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Review Article

Therapeutic Cancer Vaccines: Current Evidence on Immunogenicity, Clinical Efficacy, Safety, and Emerging Challenges.

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Abstract

Background:
Cancer is a leading cause of death globally and is significantly more difficult to treat than other diseases owing to tumor heterogeneity. Treatment of advanced cancers with conventional therapies such as chemotherapy or checkpoint inhibitors is plagued by a high incidence of recurrence and treatment resistance. The high specificity of cancer vaccines and their ability to target multiple neoantigens simultaneously provide avenues for circumventing tumor heterogeneity. This review aimed to provide a comprehensive overview of the current literature on cancer vaccines, with particular emphasis on their immunogenicity, efficacy, and safety.
Methodology:
PubMed and Web of Science databases were searched for primary research articles on cancer vaccines published in English within the past five years and available free of charge. A total of 45 articles were included in the review. Findings were stratified according to vaccine platform into nucleic acid, peptide, cell-based, and vector-based vaccines.
Results:
Cancer vaccines across all platforms demonstrated significant immunogenicity, including long-term immune responses. Vaccine-induced immune responses were observed in CD8+ and CD4+ T cells as well as B cells. Substantial, although ultimately inconclusive, clinical efficacy was reported across vaccine platforms. The greatest clinical benefit was observed when cancer vaccines were administered in the adjuvant setting; however, clinical benefit was not consistently correlated with immunogenicity. Cancer vaccines also demonstrated a safety profile that was generally preferable to that of conventional therapies. Small, uncontrolled trials and lengthy and expensive production processes were identified as major challenges in the field.
Conclusion:
Cancer vaccines demonstrate considerable potential as safe and effective therapeutic strategies to supplement conventional approaches to cancer treatment. However, further well-designed research is required to establish definitive effect sizes, clarify the relationship between immunogenicity and clinical benefit, and overcome practical barriers to their widespread clinical implementation.
Keywords:
Cancer Vaccines, Immunogenicity, Vaccine, Immunotherapy, Antigens, Neoplasm, Treatment Outcome, Neoplasms

Introduction

Vaccines are among the most important and successful medical achievements in human history. Infectious diseases such as polio, measles, diphtheria, tetanus, pertussis, and hepatitis were leading causes of infant mortality before vaccines were developed. Most survivors experienced debilitating complications, including paralytic poliomyelitis and visual and neurological impairments [1]. The advent of vaccines has nearly eradicated these conditions. Since the WHO's introduction of the Expanded Program on Immunization in 1974, vaccination has averted an estimated 146 million infant deaths, accounting for 40% of the reduction in global infant mortality [2].

Generally, vaccines work by introducing an antigen into the body under safe conditions to prime the adaptive immune system to produce long-lived memory cells specific to the antigen [3]. Subsequent exposure to the antigen rapidly activates memory cells, enabling a faster and more effective secondary immune response compared with naïve immune cells [4]. Vaccines are classified by the means of antigen delivery or the types of antigens delivered. Subtypes include, but are not limited to, live-attenuated vaccines, nucleic acid vaccines, antigen-presenting cell vaccines, subunit (protein/polysaccharide/peptide) vaccines, toxoid vaccines, and viral or bacterial vector vaccines [3]. Globally, cancer is a leading cause of mortality and one of the most prevalent chronic health conditions, with both statistics rising. In 2022, the International Agency for Research on Cancer reported approximately 20 million new cases of cancer and approximately 9.7 million cancer deaths [5]. Lung cancer was the most commonly diagnosed and the leading cause of cancer deaths. Cancer screening, treatment, and care impose an immense economic burden on patients, families, and governments alike. The global economic cost of cancer over the thirty-year period between 2020 and 2050 was estimated to reach 25.2 trillion dollars (at 2017 prices), equivalent to an annual 0.55% tax on the global gross domestic product [6].

Cancer is a disease characterized by mutant body cells that replicate uncontrollably and are subject to selection for their survival [7]. These cells may severely disrupt tissue structure and function or spread to distant sites from their site of origin (metastasis). Mutations that cause cancer can be spontaneous or catalyzed by risk factors such as genetic susceptibility, exposure to unsafe levels of radiation, carcinogenic chemicals, or pathogens like HPV, among others. These mutations commonly occur in genes that regulate processes such as the cell cycle, DNA repair, apoptosis, autophagy, immunity, and cellular metabolism, resulting in either gain or loss of function [8]. The resulting gene is known as an oncogene. Oncogenes result in either excessive replication or exaggerated cell survival. Either effect leads to a mutant cell population that far exceeds the normal cell population. This, together with the surrounding connective tissues and recruited immune cells, comprises a tissue mass known as a tumor, which is a central target for cancer treatment and a measure of disease progression.

The cancer-immunity cycle describes how the immune system responds to tumors. Antigens released from dying tumor cells are presented by antigen-presenting cells (APCs) to T cells in lymph nodes. Tumor-associated antigens (TAAs) are overexpressed normal antigens, whereas tumor-specific antigens (TSAs), or neoantigens, arise from mutations unique to cancer cells [9]. T-cell activation drives differentiation and chemokine production (e.g., CXCL-9), promoting lymphocyte migration and tumor infiltration. Tumor infiltration may be absent (immune desert), partial (immune excluded), or extensive (immune infiltrated) [10].

Tumor recognition requires peptide–MHC interaction with T-cell receptors. Subsequent cytotoxic activity is regulated by co-inhibitory signals such as PD-1/PD-L1. Without sufficient inhibition, cancer cells undergo apoptosis and are cleared. Tumors employ a variety of mechanisms to evade key stages of the cycle, for example by upregulating PD-L1, providing targets for immunotherapies such as checkpoint inhibitors to restore effective immune responses [10]. Cancer's high mutability and rapid proliferation result in rapidly changing cancer cell populations [11]. As a result, most treatment methods unfortunately serve as a selection pressure for cancer cells that are resistant, less immunogenic, and more proliferative [7]. The standard of care in cancer treatment comprises non-targeted approaches such as chemotherapy, radiotherapy, and surgery, as well as targeted treatments such as adoptive cell therapy, ICIs, and monoclonal antibodies, to name but a few [12,13]. While successful for milder forms, these treatments are not effective for many aggressive, late-stage, treatment-resistant, or highly tumorigenic cancers, often resulting in high recurrence rates. Despite the standard of care, surgery for glioblastoma has a nearly 100% recurrence rate and a 5-year survival of generally less than 5% [14]. Standard treatments for resectable colorectal cancer and pancreatic ductal adenocarcinoma (PDAC) have less than 20% 5-year survival, and few effective treatments for relapses exist [15]. Though revolutionary, immune checkpoint blockers (ICBs) still result in resistance and relapse in most non-small cell lung cancer patients [13]. These cases present an urgent need for novel therapies for such cancers. Cancer vaccines are one such therapy. The approach has increasingly piqued researchers' interest in recent years owing to its various utilities. PDACs have less than 5% sensitivity to ICIs, but recent evidence highlights the potential of neoantigen delivery systems, such as cancer vaccines, to activate T-cells and improve patient outcomes [16]. The ability of cancer vaccines to target specific TAAs provides a means to counteract immune tolerance in ICB-resistant tumors [13].

