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REVIEW

Current progress in neoantigen-based dendritic cell vaccines for solid tumors

Yuting Li[1]*, Abudukadierjiang Abudureheman[1]*, Jianming Xu[2]

[1]Department of Oncology, The First Medical Center, Chinese PLA General Hospital/Medical School of Chinese PLA, Beijing 100853, China; [2]Department of Oncology, The Fifth Medical Center of the PLA General Hospital, Beijing 100071, China

ABSTRACT Immunotherapy, particularly immune checkpoint inhibitors (ICIs) programmed death-ligand 1/programmed death-1 (PD-L1/PD-1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), has heralded a new era of tumor treatment. Although ICIs have clinical benefits, their complex heterogeneity and diverse resistance mechanisms critically limit their efficacy. Neoantigens, arising from tumor-specific alterations, offer novel targets for individualized immunotherapy, because of their high immunogenicity and tumor specificity. In the past decade, neoantigen-based tumor vaccines have been demonstrated to be a promising immunotherapy strategy to prime the tumor-specific immune response. These therapeutic vaccines include peptide vaccines, nucleic acid vaccines, and dendritic cell (DC) vaccines, and are categorized according to the neoantigen source and delivery method. *In vivo*, neoantigens are processed and presented by antigen-presenting cells (APCs) *via* the peptide-Major Histocompatibility Complex (pMHC) for T cell recognition, thereby triggering specific immune responses. Because DCs, the most potent APCs, play crucial roles in antitumor immunity, neoantigen-based DC vaccines provide a promising therapeutic strategy. A series of global clinical trials are exploring the safety, feasibility, and efficacy of neoantigen-based DC vaccines in tumors. This review focuses on current progress in clinical research on neoantigen-based DC vaccines in the treatment of solid tumors.

KEYWORDS Neoantigen; dendritic cell; vaccines; immunotherapy; solid tumor

Introduction

In the past decade, the discovery of immune checkpoints and the development of immune checkpoint inhibitors (ICIs) have led to an unprecedented revolution in tumor treatment and a new era of immunotherapy in oncology, by addressing the limitations of traditional chemotherapy and radiotherapy[1,2]. Extensive clinical evidence has demonstrated the feasibility and efficacy of ICIs against programmed death-ligand 1/programmed death-1 (PD-L1/ PD-1) or cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) in various types of solid tumors[3-5]. Nevertheless, ICIs are not sufficiently effective to meet clinical requirements, and only a subset of patients achieve durable survival benefits[6]. This limited ICI treatment efficacy is attributable to resistance to ICIs, which is induced by multiple complex mechanisms, including neoantigen loss; defects in antigen presentation and interferon signaling; immunosuppressive molecule expression; T cell exclusion; and alterations in metabolism, the microbiome, and epigenetics[7,8]. Additionally, the high intertumoral and intratumoral heterogeneity of solid tumors remains a critical limitation that further challenges the effectiveness of immunotherapy[9-11]. Consequently, research efforts have increasingly focused on identifying novel therapeutic targets to explore more effective immunotherapy strategies. Neoantigens, derived from tumor-specific mutations, have emerged as promising targets for personalized immunotherapy, owing to their strong tumor specificity and immunogenicity[12].

In recent years, personalized neoantigen vaccines have been demonstrated to potentially elicit specific and durable antitumor immune responses that effectively prevent tumor progress[13-16]. According to the neoantigen source and delivery method, therapeutic neoantigen vaccines are categorized into several types, including peptide-based vaccines, nucleic acid-based vaccines, and dendritic cell

*These authors contributed equally to this work.
Correspondence to: Jianming Xu
E-mail: jmxu2003@163.com
ORCID ID: https://orcid.org/0000-0003-4467-6021
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(DC)-based vaccines[17]. The core mechanism of these neoantigen vaccines is priming strong and long-lasting neoantigen-specific T cell responses, which are inseparable from the processing and presentation of neoantigens by antigen presenting cells (APCs). Generally, in APCs, neoantigens are processed and transported to major histocompatibility complex (MHC) molecules and are ultimately presented on cell surfaces in the form of peptide-MHC complexes. Subsequent recognition of these complexes by T cell receptors (TCRs) initiates a targeted immune response. DCs, the strongest professional APCs, are an attractive platform for manufacturing neoantigen vaccines. DC vaccines, particularly those in which patient-derived DCs are loaded with antigens *in vitro* and then reintroduced into patients to prime specific T cell responses, are known for their stability, safety, and reliability[18,19]. Notably, sipuleucel-T, an autologous DC vaccine loaded with fusion proteins, was the first therapeutic cancer vaccine to be approved by the U.S. Food & Drug Administration (FDA) for prostate cancer treatment, on the basis of significant improvement in overall survival[20].

Neoantigen-based DC vaccines are a prospective strategy for precise and efficient tumor eradication. Clinical studies are increasingly evaluating the feasibility, safety, and preliminary efficacy of neoantigen-based DC vaccines in various tumor types. Although some reviews have summarized research progress in DC vaccines in cancer, few have specifically described neoantigen-based DC vaccines across the spectrum of solid tumors[21-26]. In this review, we describe current clinical progress in various types of neoantigen-based DC vaccines for solid tumors and discuss their potential.

Neoantigens

Tumorigenesis is driven by genetic changes such as DNA mutations, chromosomal alterations, and epigenetic modifications, which ultimately alter the growth and proliferation of tumor cells[27]. These genomic alterations result in the production of altered or novel proteins, which are recognized by the immune system as "non-self" proteins, referred to as neoantigens[28]. Neoantigens are presented exclusively on the surfaces of tumor cells in complex with MHC molecules. These antigens are promising targets for cancer immunotherapy, because neoantigen-specific T cells specifically recognize and target tumor cells, thereby priming potent antitumor immune responses without harming normal tissues. Therapeutic neoantigen-based vaccines have been designed to prime effective and lasting tumor-specific immune responses, thus addressing a major limitation of traditional cancer therapies that arises from tumor heterogeneity[29].

