy.[241] Advances in biomarker profiling, understanding of clinical DC biology and immune resistance mechanisms, will together enable the development of more effective and personalized DC vaccines.[13,142,242] We believe that DC vaccines will play a crucial role in sensitizing and priming 'immune cold' tumors to overcome ICB resistance in various cancers.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

There is no relevant new data or dataset associated with this manuscript.

References

1. Gardner A, de Mingo Pulido Á, Ruffell B. Dendritic cells and their role in immunotherapy. Front Immunol. 2020;11:924. doi:10.3389/fimmu.2020.00924.
2. Lee YS, Radford KJ. The role of dendritic cells in cancer. Int Rev Cell Mol Biol. 2019;348:123–178. doi:10.1016/bs.ircmb.2019.07.006.
3. Steinman RM, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. J Exp Med. 1973;137(5):1142–1162. doi:10.1084/jem.137.5.1142.
4. Lanzavecchia A, Sallusto F. Ralph M. Steinman 1943–2011. Cell. 2011;147(6):1216–1217. doi:10.1016/j.cell.2011.11.040.
5. Randolph GJ. Dendritic cells: the first step. J Exp Med. 2021;218(3). doi:10.1084/jem.20202077.
6. Zhao L, Zhang S, Kepp O, Kroemer G, Liu P. Dendritic cell transfer for cancer immunotherapy. Int Rev Cell Mol Biol. 2022;370:33–64. doi:10.1016/bs.ircmb.2022.03.003.
7. Heras-Murillo I, Adán-Barrientos I, Galán M, Wculek SK, Sancho D. Dendritic cells as orchestrators of anticancer immunity and immunotherapy. Nat Rev Clin Oncol. 2024;21(4):257–277. doi:10.1038/s41571-024-00859-1.

8. Eisenbarth SC. Dendritic cell subsets in T cell programming: location dictates function. Nat Rev Immunol. 2019;19(2):89–103. doi:10.1038/s41577-018-0088-1.

9. Jhunjhunwala S, Hammer C, Delamarre L. Antigen presentation in cancer: insights into tumour immunogenicity and immune evasion. Nat Rev Cancer. 2021;21(5):298–312. doi:10.1038/s41568-021-00339-z.

10. Mulder WJM, Ochando J, Joosten LAB, Fayad ZA, Netea MG. Therapeutic targeting of trained immunity. Nat Rev Drug Discov. 2019;18(7):553–566. doi:10.1038/s41573-019-0025-4.

11. Laureano RS, Vanmeerbeek I, Sprooten J, Govaerts J, Naulaerts S, Garg AD. The cell stress and immunity cycle in cancer: toward next generation of cancer immunotherapy. Immunol Rev. 2024;321 (1):71–93. doi:10.1111/imr.13287.

12. Joffre OP, Segura E, Savina A, Amigorena S. Cross-presentation by dendritic cells. Nat Rev Immunol. 2012;12(8):557–569. doi:10.1038/nri3254.

13. Hato L, Vizcay A, Eguren I, Pérez-Gracia JL, Rodríguez J, Gállego Pérez-Larraya J, Sarobe P, Inogés S, Díaz de Cerio AL, Santisteban M. Dendritic cells in cancer immunology and immunotherapy. Cancers (Basel). 2024;16(5):981. doi:10.3390/cancers16050981.

14. Soltani S, Mahmoudi M, Farhadi E. Dendritic cells Currently under the Spotlight; classification and subset based upon new markers. Immunol Invest. 2021;50(6):646–661. doi:10.1080/08820139.2020.1783289.

15. Luo Y, Shreeder B, Jenkins JW, Shi H, Lamichhane P, Zhou K, Bahr DA, Kurian S, Jones KA, Daum JI. et al. Th17-inducing dendritic cell vaccines stimulate effective CD4 T cell-dependent antitumor immunity in ovarian cancer that overcomes resistance to immune checkpoint blockade. J Immunother Cancer. 2023;11 (11): doi:10.1136/jitc-2023-007661.

16. Garg AD, Agostinis P. Cell death and immunity in cancer: from danger signals to mimicry of pathogen defense responses. Immunol Rev. 2017;280(1):126–148. doi:10.1111/imr.12574.

17. Naulaerts S, Datsi A, Borras DM, Antoranz Martinez A, Messiaen J, Vanmeerbeek I, Sprooten J, Laureano RS, Govaerts J, Panovska D. et al. Multiomics and spatial mapping characterizes human CD8+ T cell states in cancer. Sci Transl Med. 2023;15: eadd1016. doi:10.1126/scitranslmed.add1016.

18. Zhou H, Ma Y, Liu F, Li B, Qiao D, Ren P, Wang M. Current advances in cancer vaccines targeting NY-ESO-1 for solid cancer treatment. Front Immunol. 2023;14:1255799. doi:10.3389/fimmu.2023.1255799.

19. Fang S, Agostinis P, Salven P, Garg AD. Decoding cancer cell death-driven immune cell recruitment: an in vivo method for site-of-vaccination analyses. Meth Enzymol. 2020;636:185–207. doi:10.1016/bs.mie.2019.04.013.

20. Vanmeerbeek I, Naulaerts S, Sprooten J, Laureano RS, Govaerts J, Trotta R, Pretto S, Zhao S, Cafarello ST, Verelst J. et al. Targeting conserved TIM3+VISTA+ tumor-associated macrophages overcomes resistance to cancer immunotherapy. Sci Adv. 2024;10: eadm8660. doi:10.1126/sciadv.adm8660.

21. Garg AD. The dynamic interface of genetics and immunity: toward future horizons in health & disease. Genes Immun. 2023;24:155–158. doi:10.1038/s41435-023-00213-y.

22. Kang M-H, Bae Y-S. IL-33 and IL-33-derived DC-based tumor immunotherapy. Exp Mol Med. 2024;56(6):1340–1347. doi:10.1038/s12276-024-01249-4.

23. Miah MA, Yoon C-H, Kim J, Jang J, Seong Y-R, Bae Y-S. CISH is induced during DC development and regulates DC-mediated CTL activation. Eur J Immunol. 2012;42(1):58–68. doi:10.1002/eji.201141846.

24. Perez CR, De Palma M. Engineering dendritic cell vaccines to improve cancer immunotherapy. Nat Commun. 2019;10(1):5408. doi:10.1038/s41467-019-13368-y.

25. Lee W-C, Cheng C-H, Lee C-F, Hsu H-Y, Hsu P-Y, Wu T-J, Chan K-M. Enhancement of dendritic cell immunotherapy by recalling antigens for hepatocellular carcinoma in mice. Immunotherapy. 2022;14(15):1225–1236. doi:10.2217/imt-2021-0254.

26. Ginhoux F, Guilliams M, Merad M. Expanding dendritic cell nomenclature in the single-cell era. Nat Rev Immunol. 2022;22 (2):67–68. doi:10.1038/s41577-022-00675-7.

27. Anderson DA, Dutertre C-A, Ginhoux F, Murphy KM. Genetic models of human and mouse dendritic cell development and function. Nat Rev Immunol. 2021;21(2):101–115. doi:10.1038/s41577-020-00413-x.

28. Kvedaraite E, Ginhoux F. Human dendritic cells in cancer. Sci Immunol. 2022;7:eabm9409. doi:10.1126/sciimmunol.abm9409.

29. Chen MY, Zhang F, Goedegebuure SP, Gillanders WE. Dendritic cell subsets and implications for cancer immunotherapy. Front Immunol. 2024;15:1393451. doi:10.3389/fimmu.2024.1393451.

30. Zhu H, Chelysheva I, Pollard AJ, O'Connor D. Spotlight on systems vaccinology: a novel approach to elucidate correlates of protection. Genes Immun. 2024;25(4):336–337. doi:10.1038/s41435-023-00247-2.

31. Johnson P, Rosendahl N, Radford KJ. Conventional type 1 dendritic cells (cDC1) as cancer therapeutics: challenges and opportunities. Expert Opin Biol Ther. 2022;22(4):465–472. doi:10.1080/14712598.2022.1994943.

32. Zimmermannova O, Ferreira AG, Pereira C-F. Orchestrating an immune response to cancer with cellular reprogramming. Genes Immun. 2024;25(1):95–97. doi:10.1038/s41435-023-00237-4.

33. Gerhard GM, Bill R, Messemaker M, Klein AM, Pittet MJ. Tumor-infiltrating dendritic cell states are conserved across solid human cancers. J Exp Med. 2021;218(1). doi:10.1084/jem.20200264.

34. Collin M, McGovern N, Haniffa M. Human dendritic cell subsets. Immunology. 2013;140(1):22–30. doi:10.1111/imm.12117.

35. Brown CC, Gudjonson H, Pritykin Y, Deep D, Lavallée V-P, Mendoza A, Fromme R, Mazutis L, Ariyan C, Leslie C. et al. Transcriptional basis of mouse and human dendritic cell heterogeneity. Cell. 2019;179(4):846–863.e24. doi:10.1016/j.cell.2019.09.035.

36. See P, Dutertre C-A, Chen J, Günther P, McGovern N, Irac SE, Gunawan M, Beyer M, Händler K, Duan K. et al. Mapping the human DC lineage through the integration of high-dimensional techniques. Science. 2017;356(6342). doi:10.1126/science.aag3009.