Cancer vaccines also provide a means to target multiple TAAs using a single treatment. Clinical trials applying dendritic cell vaccines to treat glioblastoma indicate the utility of cancer vaccines in providing more specific targets at stages of the previously described cancer immunity cycle [14]. Cancer vaccines may also provide a cheaper approach to personalized therapies compared to alternatives like adoptive cell therapy [15]. Generally, cancer vaccines function by eliciting the host's adaptive immune response against neoantigens, with the goal of preventing or slowing tumor growth over the long term. The various mechanisms by which cancer vaccines achieve this allow them to target a wider array of cancer immune-evasion strategies than conventional immune-checkpoint inhibitors. Being relatively new, most cancer vaccines are still in the trial phase, and the literature is comprised mostly of independent studies reporting on these trials. This review aims to provide a comprehensive summary of the literature to broaden our understanding of cancer vaccines and their function, while reporting on the current state of the research and emerging themes in the field.

Methodology

Search Strategy

A structured literature search was conducted using PubMed and Web of Science to identify relevant studies on therapeutic cancer vaccines. PubMed served as the primary database because of its extensive coverage of peer-reviewed biomedical literature. The search strategy incorporated relevant keywords, Medical Subject Headings (MeSH), Boolean operators, and field tags related to cancer vaccines. The complete PubMed search strategy, including the keywords, MeSH terms, and field tags used, is presented in Table 1 of the Appendix.

The initial PubMed search yielded 95,604 records. Filters were applied to restrict the search to articles published from 2020 onward, available as free full text, and reporting primary research, resulting in 628 records. Clinical trials were prioritized to capture recent developments in therapeutic cancer vaccine research. Studies not conducted in humans and articles without an English-language version were subsequently excluded, leaving 624 records. A supplementary search was conducted in Web of Science using keywords similar to those applied in PubMed. MeSH terminology and PubMed-specific field tags were omitted where they were not applicable to the Web of Science database.

Eligibility Criteria

Studies were considered eligible if they investigated therapeutic cancer vaccines, reported primary research findings, were published in English, and were relevant to the immunogenicity, clinical efficacy, safety, mechanisms of action, or development of cancer vaccines. Preference was given to studies published from 2020 onward and involving human participants. Studies focusing primarily on prophylactic vaccination, including HPV vaccination, were excluded because the present review focused on therapeutic cancer vaccines. Articles primarily concerning COVID-19, HIV, or tuberculosis vaccines were also excluded. Secondary and tertiary literature, duplicate records, non-English articles, and studies that were not directly relevant to the objectives of the review were excluded from the principal study selection.

Study Selection

Following application of the initial PubMed filters, 624 records remained for further screening. Preliminary screening of titles and abstracts revealed that a substantial proportion of the retrieved records concerned COVID-19 vaccines. Exclusion of these records using the search queries provided in Table 1 reduced the number of records to 502. Studies related to HPV vaccination were subsequently excluded to maintain the review's focus on therapeutic rather than preventive cancer vaccines, reducing the number of records to 366. Further title and abstract screening identified studies related primarily to HIV and tuberculosis, which were also excluded, leaving 288 records. The remaining titles and abstracts were screened for relevance to the review objectives. Studies that did not address therapeutic cancer vaccination or outcomes relevant to the scope of the review were excluded, leaving 96 potentially eligible articles. Following further assessment, 38 studies identified through PubMed were included. The Web of Science search was screened independently. After removing duplicates of PubMed records, secondary or tertiary research, and non-open-access articles, 23 records remained. Screening of titles and abstracts resulted in the inclusion of 3 additional studies. A further 4 articles were identified through citation tracking and supplementary reading. These articles were retained because they provided important contextual, mechanistic, or supporting evidence relevant to the interpretation of therapeutic cancer vaccine research. Overall, 45 articles were included in the review. The literature identification and study-selection process is summarized in Figure 1.

Data Extraction and Synthesis

All included articles were reviewed in full. Relevant information was extracted on the type of cancer vaccine, mechanism of action, manufacturing or production approach, immunogenicity, clinical efficacy, safety, and treatment-related adverse events. Studies were classified according to the principal vaccine platform investigated into four categories: nucleic acid-based, peptide-based, cell-based, and vector-based vaccines. Findings were synthesized narratively within each vaccine category. The synthesis focused primarily on vaccine-induced immune responses, including CD4+ and CD8+ T-cell responses and, where reported, B-cell responses; measures of clinical efficacy, including recurrence, progression-free survival, disease-free survival, and overall survival; and the incidence and severity of treatment-related adverse events. Common findings, inconsistencies across studies, and methodological or practical limitations were also examined to characterize the current evidence regarding the immunogenicity, clinical efficacy, safety, and translational challenges of therapeutic cancer vaccines.

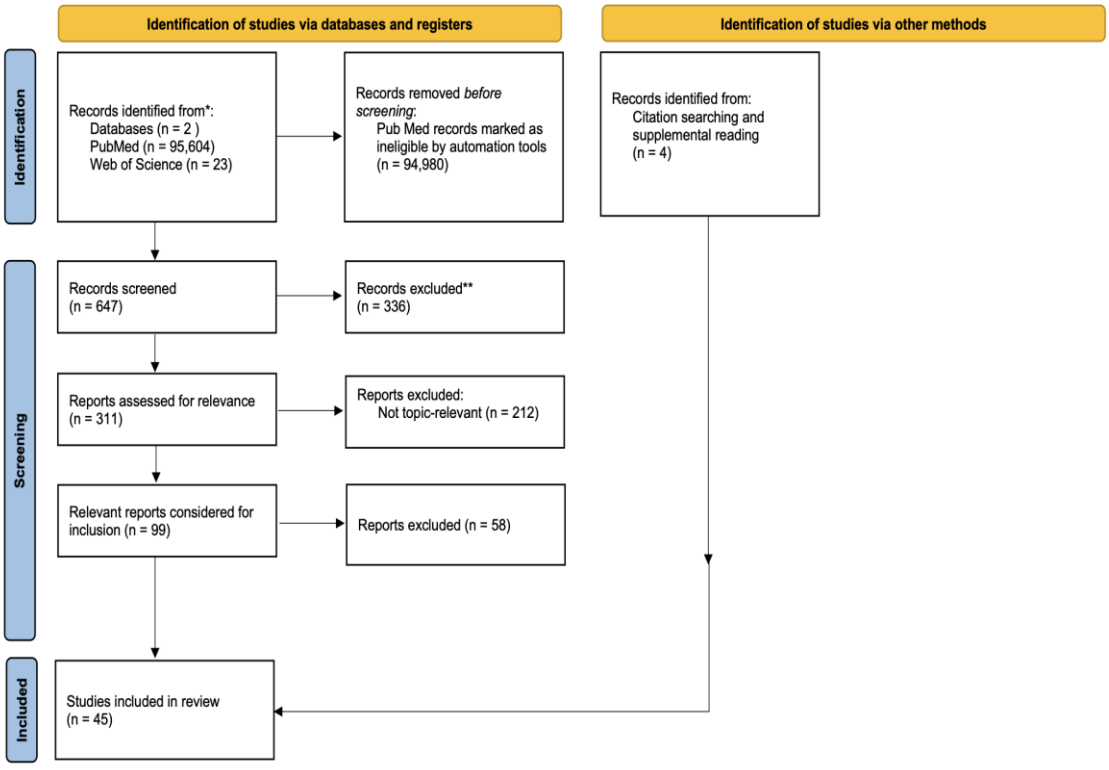

Figure 1: A flow diagram summarizing the process of study selection.

Nucleic Acid Cancer Vaccines

Nucleic acid vaccines have attracted considerable interest in recent years, particularly following the widespread application of mRNA vaccine technology during the COVID-19 pandemic. In therapeutic oncology, nucleic acid vaccines deliver DNA or RNA encoding tumor-associated antigens or neoantigens into host cells. Expression of the encoded antigen allows subsequent processing and presentation through major histocompatibility complex (MHC) pathways, thereby priming antigen-specific adaptive immune responses [17]. MHC-II presentation may additionally involve secretion of the synthesized antigen or uptake of antigen-containing cells by antigen-presenting cells (APCs). These mechanisms are illustrated in Figure 2B and C. Nucleic acids may also stimulate innate immunity independently of antigen expression; however, excessive nonspecific immune activation is undesirable because of the potential for inflammatory or autoimmune responses [17].