The efficacy of neoantigen-based vaccines substantially depends on the immunogenicity and quality of targeted neoantigens; therefore, the major issue in neoantigen vaccine design is the identification of reliable immunogenic neoantigens[30]. An ideal neoantigen, arising from tumor-specific somatic mutation, is effectively presented *via* peptide-MHCs with high TCR affinity. The rapid advancement of next-generation sequencing techniques and bioinformatic analysis has rapidly accelerated neoantigen identification and substantially promoted the clinical application of neoantigen-based therapy strategies[31-41]. In the initial step of neoantigen identification, whole exome sequencing of tumors and blood cells is performed to identify the DNA sequences arising from non-synonymous mutations, such as single-nucleotide variants, insertions, deletions, and frameshift mutations, which eventually produce the novel neoantigen[35]. Subsequently, RNA sequencing of tumors and bioinformatic tools are applied to rank and filter candidate neoantigens, and further identify potential immunogenic mutations[33]. MHC binding affinity is a critical factor for effective presentation of neoantigen peptides (neopeptides). Use of mass spectrometry and next-generation sequencing techniques, together with machine learning and bioinformatics algorithms, profoundly improves the detection and prediction of HLA-binding neopeptides[34,42-44]. After these steps, screened neoantigen candidates are subjected to further evaluation to detect induced neoantigen-specific T cell responses through *in vitro* experiments. These *in vitro* assays, such as enzyme-linked immunospot (ELISpot) assays and intracellular cytokine staining, complement in silico neoantigen prediction algorithms by directly assessing the immunogenicity of neoantigens in a patient-specific context. Finally, the identified neoantigens are produced and delivered *via* distinct platforms, including synthetic neopeptides (short/long peptides typically administered with adjuvants), nucleic acid-based vectors (RNA/DNA encoding neoantigens), and autologous DC vaccines (autologous DCs *ex vivo* loaded with neoantigens), as illustrated in **Figure 1**. Neoantigen-based vaccines developed *via* these platforms can stimulate,

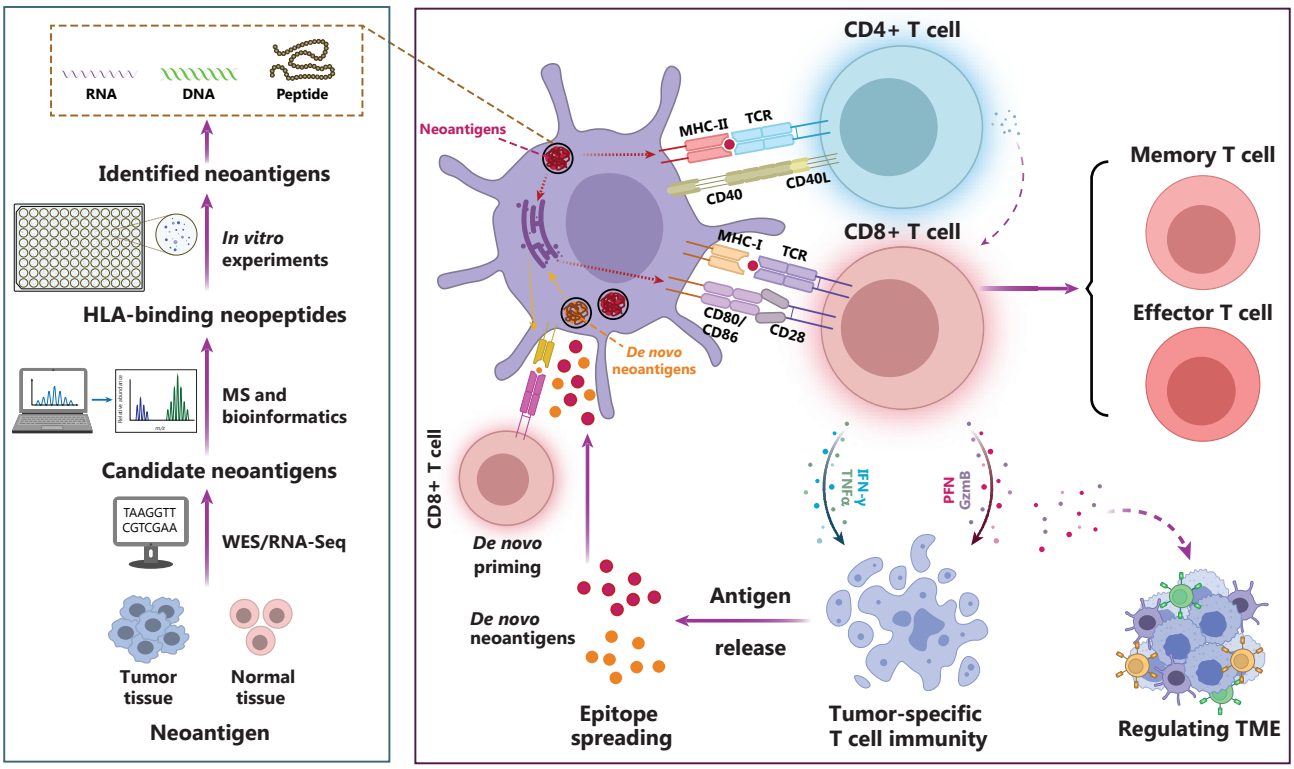


Figure 1 Neoantigen identification and mechanism of neoantigen-based DC vaccines priming specific antitumor immunity. Left: Personalized neoantigen identification. Tumor and matched normal tissues undergo whole exome sequencing and RNA sequencing. Candidate neoantigens derived from nonsynonymous mutations are bioinformatically screened. High-affinity HLA-binding neopeptides are predicted with mass spectrometry and computational algorithms, and immunogenicity validation (e.g., ELISpot) is performed. Validated neoantigens are converted to various formats (e.g., RNA, DNA, or peptides) for loading onto patient-derived moDCs to generate the vaccine. Right: Neoantigen DC vaccine-induced antitumor immunity. Activated DCs present MHC-II-restricted neopeptides to CD4+ T cells, which license DCs (e.g., *via* CD40L:CD40) for cross-presentation on MHC-I, thereby activating CD8+ T cells. Nucleic acid-based neoantigens are processed and presented by DCs for CD8+ T cell activation *via* recognition of the MHC-I complex and TCR, with co-stimulatory signals (e.g., CD80/CD86:CD28). Activated CD8+ T cells differentiate into memory T cells (sustained immunity) and effector T cells. Effectors target and lyse neoantigen-presenting tumor cells and secrete cytokines modulating the tumor microenvironment. Lysed tumor cells may release *de novo* neoantigens, which are taken up by DCs, thus priming *de novo* T cell responses (epitope spreading).

amplify, and diversify tumor-specific T cell responses, while exhibiting clinically favorable feasibility and safety profiles.