37. Villani A-C, Satija R, Reynolds G, Sarkizova S, Shekhar K, Fletcher J, Griesbeck M, Butler A, Zheng S, Lazo S. et al. Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes, and progenitors. Science. 2017;356(6335). doi:10.1126/science.aah4573.

38. Fu C, Ma T, Zhou L, Mi Q-S, Jiang A. Dendritic cell-based vaccines against cancer: challenges, advances and future opportunities. Immunol Invest. 2022;51(8):2133–2158. doi:10.1080/08820139.2022.2109486.

39. Guilliams M, Ginhoux F, Jakubzick C, Naik SH, Onai N, Schraml BU, Segura E, Tussiwand R, Yona S. Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny. Nat Rev Immunol. 2014;14(8):571–578. doi:10.1038/nri3712.

40. Schlitzer A, Sivakamasundari V, Chen J, Sumatoh HRB, Schreuder J, Lum J, Malleret B, Zhang S, Larbi A, Zolezzi F. et al. Identification of cDC1- and cDC2-committed DC progenitors reveals early lineage priming at the common DC progenitor stage in the bone marrow. Nat Immunol. 2015;16(7):718–728. doi:10.1038/ni.3200.

41. Fu C, Zhou L, Mi Q-S, Jiang A. Plasmacytoid dendritic cells and cancer immunotherapy. Cells. 2022;11(2):222. doi:10.3390/cells11020222.

42. Carpentier S, Vu Manh T-P, Chelbi R, Henri S, Malissen B, Haniffa M, Ginhoux F, Dalod M. Comparative genomics analysis of mononuclear phagocyte subsets confirms homology between lymphoid tissue-resident and dermal XCR1(+) DCs in mouse and human and distinguishes them from langerhans cells. J Immunol Methods. 2016;432:35–49. doi:10.1016/j.jim.2016.02.023.

43. Rodrigues PF, Tussiwand R. Novel concepts in plasmacytoid dendritic cell (pDC) development and differentiation. Mol Immunol. 2020;126:25–30. doi:10.1016/j.molimm.2020.07.006.

44. Dress RJ, Dutertre C-A, Giladi A, Schlitzer A, Low I, Shadan NB, Tay A, Lum J, Kairi MFBM, Hwang YY. et al. Plasmacytoid dendritic cells develop from Ly6D+ lymphoid progenitors distinct from the myeloid lineage. Nat Immunol. 2019;20(7):852–864. doi:10.1038/s41590-019-0420-3.

45. Rodrigues PF, Alberti-Servera L, Eremin A, Grajales-Reyes GE, Ivanek R, Tussiwand R. Distinct progenitor lineages contribute to the heterogeneity of plasmacytoid dendritic cells. Nat Immunol. 2018;19(7):711–722. doi:10.1038/s41590-018-0136-9.

46. Sprooten J, Agostinis P, Garg AD. Type I interferons and dendritic cells in cancer immunotherapy. Int Rev Cell Mol Biol. 2019;348:217–262. doi:10.1016/bs.ircmb.2019.06.001.

47. Medler T, Patel JM, Alice A, Baird JR, Hu H-M, Gough MJ. Activating the nucleic acid-sensing machinery for anticancer immunity. Int Rev Cell Mol Biol. 2019;344:173–214. doi:10.1016/bs.ircmb.2018.08.006.

48. Gilliet M, Boonstra A, Paturel C, Antonenko S, Xu X-L, Trinchieri G, O'Garra A, Liu Y-J. The development of murine plasmacytoid dendritic cell precursors is differentially regulated by FLT3-ligand and granulocyte/macrophage colony-stimulating factor. J Exp Med. 2002;195(7):953–958. doi:10.1084/jem.20020045.

49. Siegal FP, Kadowaki N, Shodell M, Fitzgerald-Bocarsly PA, Shah K, Ho S, Antonenko S, Liu YJ. The nature of the principal type 1 interferon-producing cells in human blood. Science. 1999;284 (5421):1835–1837. doi:10.1126/science.284.5421.1835.

50. Garg AD. Immunology of cell death in cancer and infection. Genes Immun. 2022;23(8):241–243. doi:10.1038/s41435-022-00184-6.

51. Lauterbach H, Bathke B, Gilles S, Traidl-Hoffmann C, Luber CA, Fejer G, Freudenberg MA, Davey GM, Vremec D, Kallies A. et al. Mouse CD8α+ DCs and human BDCA3+ DCs are major producers of ifn-λ in response to poly IC. J Exp Med. 2010;207 (12):2703–2717. doi:10.1084/jem.20092720.

52. Pilones KA, Charpentier M, Garcia-Martinez E, Demaria S. IL15 synergizes with radiotherapy to reprogram the tumor immune contexture through a dendritic cell connection. Oncoimmunology. 2020;9(1):1790716. doi:10.1080/2162402X.2020.1790716.

53. Broz ML, Binnewies M, Boldajipour B, Nelson AE, Pollack JL, Erle DJ, Barczak A, Rosenblum MD, Daud A, Barber DL. et al. Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. Cancer Cell. 2014;26(5):638–652. doi:10.1016/j.ccell.2014.09.007.

54. Salmon H, Idoyaga J, Rahman A, Leboeuf M, Remark R, Jordan S, Casanova-Acebes M, Khudoynazarova M, Agudo J, Tung N. et al. Expansion and activation of CD103+ dendritic cell progenitors at the tumor site enhances tumor responses to therapeutic PD-L1 and BRAF inhibition. Immunity. 2016;44(4):924–938. doi:10.1016/j.immuni.2016.03.012.

55. Qiu CC, Kotredes KP, Cremers T, Patel S, Afanassiev A, Slifker M, Gallucci S, Gamero AM. Targeted Stat2 deletion in conventional dendritic cells impairs CTL responses but does not affect antibody production. Oncoimmunology. 2020;10(1):1860477. doi:10.1080/2162402X.2020.1860477.

56. Borràs DM, Verbandt S, Ausserhofer M, Sturm G, Lim J, Verge GA, Vanmeerbeek I, Laureano RS, Govaerts J, Sprooten J. et al. Single cell dynamics of tumor specificity vs bystander activity in CD8+ T cells define the diverse immune landscapes in colorectal cancer. Cell Discov. 2023;9(1):114. doi:10.1038/s41421-023-00605-4.

57. Lazear HM, Nice TJ, Diamond MS. Interferon-λ: immune functions at barrier surfaces and beyond. Immunity. 2015;43(1):15–28. doi:10.1016/j.immuni.2015.07.001.

58. Horton BL, Fessenden TB, Spranger S. Tissue site and the cancer immunity cycle. Trends Cancer. 2019;5(10):593–603. doi:10.1016/j.trecan.2019.07.006.

59. Böttcher JP, Reis e Sousa C. The role of type 1 conventional dendritic cells in cancer immunity. Trends Cancer. 2018;4 (11):784–792. doi:10.1016/j.trecan.2018.09.001.

60. Bennett SR, Carbone FR, Karamalis F, Miller JF, Heath WR. Induction of a CD8+ cytotoxic T lymphocyte response by cross-priming requires cognate CD4+ T cell help. J Exp Med. 1997;186(1):65–70. doi:10.1084/jem.186.1.65.

61. Lei X, Wang Y, Broens C, Borst J, Xiao Y. Immune checkpoints targeting dendritic cells for antibody-based modulation in cancer. Int Rev Cell Mol Biol. 2024;382:145–179. doi:10.1016/bs.ircmb.2023.07.006.

62. Jeon D, McNeel DG. Toll-like receptor agonist combinations augment mouse T-cell anti-tumor immunity via IL-12- and interferon ß-mediated suppression of immune checkpoint receptor expression. Oncoimmunology. 2022;11(1):2054758. doi:10.1080/2162402X.2022.2054758.

63. Nizzoli G, Krietsch J, Weick A, Steinfelder S, Facciotti F, Gruarin P, Bianco A, Steckel B, Moro M, Crosti M. et al. Human CD1c+ dendritic cells secrete high levels of IL-12 and potently prime cytotoxic T-cell responses. Blood. 2013;122(6):932–942. doi:10.1182/blood-2013-04-495424.

64. Reindl LM, Albinger N, Bexte T, Müller S, Hartmann J, Ullrich E. Immunotherapy with NK cells: recent developments in gene modification open up new avenues. Oncoimmunology. 2020;9 (1):1777651. doi:10.1080/2162402X.2020.1777651.

65. Li Q, Li Y, Wang Y, Xu L, Guo Y, Wang Y, Wang L, Guo C. Oral administration of Bifidobacterium breve promotes antitumor efficacy via dendritic cells-derived interleukin 12. Oncoimmunology. 2021;10(1):1868122. doi:10.1080/2162402X.2020.1868122.

66. Angelova M, Mascaux C, Galon J. Evasion before invasion: pre-cancer immunosurveillance. Oncoimmunology. 2021;10 (1):1912250. doi:10.1080/2162402X.2021.1912250.

67. Mahnke K, Schmitt E, Bonifaz L, Enk AH, Jonuleit H. Immature, but not inactive: the tolerogenic function of immature dendritic cells. Immunol Cell Biol. 2002;80(5):477–483. doi:10.1046/j.1440-1711.2002.01115.x.