Development of personalized nucleic acid cancer vaccines commonly begins with genomic characterization of tumor and/or blood samples using next-generation sequencing [18]. Whole-exome sequencing is used to identify tumor-specific mutations and determine the patient's human leukocyte antigen (HLA) profile, while RNA sequencing can help establish whether candidate mutations are transcriptionally expressed. Candidate neoantigens are subsequently prioritized, and synthetic DNA plasmids or mRNA constructs encoding selected antigens are produced using nucleic acid synthesis and amplification techniques [19].

Because production workflows vary among vaccine developers and study protocols, this process represents a general rather than universal framework for personalized nucleic acid vaccine development. DNA cancer vaccines are generally administered as plasmid formulations, often by intramuscular injection, whereas some mRNA formulations may be administered intravenously [16,18,20]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been used as an adjuvant to enhance immune priming by promoting recruitment and activation of dendritic cells [20–22].

Following cellular uptake, plasmid DNA must enter the nucleus and undergo transcription before the resulting mRNA can be exported to the cytoplasm and translated. The synthesized antigen is subsequently processed and presented through MHC-I and/or MHC-II pathways. DNA plasmids have also been incorporated into heterologous prime-boost strategies. Autio et al. (2023), for example, reported anti-tumor immune responses in patients with prostate cancer receiving a vaccine-based immunotherapy regimen that incorporated a DNA plasmid component [23]. mRNA vaccines bypass the requirement for nuclear entry because translation can occur directly in the cytoplasm. They are commonly formulated within lipid-based nanoparticles to protect RNA from extracellular degradation and facilitate intracellular delivery [16–18].

An important advantage of mRNA platforms is their capacity to encode multiple antigens within a single therapeutic formulation. Weber et al. (2024), for example, evaluated an individualized mRNA vaccine targeting as many as 34 neoantigens [18]. This multiplexing capacity may be particularly advantageous in heterogeneous tumors.

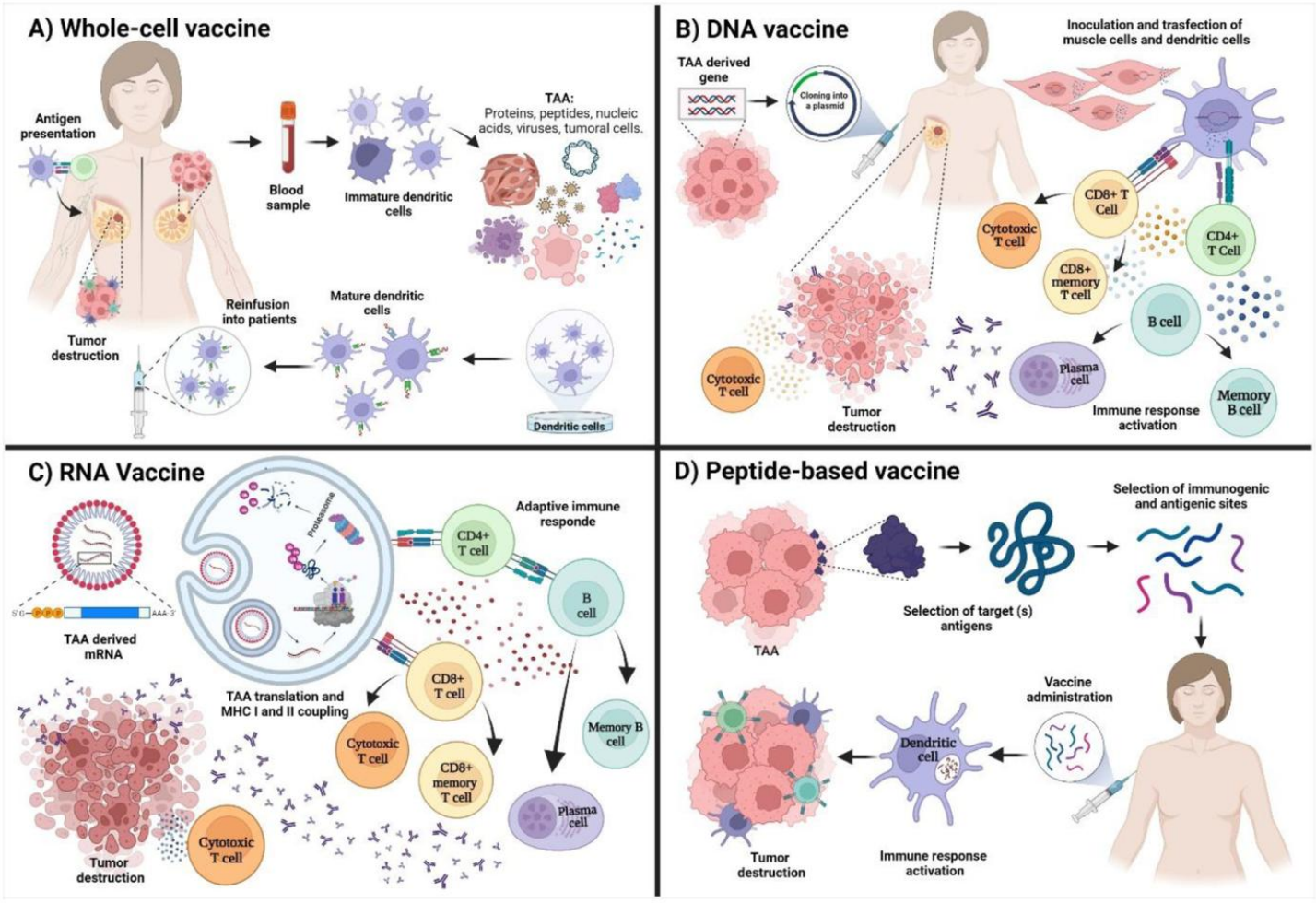

Figure 2: Schematic representation of the mechanisms of action of cell-based (A), nucleic acid-based (B and C), and peptide-based (D) therapeutic cancer vaccines [31].

Nucleic acid vaccines also offer practical advantages in manufacturing. DNA vaccines are generally simpler and less costly to produce than many individualized cellular platforms [21], while nucleic acid vaccines overall avoid the need for extensive ex vivo cell culture [17,24]. Their modular design facilitates rapid modification and personalization according to the antigenic profile of an individual tumor. These characteristics make nucleic acid platforms particularly attractive for targeting tumor heterogeneity, although individualized sequencing, antigen selection, and manufacturing continue to impose logistical constraints. Clinical studies demonstrate substantial immunogenicity, particularly the induction of durable antigen-specific T-cell responses. In patients with pancreatic ductal adenocarcinoma (PDAC), Sethna et al. (2025) reported that a personalized mRNA-lipoplex neoantigen vaccine, administered after surgery in combination with a PD-1 inhibitor, generated de novo CD8+ T-cell clones that remained detectable at substantial frequencies and functional levels in 86% of vaccine responders for approximately three years [16]. Vaccine responders also experienced longer recurrence-free survival than non-responders. Similarly, Weber et al. (2024) reported improved recurrence-free survival with individualized mRNA-4157 (V940) plus pembrolizumab compared with pembrolizumab alone in patients with resected high-risk melanoma [18].