Neoantigen-based DC vaccines

Theoretical potential of neoantigen-based DC vaccines

Neoantigen-based DC vaccines are designed to theoretically elicit robust and durable tumor-specific immune responses, by integrating the precision of tumor-specific antigen targeting with the immunostimulatory functions of DCs. The rationale for their efficacy is based on the following interconnected mechanisms (**Figure 1**). (i) The nature of neoantigens: Neoantigens, derived from tumor-specific somatic mutations, bypass central tolerance mechanisms and consequently enable DCs to prime high-affinity T cells devoid of self-tolerance constraints. This process overcomes a critical limitation of tumor-associated antigen (TAA)-targeted vaccines, which often trigger weak or transient responses, because of pre-existing immune tolerance. (ii) DC-mediated antigen presentation and T cell priming:

DCs are professional APCs uniquely equipped to process and present tumor-derived neoantigens *via* both MHC-I and MHC-II pathways. This dual presentation activates CD8+ cytotoxic T lymphocytes and CD4+ T helper cells, respectively[45,46]. Neoantigen-based DCs migrate to secondary lymphoid organs, where they cross-present exogenous antigens on MHC class I molecules to naïve CD8+ T cells. Concurrently, MHC class II-restricted neoantigen presentation to CD4+ T cells promotes clonal expansion of cytotoxic T lymphocytes and fosters the development of immunological memory. The provision of co-stimulatory signals (e.g., CD80/CD86-CD28 interactions) and cytokines (e.g., IL-12) by activated DCs prevents T cell anergy, and drives the differentiation of effector and memory T cell subsets[47]. (iii) Epitope spreading and diverse antitumor immunity: Neoantigen-specific T cell responses may initiate epitope spreading, wherein immune recognition expands to additional tumor antigens beyond the vaccine-targeted neoantigens. This phenomenon broadens the immune repertoire, decreases the risk of tumor immune escape because of antigen loss, and contributes to long-term immunological surveillance[18,48]. (iv) Generation of memory T cell pools: DCs promote the differentiation of central memory T cells and stem-like memory T cells, which exhibit self-renewal capacity and longevity. These subsets serve as reservoirs for rapid effector T cell expansion after antigen re-exposure, thereby underpinning durable antitumor immunity. Preclinical models have demonstrated that the persistence of neoantigen-specific central memory T cell populations in lymphoid tissues and the circulation enables prolonged tumor control. (v) Modulation of the tumor microenvironment (TME): Neoantigen-activated T cells secrete pro-inflammatory cytokines (e.g., IFN-γ and TNF-α), which reprogram the immunosuppressive TME by attenuating regulatory T cell activity, inhibiting myeloid-derived suppressor cells, and enhancing DC maturation. Consequently, a self-reinforcing cycle of immune activation further sustains antitumor efficacy.

Neoantigen-based DC vaccines integrate the precision of tumor-specific antigen targeting with the immunostimulatory functions of DCs, thereby fostering a multifaceted adaptive immune response capable of overcoming tolerance, diversifying antigen recognition, and establishing enduring memory. These vaccines therefore provide a promising modality for achieving durable clinical responses in solid tumors, particularly when they are combined with ICIs to counteract T cell exhaustion mechanisms.

Preparation of neoantigen-based DC vaccines

The effective presentation of neoantigens on APCs critically influences the therapeutic efficacy of neoantigen vaccines. DCs, the most potent professional APCs, serve as ideal antigen delivery vehicles and are frequently used in clinical trials of neoantigen vaccines. According to their developmental origin and function, DCs are typically categorized into distinct subtypes, including conventional DCs (cDC1 and cDC2), plasmacytoid DCs, and monocyte-derived DCs (moDC)[49]. Among these, the cDC1 (CD123−CD11c+CD141+CLEC9A+) subset is critical in initiating immune responses by priming both CD4+ and CD8+ T cells in syngeneic tumor models, whereas the cDC2 (CD123−CD11c+CD1c+CLEC9A−) subset is important for priming CD4 responses. The plasmacytoid DC (CD123+CD11c−CD303+CD304+) subset produces type I interferons. Moreover, the moDC (CD16−CD11c+) subset, driven primarily by inflammation, may prime T cell responses after chemotherapy or viral infection.

The manufacturing process of neoantigen-based DC vaccines involves several critical approaches, particularly focusing on moDCs, the most prevalent type of DCs in the blood. A brief overview of the key approaches (**Figure 2**) is as follows. (i) Isolation of monocytes: Peripheral blood mononuclear cells are collected from patients *via* leukapheresis and prepared for further isolation and purification with density gradient centrifugation or magnetic-activated cell sorting. (ii) Differentiation into moDCs: Isolated monocytes are cultured in the presence of specific cytokines (GM-CSF and IL-4), which promote their differentiation into monocyte-derived DCs. (iii) Loading of neoantigens: In moDC culture, neoantigens (e.g., nucleic acid, peptides, proteins, or tumor lysates) are loaded with immature DCs for fusion into a tumor vaccine. (iv) Maturation of DCs: Immature DCs are further cultured with a cocktail containing a series of stimulation factors (e.g., TNF-α, IL-1β, IL-6, IFN-γ, and prostaglandin E2) and simultaneously pulsed with neoantigens[50,51]. Subsequently, mature DCs loaded with neoantigens undergo quality control assessment and are reinfused into patients, as part of personalized immunotherapy regimens.

According to the neoantigen source, neoantigen-based DC vaccines are categorized into the following types. (i) Neopeptide-based DC vaccines: DCs loaded with in