68. Galluzzi L, Yamazaki T, Kroemer G. Linking cellular stress responses to systemic homeostasis. Nat Rev Mol Cell Biol. 2018;19(11):731–745. doi:10.1038/s41580-018-0068-0.

69. Xu Y, Liu F, He D, Han L, Zheng X, Hu M, Chen P. Monocyte-derived immature dendritic cells negatively regulate hepatic stellate cells in vitro by secreting IL-10. Immunobiology. 2023;228 (2):152315. doi:10.1016/j.imbio.2022.152315.

70. Liu S, Zhang Y, Ren J, Li J. Microbial DNA recognition by cGAS-sting and other sensors in dendritic cells in inflammatory bowel diseases. Inflamm Bowel Dis. 2015;21(4):901–911. doi:10.1097/MIB.0000000000000299.

71. Palucka K, Banchereau J. Cancer immunotherapy via dendritic cells. Nat Rev Cancer. 2012;12(4):265–277. doi:10.1038/nrc3258.

72. Mahnke K, Enk AH. Dendritic cells: key cells for the induction of regulatory T cells? Curr Top Microbiol Immunol. 2005;293:133–150. doi:10.1007/3-540-27702-1_7.

73. Roncarolo MG, Levings MK, Traversari C. Differentiation of T regulatory cells by immature dendritic cells. J Exp Med. 2001;193(2):F5–9. doi:10.1084/jem.193.2.f5.

74. Zafar S, Sorsa S, Siurala M, Hemminki O, Havunen R, Cervera-Carrascon V, Santos JM, Wang H, Lieber A, De Gruijl T. et al. CD40L coding oncolytic adenovirus allows long-term survival of humanized mice receiving dendritic cell therapy. Oncoimmunology. 2018;7(10):e1490856. doi:10.1080/2162402X.2018.1490856.

75. Ho NI, Huis in 't, Raaijmakers TK, Veld LGM, Raaijmakers TK, Adema GJ. Adjuvants enhancing cross-presentation by dendritic cells: the key to more effective vaccines? Front Immunol. 2018;9:2874. doi:10.3389/fimmu.2018.02874.

76. Li X, Dong W, Nalin AP, Wang Y, Pan P, Xu B, Zhang Y, Tun S, Zhang J, Wang L-S. et al. The natural product chitosan enhances the anti-tumor activity of natural killer cells by activating dendritic cells. Oncoimmunology. 2018;7(6):e1431085. doi:10.1080/2162402X.2018.1431085.

77. Krzastek SC, Goliadze E, Zhou S, Petrossian A, Youniss F, Sundaresan G, Wang L, Zweit J, Guruli G. Dendritic cell trafficking in tumor-bearing mice. Cancer Immunol Immunother. 2018;67 (12):1939–1947. doi:10.1007/s00262-018-2187-z.

78. Santillo BT, Reis DDS, da Silva LT, Romani NT, Duarte AJDS, Oshiro TM. Phenotypic and functional profile of ifn-α-differentiated dendritic cells (IFN-DCs) from HIV-infected individuals. Hum Vaccin Immunother. 2019;15(9):2140–2149. doi:10.1080/21645515.2018.1547603.

79. Land WG, Agostinis P, Gasser S, Garg AD, Linkermann A. Damp—induced allograft and tumor rejection: the circle is closing. Am J Transpl. 2016;16(12):3322–3337. doi:10.1111/ajt.14012.

80. Zom GG, Willems MMJHP, Khan S, van der Sluis TC, Kleinovink JW, Camps MGM, van der Marel GA, Filippov DV, Melief CJM, Ossendorp F. Novel TLR2-binding adjuvant induces enhanced T cell responses and tumor eradication. J Immunother Cancer. 2018;6(1):146. doi:10.1186/s40425-018-0455-2.

81. Garg AD, Galluzzi L, Apetoh L, Baert T, Birge RB, Bravo-San Pedro JM, Breckpot K, Brough D, Chaurio R, Cirone M. et al. Molecular and translational classifications of damps in immunogenic cell death. Front Immunol. 2015;6:588. doi:10.3389/fimmu.2015.00588.

82. Umansky V, Adema GJ, Baran J, Brandau S, Van Ginderachter JA, Hu X, Jablonska J, Mojsilovic S, Papadaki HA, Pico de Coaña Y. et al. Interactions among myeloid regulatory cells in cancer. Cancer Immunol Immunother. 2019;68(4):645–660. doi:10.1007/s00262-018-2200-6.

83. Qian D, Li J, Huang M, Cui Q, Liu X, Sun K. Dendritic cell vaccines in breast cancer: immune modulation and immunotherapy. Biomed Pharmacother. 2023;162:114685. doi:10.1016/j.biopha.2023.114685.

84. Hassan Venkatesh G, Abou Khouzam R, Shaaban Moustafa Elsayed W, Ahmed Zeinelabdin N, Terry S, Chouaib S. Tumor hypoxia: an important regulator of tumor progression or a potential modulator of tumor immunogenicity? Oncoimmunology. 2021;10(1):1974233. doi:10.1080/2162402X.2021.1974233.

85. Wang Y-M, Qiu J-J, Qu X-Y, Peng J, Lu C, Zhang M, Zhang M-X, Qi X-L, Lv B, Guo J-J. et al. Accumulation of dysfunctional tumor-infiltrating PD-1+ DCs links PD-1/PD-L1 blockade immunotherapeutic response in cervical cancer. Oncoimmunology. 2022;11(1):2034257. doi:10.1080/2162402X.2022.2034257.

86. Tormoen GW, Crittenden MR, Gough MJ. Role of the immunosuppressive microenvironment in immunotherapy. Adv Radiat Oncol. 2018;3(4):520–526. doi:10.1016/j.adro.2018.08.018.

87. Fu C, Jiang A. Dendritic cells and CD8 T cell immunity in tumor microenvironment. Front Immunol. 2018;9:3059. doi:10.3389/fimmu.2018.03059.

88. Wang Y, Xiang Y, Xin VW, Wang X-W, Peng X-C, Liu X-Q, Wang D, Li N, Cheng J-T, Lyv Y-N. et al. Dendritic cell biology and its role in tumor immunotherapy. J Hematol Oncol. 2020;13(1):107. doi:10.1186/s13045-020-00939-6.

89. DeBenedette M, Gamble A, Norris M, Horvatinovich J, Nicolette CA. A review of the clinical experience with CMN-001, a tumor RNA loaded dendritic cell immunotherapy for the treatment of metastatic renal cell carcinoma. Hum Vaccin Immunother. 2023;19(2):2220629. doi:10.1080/21645515.2023.2220629.

90. Zhou N, Li S, Zhang F, Chen C, Li Y. Matrine combined with mammalian target of Rapamycin inhibitor enhances anti-tumor efficacy of dendritic cell vaccines in hepatocellular carcinoma. Bioengineered. 2022;13(4):9274–9283. doi:10.1080/21655979.2022.2037855.

91. Dillman RO, Nistor GI, Keirstead HS. Autologous dendritic cells loaded with antigens from self-renewing autologous tumor cells as patient-specific therapeutic cancer vaccines. Hum Vaccin Immunother. 2023;19(1):2198467. doi:10.1080/21645515.2023.2198467.

92. Scheper W. Mapping the landscape of T cell-recognized neoantigens in cancer patients. Genes Immun. 2023;24(6):287–288. doi:10.1038/s41435-023-00230-x.

93. Lu Y, Shi Y, You J. Strategy and clinical application of up-regulating cross presentation by DCs in anti-tumor therapy. J Control Release. 2022;341:184–205. doi:10.1016/j.jconrel.2021.11.011.

94. Sadeghzadeh M, Bornehdeli S, Mohahammadrezakhani H, Abolghasemi M, Poursaei E, Asadi M, Zafari V, Aghebati-Maleki L, Shanehbandi D. Dendritic cell therapy in cancer treatment; the state-of-the-art. Life Sci. 2020;254:117580. doi:10.1016/j.lfs.2020.117580.

95. Wculek SK, Cueto FJ, Mujal AM, Melero I, Krummel MF, Sancho D. Dendritic cells in cancer immunology and immunotherapy. Nat Rev Immunol. 2020;20(1):7–24. doi:10.1038/s41577-019-0210-z.

96. Harari A, Graciotti M, Bassani-Sternberg M, Kandalaft LE. Antitumour dendritic cell vaccination in a priming and boosting approach. Nat Rev Drug Discov. 2020;19(9):635–652. doi:10.1038/s41573-020-0074-8.

97. Gu Y-Z, Zhao X, Song X-R. Ex vivo pulsed dendritic cell vaccination against cancer. Acta Pharmacol Sin. 2020;41(7): doi:10.1038/s41401-020-0415-5.

98. Han P, Hanlon D, Sobolev O, Chaudhury R, Edelson RL. Ex vivo dendritic cell generation-A critical comparison of current approaches. Int Rev Cell Mol Biol. 2019;349:251–307. doi:10.1016/bs.ircmb.2019.10.003.

99. Giri B, Sharma P, Jain T, Ferrantella A, Vaish U, Mehra S, Garg B, Iyer S, Sethi V, Malchiodi Z. et al. Hsp70 modulates immune response in pancreatic cancer through dendritic cells. Oncoimmunology. 2021;10(1):1976952. doi:10.1080/2162402X.2021.1976952.