Evidence from DNA vaccines also supports sustained immunogenicity, although clinical benefit has not always paralleled immune responses. Disis et al. (2022) found that 100- and 500-µg doses of an ERBB2 intracellular-domain DNA vaccine induced greater ERBB2-specific T-cell responses than a 10-µg dose in patients with advanced ERBB2-positive breast cancer, with Th1 cells constituting a prominent response [20]. However, progression-free survival did not differ significantly among dose groups. Szymura et al. (2024) reported stable disease or better among participants receiving a personalized neoantigen DNA vaccine for lymphoplasmacytic lymphoma, with a median progression-free interval of six years [19]. Vaccination was associated with expansion of neoantigen-specific T cells, particularly CD8+ cells, as well as changes in myeloid signaling and downregulation of pathways associated with lymphoma growth. Long-term durability was further demonstrated by Tonelli et al. (2024), who observed antigen-specific T-cell responses in approximately 60% of patients during 15-year follow-up of a DNA vaccine trial for PSA-recurrent prostate cancer, with responses persisting in some participants [21].

Overall, nucleic acid cancer vaccines have demonstrated an acceptable tolerability profile. Disis et al. (2022) reported predominantly grade 1–2 adverse events and no observed autoimmune events attributable to the plasmid vaccine [20]. Weber et al. (2024) similarly reported a predominance of lower-grade adverse events, although grade 3 events occurred more frequently in the vaccine-containing treatment arm [18]. Szymura et al. (2024) reported one participant with grade 3 toxicity that resolved within two months, while commonly observed lower-grade events included fatigue, diarrhea, anemia, and hyperglycemia [19]. Importantly, Tonelli et al. (2024) reported no adverse events considered possibly related to vaccination during long-term follow-up [21]. Collectively, these studies suggest that nucleic acid vaccines can generate durable immune responses with generally manageable toxicity, although the relationship between immunogenicity and clinical benefit remains incompletely defined.

Peptide Cancer Vaccines

Peptide cancer vaccines introduce synthetic tumor-associated or neoantigen-derived peptides that are taken up and processed by APCs, leading to activation of antigen-specific adaptive immune responses, as illustrated in Figure 2D. Development typically begins with genomic and/or transcriptomic characterization of tumor tissue to identify candidate neoantigens [25]. Selected epitopes are then synthesized as either short or long peptides. Short peptides, generally 8–12 amino acids in length, are designed primarily for direct presentation through MHC-I and activation of CD8+ T cells, whereas longer peptides, commonly 25–35 amino acids, require intracellular processing by APCs and may support broader CD4+ and CD8+ responses [22,26].

Peptide formulation represents an important determinant of vaccine performance. Although aqueous or buffer-based formulations are relatively straightforward to manufacture, peptide stability—particularly for longer sequences—may be problematic [27]. Alternative delivery approaches, including liposomal systems and virus-like particles, have therefore been explored to improve peptide stability and immunogenicity [28,29]. Heitmann et al. (2024) additionally demonstrated the feasibility of a warehouse-based approach in which pre-manufactured peptides can be selected according to an individual patient's immunopeptidomic profile, potentially shortening the time required for personalized vaccine production [30].

Peptide vaccines generally require potent adjuvants because isolated peptides provide limited innate immune stimulation [22]. Commonly used adjuvants include Montanide ISA-51, poly-ICLC, CpG-containing agents, GM-CSF, and Toll-like receptor agonists such as imiquimod [22,31]. These agents enhance immunogenicity through mechanisms including recruitment and activation of innate immune cells and prolonged antigen exposure at the injection site [32]. Peptide vaccines are commonly administered intradermally or subcutaneously, frequently as multiple-dose regimens and often in combination with conventional or immune-based anticancer therapies [27,33].

Evidence regarding their immunogenicity is generally favorable but heterogeneous. Platten et al. (2021) observed vaccine-induced immune responses in 93.3% of patients receiving a mutant IDH1 peptide vaccine for glioma, with responses occurring across multiple HLA alleles and involving both cellular and humoral immunity [33]. Emmers et al. (2025) reported vaccine-induced CD8+ and CD4+ T-cell responses in 83% and 62% of patients, respectively, following an LRPAP1 synthetic long-peptide vaccine in checkpoint-resistant NSCLC [34]. Peptide vaccines can also induce antigen-specific B-cell responses, including IgG production, which may contribute to antibody-dependent cellular cytotoxicity [35,36].

However, immunogenicity has not been consistent across studies. Heitmann et al. (2024) detected a vaccine-induced T-cell response in only one patient during the reported trial period, and most participants did not achieve the intended immunogenicity endpoint [30]. Similarly, O'Shea et al. (2023) observed a greater increase in vaccine-induced cytotoxic T lymphocytes among vaccinated women with ductal carcinoma in situ than among unvaccinated controls, although the between-group difference was not statistically significant [27]. These findings illustrate the variability of peptide-vaccine immunogenicity according to antigen selection, formulation, tumor type, host characteristics, and therapeutic context.

Clinical efficacy is similarly promising but not yet definitive. In the study by Platten et al. (2021), patients who mounted a vaccine response had a two-year progression-free survival rate of 82%, whereas patients without a vaccine response experienced disease

progression within two years [33]. Ueda et al. (2021) reported a median overall survival of 10 months among immune responders receiving a WT1-targeted peptide vaccine compared with 4.1 months among non-responders [37]. However, not all studies have demonstrated meaningful survival benefits. Emmers et al. (2025) observed numerically longer survival in patients deriving clinical benefit from vaccination, but the difference was not statistically significant [34]. More importantly, a phase III randomized controlled trial by Makino et al. (2024) found no improvement in relapse-free survival with an adjuvant five-peptide vaccine following curative resection of esophageal squamous cell carcinoma [38]. These inconsistencies indicate that immunogenicity alone cannot be assumed to translate into improved clinical outcomes.

Peptide vaccines have generally demonstrated favorable tolerability. Most reported treatment-related toxicities have been grade 1–2, with serious vaccine-attributable events uncommon [30,33,35]. Injection-site reactions are among the most frequently reported adverse events. Other events include fever, neutropenia, and febrile neutropenia [37]. Thus, peptide vaccines appear to offer a favorable safety profile, although their variable immunogenicity and uncertain clinical efficacy remain important challenges.

Cell-Based Cancer Vaccines

Cell-based cancer vaccines use autologous or otherwise prepared cells as the principal vehicle for antigen presentation and immune activation. Dendritic cell (DC) vaccines represent the most extensively investigated platform in this category. DCs are commonly generated from monocyte precursors collected through leukapheresis [39]. After ex vivo differentiation, immature DCs can be loaded with tumor lysates, peptides, or nucleic acids encoding tumor-associated antigens. Alternatively, they may be electroporated with mRNA or genetically modified to express selected antigens [22,40]. Antigen-loaded cells are subsequently matured using inflammatory cytokines, microbial products, or related stimuli before administration [42,43]. Because dendritic cells are professional APCs, they can directly present vaccine-associated antigens to T cells rather than relying on endogenous APC uptake of an injected antigen. Following administration, loaded DCs may additionally transfer tumor antigens to endogenous cross-presenting DC populations, potentially amplifying immune activation [39]. GM-CSF and Toll-like receptor agonists have been used to enhance DC-vaccine activity [44]. Vaccines may be administered intradermally, subcutaneously, or intravenously [39,44]. Their overall mechanism is represented in Figure 2A.

Compared with several non-cellular platforms, DC vaccines provide controlled ex vivo antigen loading and presentation and may be particularly useful when broad tumor lysates are used to address tumor heterogeneity [14]. However, these potential advantages must be balanced against the complexity, time, and cost of individualized cell collection, culture, maturation, and quality control. Comparative evidence also suggests that the clinical advantage of DC vaccination is context dependent. For example, a study comparing dendritic-cell and peptide-based vaccination in patients with stage III/IV melanoma found no significant difference in survival between the two approaches [47].