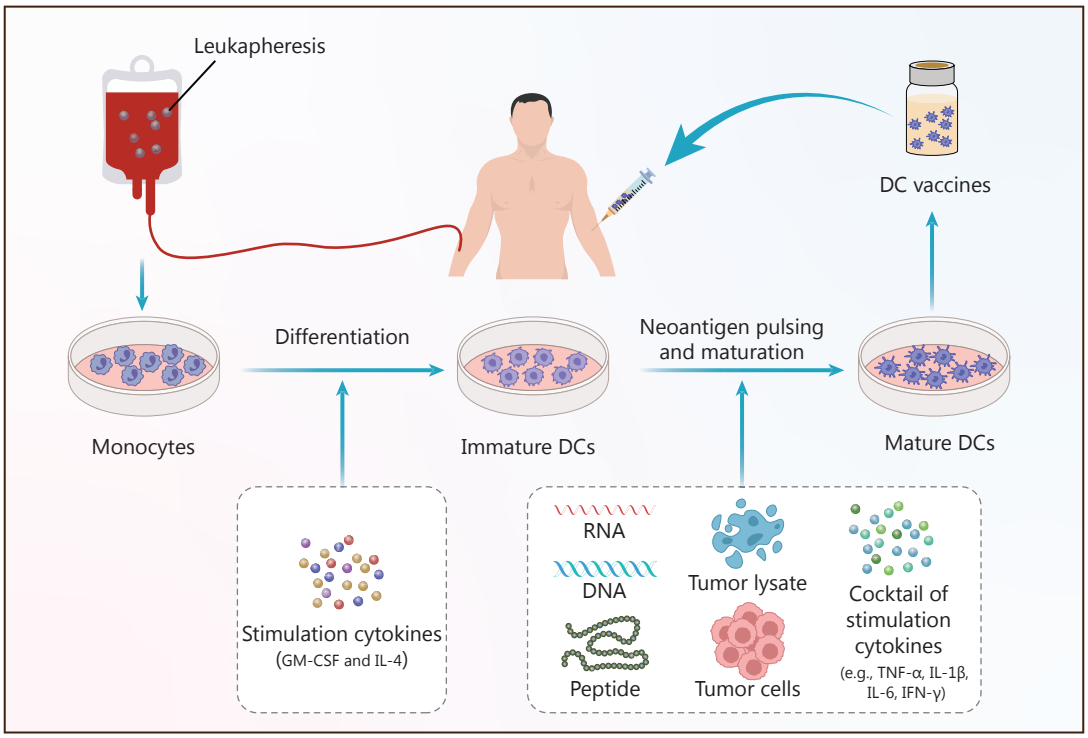


Figure 2 Overview of the manufacturing process of personalized neoantigen-based DC vaccines. A typical basic process of manufacturing neoantigen-based DC vaccines by using monocyte-derived dendritic cells is depicted. First, patients' peripheral blood mononuclear cells collected *via* leukapheresis are isolated and purified for collection of monocytes. Subsequently, monocytes are cultured and differentiated into immature DCs with the addition of a series of stimulatory cytokines. Subsequently, neoantigens (e.g., nucleic acid, peptides, tumor cells, or lysates) are loaded with immature DCs for further cultivation of mature DCs with the addition of a cocktail of stimulation factors. Finally, neoantigen-loaded DCs are collected for quality testing and ultimately used for vaccination in patients.

silico-predicted synthetic peptides enable precise targeting of immunodominant neoantigens with defined HLA restriction, thereby maximizing specificity. However, their efficacy heavily depends on accurate neoantigen prediction and HLA typing. (ii) Nucleic acid-based DC vaccines: DCs transfected with mRNA/DNA drive endogenous antigen processing, and facilitate concurrent MHC class I/II presentation and multi-epitope immunity without HLA limitation, thus offering broad potential coverage. However, the need for efficient transfection remains a consideration. (iii) Whole tumor lysate-based DC vaccines: Although procuring sufficient tumor tissue to generate adequate lysate protein for DC loading remains a challenge, DCs loaded with whole tumor lysates, delivering a broad spectrum of undefined tumor-derived antigens, including both neoantigens and shared tumor-associated antigens, provide broad coverage against heterogeneous tumors and counter clonal evolution.

Clinical trials of neoantigen-based DC vaccines in solid tumors

In 2010, sipuleucel-T was the first antigen-loaded DC vaccine approved by the FDA for the treatment of metastatic castration resistant prostate cancer, on the basis of a 4.1-month improvement in median overall survival (mOS) and a 22% lower risk of death in the sipuleucel-T group compared with controls[20]. Sipuleucel-T is an autologous DC vaccine loaded with a recombinant fusion protein (PA2024) including primarily the TAAs of prostatic acid phosphatase. However, TAAs lack the high tumor specificity of tumor-specific antigens (TSAs), namely neoantigens. Therefore, current DC vaccine research has shifted toward the development, optimization, and clinical evaluation of neoantigen-based DC vaccines. The superior safety profiles of neoantigen-based DC vaccines have been

demonstrated in a series of clinical trials. In the following sections, we further discuss clinical investigations of neoantigen-based DC vaccines in solid tumors.

Neopeptide-based DC vaccines in various solid tumors

Clinical trials are increasingly providing compelling evidence supporting the successful translation of neoantigen peptide-based DC vaccines from concept to clinical application across various cancers. This progress has been facilitated by advancements in neoantigen discovery pipelines that leverage cutting-edge biocomputational methods, whole-exome and RNA sequencing, and mass spectrometry-based immunopeptidomics, as well as functional validation of potential epitopes *in vitro*. These studies (summarized in **Table 1**) have promoted the development and clinical application of personalized immunotherapies for solid tumors.

Hepatocellular carcinoma (HCC)

A pilot trial (NCT04147078) was conducted to evaluate the safety and efficacy of an adjuvant personalized neoantigen peptide pulsed autologous DC vaccine (Neo-DCVac-02) in postoperative patients with locally advanced solid tumors. The most recent results of this study were presented at the 2024 ASCO conference[52]. Among 13 patients with postoperative HCC, Neo-DCVac-02 was found to be safe and well tolerated, and no treatment-related adverse events (TRAEs) exceeding grade 2 were observed. Notably, the patients receiving this DC vaccine exhibited a significant delay in HCC recurrence, with 1- and 2-year recurrence-free survival of 84.6% and 60%, respectively. Additionally, neoantigen-specific immune responses were observed, particularly in patients not prone to relapse. These findings demonstrated the safety, tolerability, and immunogenicity of Neo-DCVac-02 in postoperative patients with HCC, thereby highlighting its strong potential to prevent relapse after surgery. Furthermore, a phase II trial (NCT03067493) was conducted to investigate the safety, efficacy, and immunologic effects of a combination immunotherapy comprising a neoantigen peptide-loaded DC vaccine and neoantigen-activated T cell therapy in preventing HCC recurrence. In the first stage of the trial, 10 patients with HCC who had previously undergone surgical resection or radiofrequency ablation were enrolled. Neoantigen-specific T cell responses were detected in 70% of vaccinated patients, and correlated with strong and durable immunity that was significantly associated with prolonged disease-free survival (DFS)[53]. These results provided evidence supporting a novel immunotherapy based on neopeptide-loaded DC vaccine in the prevention of HCC recurrence after surgery or radiofrequency ablation.