100. DeVette CI, Gundlapalli H, Lai S-CA, McMurtrey CP, Hoover AR, Gurung HR, Chen WR, Welm AL, Hildebrand WH. A pipeline for identification and validation of tumor-specific antigens in a mouse model of metastatic breast cancer. Oncoimmunology. 2020;9(1):1685300. doi:10.1080/2162402X.2019.1685300.

101. Fecci PE, Sampson JH. The current state of immunotherapy for gliomas: an eye toward the future. J Neurosurg. 2019;131(3):657–666. doi:10.3171/2019.5.JNS181762.

102. Hensler M, Rakova J, Kasikova L, Lanickova T, Pasulka J, Holicek P, Hraska M, Hrnciarova T, Kadlecova P, Schoenenberger A. et al. Peripheral gene signatures reveal distinct cancer patient immunotypes with therapeutic implications for autologous DC-based vaccines. Oncoimmunology. 2022;11(1):2101596. doi:10.1080/2162402X.2022.2101596.

103. Abbaspour M, Akbari V. Cancer vaccines as a targeted immunotherapy approach for breast cancer: an update of clinical evidence. Expert Rev Vaccines. 2022;21(3):337–353. doi:10.1080/14760584.2022.2021884.

104. León B, López-Bravo M, Ardavín C. Monocyte-derived dendritic cells formed at the infection site control the induction of protective T helper 1 responses against Leishmania. Immunity. 2007;26:519–531. doi:10.1016/j.immuni.2007.01.017.

105. Segura E, Touzot M, Bohineust A, Cappuccio A, Chiocchia G, Hosmalin A, Dalod M, Soumelis V, Amigorena S. Human inflammatory dendritic cells induce Th17 cell differentiation. Immunity. 2013;38(2):336–348. doi:10.1016/j.immuni.2012.10.018.

106. Nutt SL, Chopin M. Transcriptional networks driving dendritic cell differentiation and function. Immunity. 2020;52(6):942–956. doi:10.1016/j.immuni.2020.05.005.

107. Truxova I, Hensler M, Skapa P, Halaska MJ, Laco J, Ryska A, Spisek R, Fucikova J. Rationale for the combination of dendritic cell-based vaccination approaches with chemotherapy agents. Int Rev Cell Mol Biol. 2017;330:115–156. doi:10.1016/bs.ircmb.2016.09.003.

108. Petroni G, Buqué A, Coussens LM, Galluzzi L. Targeting oncogene and non-oncogene addiction to inflame the tumour microenvironment. Nat Rev Drug Discov. 2022;21(6):440–462. doi:10.1038/s41573-022-00415-5.

109. Schaller TH, Sampson JH. Advances and challenges: dendritic cell vaccination strategies for glioblastoma. Expert Rev Vaccines. 2017;16(1):27–36. doi:10.1080/14760584.2016.1218762.

110. Sutherland SIM, Ju X, Horvath LG, Clark GJ. Moving on from sipuleucel-t: new dendritic cell vaccine strategies for prostate cancer. Front Immunol. 2021;12:641307. doi:10.3389/fimmu.2021.641307.

111. Lavin Y, Kobayashi S, Leader A, Amir E-AD, Elefant N, Bigenwald C, Remark R, Sweeney R, Becker CD, Levine JH. et al. Innate immune landscape in early lung adenocarcinoma by paired single-cell analyses. Cell. 2017;169(4):750–765.e17. doi:10.1016/j.cell.2017.04.014.

112. Laoui D, Keirsse J, Morias Y, Van Overmeire E, Geeraerts X, Elkrim Y, Kiss M, Bolli E, Lahmar Q, Sichien D. et al. The tumour microenvironment harbours ontogenically distinct dendritic cell populations with opposing effects on tumour immunity. Nat Commun. 2016;7(1):13720. doi:10.1038/ncomms13720.

113. Filin IY, Kitaeva KV, Rutland CS, Rizvanov AA, Solovyeva VV. Recent advances in experimental dendritic cell vaccines for cancer. Front Oncol. 2021;11:730824. doi:10.3389/fonc.2021.730824.

114. Gerlini G, Susini P, Sestini S, Brandani P, Giannotti V, Borgognoni L. Langerhans cells in sentinel lymph nodes from melanoma patients. Cancers (Basel). 2024;16(10):1890. doi:10.3390/cancers16101890.

115. Chung DJ, Carvajal RD, Postow MA, Sharma S, Pronschinske KB, Shyer JA, Singh-Kandah S, Dickson MA, D'Angelo SP, Wolchok JD. et al. Langerhans-type dendritic cells electroporated with TRP-2 mRNA stimulate cellular immunity against melanoma: results of a phase I vaccine trial. Oncoimmunology. 2017;7(1):e1372081. doi:10.1080/2162402X.2017.1372081.

116. Tel J, Aarntzen EHJG, Baba T, Schreibelt G, Schulte BM, Benitez-Ribas D, Boerman OC, Croockewit S, Oyen WJG, van Rossum M. et al. Natural human plasmacytoid dendritic cells induce antigen-specific T-cell responses in melanoma patients. Cancer Res. 2013;73(3):1063–1075. doi:10.1158/0008-5472.CAN-12-2583.

117. Schreibelt G, Bol KF, Westdorp H, Wimmers F, Aarntzen EHJG, Duiveman-de Boer T, van de Rakt MWMM, Scharenborg NM, de Boer AJ, Pots JM. et al. Effective clinical responses in metastatic melanoma patients after vaccination with primary myeloid dendritic cells. Clin Cancer Res. 2016;22(9):2155–2166. doi:10.1158/1078-0432.CCR-15-2205.

118. Huber A, Dammeijer F, Aerts JGJV, Vroman H. Current state of dendritic cell-based immunotherapy: opportunities for in vitro antigen loading of different DC subsets? Front Immunol. 2018;9:2804. doi:10.3389/fimmu.2018.02804.

119. Charles J, Chaperot L, Hannani D, Bruder Costa J, Templier I, Trabelsi S, Gil H, Moisan A, Persoons V, Hegelhofer H. et al. An innovative plasmacytoid dendritic cell line-based cancer vaccine primes and expands antitumor T-cells in melanoma patients in a first-in-human trial. Oncoimmunology. 2020;9(1):1738812. doi:10.1080/2162402X.2020.1738812.

120. Bloemendal M, Bol KF, Boudewijns S, Gorris MAJ, de Wilt JHW, Croockewit SAJ, van Rossum MM, de Goede AL, Petry K, Koornstra RHT. et al. Immunological responses to adjuvant vaccination with combined CD1c+ myeloid and plasmacytoid dendritic cells in stage III melanoma patients. Oncoimmunology. 2022;11(1):2015113. doi:10.1080/2162402X.2021.2015113.

121. Bercovici N, Haicheur N, Massicard S, Vernel-Pauillac F, Adotevi O, Landais D, Gorin I, Robert C, Prince HM, Grob J-J. et al. Analysis and characterization of antitumor T-cell response after administration of dendritic cells loaded with allogeneic tumor lysate to metastatic melanoma patients. J Immunother. 2008;31(1):101–112. doi:10.1097/CJI.0b013e318159f5ba.

122. Fučíková J, Rožková D, Ulčová H, Budinský V, Sochorová K, Pokorná K, Bartůňková J, Špíšek R. Poly I: C-activated dendritic cells that were generated in CellGro for use in cancer immunotherapy trials. J Transl Med. 2011;9(1):223. doi:10.1186/1479-5876-9-223.

123. Irvine AS, Trinder PK, Laughton DL, Ketteringham H, McDermott RH, Reid SC, Haines AM, Amir A, Husain R, Doshi R. et al. Efficient nonviral transfection of dendritic cells and their use for in vivo immunization. Nat Biotechnol. 2000;18(12):1273–1278. doi:10.1038/82383.

124. Wan Y, Bramson J, Carter R, Graham F, Gauldie J. Dendritic cells transduced with an adenoviral vector encoding a model tumor-associated antigen for tumor vaccination. Hum Gene Ther. 1997;8(11):1355–1363. doi:10.1089/hum.1997.8.11-1355.

125. Ishida T, Chada S, Stipanov M, Nadaf S, Ciernik FI, Gabrilovich DI, Carbone DP. Dendritic cells transduced with wild-type p53 gene elicit potent anti-tumour immune responses. Clin Exp Immunol. 1999;117(2):244–251. doi:10.1046/j.1365-2249.1999.00913.x.

126. Orentas RJ, Schauer D, Bin Q, Johnson BD. Electrofusion of a weakly immunogenic neuroblastoma with dendritic cells produces a tumor vaccine. Cell Immunol. 2001;213(1):4–13. doi:10.1006/cimm.2001.1864.

127. Kjaergaard J, Shimizu K, Shu S. Electrofusion of syngeneic dendritic cells and tumor generates potent therapeutic vaccine. Cell Immunol. 2003;225(2):65–74. doi:10.1016/j.cellimm.2003.09.005.

128. Tanaka H, Shimizu K, Hayashi T, Shu S. Therapeutic immune response induced by electrofusion of dendritic and tumor cells. Cell Immunol. 2002;220(1):1–12. doi:10.1016/S0008-8749(03)00009-1.