Clinical studies nevertheless demonstrate substantial immunogenicity. Van 'T Land et al. (2024) observed increased frequencies of effector-memory CD4+ T cells and vaccine-induced T-cell infiltration of tumors following repeated DC vaccination in patients with resected pancreatic cancer [39]. Berneman et al. (2025) reported antigen-specific type 1 CD4+ and CD8+ T-cell responses following WT1-mRNA DC vaccination, with these responses associated with higher disease-control rates and overall survival [40]. Chung et al. (2022) similarly demonstrated clonal expansion of CD4+ and CD8+ T cells following Langerhans-type dendritic-cell vaccination in patients with multiple myeloma after autologous stem-cell transplantation [41]. These findings support the ability of DC vaccines to induce cellular immunity in both solid tumors and hematologic malignancies.

The magnitude of response, however, varies considerably. Some studies have reported heterogeneous immune responses with limited or absent associations between immunogenicity and survival [45]. Repeated vaccination may also be important for achieving sustained benefit. Van 'T Land et al. (2024), for example, reported disease recurrence within two years in 80% of participants who received fewer than five vaccinations [39].

Clinical outcomes provide further evidence of potential benefit. Van 'T Land et al. (2024) reported a two-year recurrence-free survival rate of 64% in patients with resected pancreatic cancer receiving DC-based immunotherapy [39]. In glioblastoma, a phase III study of an autologous tumor lysate-loaded DC vaccine reported higher survival proportions at 48 and 60 months among vaccinated patients compared with external standard-of-care controls, with corresponding findings also reported in recurrent disease [14]. Among patients with recurrent glioblastoma, vaccination was associated with a reported 42% relative reduction in the risk of death. These findings are noteworthy given the highly immunosuppressive biology of glioblastoma, although interpretation depends on the design and comparator framework of the individual study.

Combination approaches may further enhance the activity of DC vaccines. In resectable PDAC, a DC-based vaccine administered with anti-PD-1 and anti-CD137 therapy produced numerically greater disease-free survival than vaccine plus anti-PD-1 or vaccination alone [49]. Patient characteristics may also influence treatment outcomes. Bulgarelli et al. (2025) reported greater relapse-free survival among women and patients younger than 60 years in a phase II study of DC-based immunotherapy for stage III/IV melanoma [46]. These observations suggest that vaccine efficacy is likely influenced by both tumor biology and host characteristics.

DC vaccines are generally well tolerated, although clinically significant toxicities have been reported. Van 'T Land et al. (2024) documented only one grade 3 vaccine-related event, with injection-site reactions accounting for most remaining toxicities [39]. Chung et al. (2022) reported no vaccine-related adverse events exceeding grade 1 apart from local hypersensitivity reactions [41]. Bulgarelli et al. (2025) reported limited grade 3 toxicity, including injection-site and gastrointestinal events, some of which were attributed to accompanying low-dose IL-2 [46]. Conversely, Bota et al. (2022) reported seizures in 33% of participants in a phase II glioblastoma vaccine study, including one event resulting in discontinuation [44]. Vincent et al. (2023) reported grade 3 leukopenia, grade 4 neutropenia, and one dose-limiting injection-site reaction, although the overall intervention was considered tolerable [45].

Alternative cell-based approaches are also being explored. Fang et al. (2025) investigated an experimental strategy using autologous tumor cells as an immunogenic component in a preclinical model [48]. Tumor cells were modified using Salmonella typhimurium, inactivated by flash freezing, and combined with L-arginine. The proposed mechanism involves enhanced tumor-antigen presentation, macrophage repolarization from an immunosuppressive M2

phenotype toward an inflammatory M1 phenotype, and nitric oxide-mediated pyroptosis. The authors also proposed that this approach could substantially shorten manufacturing time compared with conventional adoptive-cell approaches. Because these findings derive from preclinical work, however, their clinical relevance remains to be established.

Vector-Based Cancer Vaccines

Vector-based cancer vaccines use modified viral or bacterial organisms to deliver tumor antigens or genetic material encoding those antigens. Viral vectors are typically engineered to express one or more tumor-associated antigens and may additionally encode immunostimulatory or co-stimulatory molecules [50]. Recombinant genetic constructs encoding selected antigens are introduced into production systems to generate the final viral vector [51]. Bacterial vectors can similarly be attenuated and genetically modified to express or deliver tumor-associated targets.

Following administration, vector systems infect host cells or are taken up by APCs, resulting in antigen expression, processing, and presentation to T cells. An important theoretical advantage is their capacity to induce both antigen-specific adaptive immunity and innate antiviral or antibacterial signaling [52]. Poxvirus-based systems have been frequently investigated because of their relatively high antigen-carrying capacity and intrinsic immunogenic properties [50,53,54]. Adenoviral vectors are also widely studied because they can accommodate substantial genetic payloads [51]. Bacterial vectors offer additional potential advantages related to preferential localization within tumor tissue, including hypoxic tumor regions.

Human studies demonstrate substantial immunogenicity, particularly when vector vaccines are combined with immune-checkpoint blockade. D'Alise et al. (2024) reported antigen-specific T-cell responses in all evaluable patients receiving a personalized viral-vector vaccine together with anti-PD-1 therapy, with responses persisting for up to seven months [51]. Lassoued et al. (2025) observed more than a twofold increase in intratumoral CD4+ and CD8+ T-cell density among patients with localized prostate cancer treated with PROSTVAC plus nivolumab [53]. Tan et al. (2022) similarly reported increased IFN-γ- and granzyme B-expressing CD8+ T cells following an adenoviral-vector vaccine in patients with advanced adenocarcinoma [52].

Not all studies have demonstrated comparable immune effects. Madan et al. (2023) found no meaningful difference in antigen-specific responses between PROSTVAC plus flutamide and flutamide alone in patients with non-metastatic castration-resistant prostate cancer [55]. Such findings suggest that the biological effects of vector-based vaccination may depend substantially on the vaccine construct, tumor type, disease stage, and accompanying treatment.

Evidence for clinical efficacy remains mixed. Sonpavde et al. (2022) terminated a phase II study of CV301 combined with atezolizumab in advanced urothelial carcinoma after preliminary findings indicated futility [50]. By contrast, Rajan et al. (2022) reported six-month progression-free survival rates of 50% and 75% in two cohorts receiving CV301 in combination with anti-PD-1 therapy for non-squamous NSCLC [56]. However, because the study did not establish whether these outcomes exceeded those expected with checkpoint inhibition alone, the independent contribution of the vaccine remained uncertain. Preclinical studies of bacterial vectors have also demonstrated immunogenic activity, but their therapeutic benefit in humans has yet to be established [57]. Collectively, these findings reinforce the broader observation that robust vaccine-induced immune responses do not necessarily translate into proportional clinical benefit [52].

Vector vaccines have generally been tolerable in early-phase clinical studies. D'Alise et al. (2024) reported no serious vaccine-related adverse events [51], while Tan et al. (2022) reported predominantly grade 1–2 treatment-related events [52]. Lassoued et al. (2025) identified injection-site reactions, anemia, and fatigue among the most common toxicities [53]. One participant developed persistent grade 2 xerostomia that affected quality of life beyond one year. Madan et al. (2023) reported that most treatment-related events exceeding grade 2 consisted of self-limiting injection-site reactions [55]. Other reported events across studies included decreased appetite, diarrhea, and acute kidney injury [50]. Overall, the safety profile appears acceptable, but interpretation remains limited by small cohorts and heterogeneous combination regimens.