Additionally, an open-label, single-arm, phase II trial (NCT04912765) was initiated to evaluate the safety and efficacy of a neoantigen-loaded DC vaccine combined with nivolumab as adjuvant therapy in patients with resected HCC or liver metastases from colorectal cancer. Data including recurrence-free survival 24 months after surgery and neoantigen-specific immune responses will be collected for efficacy evaluation.

Lung cancer

For advanced lung cancers, a single arm pilot study (NCT02956551) was initiated to investigate the safety and efficacy of personalized neopeptide-pulsed DC vaccine (Neo-DCVac)[51]. That study enrolled 12 patients in whom multiline standard treatment had failed, each of whom received an autologous DC vaccine pulsed with 12–30 neopeptides. Only grade 1–2 adverse events were observed, and no treatment delays occurred because of toxicity. The study yielded promising results, with an objective response rate of 25%, disease control rate of 75%, median progression-free survival of 5.5 months, and mOS of 7.9 months. Additionally, IFN-γ ELISpot assays and intracellular cytokine staining confirmed that Neo-DCVac effectively primed antigen-specific T cell responses. This study conclusively demonstrated the safety and potential efficacy of Neo-DCVac in patients with advanced lung cancer.

Gastric cancer

One study (NCT03185429) was designed to evaluate the safety, tolerability, efficacy, and feasibility of neoantigen-loaded autologous DC vaccines in 20 patients with advanced gastrointestinal solid tumors[54]. In that trial, one patient achieved complete regression for 25 months as of October 2021, after ICI treatment combined with a personalized neopeptide-loaded DC vaccine (Neo-MoDC). ELISpot assays and TCR sequencing revealed that Neo-MoDC successfully induced a robust neoantigen-specific T cell response, along with a significant increase in high-frequency TCR clones post-vaccination. This case of complete and durable tumor regression supports the potential of combining neoantigen-based DC vaccines with ICIs as an optimized immunotherapy strategy for patients with advanced gastric cancers.

Table 1 Clinical trials of neopeptide-based DC vaccines in solid tumors

Neoantigen source	NCT number	Tumor types	Phase	Status	Interventions	Enrollment	Data start	Data end
Neoantigen peptides	CTR20240064	GBM	Phase I	Ongoing	Personalized DC vaccine	12	2024-01-08	NA
Tumor specific peptides	NCT00683670	Melanoma	Phase I	Completed	Cyclophosphamide followed by mature DC vaccine	17	2008-08-01	2016-06-01 (actual)
Neoantigen peptides	NCT04879888	Breast cancer	Phase I	Completed	Peptide-pulsed autologous DCs, intradermal vaccination	9	2016-08-01 (actual)	2017-07-30 (actual)
Neoantigen peptides	NCT04105582	Triple-negative breast cancer	Phase I	Completed	DCs pulsed with synthetic peptide	5	2019-08-01 (actual)	2022-02-01 (actual)
Neoantigen peptides	NCT03205930	Non-small cell lung cancer	Phase I/II	Unknown	Neoantigen multiple target antigen stimulating cell therapy (Neo-MASCT)	20	2017-08 (estimated)	2019-11 (estimated)
Neoantigen peptides	NCT02956551	Lung cancer	Phase I	Unknown	DC vaccine, subcutaneous administration	20	2016-11-30 (actual)	2020-6-1 (estimated)
Neoantigen peptides	ChiCTR2000040715	Spinal metastasis of lung cancer	Phase II	Unknown	DC vaccine immunotherapy or best treatment (chemotherapy or targeted drug therapy)	20	2020-12-03	2022-11-30
Tumor specific antigen	NCT03185429	Gastric cancer	Not applicable	Unknown	DC vaccine, subcutaneous injection	20	2017-12-01 (estimated)	2019-06-01 (estimated)
Neoantigen peptides	NCT04627246	Pancreatic adenocarcinoma	Phase I	Active, not recruiting	Autologous DC vaccine loaded with personalized peptides (PEP-DC vaccine)	14	2020-9-11 (actual)	2028-09 (estimated)
Public neoantigen peptides	NCT03592888	Pancreatic ductal adenocarcinoma	Phase I	Completed	mDC3/8-KRAS vaccine	29	2018-11-20 (actual)	2024-02-12 (actual)
Neoantigen peptides	NCT03067493	Hepatocellular carcinoma	Phase II	Unknown	Neo-MASCT	98	2017-7-25 (estimated)	2023-3-31 (estimated)
TAA-CEA and frameshift-derived neopeptides	NCT01885702	Colorectal cancer	Phase I/II	Active, not recruiting	DC vaccine	25	2010-10-01	2024-12-01 (estimated)
Neoantigen long peptides	NCT03300843	Melanoma Gastrointestinal cancer Breast cancer Ovarian cancer Pancreatic cancer	Phase II	Terminated	Peptide loaded DC vaccine	1	2018-04-11 (actual)	2019-09-16 (actual)
Neoantigen peptides	NCT04147078	Gastric cancer Hepatocellular carcinoma Non-small cell lung cancer Colorectal cancer	Phase I	Recruiting	DC vaccine, subcutaneous administration	80	2019-06-01 (actual)	2026-06-01 (estimated)
Neoantigen peptides	CTR20232435	Solid tumor	Phase I	Ongoing	Personized DC vaccine	15	2023-08-21	NA

Pancreatic cancer

In pancreatic cancers, a phase Ib study (CHUV-DO-0017_PC-PEPDC_2017) was conducted to evaluate the safety, tolerability, and feasibility of a treatment regimen consisting of autologous DC pulsed with personalized neoantigen peptides (PEP-DC), standard chemotherapy, aspirin, and subsequent nivolumab. Notably, that study used an innovative pipeline, NeoDisc, for the identification and prioritization of neoantigens[55]. Another study (NCT03300843) was aimed at assessing the clinical response to DC vaccines pulsed with neoantigen long peptides in patients with epithelial cancers, including pancreatic cancer. However, that study has since been terminated, and only one patient was enrolled. Targeting public neoantigens has emerged as an attractive alternative approach for DC vaccines, because of the more cost-effective and straightforward manufacturing process of public than personalized neoantigens. An ongoing phase I study (NCT03592888) is evaluating the safety and efficacy of a DC vaccine loaded with peptides derived from KRAS mutations in patients with pancreatic ductal adenocarcinoma. This study includes primarily patients with pancreatic ductal adenocarcinoma with pathologically confirmed KRAS(G12D–), KRAS(G12V–), KRAS(G12R–), or KRAS(G12C–) mutations who have high risk of recurrence.