129. Copland MJ, Baird MA, Rades T, McKenzie JL, Becker B, Reck F, Tyler PC, Davies NM. Liposomal delivery of antigen to human dendritic cells. Vaccine. 2003;21(9–10):883–890. doi:10.1016/S0264-410X(02)00536-4.

130. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB. et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411–422. doi:10.1056/NEJMoa1001294.

131. Higano CS, Small EJ, Schellhammer P, Yasothan U, Gubernick S, Kirkpatrick P, Kantoff PW. Sipuleucel-T. Nat Rev Drug Discov. 2010;9(7):513–514. doi:10.1038/nrd3220.

132. Cheever MA, Higano CS. PROVENGE (sipuleucel-t) in prostate cancer: the first DC-approved therapeutic cancer vaccine. Clin Cancer Res. 2011;17(11):3520–3526. doi:10.1158/1078-0432.CCR-10-3126.

133. Handy CE, Antonarakis ES. Sipuleucel-T for the treatment of prostate cancer: novel insights and future directions. Future Oncol. 2018;14:907–917. doi:10.2217/fon-2017-0531.

134. Zhou J, Wang H. Spotlight—author's view for "metabolic glycan labeling immobilizes dendritic cell membrane and enhances antitumorefficacy of dendritic cell vaccine". Genes Immun. 2024;25(3):259–260. doi:10.1038/s41435-023-00245-4.

135. Dhar R, Seethy A, Singh S, Pethusamy K, Srivastava T, Talukdar J, Rath GK, Karmakar S. Cancer immunotherapy: recent advances and challenges. J Cancer Res Ther. 2021;17(4):834–844. doi:10.4103/jcrt.JCRT_1241_20.

136. Lagos KJ, Buzzá HH, Bagnato VS, Romero MP. Carbon-based materials in photodynamic and photothermal therapies applied to tumor destruction. Int J Mol Sci. 2021;23(1):22. doi:10.3390/ijms23010022.

137. Vanmeerbeek I, Borras DM, Sprooten J, Bechter O, Tejpar S, Garg AD. Early memory differentiation and cell death resistance in T cells predicts melanoma response to sequential anti-CTLA4 and anti-PD1 immunotherapy. Genes Immun. 2021;22(2):108–119. doi:10.1038/s41435-021-00138-4.

138. Hendrickson PG, Olson M, Luetkens T, Weston S, Han T, Atanackovic D, Fine GC. The promise of adoptive cellular immunotherapies in hepatocellular carcinoma. Oncoimmunology. 2020;9(1):1673129. doi:10.1080/2162402X.2019.1673129.

139. Faghfuri E, Shadbad MA, Faghfouri AH, Soozangar N. Cellular immunotherapy in gastric cancer: adoptive cell therapy and dendritic cell-based vaccination. Immunotherapy. 2022;14(6):475–488. doi:10.2217/imt-2021-0285.

140. Ghiringhelli F, Thibaudin M. Targeting CTLA-4: a possible solution for microsatellite-stable colorectal cancer. Genes Immun. 2023;24(6):283–284. doi:10.1038/s41435-023-00223-w.

141. Wei F, Sasada T. Circulating cytokine signatures as a soluble biomarker of immune checkpoint inhibitor therapy in non-small-cell lung cancer. Genes Immun. 2024;25(1):89–91. doi:10.1038/s41435-023-00236-5.

142. Li P, Jia L, Bian X, Tan S. Application of engineered dendritic cell vaccines in cancer immunotherapy: challenges and opportunities.

Curr Treat Options Oncol. 2023;24(12):1703–1719. doi:10.1007/s11864-023-01143-7.

143. Laureano RS, Sprooten J, Vanmeerbeerk I, Borras DM, Govaerts J, Naulaerts S, Berneman ZN, Beuselinck B, Bol KF, Borst J. et al. Trial watch: dendritic cell (dc)-based immunotherapy for cancer. Oncoimmunology. 2022;11(1):2096363. doi:10.1080/2162402X.2022.2096363.

144. Vedunova M, Turubanova V, Vershinina O, Savyuk M, Efimova I, Mishchenko T, Raedt R, Vral A, Vanhove C, Korsakova D. et al. DC vaccines loaded with glioma cells killed by photodynamic therapy induce Th17 anti-tumor immunity and provide a four-gene signature for glioma prognosis. Cell Death Dis. 2022;13 (12):1062. doi:10.1038/s41419-022-05514-0.

145. Caslin HL, Abebayehu D, Pinette JA, Ryan JJ. Lactate is a metabolic mediator that shapes immune cell fate and function. Front Physiol. 2021;12:688485. doi:10.3389/fphys.2021.688485.

146. Adamik J, Munson PV, Maurer DM, Hartmann FJ, Bendall SC, Argüello RJ, Butterfield LH. Immuno-metabolic dendritic cell vaccine signatures associate with overall survival in vaccinated melanoma patients. Nat Commun. 2023;14(1):7211. doi:10.1038/s41467-023-42881-4.

147. Sprooten J, Vanmeerbeek I, Datsi A, Govaerts J, Naulaerts S, Laureano RS, Borràs DM, Calvet A, Malviya V, Kuballa M. et al. Lymph node and tumor-associated PD-L1+ macrophages antagonize dendritic cell vaccines by suppressing CD8+ T cells. Cell Rep Med. 2024;5(1):101377. doi:10.1016/j.xcrm.2023.101377.

148. Han J, Bhatta R, Liu Y, Bo Y, Elosegui-Artola A, Wang H. Metabolic glycan labeling immobilizes dendritic cell membrane and enhances antitumor efficacy of dendritic cell vaccine. Nat Commun. 2023;14(1):5049. doi:10.1038/s41467-023-40886-7.

149. Basirjafar P, Zandvakili R, Masoumi J, Zainodini N, Taghipour Z, Khorramdelazad H, Yousefi S, Tavakoli T, Vatanparast M, Safdel S. et al. Leptin/lipopolysaccharide-treated dendritic cell vaccine improved cellular immune responses in an animal model of breast cancer. Immunopharmacol Immunotoxicol. 2024;46(1):73–85. doi:10.1080/08923973.2023.2253989.

150. Chan L, Mehrani Y, Wood GA, Bridle BW, Karimi K. Dendritic cell-based vaccines recruit neutrophils to the local draining lymph nodes to prime natural killer cell responses. Cells. 2022;12(1):121. doi:10.3390/cells12010121.

151. Ferris ST, Ohara RA, Ou F, Wu R, Huang X, Kim S, Chen J, Liu T-T, Schreiber RD, Murphy TL. et al. cDC1 vaccines drive tumor rejection by direct presentation independently of Host cDC1. Cancer Immunol Res. 2022;10(8):920–931. doi:10.1158/2326-6066.CIR-21-0865.

152. da Silva SF, Murta EF, Michelin MA. ICAM2 is related to good prognosis in dendritic cell immunotherapy for cancer. Immunotherapy. 2024;16(3):173–185. doi:10.2217/imt-2021-0097.

153. Groux H, O'Garra A, Bigler M, Rouleau M, Antonenko S, de Vries JE, Roncarolo MG. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. Nature. 1997;389(6652):737–742. doi:10.1038/39614.

154. Sultan H, Takeuchi Y, Ward JP, Sharma N, Liu T-T, Sukhov V, Firulyova M, Song Y, Ameh S, Brioschi S. et al. Neoantigen-specific cytotoxic Tr1 CD4 T cells suppress cancer immunotherapy. Nature. 2024. doi:10.1038/s41586-024-07752-y.

155. Schwarze JK, Tijtgat J, Awada G, Cras L, Vasaturo A, Bagnall C, Forsyth R, Dufait I, Tuyaerts S, Van Riet I. et al. Intratumoral administration of CD1c (BDCA-1)+ and CD141 (BDCA-3)+ myeloid dendritic cells in combination with talimogene laherparepvec in immune checkpoint blockade refractory advanced melanoma patients: a phase I clinical trial. J Immunother Cancer. 2022;10(9): doi:10.1136/jitc-2022-005141.

156. Carpenter EL, Van Decar S, Adams AM, O'Shea AE, McCarthy P, Chick RC, Clifton GT, Vreeland T, Valdera FA, Tiwari A. et al. Prospective, randomized, double-blind phase 2B trial of the TLPO and TLPLDC vaccines to prevent recurrence of resected stage III/IV melanoma: a prespecified 36-month analysis. J Immunother Cancer. 2023;11(8): doi:10.1136/jitc-2023-006665.

157. Dasyam N, Sharples KJ, Barrow C, Huang Y, Bauer E, Mester B, Wood CE, Authier-Hall A, Dzhelali M, Ostapowicz T. et al. A randomised controlled trial of long NY-ESO-1 peptide-pulsed autologous dendritic cells with or without alpha-galactosylceramide in high-risk melanoma. Cancer Immunol Immunother. 2023;72(7):2267–2282. doi:10.1007/s00262-023-03400-y.

158. Adams AM, Carpenter EL, Clifton GT, Vreeland TJ, Chick RC, O'Shea AE, McCarthy PM, Kemp Bohan PM, Hickerson AT, Valdera FA. et al. Divergent clinical outcomes in a phase 2B trial of the TLPLDC vaccine in preventing melanoma recurrence and the impact of dendritic cell collection methodology: a randomized clinical trial. Cancer Immunol Immunother. 2023;72(3):697–705. doi:10.1007/s00262-022-03272-8.