Figure 2. Schematic representation of the mechanisms of action of cell-based (A), nucleic acid-based (B and C), and peptide-based (D) therapeutic cancer vaccines [31].

Discussion

This review synthesized current evidence on therapeutic cancer vaccines across four major platforms—nucleic acid, peptide, cell-based, and vector-based vaccines—with particular emphasis on immunogenicity, clinical efficacy, safety, mechanisms of action, and manufacturing considerations. Across platforms, therapeutic vaccination was capable of inducing tumor antigen-specific cellular immune responses involving both CD4+ and CD8+ T cells, while some peptide-based approaches also generated measurable humoral responses. Clinical outcomes, however, were considerably more heterogeneous than immunological outcomes and varied according to vaccine platform, tumor type, disease setting, patient characteristics, and accompanying therapy.

One of the most consistent observations was the durability of vaccine-induced immunity. Antigen-specific responses persisted for months or years in several studies [16,21], consistent with the generation and maintenance of memory T-cell populations. Nevertheless, durable immunogenicity should not be equated with the magnitude or clinical effectiveness of the immune response. Many vaccine regimens required repeated dosing or booster administration, and several depended on immunostimulatory adjuvants such as GM-CSF, Toll-like receptor agonists, poly-ICLC, or Montanide ISA-51 [21,22]. Peptide vaccines appeared particularly dependent on adjuvant support, consistent with their comparatively limited intrinsic capacity to activate innate immune pathways [58].

A major advantage of therapeutic cancer vaccination is the ability to tailor antigenic specificity. Nucleic acid and personalized peptide vaccines can incorporate multiple tumor-specific targets, potentially addressing intratumoral heterogeneity and reducing the likelihood of immune escape through loss of a single antigen. Peptide design additionally permits selective targeting of MHC-I- or MHC-II-restricted responses and thereby facilitates modulation of CD8+ and CD4+ T-cell activation [26]. Some peptide vaccines also generated antigen-specific IgG responses [33], providing a potential complementary mechanism of tumor-cell killing through antibody-dependent cellular cytotoxicity.

Despite these immunological advantages, a central finding of this review is the inconsistent relationship between immunogenicity and clinical efficacy. Robust vaccine-induced immune responses did not uniformly correspond to improved progression-free or overall

survival [20,27,50,55]. This discrepancy may partly reflect the immunosuppressive tumor microenvironment, where vaccine-activated lymphocytes may encounter checkpoint signaling, immunosuppressive myeloid populations, metabolic restriction, or impaired antigen presentation. Importantly, some studies demonstrated vaccine-associated alterations in tumor microenvironment signaling [19], suggesting that rational combinations targeting both systemic immune priming and local immunosuppression may improve therapeutic effectiveness.

The available evidence also suggests that cancer vaccines may be most useful as components of multimodal treatment rather than as isolated therapies. Several encouraging outcomes were reported when vaccination was combined with immune-checkpoint inhibitors or other standard therapies [14,16,18,49]. This observation is biologically plausible because vaccination can expand tumor-specific lymphocyte populations, whereas checkpoint inhibition may facilitate their activity within immunosuppressive tumor environments. Nevertheless, the magnitude of added benefit differs substantially across cancer types, and some combination studies have failed to demonstrate meaningful clinical efficacy [50]. It is therefore premature to regard any single combination strategy as universally effective.

The distinction between the adjuvant treatment setting and the use of vaccines as therapeutic adjuncts is also important. Several of the strongest findings emerged in patients with resected or minimal residual disease, including melanoma, pancreatic cancer, glioblastoma, and other malignancies [14,16,18,39]. Lower tumor burden and reduced immunosuppression may provide a more favorable environment for vaccine-induced immunity than advanced metastatic disease. Future trials should therefore evaluate not only which vaccine platform is optimal, but also the disease stage, tumor burden, biomarker profile, and treatment sequence most likely to generate meaningful benefit.

Patient-level characteristics may further modify vaccine efficacy. Age and sex were associated with differences in clinical outcome in at least one DC-vaccine study [46], while HLA type, antigen presentation, baseline immunity, tumor mutational profile, and previous treatment are also central to personalized vaccine design. Such heterogeneity may partly explain the variable results observed between apparently similar vaccine approaches.

Across platforms, safety findings were generally favorable. Most vaccine-related adverse events were grade 1–2, with local injection-site reactions among the most frequently reported events [21,39,51–53]. Serious toxicities occurred in some studies, including hematological events, seizures, and persistent treatment-related symptoms [44,45,53], demonstrating that therapeutic vaccination cannot be considered entirely risk free. Moreover, many vaccines were administered alongside checkpoint inhibitors, cytokines, chemotherapy, or other therapies, making attribution of toxicity to the vaccine itself difficult. Overall, however, the available evidence suggests that therapeutic cancer vaccination can generally be delivered with manageable toxicity.

Limitations

Several limitations affect both the underlying literature and the conclusions that can be drawn from this review. Most importantly, much of the available clinical evidence derives from phase I or phase II studies with small sample sizes. Some studies enrolled only a few participants, while sample sizes of approximately 25 patients were common [25]. Early-phase trials are primarily designed to evaluate safety, feasibility, and dose selection rather than definitive therapeutic efficacy. Consequently, many studies were inadequately powered to detect clinically meaningful differences in progression-free or overall survival.

Small sample sizes were frequently accompanied by the absence of randomized control groups and limited population diversity [35]. These characteristics restrict both internal validity and generalizability and complicate comparisons across vaccine platforms. Differences in tumor type, disease stage, previous treatment, vaccine formulation, dosing schedule, adjuvant use, combination therapy, and immunological assays further increase heterogeneity. Consequently, apparent differences between vaccine platforms should be interpreted cautiously rather than as evidence of superiority of one approach over another.

Manufacturing represents another major translational challenge. Personalized cancer vaccines frequently require tumor sampling, whole-exome sequencing, RNA sequencing, HLA typing, computational neoantigen prediction, candidate prioritization, and individualized manufacturing. These processes may be time consuming and expensive, particularly because tumor heterogeneity requires assessment of large genomic datasets while neoantigen prediction remains imperfect [33]. D'Alise et al. (2024) reported production timelines of approximately 8–16 weeks for personalized cancer vaccination [51]. Such delays may be clinically important in rapidly progressive or metastatic malignancies.

Platform-specific production challenges also remain. mRNA and peptide products require formulation strategies that preserve molecular stability, whereas cell-based vaccines involve technically demanding ex vivo culture, antigen loading, maturation, and quality-control procedures. These complexities add to the cost of treatment, particularly when vaccines are combined with already expensive systemic therapies.

Several emerging approaches may mitigate these barriers. The peptide "warehouse" strategy described by Heitmann et al. (2024) could shorten personalized vaccine production by selecting antigens from pre-manufactured peptide libraries, although this may reduce the degree of individualization [30]. Likewise, experimental cell-based manufacturing strategies such as that proposed by Fang et al. (2025) may substantially shorten production time [48], although such findings remain preclinical and require validation in human trials.

These limitations emphasize the need for adequately powered, multicenter, randomized phase III trials using standardized clinical and immunological endpoints. Future studies should also incorporate prospective biomarker strategies capable of identifying patients most likely to benefit from specific vaccine platforms and combinations.