Melanoma

By early 2015, researchers had already begun to explore neoantigen-based DC vaccines in advanced melanoma[18]. The observed increase in neoantigen-specific immune responses, along with the enhanced diversity of the TCR repertoire induced by neoantigen-loaded DC vaccines, sparked substantial interest in the field of neoantigen-based DC vaccines for melanoma.

Whole tumor lysate-based DC vaccines in various solid tumors

Whole tumor antigens, typically derived from whole tumor lysates, contain a wide range of both TAAs and TSAs, which can stimulate powerful and extensive T cells with multiple clones, and subsequently prevent the emergence of immune resistant tumor variants, thus providing an ideal source for DC vaccine pulsing[56]. Research on DC vaccines pulsed with whole tumor antigens is increasing, and some studies have indicated promising potential across various tumor types (**Table 2**).

Ovarian cancer (OC)

OCDC, a personalized DC vaccine pulsed with oxidized autologous whole-tumor cell lysate, has shown potential efficacy in patients with OC[57]. In a pilot trial (NCT01132014), 25 patients with platinum-treated, immunotherapy-naïve, recurrent OC were enrolled in a 1:2:2 ratio across 3 arms: OCDC alone, OCDC with bevacizumab (Bev/OCDC), and OCDC with bevacizumab and low-dose cyclophosphamide (Cy/Bev/OCDC)[58]. OCDC vaccination successfully primed specific T cell responses without severe adverse events, and correlated with prolonged survival. Notably, patients in the Cy/Bev/OCDC arm exhibited a significantly higher OS at 2 years than those in the Bev/OCDC arm or a matched historical control group. More importantly, OCDC promoted the induction and expansion of new high-affinity T cell clones, as well as enhanced neoantigen recognition.

Building on this robust antitumor immunity, a clinical study (NCT01312376) evaluated adoptive transfer therapy by using *in vitro*-expanded, OCDC-primed autologous peripheral blood T cells. In that study, 17 patients with platinum-resistant OC completed a combination treatment comprising OCDC administration, followed by the transfer of vaccine-primed T cells, and subsequent bevacizumab maintenance along with continued OCDC vaccination[59]. This combination therapy was effective, and achieved a disease control rate of 70.5% and a mOS of 14.2 months. Additionally, the treatment was immunogenic, thus promoting the reinvigoration of antitumor immunity. Therefore, OCDC, with its favorable safety profile, effective clinical responses, and ability to elicit robust antitumor immunity, holds promise for various combination strategies in patients with OC.

Beyond autologous tumor lysates, allogeneic tumor cells killed by high hydrostatic pressure have emerged as an attractive source for generating personalized DC vaccines, such as DCVAC/OvCA. A phase II clinical trial (SOV02, NCT02107950) was conducted to evaluate the efficacy of DCVAC/OvCA in combination with standard carboplatin and gemcitabine in patients with recurrent platinum-sensitive epithelial OC (EOC)[60]. The final results demonstrated that this combination therapy significantly decreased the risk of death by 62% as a second-line OC treatment, and achieved an OS improvement of 13.4 months with respect to that in the control group (35.5 *vs*. 22.1 months). These findings highlight the efficacy of DCVAC/OvCA based immunotherapy in treating OC. This trial revealed a significant improvement in PFS in patients with EOC receiving first-line treatment with DCVAC/OvCA after standard chemotherapy[12]. Interestingly, the benefits of this sequential therapy were

Table 2 Clinical trials of whole tumor lysate-based DC vaccines in solid tumors

Neoantigen source	NCT number	Tumor types	Phase	Status	Interventions	Enrollment	Data start	Data end
Autologous tumor lysate	NCT02301611	Melanoma	Phase II	Completed	Autologous tumor lysate, particle-loaded DC (TLPLDC) or placebo	184	2015-01-01	2022-05-11 (actual)
Lysate from autologous oxidized tumor cells	NCT01132014	Ovarian cancer	Phase I	Completed	OCDC, an autologous vaccine comprising autologous dendritic cells (DCs) loaded *in vitro* with lysate from autologous oxidized tumor cells	67	2010-05-01	2018-05-30 (actual)
Allogeneic tumor cells killed by high hydrostatic pressure	NCT02107950	Ovarian carcinoma	Phase II	Completed	DCVAC/OvCa in parallel with chemotherapy or standard of care	71	2013-11-01	2017-05-17 (actual)
Allogeneic tumor cells killed by high hydrostatic pressure	NCT02107937	Epithelial ovarian carcinoma	Phase II	Completed	DCVAC/OvCa with standard of care or sequentially after standard of care	136	2013-11-01 (actual)	2021-11 (actual)
Genetically modified tumor cells or tumor-associated antigens	NCT03914768	Diffuse intrinsic pontine glioma or glioblastoma	Phase I	Unknown	Immunomodulatory DC vaccine targeting DIPG and GBM	10	2019-03-31 (actual)	2022-12-31 (estimated)
Autologous tumor lysate	NCT00045968	Glioblastoma	Phase III	Unknown	DC immunotherapy	348	2006-12-01	2022-11 (estimated)
Lysate from autologous oxidized tumor cells	NCT01312376	Ovarian carcinoma Fallopian tube cancer Primary peritoneal cancer	Phase I	Terminated	Adoptive transfer of vaccine-primed T cells combined with vaccine boost and bevacizumab	18	2011-03-01	2019-01 (actual)

observed only in patients who received DCVAC/OvCA after, rather than in parallel with, chemotherapy.

The findings of another open-label, randomized phase II clinical trial (SOV01, NCT02107937) further revealed a significant improvement in PFS in patients with EOC receiving first-line treatment with DCVAC/OvCA after standard chemotherapy[61]. Given that the benefits of this sequential therapy strategy were observed only in patients administered this treatment after (rather than in parallel with) chemotherapy, subsequent investigations focused on immune characterization and biomarker exploration in patients with EOC. Notably, patients with below-median TMB and insufficient CD8+ T cell infiltration were most likely to benefit from DCVAC/OvCA therapy[62]. These findings suggest the promising potential of DCVAC/OvCA to prime anticancer immunity in patients with immunologically "cold" EOC, thereby offering a new avenue for personalized immunotherapy in this subset of patients.