159. Vogelzang NJ, Beer TM, Gerritsen W, Oudard S, Wiechno P, Kukielka-Budny B, Samal V, Hajek J, Feyerabend S, Khoo V. et al. Efficacy and safety of autologous dendritic cell–based immunotherapy, Docetaxel, and prednisone vs placebo in patients with metastatic castration-resistant prostate cancer. JAMA Oncol. 2022;8(4):546–552. doi:10.1001/jamaoncol.2021.7298.

160. Thomsen LCV, Honoré A, Reisæter LAR, Almås B, Børretzen A, Helle SI, Førde K, Kristoffersen EK, Kaada SH, Melve GK. et al. A phase I prospective, non-randomized trial of autologous dendritic cell-based cryoimmunotherapy in patients with metastatic castration-resistant prostate cancer. Cancer Immunol Immunother. 2023;72(7):2357–2373. doi:10.1007/s00262-023-03421-7.

161. Wei XX, Kwak L, Hamid A, He M, Sweeney C, Flanders SC, Harmon M, Choudhury AD. Outcomes in men with metastatic castration-resistant prostate cancer who received sipuleucel-T and no immediate subsequent therapy: experience at Dana Farber and in the PROCEED registry. Prostate Cancer Prostatic Dis. 2022;25 (2):314–319. doi:10.1038/s41391-022-00493-x.

162. Tryggestad AMA, Axcrona K, Axcrona U, Bigalke I, Brennhovd B, Inderberg EM, Hønnåshagen TK, Skoge LJ, Solum G, Saebøe-Larssen S. et al. Long-term first-in-man phase I/II study of an adjuvant dendritic cell vaccine in patients with high-risk prostate cancer after radical prostatectomy. Prostate. 2022;82 (2):245–253. doi:10.1002/pros.24267.

163. Liau LM, Ashkan K, Brem S, Campian JL, Trusheim JE, Iwamoto FM, Tran DD, Ansstas G, Cobbs CS, Heth JA. et al. Association of autologous tumor lysate-loaded dendritic cell vaccination with extension of survival among patients with newly diagnosed and recurrent glioblastoma: a phase 3 prospective externally controlled cohort trial. JAMA Oncol. 2023;9(1):112–121. doi:10.1001/jamaoncol.2022.5370.

164. Bota DA, Taylor TH, Piccioni DE, Duma CM, LaRocca RV, Kesari S, Carrillo JA, Abedi M, Aiken RD, Hsu FPK. et al. Phase 2 study of AV-GBM-1 (a tumor-initiating cell targeted dendritic cell vaccine) in newly diagnosed glioblastoma patients: safety and efficacy assessment. J Exp Clin Cancer Res. 2022;41(1):344. doi:10.1186/s13046-022-02552-6.

165. Hu JL, Omofoye OA, Rudnick JD, Kim S, Tighiouart M, Phuphanich S, Wang H, Mazer M, Ganaway T, Chu RM. et al. A phase I study of autologous dendritic cell vaccine pulsed with allogeneic stem-like cell line lysate in patients with newly diagnosed or recurrent glioblastoma. Clin Cancer Res. 2022;28 (4):689–696. doi:10.1158/1078-0432.CCR-21-2867.

166. Chung DJ, Sharma S, Rangesa M, DeWolf S, Elhanati Y, Perica K, Young JW. Langerhans dendritic cell vaccine bearing mRNA-encoded tumor antigens induces antimyeloma immunity after autotransplant. Blood Adv. 2022;6(5):1547–1558. doi:10.1182/bloodadvances.2021005941.

167. Chung DJ, Shah N, Wu J, Logan B, Bisharat L, Callander N, Cheloni G, Anderson K, Chodon T, Dhakal B. et al. Randomized phase II trial of dendritic cell/myeloma fusion vaccine with lenalidomide maintenance after upfront autologous hematopoietic cell transplantation for multiple myeloma: BMT CTN 1401. Clin Cancer Res. 2023;29(23):4784–4796. doi:10.1158/1078-0432.CCR-23-0235.

168. Zhong R, Ling X, Cao S, Xu J, Zhang B, Zhang X, Wang H, Han B, Zhong H. Safety and efficacy of dendritic cell-based immunotherapy (DCVAC/DCVAC) combined with carboplatin/pemetrexed for patients with advanced non-squamous non-small-cell lung cancer without oncogenic drivers. ESMO Open. 2022;7 (1):100334. doi:10.1016/j.esmoop.2021.100334.

169. Liu Q, Lou Y, Li L, Yang G, Cui H, Cheng Z, Li Y, Liu M, Deng C, Wan D. et al. A single-arm phase II study to evaluate efficacy and safety of first-line treatment with DCVAC/LuCa. Standard Of Care Chemother And Shenqi Fuzheng Injection In Adv (Stage IIIB/IV) Non-Small Cell Lung Cancer Patients Integr Cancer Ther. 2022;21:15347354221083968. doi:10.1177/15347354221083968.

170. Fucikova J, Hensler M, Kasikova L, Lanickova T, Pasulka J, Rakova J, Drozenova J, Fredriksen T, Hraska M, Hrnciarova T. et al. An autologous dendritic cell vaccine promotes anticancer immunity in patients with ovarian cancer with Low mutational burden and cold tumors. Clin Cancer Res. 2022;28(14):3053–3065. doi:10.1158/1078-0432.CCR-21-4413.

171. Rob L, Cibula D, Knapp P, Mallmann P, Klat J, Minar L, Bartos P, Chovanec J, Valha P, Pluta M. et al. Safety and efficacy of dendritic cell-based immunotherapy DCVAC/OvCa added to first-line chemotherapy (carboplatin plus paclitaxel) for epithelial ovarian cancer: a phase 2, open-label, multicenter, randomized trial. J Immunother Cancer. 2022;10(1): doi:10.1136/jitc-2021-003190.

172. Vincent BG, File DM, McKinnon KP, Moore DT, Frelinger JA, Collins EJ, Ibrahim JG, Bixby L, Reisdorf S, Laurie SJ. et al. Efficacy of a dual-epitope dendritic cell vaccine as part of combined immunotherapy for HER2-expressing breast tumors. J Immunol. 2023;211(2):219–228. doi:10.4049/jimmunol.2300077.

173. Nickles E, Dharmadhikari B, Yating L, Walsh RJ, Koh LP, Poon M, Tan LK, Wang L-Z, Ang Y, Asokumaran Y. et al. Dendritic cell therapy with CD137L-DC-EBV-vax in locally recurrent or metastatic nasopharyngeal carcinoma is safe and confers clinical benefit. Cancer Immunol Immunother. 2022;71(6):1531–1543. doi:10.1007/s00262-021-03075-3.

174. Zhou Y, Li M, Zhang B, Yang C, Wang Y, Zheng S, Tang L, Zhou C, Qian G, Huang Y. et al. A pilot study of multi-antigen stimulated cell therapy-I plus camrelizumab and apatinib in patients with advanced bone and soft-tissue sarcomas. BMC Med. 2023;21(1):470. doi:10.1186/s12916-023-03132-x.

175. Koeneman BJ, Schreibelt G, Gorris MAJ, Hins-de Bree S, Westdorp H, Ottevanger PB, de Vries IJM. Dendritic cell vaccination combined with carboplatin/paclitaxel for metastatic endometrial cancer patients: results of a phase I/II trial. Front Immunol. 2024;15:1368103. doi:10.3389/fimmu.2024.1368103.

176. Master VA, Uzzo RG, Bratlavsky G, Karam JA. Autologous dendritic vaccine therapy in metastatic kidney cancer: the ADAPT trial and beyond. Eur Urol Focus. 2022;8(3):651–653. doi:10.1016/j.euf.2022.04.003.

177. Dietz MV, Quintelier KLA, van Kooten JP, de Boer NL, Vink M, Brandt-Kerkhof ARM, Verhoef C, Saeys Y, Aerts JGJV, Willemsen M. et al. Adjuvant dendritic cell-based immunotherapy after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with malignant peritoneal mesothelioma: a phase II clinical trial. J Immunother Cancer. 2023;11(8): doi:10.1136/jitc-2023-007070.

178. Lau SP, Klaase L, Vink M, Dumas J, Bezemer K, van Krimpen A, van der Breggen R, Wismans LV, Doukas M, de Koning W. et al. Autologous dendritic cells pulsed with allogeneic tumour cell lysate induce tumour-reactive T-cell responses in patients with pancreatic cancer: a phase I study. Eur J Cancer. 2022;169:20–31. doi:10.1016/j.ejca.2022.03.015.

179. Cheng X, Wang J, Qiu C, Jin Y, Xia B, Qin R, Hu H, Yan J, Zhang X, Xu J. Feasibility of iNKT cell and PD-1+CD8+ T cell-based immunotherapy in patients with lung adenocarcinoma: preliminary results of a phase I/II clinical trial. Clin Immunol. 2022;238:108992. doi:10.1016/j.clim.2022.108992.