Conclusion

Therapeutic cancer vaccines represent a rapidly evolving approach to cancer immunotherapy with the potential to generate highly specific, personalized, and durable anti-tumor immune responses. Current evidence demonstrates substantial immunogenicity across nucleic acid-, peptide-, cell-, and vector-based platforms, while several studies have also reported encouraging improvements in recurrence and survival outcomes. However, immunogenicity does not consistently translate into clinical efficacy, and the magnitude of therapeutic benefit remains uncertain across many tumor types. The most encouraging findings generally arise when cancer vaccines are integrated with other anticancer therapies or administered in settings of relatively low residual disease burden. Future research should

therefore focus on identifying the optimal vaccine platform, antigen-selection strategy, disease setting, treatment combination, and patient population rather than considering cancer vaccines as a uniform therapeutic class. Progress will also depend on improving neoantigen prediction, antigen-delivery systems, manufacturing speed, scalability, and cost-effectiveness. Most importantly, larger randomized controlled trials are required to establish clinically meaningful effect sizes and determine whether improvements in immune response translate into durable gains in progression-free and overall survival. Addressing these scientific and logistical challenges will be essential before therapeutic cancer vaccines can be incorporated routinely into cancer care.

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References

1. Montero DA, Vidal RM, Velasco J, Carreño LJ, Torres JP, Benachi O MA, et al. Two centuries of vaccination: historical and conceptual approach and future perspectives. Front Public Health. 2024;11:1326154. doi:10.3389/fpubh.2023.1326154.
2. Shattock AJ, Johnson HC, Sim SY, Carter A, Lambach P, Hutubessy RCW, et al. Contribution of vaccination to improved survival and health: modelling 50 years of the Expanded Programme on Immunization. Lancet. 2024;403(10441):2307-16. doi:10.1016/S0140-6736(24)00850-X.
3. Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. Nat Rev Immunol. 2021;21(2):83-100. doi:10.1038/s41577-020-00479-7.
4. Lam N, Lee Y, Farber DL. A guide to adaptive immune memory. Nat Rev Immunol. 2024;24(11):810-29. doi:10.1038/s41577-024-01040-6.
5. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63. doi:10.3322/caac.21834.
6. Chen S, Cao Z, Prettner K, Kuhn M, Yang J, Jiao L, et al. Estimates and projections of the global economic cost of 29 cancers in 204 countries and territories from 2020 to 2050. JAMA Oncol. 2023;9(4):465-72. doi:10.1001/jamaoncol.2022.7826.
7. Brown JS, Amend SR, Austin RH, Gatenby RA, Hammarlund EU, Pienta KJ. Updating the definition of cancer. Mol Cancer Res. 2023;21(11):1142-7. doi:10.1158/1541-7786.MCR-23-0411.
8. Tornesello ML. TP53 mutations in cancer: molecular features and therapeutic opportunities (Review). Int J Mol Med. 2025;55(1):7. doi:10.3892/ijmm.2024.5448.
9. Jiani W, Qin T, Jie M. Tumor neoantigens and tumor immunotherapies. Aging Med (Milton). 2024;7(2):224-30. doi:10.1002/agm2.12295.
10. Mellman I, Chen DS, Powles T, Turley SJ. The cancer-immunity cycle: indication, genotype, and immunotype. Immunity. 2023;56(10):2188-205. doi:10.1016/j.immuni.2023.09.011.
11. Novikov NM, Zolotaryova SY, Gautreau AM, Denisov EV. Mutational drivers of cancer cell migration and invasion. Br J Cancer. 2021;124(1):102-14. doi:10.1038/s41416-020-01149-0.
12. Ding Z, Li Q, Zhang R, Xie L, Shu Y, Gao S, et al. Personalized neoantigen pulsed dendritic cell vaccine for advanced lung cancer. Signal Transduct Target Ther. 2021;6(1):26. doi:10.1038/s41392-020-00448-5.
13. Besse B, Felip E, Campelo RG, Cobo M, Mascaux C, Madroszyk A, et al. Randomized open-label controlled study of cancer vaccine OSE2101 versus chemotherapy in HLA-A2-positive patients with advanced non-small-cell lung cancer with resistance to immunotherapy: ATALANTE-1. Ann Oncol. 2023;34(10):920-33. doi:10.1016/j.annonc.2023.07.006.
14. Liau LM, Ashkan K, Brem S, Campian JL, Trusheim JE, Iwamoto FM, 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):112-21. doi:10.1001/jamaoncol.2022.5370.
15. Pant S, Wainberg ZA, Weekes CD, Furqan M, Kasi PM, Devoe CE, et al. Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: the phase 1 AMPLIFY-201 trial. Nat Med. 2024;30(2):531-42. doi:10.1038/s41591-023-02760-3.
16. Sethna Z, Guasp P, Reiche C, Milighetti M, Ceglia N, Patterson E, et al. RNA neoantigen vaccines prime long-lived CD8+ T cells in pancreatic cancer. Nature. 2025;639(8056):1042-51. doi:10.1038/s41586-024-08508-4.
17. Liao HC, Liu S. Advances in nucleic acid-based cancer vaccines. J Biomed Sci. 2025;32(1):10. doi:10.1186/s12929-024-01102-w.
18. Weber JS, Carlino MS, Khattak A, Meniawy T, Ansstas G, Taylor MH, et al. Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study. Lancet. 2024;403(10427):632-44. doi:10.1016/S0140-6736(23)02268-7.
19. Szymura SJ, Wang L, Zhang T, Cha S, Song J, Dong Z, et al. Personalized neoantigen vaccines as early intervention in untreated patients with lymphoplasmacytic lymphoma: a non-randomized phase 1 trial. Nat Commun. 2024;15(1):6874. doi:10.1038/s41467-024-50880-2.
20. Disis MLN, Guthrie KA, Liu Y, Coveler AL, Higgins DM, Childs JS, et al. Safety and outcomes of a plasmid DNA vaccine encoding the ERBB2 intracellular domain in patients with advanced-stage ERBB2-positive breast cancer: a phase 1 nonrandomized clinical trial. JAMA Oncol. 2023;9(1):71-8. doi:10.1001/jamaoncol.2022.5143.
21. Tonelli TP, Eickhoff JC, Johnson LE, Liu G, McNeel DG. Long-term follow up of patients treated with a DNA vaccine (pTVG-hp) for PSA-recurrent prostate cancer. Hum Vaccin Immunother. 2024;20(1):2395680. doi:10.1080/21645515.2024.2395680.
22. Fan T, Zhang M, Yang J, Zhu Z, Cao W, Dong C. Therapeutic cancer vaccines: advancements, challenges and prospects. Signal Transduct Target Ther. 2023;8(1):450. doi:10.1038/s41392-023-01674-3.
23. Autio KA, Higano CS, Nordquist L, Appleman LJ, Zhang T, Zhu X, et al. First-in-human, phase 1 study of PF-06753512, a vaccine-based immunotherapy regimen (VBIR), in non-metastatic hormone-sensitive biochemical recurrence and metastatic castration-resistant prostate cancer (mCRPC). J Immunother Cancer. 2023;11(3). doi:10.1136/jitc-2022-005702.
24. Rojas LA, Sethna Z, Soares KC, Olcese C, Pang N, Patterson E, et al. Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. Nature. 2023;618(7963):144-50. doi:10.1038/s41586-023-06063-y.
25. Ramirez CA, Becker-Hapak M, Singhal K, Russler-Germain DA, Frenkel F, Barnell EK, et al. Neoantigen landscape supports feasibility of personalized cancer vaccine for follicular