Melanoma

The early exploration of tumor lysate loaded DCs indicated a potential moderate response in patients with melanoma[63]. Since then, the application of TLPLDC, a DC vaccine loaded with tumor lysate-loaded particles, has shown significant improvements in both OS and DFS in patients with melanoma[64-66]. In a phase I/II clinical trial (NCT02301611), a total of 187 patients with stage III/IV melanoma were randomly allocated in a 2:1 ratio to groups treated with the tumor lysate-loaded particle only vaccine (TLPO) or TLPLDC vaccine, with a median follow-up of 35.8 months. The TLPLDC group demonstrated superior outcomes to the

placebo group (OS of 94.2% *vs.*70%, and DFS of 55.8% *vs.* 30%)[66]. Nevertheless, because no significant differences in OS and DFS were observed between the TLPLDC and TLPO groups, a phase III trial is necessary for further exploration.

Glioblastoma

In past decades, research on DCs loaded with tumor lysate has demonstrated the acceptable safety and toxicity profile of this treatment in glioblastoma (GBM)[67,68]. In a phase III clinical trial (NCT00045968), a DC vaccine loaded with autologous tumor lysate (DCVax-L) pulsed with standard of care temozolomide was administered to 331 participants with GBM. In that study, patients with newly diagnosed GBM (nGBM) or recurrent GBM (rGBM) were compared with a contemporaneous matched external cohort receiving standard of care treatment[69]. DCVax-L increased the 4-year survival rate to 15.7% in the nGBM cohort (n = 232), compared with 9.9% in controls. In the rGBM cohort (n = 64), compared with the control group, the DCVax-L group showed a significantly higher mOS (13.2 m *vs.* 7.8 m), and the 1- and 2-year survival rates were 54.1% *vs.* 30.8%, and 20.7% *vs.* 9.6%, respectively. That study was the first large phase III clinical trial in nearly 20 years to successfully extend OS in newly diagnosed patients with GBM, thus offering new perspectives and hope for GBM treatment. In the future, DCVax-L therapy might potentially be combined with other treatments, including ICIs, cytokines, targeted therapies, chemotherapy, or oncolytic virus therapies.

DC vaccines loaded with tumor lysates are a promising treatment strategy with potential therapeutic efficacy demonstrated in small-scale clinical trials across multiple types of advanced malignant solid tumors, including head and neck, kidney, and prostate tumors, as well as recurrent rectal carcinoma[70-72].

RNA-based DC vaccines in various solid tumors

During the COVID-19 pandemic, mRNA vaccines with high safety and rapid production markedly promoted the field of immunotherapy, particularly in cancer treatment[15]. Because of its ability to effectively elicit sufficient and lasting expression of antigens without integrating into the host genome, mRNA is a compelling platform for neoantigen-based DC vaccines. Generally, mRNAs encoding neoantigens are introduced into DCs, translated into proteins, and eventually endogenously processed and presented on DCs as neopeptides, *via* peptide-MHC complexes, for priming specific T cell responses. Although clinical trials focusing on mRNA-based DC vaccines targeting neoantigens remain scarcer than those investigating neopeptide-based DC vaccines (**Table 3**), preliminary reports from clinical trials have confirmed that neoantigen-encoding mRNA DC vaccines demonstrate robust safety profiles and potent immunogenicity in tumors.

Hepatocellular carcinoma

At the 2024 ASCO conference, Liang (NCT03674073) presented a personalized neoantigen-based mRNA-loaded DC vaccine combined with ablation for HCC treatment[73]. In that trial, 24 patients with HKLC stage IIa HCC were enrolled and assigned in a 1:1 ratio to either a DC vaccine plus ablation arm or an ablation-only control arm. In the vaccination arm, compared with the control arm, the patients showed a significantly lower recurrence rate of HCC at both 1 year (18.2% *vs.* 33.3%) and 2 years (36.4% *vs.* 51.4%). This mRNA-based DC vaccine was not only demonstrated to be highly safe, with only grade 1–2 adverse events observed, but also showed robust immunogenicity, according to detection of neoantigen-specific T cell responses to 60%–90% of neopeptides among vaccinated patients. Of note, the effector memory subtype of CD4 and CD8 T cells increased, whereas PD-1+ T cells decreased, in the peripheral blood of patients after vaccination. These results indicated the durable and robust specific immune response primed by the mRNA-based DC vaccines with high safety.

Lung cancer

The recently reported results of a phase I clinical trial have revealed the potent potential of neoantigen-encoding mRNA based DC vaccines in early resectable NSCLC[74,75]. In that study, 6 patients diagnosed with early-stage NSCLC eligible for surgical resection received mRNA-based DC vaccine treatment after the operation. The median time from surgery to the first vaccination was 198 days. No serious AEs were found, and only grade 1–2 AEs were observed in all patients. Three patients achieved relapse-free survival during as many as 2 years' follow-up after the last vaccination. Additionally, the neoantigen based mRNA loaded DC vaccine significantly induced long-lasting neoantigen-specific T cells with diverse and polyclonal phenotypes, thereby contributing to the potent T cell response against tumor cells. This study demonstrated the feasibility, safety, and immunogenicity of a neoantigen-based mRNA DC vaccine, as an adjuvant therapy, in early resected NSCLC. Another phase Ib/IIa clinical trial (NCT05886439) is recruiting patients to evaluate the

Table 3 Clinical trials of DC vaccines loaded with neoantigens encoding mRNA or other personalized neoantigens in solid tumors