180. Garg AD, Coulie PG, Van den Eynde BJ, Agostinis P. Integrating Next-generation dendritic cell vaccines into the current cancer immunotherapy landscape. Trends Immunol. 2017;38 (8):577–593. doi:10.1016/j.it.2017.05.006.

181. Lee K-W, Yam JWP, Mao X. Dendritic cell vaccines: a shift from conventional approach to new generations. Cells. 2023;12 (17):2147. doi:10.3390/cells12172147.

182. Garg AD, Vara Perez M, Schaaf M, Agostinis P, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: dendritic cell-based anticancer immunotherapy. Oncoimmunology. 2017;6:e1328341. doi:10.1080/2162402X.2017.1328341.

183. Zhu P, Li S-Y, Ding J, Fei Z, Sun S-N, Zheng Z-H, Wei D, Jiang J, Miao J-L, Li S-Z. et al. Combination immunotherapy of glioblastoma with dendritic cell cancer vaccines, anti-PD-1 and poly I. C J Pharm Anal. 2023;13(6):616–624. doi:10.1016/j.jpha.2023.04.012.

184. Najafi S, Mortezaee K. Advances in dendritic cell vaccination therapy of cancer. Biomed Pharmacother. 2023;164:114954. doi:10.1016/j.biopha.2023.114954.

185. Fucikova J, Coosemans A, Orsulic S, Cibula D, Vergote I, Galluzzi L, Spisek R. Immunological configuration of ovarian carcinoma: features and impact on disease outcome. J Immunother Cancer. 2021;9(10): doi:10.1136/jitc-2021-002873.

186. Jiang Y-Q, Wang Z-X, Zhong M, Shen L-J, Han X, Zou X, Liu X-Y, Deng Y-N, Yang Y, Chen G-H. et al. Investigating mechanisms of response or resistance to immune checkpoint inhibitors by analyzing cell-cell communications in tumors before and after programmed cell death-1 (PD-1) targeted therapy: an integrative analysis using single-cell RNA and Bulk-rna sequencing data. Oncoimmunology. 2021;10:1908010. doi:10.1080/2162402X.2021.1908010.

187. Kato S, Okamura R, Kumaki Y, Ikeda S, Nikanjam M, Eskander R, Goodman A, Lee S, Glenn ST, Dressman D. et al. Expression of TIM3/VISTA checkpoints and the CD68 macrophage-associated marker correlates with anti-PD1/PDL1 resistance: implications of immunogram heterogeneity. Oncoimmunology. 2020;9 (1):1708065. doi:10.1080/2162402X.2019.1708065.

188. Sun Q, Hong Z, Zhang C, Wang L, Han Z, Ma D. Immune checkpoint therapy for solid tumours: clinical dilemmas and future trends. Signal Transduct Target Ther. 2023;8(1):320. doi:10.1038/s41392-023-01522-4.

189. Kim H, Choi J-M, Lee K-M. Immune checkpoint blockades in triple-negative breast cancer: current state and molecular mechanisms of resistance. Biomedicines. 2022;10(5):1130. doi:10.3390/biomedicines10051130.

190. Jin C, Ali A, Iskantar A, Fotaki G, Wang H, Essand M, Karlsson-Parra A, Yu D. Intratumoral administration of pro-inflammatory allogeneic dendritic cells improved the anti-tumor response of systemic anti-CTLA-4 treatment via unleashing a T cell-dependent response. Oncoimmunology. 2022;11(1):2099642. doi:10.1080/2162402X.2022.2099642.

191. Jang A, Lichterman JN, Zhong JY, Shoag JE, Garcia JA, Zhang T, Barata PC. Immune approaches beyond traditional immune checkpoint inhibitors for advanced renal cell carcinoma. Hum Vaccin Immunother. 2023;19(3):2276629. doi:10.1080/21645515.2023.2276629.

192. Hotchkiss KM, Batich KA, Mohan A, Rahman R, Piantadosi S, Khasraw M. Dendritic cell vaccine trials in gliomas: Untangling the lines. Neuro Oncol. 2023;25(10):1752–1762. doi:10.1093/neuonc/noad088.

193. Mukherji R, Debnath D, Hartley ML, Noel MS. The role of immunotherapy in pancreatic cancer. Curr Oncol. 2022;29 (10):6864–6892. doi:10.3390/curroncol29100541.

194. Yuan B, Wang G, Tang X, Tong A, Zhou L. Immunotherapy of glioblastoma: recent advances and future prospects. Hum Vaccin Immunother. 2022;18(5):2055417. doi:10.1080/21645515.2022.2055417.

195. Lim M, Weller M, Idbaih A, Steinbach J, Finocchiaro G, Raval RR, Ansstas G, Baehring J, Taylor JW, Honnorat J. et al. Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter. Neuro Oncol. 2022;24(11):1935–1949. doi:10.1093/neuonc/noac116.

196. Reardon DA, Brandes AA, Omuro A, Mulholland P, Lim M, Wick A, Baehring J, Ahluwalia MS, Roth P, Bähr O. et al. Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the checkmate 143 phase 3 randomized clinical trial. JAMA Oncol. 2020;6(7):1003–1010. doi:10.1001/jamaoncol.2020.1024.

197. Sprooten J, Vankerckhoven A, Vanmeerbeek I, Borras DM, Berckmans Y, Wouters R, Laureano RS, Baert T, Boon L, Landolfo C. et al. Peripherally-driven myeloid NFkB and IFN/ISG responses predict malignancy risk, survival, and immunotherapy regime in ovarian cancer. J Immunother Cancer. 2021;9(11): doi:10.1136/jitc-2021-003609.

198. Shamshiripour P, Nikoobakht M, Mansourinejad Z, Ahmadvand D, Akbarpour M. A comprehensive update to dendritic cell therapy for glioma: a systematic review and meta-analysis. Expert Rev Vaccines. 2022;21(4):513–531. doi:10.1080/14760584.2022.2027759.

199. Caro AA, Deschoemaeker S, Allonsius L, Coosemans A, Laoui D. Dendritic cell vaccines: a promising approach in the fight against ovarian cancer. Cancers (Basel). 2022;14(16):4037. doi:10.3390/cancers14164037.

200. Yu J, Sun H, Cao W, Song Y, Jiang Z. Research progress on dendritic cell vaccines in cancer immunotherapy. Exp Hematol Oncol. 2022;11(1):3. doi:10.1186/s40164-022-00257-2.

201. Salehi-Rad R, Lim RJ, Du Y, Tran LM, Li R, Ong SL, Ling Huang Z, Dumitras C, Zhang T, Park SJ. et al. CCL21-DC in situ vaccination in murine NSCLC overcomes resistance to immunotherapy and generates systemic tumor-specific immunity. J Immunother Cancer. 2023;11(9): doi:10.1136/jitc-2023-006896.

202. Jie J, Liu G, Feng J, Huo D, Wu Y, Yuan H, Tai G, Ni W. MF59 promoted the combination of CpG ODN1826 and MUC1-MBP vaccine-induced antitumor activity involved in the enhancement of DC maturation by prolonging the local retention time of antigen and down-regulating of IL-6/STAT3. Int J Mol Sci. 2022;23 (18):10887. doi:10.3390/ijms231810887.

203. Liang T, Tong W, Ma S, Chang P. Standard therapies: solutions for improving therapeutic effects of immune checkpoint inhibitors on colorectal cancer. Oncoimmunology. 2020;9(1):1773205. doi:10.1080/2162402X.2020.1773205.

204. Grypari IM, Zolota V, Tzelepi V. Radical or not-so-radical prostatectomy: do surgical margins matter? Cancers (Basel). 2021. 14. 10 .3390/cancers14010013.

205. Yang J, Eresen A, Shangguan J, Ma Q, Yaghmai V, Zhang Z. Irreversible electroporation ablation overcomes tumor-associated immunosuppression to improve the efficacy of DC vaccination in a mice model of pancreatic cancer. Oncoimmunology. 2021;10 (1):1875638. doi:10.1080/2162402X.2021.1875638.

206. Vanmeerbeek I, Sprooten J, De Ruysscher D, Tejpar S, Vandenberghe P, Fucikova J, Spisek R, Zitvogel L, Kroemer G, Galluzzi L. et al. Trial watch: chemotherapy-induced immunogenic cell death in immuno-oncology. Oncoimmunology. 2020;9 (1):1703449. doi:10.1080/2162402X.2019.1703449.

207. Sprooten J, Laureano RS, Vanmeerbeek I, Govaerts J, Naulaerts S, Borras DM, Kinget L, Fucíková J, Špíšek R, Jelínková LP. et al. Trial watch: chemotherapy-induced immunogenic cell death in oncology. Oncoimmunology. 2023;12(1):2219591. doi:10.1080/2162402X.2023.2219591.

208. Guan H, Wu Y, Li LU, Yang Y, Qiu S, Zhao Z, Chu X, He J, Chen Z, Zhang Y. et al. Tumor neoantigens: novel strategies for application of cancer immunotherapy. Oncol Res. 2023;31(4):437–448. doi:10.32604/or.2023.029924.

209. Hannani D, Leplus E, Laulagnier K, Chaperot L, Plumas J. Leveraging a powerful allogeneic dendritic cell line towards neoantigen-based cancer vaccines. Genes Cancer. 2023;14:3–11. doi:10.18632/genesandcancer.229.

210. Zhang X, Xu Z, Dai X, Zhang X, Wang X. Research progress of neoantigen-based dendritic cell vaccines in pancreatic cancer. Front Immunol. 2023;14:1104860. doi:10.3389/fimmu.2023.1104860.

211. Liu G, Zhang Z, Wu Y, Feng J, Lan Y, Dong D, Liu Y, Yuan H, Tai G, Li S. et al. Anti-PD-L1 antibody reverses the immune tolerance induced by multiple MUC1-MBP vaccine immunizations by increasing the CD80/PD-L1 ratio, resulting in DC maturation, and decreasing treg activity in B16-MUC1 melanoma-bearing mice. Int Immunopharmacol. 2023;121:110487. doi:10.1016/j.intimp.2023.110487.

212. Liu Y, Pagacz J, Wolfgeher DJ, Bromerg KD, Gorman JV, Kron SJ. Senescent cancer cell vaccines induce cytotoxic T cell responses targeting primary tumors and disseminated tumor cells. J Immunother Cancer. 2023;11(2): doi:10.1136/jitc-2022-005862.

213. Mestrallet G, Sone K, Bhardwaj N. Strategies to overcome DC dysregulation in the tumor microenvironment. Front Immunol. 2022;13:980709. doi:10.3389/fimmu.2022.980709.

214. Wang R, Zhu T, Hou B, Huang X. An iPSC-derived exosome-pulsed dendritic cell vaccine boosts antitumor immunity in melanoma. Mol Ther. 2023;31(8):2376–2390. doi:10.1016/j.ymthe.2023.06.005.

215. Gea-Mallorquí E, Rowland-Jones S. Dc-targeting lentivectors for cancer immunotherapy. Immunother Adv. 2023;3(1):ltad023. doi:10.1093/immadv/ltad023.

216. Meng L, Teng Z, Yang S, Wang N, Guan Y, Chen X, Liu Y. Biomimetic nanoparticles for DC vaccination: a versatile approach to boost cancer immunotherapy. Nanoscale. 2023;15 (14):6432–6455. doi:10.1039/d2nr07071e.

217. Zhang M, Wang Y, Chen X, Zhang F, Chen J, Zhu H, Li J, Chen Z, Wang A, Xiao Y. et al. DC vaccine enhances CAR-T cell antitumor activity by overcoming T cell exhaustion and promoting T cell infiltration in solid tumors. Clin Transl Oncol. 2023;25 (10):2972–2982. doi:10.1007/s12094-023-03161-1.

218. Sun S, Ding Z, Gao L, Hammock BD, Huang X, Xu ZP, Wang X, Cheng Q, Mo F, Shi W. et al. A dendritic/tumor fusion cell vaccine enhances efficacy of nanobody-based CAR-T cells against solid tumor. Theranostics. 2023;13(14):5099–5113. doi:10.7150/thno.84946.

219. Tai Y, Chen M, Wang F, Fan Y, Zhang J, Cai B, Yan L, Luo Y, Li Y. The role of dendritic cells in cancer immunity and therapeutic strategies. Int Immunopharmacol. 2024;128:111548. doi:10.1016/j.intimp.2024.111548.

220. Tang L, Zhang R, Zhang X, Yang L. Personalized neoantigen-pulsed DC vaccines: advances in clinical applications. Front Oncol. 2021;11:701777. doi:10.3389/fonc.2021.701777.

221. Constantino J, Gomes C, Falcão A, Cruz MT, Neves BM. Antitumor dendritic cell-based vaccines: lessons from 20 years of clinical trials and future perspectives. Transl Res. 2016;168:74–95. doi:10.1016/j.trsl.2015.07.008.

222. Anguille S, Smits EL, Lion E, van Tendeloo VF, Berneman ZN. Clinical use of dendritic cells for cancer therapy. Lancet Oncol. 2014;15(7):e257–67. doi:10.1016/S1470-2045(13)70585-0.

223. Tesfatsion DA. Dendritic cell vaccine against leukemia: advances and perspectives. Immunotherapy. 2014;6(4):485–496. doi:10.2217/imt.14.12.

224. Jung N-C, Lee J-H, Chung K-H, Kwak YS, Lim D-S. Dendritic cell-based immunotherapy for solid tumors. Transl Oncol. 2018;11 (3):686–690. doi:10.1016/j.tranon.2018.03.007.

225. Verheye E, Bravo Melgar J, Deschoemaeker S, Raes G, Maes A, De Bruyne E, Menu E, Vanderkerken K, Laoui D, De Veirman K. Dendritic cell-based immunotherapy in multiple myeloma: challenges, opportunities, and future directions. Int J Mol Sci. 2022;23 (2):904. doi:10.3390/ijms23020904.

226. Vaes RDW, Reynders K, Sprooten J, Nevola KT, Rouschop KMA, Vooijs M, Garg AD, Lambrecht M, Hendriks LEL, Rucevic M. et al. Identification of potential prognostic and predictive immunological biomarkers in patients with stage I and Stage III non-Small cell lung cancer (NSCLC): a prospective exploratory study. Cancers (Basel). 2021;13(24):6259. doi:10.3390/cancers13246259.

227. Preusser M, van den Bent MJ. Autologous tumor lysate-loaded dendritic cell vaccination (DCVax-l) in glioblastoma:

breakthrough or fata morgana? Neuro Oncol. 2023;25(4):631–634. doi:10.1093/neuonc/noac281.

228. Backer RA, Probst HC, Clausen BE. Classical DC2 subsets and monocyte-derived DC: delineating the developmental and functional relationship. Eur J Immunol. 2023;53(3):e2149548. doi:10.1002/eji.202149548.

229. Murphy TL, Murphy KM. Dendritic cells in cancer immunology. Cell Mol Immunol. 2022;19(1):3–13. doi:10.1038/s41423-021-00741-5.

230. Del Prete A, Salvi V, Soriani A, Laffranchi M, Sozio F, Bosisio D, Sozzani S. Dendritic cell subsets in cancer immunity and tumor antigen sensing. Cell Mol Immunol. 2023;20(5):432–447. doi:10.1038/s41423-023-00990-6.

231. Mastelic-Gavillet B, Sarivalasis A, Lozano LE, Lofek S, Wyss T, Melero I, de Vries IJM, Harari A, Romero P, Kandalaft LE. et al. Longitudinal analysis of DC subsets in patients with ovarian cancer: implications for immunotherapy. Front Immunol. 2023;14:1119371. doi:10.3389/fimmu.2023.1119371.

232. Zhou T, Wang H-W. Antigen loss after targeted immunotherapy in hematological malignancies. Clin Lab Med. 2021;41(3):341–357. doi:10.1016/j.cll.2021.04.005.

233. Dhatchinamoorthy K, Colbert JD, Rock KL. Cancer immune evasion through loss of MHC class I antigen presentation. Front Immunol. 2021;12:636568. doi:10.3389/fimmu.2021.636568.

234. Schoenfeld AJ, Hellmann MD. Acquired resistance to immune checkpoint inhibitors. Cancer Cell. 2020;37(4):443–455. doi:10.1016/j.ccell.2020.03.017.

235. Lambrechts Y, Garg AD, Floris G, Punie K, Neven P, Nevelsteen I, Govaerts J, Richard F, Laenen A, Desmedt C. et al. Circulating biomarkers at diagnosis correlate with distant metastases of early luminal-like breast cancer. Genes Immun. 2023;24(5):270–279. doi:10.1038/s41435-023-00220-z.

236. Kinget L, Garg AD. Heritable and spatial immunogenic traits co-predict the efficacy of immunotherapy in kidney cancer. Nat Med. 2024;30:1537–1538. doi:10.1038/s41591-024-03020-8.

237. Tang XX, Shimada H, Ikegaki N. Macrophage-mediated anti-tumor immunity against high-risk neuroblastoma. Genes Immun. 2022;23(3–4):129–140. doi:10.1038/s41435-022-00172-w.

238. Vanmeerbeek I, Naulaerts S, Garg AD. Reverse translation: the key to increasing the clinical success of immunotherapy? Genes Immun. 2023;24(5):217–219. doi:10.1038/s41435-023-00217-8.

239. Kinget L, Naulaerts S, Govaerts J, Vanmeerbeek I, Sprooten J, Laureano RS, Dubroja N, Shankar G, Bosisio FM, Roussel E. et al. A spatial architecture-embedding HLA signature to predict clinical response to immunotherapy in renal cell carcinoma. Nat Med. 2024;30(6):1667–1679. doi:10.1038/s41591-024-02978-9.

240. Ogasawara M. Wilms' tumor 1 -targeting cancer vaccine: recent advancements and future perspectives. Hum Vaccin Immunother. 2024;20(1):2296735. doi:10.1080/21645515.2023.2296735.

241. Arun J, Singh A, Shashidhar E, Patel G, Verma Y, Sapcota S. The role of immunotherapy in cancer treatment: checkpoint inhibitors, car-t cells, and vaccines. Georgian Med News. 2023;(339):105–112.

242. Ding J, Zheng Y, Wang G, Zheng J, Chai D. The performance and perspectives of dendritic cell vaccines modified by immune checkpoint inhibitors or stimulants. Biochim Biophys Acta Rev Cancer. 2022;1877(5):188763. doi:10.1016/j.bbcan.2022.188763.