Neoantigen source	NCT number	Tumor types	Phase	Status	interventions	Enrollment	Data start	Data end
Neoantigen-encoding mRNA	NCT04078269	Non-small cell lung cancer	Phase I	Active, not recruiting	Dendritic cell immunotherapy	6	2019-08-26 (actual)	2025-12-31 (estimated)
Neoantigen-encoding mRNA	NCT05886439	Local advanced or metastatic NSCLC or ES-SCLC	Phase Ib/IIa	Recruiting	LK101 injection (personalized neoantigen pulsed DC vaccine) combined with pembrolizumab or durvalumab	40	2023-05-11 (actual)	2026-12-30 (estimated)
Neoantigen-encoding mRNA	NCT03674073	Hepatocellular carcinoma	Phase I	Unknown status	DC vaccine in combination with microwave ablation	24	2018-10-15 (estimated)	2020-12-15 (estimated)
TSA-encoding mRNA	NCT05270720	Ovarian cancer	Phase I	Unknown status	DCs	9	2022-09-01 (estimated)	2024-03-01 (estimated)
Neoantigen-encoding mRNA	NCT06054932	Advanced solid tumors	Phase I	Recruiting	LK101 injection (personalized neoantigen pulsed DC vaccine)	18	2023-09-05 (actual)	2026-03-30 (estimated)
Personalized neoantigens	NCT03871205	Lung cancer	Phase I	Unknown status	DC vaccine administered subcutaneously	30	2019-04-01 (estimated)	2020-12-30 (estimated)
Personalized neoantigens	NCT04912765	Resected hepatocellular carcinoma and liver metastases from colorectal cancer	Phase II	Recruiting	DC vaccine administered *via* intra-dermal injection concurrently with adjuvant nivolumab	60	2021-04-15 (actual)	2025-05-01 (estimated)
Personalized neoantigens	NCT02632019	Advanced biliary tract malignant tumor	Phase II	Unknown status	DC-precision T cells for neo-antigen combined with gemcitabine treatment	40	2015/9/1	2017-09-01 (estimated)

safety, tolerability, and efficacy of the combination of neoantigen-based mRNA-loaded DC vaccine (LK101) and pembrolizumab or durvalumab in local advanced or metastatic NSCLC and SCLC.

Additionally, in a patient with GBM, a novel combination therapy of DC vaccines loaded with multiple forms of tumor antigens (including mRNA-TAAs, mRNA-neoantigens, and tumor lysates) plus anti-PD-1 and poly I:C has been demonstrated to maximize the possibility of cure, safety, and feasibility for long-term treatment[76].

Limitations and strategies

A series of clinical trials are currently focusing on neoantigen-based DC vaccines, and the therapeutic potential of these DC vaccines in clinical practice has not yet been sufficiently realized. Therefore, further investigation and refinement of DC vaccination strategies will be essential to overcome the following limitations in DC vaccine efficacy. 1) Suboptimal T cell immune responses: DC vaccines might fail to initiate optimal T cell responses, probably because of the limited ability of monocyte-derived DCs stimulated with GM-CSF to migrate to lymph nodes—a critical step for effective T-cell-antigen interactions[77-80]. 2) Challenges in personalized neoantigen preparation: The identification and generation of immunogenic neoantigens with effective presentation under HLA restrictions is complicated. Additionally, evaluation of the sustained expression of these neoantigens is difficult. In contrast, the cultivation of DCs, which still relies on skilled and labor-intensive processes, requires further optimization. 3) Optimal

time of DC vaccine administration: Current clinical research on neoantigen DC vaccines largely comprises small-scale phase 1/2 trials in patients with advanced cancer. However, the immunosuppressive environments within advanced tumors can suppress the immune response to DC vaccines and T lymphocytes. Therefore, larger-scale clinical trials assessing the effectiveness of early DC vaccine administration are necessary. 4) Lack of predictive biomarkers: An urgent need persists for effective biomarkers to identify patients likely to benefit from neoantigen-based DC vaccine therapy early in the treatment process.

To overcome the challenges of neoantigen-based DC vaccines in solid tumors, multimodal combinatorial strategies are a critical path to enhance efficacy. Combining these vaccines with conventional therapies such as chemotherapy, which promotes antigen release and presentation, and ICIs, which counteract tumor immune evasion, remains valuable. However, a more sophisticated strategic vision must encompass advanced immunotherapies, and address logistical and temporal optimization. The integration of adoptive cell therapy using neoantigen-reactive T cells offers a potent synergistic approach for counteracting T cell exhaustion and enhancing tumor infiltration[59,81]. Furthermore, exosome loaded DC vaccines have emerged as a promising alternative or complement to traditional DC vaccines, and have been reported to successfully induce immunogenic cell death in breast cancer[82]. Early clinical exploration is underway, including several trials (e.g., NCT01550523, NCT01159288, and NCT05559177) evaluating exosome-based cancer vaccines. Moreover, alternative vaccine platforms may enhance the efficacy of neoantigen-based vaccines. Liposomal nucleic acid nanostructures (Lys-SNAs) encapsulating triple-negative breast cancer cell lysates have been shown to inhibit tumor growth; therefore, tumor lysate-loaded SNAs are potent immunotherapeutics for target-deficient malignancies[83]. Optimizing treatment timing and therapeutic sequence is critical within this strategic framework. Given the dynamic nature of tumor evolution and antigen loss, the strategic preparation of neoantigen-based DC vaccines during the disease course, particularly as postoperative adjuvant therapy, is likely to enhance effectiveness. This approach leverages the minimal residual disease state post-resection, characterized by lower tumor burden and a potentially less immunosuppressive TME, to establish potent and durable immune memory. Concurrently, dynamic biological monitoring (e.g., serial ctDNA analysis to track clonal evolution and neoantigen landscape changes) is essential to inform potential vaccine updates or therapy adjustments. Finally, to achieve the full potential of these personalized neoantigen therapies, the following key industrial and logistical challenges must be addressed: streamlining the complex, lengthy (6–8 weeks) autologous manufacturing processes; establishing robust cold chain logistics; performing rigorous quality control; and developing validated predictive biomarkers (e.g., TMB, HLA type, TCR clonality, or inflammatory gene signatures) for effective patient stratification. Large-scale phase III trials are warranted to validate the survival benefits of neoantigen-based DC vaccines, either alone or in combination with other therapies, and to establish optimal, biomarker-guided treatment sequences to advance solid tumor immunotherapy.

Conclusions

Neoantigen-based DC vaccines' safety, feasibility, and preliminary efficacy have been demonstrated in numerous clinical studies offering valuable insights into the development and optimization of tumor immunotherapy strategies. However, insufficient efficacy continues to pose a major challenge to the widespread clinical application of DC vaccines. Therefore, further efforts, such as identifying effective neoantigens, improving combination therapies, and, more importantly, achieving early use of neoantigen-based DC vaccines as a front line or even perioperative therapy, will be essential to broaden the prospects of neoantigen-based DC vaccines and provide more precise and effective personalized immunotherapies.

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Yuting Li, Jianming Xu.
Collected the data: Abudukadierjiang Abudureheman.
Contributed data or analysis tools: Yuting Li, Abudukadierjiang Abudureheman.
Performed the analysis: Yuting Li, Abudukadierjiang Abudureheman.
Wrote the paper: Yuting Li, Abudukadierjiang Abudureheman, Jianming Xu.

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