lymphoma. Blood Adv. 2024;8(15):4035-49. doi:10.1182/bloodadvances.2022007792.
26. Ninmer EK, Zhu H, Chianese-Bullock KA, Von Mehren M, Haas NB, Ross MI, et al. Multipeptide vaccines for melanoma in the adjuvant setting: long-term survival outcomes and post-hoc analysis of a randomized phase II trial. Nat Commun. 2024;15(1):2570. doi:10.1038/s41467-024-46877-6.
27. O'Shea AE, Clifton GT, Qiao N, Heckman-Stoddard BM, Wojtowicz M, Dimond E, et al. Phase II trial of nelipepimut-S peptide vaccine in women with ductal carcinoma in situ. Cancer Prev Res (Phila). 2023;16(6):333-41. doi:10.1158/1940-6207.CAPR-22-0388.
28. Sun T, Du J, Lei Y, Guo J, Zheng C, Wang D. The combination of HDACi encapsulated liposomal vaccines with oncolytic peptide QR-KLU induces an immune-mediated abscopal effect for cancer immunotherapy. J Pharm Investig. 2025;55(6):903-18. doi:10.1007/s40005-025-00736-8.
29. Tang R, Guo L, Wei T, Chen T, Yang H, Ye H, et al. Engineering PEG10-assembled endogenous virus-like particles with genetically encoded neoantigen peptides for cancer vaccination. Elife. 2024;13. doi:10.7554/eLife.98579.
30. Heitmann JS, Jung S, Wacker M, Maringer Y, Nelde A, Bauer J, et al. Warehouse-based, immunopeptidome-guided design of personalised peptide vaccines shows feasibility in clinical trial evaluation in CLL patients. Front Immunol. 2024;15:1482715. doi:10.3389/fimmu.2024.1482715.
31. Nicolás-Morales ML, Luisa-Sanjuan A, Gutiérrez-Torres M, Vences-Velázquez A, Ortuño-Pineda C, Espinoza-Rojo M, et al. Peptide-based vaccines in clinical phases and new potential therapeutic targets as a new approach for breast cancer: a review. Vaccines (Basel). 2022;10(8):1249. doi:10.3390/vaccines10081249.
32. Lorentzen CL, Martinenaite E, Kjeldsen JW, Holmstroem RB, Mørk SK, Pedersen AW, et al. Arginase-1 targeting peptide vaccine in patients with metastatic solid tumors: a phase I trial. Front Immunol. 2022;13:1023023. doi:10.3389/fimmu.2022.1023023.
33. Platten M, Bunse L, Wick A, Bunse T, Cornet LL, Harting I, et al. A vaccine targeting mutant IDH1 in newly diagnosed glioma. Nature. 2021;592(7854):463-8. doi:10.1038/s41586-021-03363-z.
34. Emmers M, Welters MJP, Dietz MV, Santegoets SJ, Boekesteijn S, Stolk A, et al. TEIPP-vaccination in checkpoint-resistant non-small cell lung cancer: a first-in-human phase I/II dose-escalation study. Nat Commun. 2025;16(1):4958. doi:10.1038/s41467-025-60281-8.
35. Ahluwalia MS, Reardon DA, Abad AP, Curry WT, Wong ET, Figel SA, et al. Phase IIa study of SurVaxM plus adjuvant temozolomide for newly diagnosed glioblastoma. J Clin Oncol. 2023;41(7):1453-65. doi:10.1200/JCO.22.00996.
36. Tobias J, Maglakelidze M, Andrić Z, Ryspayeva D, Bulat I, Nikolić I, et al. Phase II trial of HER-Vaxx, a B-cell peptide-based vaccine, in HER2-overexpressing advanced gastric cancer patients under platinum-based chemotherapy (HERIZON). Clin Cancer Res. 2024;30(18):4044-54. doi:10.1158/1078-0432.CCR-24-0742.
37. Ueda Y, Usuki K, Fujita J, Matsumura I, Aotsuka N, Sekiguchi N, et al. Phase 1/2 study evaluating the safety and efficacy of DSP-7888 dosing emulsion in myelodysplastic syndromes. Cancer Sci. 2022;113(4):1377-92. doi:10.1111/cas.15245.
38. Makino T, Miyata H, Yasuda T, Kitagawa Y, Muro K, Park J, et al. A phase 3, randomized, double-blind, multicenter, placebo-controlled study of S-588410, a five-peptide cancer vaccine as an adjuvant therapy after curative resection in patients with esophageal squamous cell carcinoma. Esophagus. 2024;21(4):447-55. doi:10.1007/s10388-024-01072-w.
39. Van 'T Land FR, Willemsen M, Bezemer K, Van Der Burg SH, Van Den Bosch TP, Doukas M, et al. Dendritic cell-based immunotherapy in patients with resected pancreatic cancer. J Clin Oncol. 2024;42(26):3083-93. doi:10.1200/JCO.23.02585.
40. Berneman ZN, De Laere M, Germonpré P, Huizing MT, Willemen Y, Lion E, et al. WT1-mRNA dendritic cell vaccination of patients with glioblastoma multiforme, malignant pleural mesothelioma, metastatic breast cancer, and other solid tumors: type 1 T-lymphocyte responses are associated with clinical outcome. J Hematol Oncol. 2025;18(1):9. doi:10.1186/s13045-025-01661-x.
41. Chung DJ, Sharma S, Rangesa M, DeWolf S, Elhanati Y, Perica K, et al. Langerhans dendritic cell vaccine bearing mRNA-encoded tumor antigens induces antimyeloma immunity after autotransplant. Blood Adv. 2022;6(5):1547-58. doi:10.1182/bloodadvances.2021005941.
42. Aerts JG, De Goeje PL, Cornelissen R, Kaijen-Lambers ME, Bezemer K, Van Der Leest CH, et al. Autologous dendritic cells pulsed with allogeneic tumor cell lysate in mesothelioma: from mouse to human. Clin Cancer Res. 2018;24(4):766-76. doi:10.1158/1078-0432.CCR-17-2522.
43. Ridolfi L, Gurrieri L, Riva N, Bulgarelli J, De Rosa F, Guidoboni M, et al. First step results from a phase II study of a dendritic cell vaccine in glioblastoma patients (CombiG-vax). Front Immunol. 2024;15:1404861. doi:10.3389/fimmu.2024.1404861.
44. Bota DA, Taylor TH, Piccioni DE, Duma CM, LaRocca RV, Kesari S, 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.
45. Vincent BG, File DM, McKinnon KP, Moore DT, Frelinger JA, Collins EJ, 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):219-28. doi:10.4049/jimmunol.2300077.
46. Bulgarelli J, Piccinini C, Scarpi E, Gentili G, Renzi L, Carloni S, et al. Adjuvant dendritic cell-based immunotherapy in melanoma: insights into immune cell dynamics and clinical evidence from a phase II trial. J Transl Med. 2025;23(1):455. doi:10.1186/s12967-025-06403-8.
47. Van Decar SG, Carpenter EL, Adams AM, Chick RC, Clifton GT, Stojadinovic A, et al. Tumor lysate particle only vaccine (TLPO) vs tumor lysate particle-loaded, dendritic cell vaccine (TLPLDC) to prevent recurrence in resected stage III/IV melanoma patients: results of a phase I/IIa trial. Cancer Treat Res Commun. 2024;41:100843. doi:10.1016/j.ctarc.2024.100843.
48. Fang T, Li L, Wang S, Li J, Nie S, Butch CJ, et al. Therapeutic adoptive cell transfer (ACT) vaccine patch: bioengineered tumor cells prime macrophage immunoregulation to prevent postsurgical tumor recurrence and metastasis. Adv Funct Mater. 2025;35(49). doi:10.1002/adfm.202510281.
49. Heumann T, Judkins C, Li K, Lim SJ, Hoare J, Parkinson R, et al. A platform trial of neoadjuvant and adjuvant antitumor vaccination alone or in combination with PD-1 antagonist and CD137 agonist antibodies in patients with resectable pancreatic adenocarcinoma. Nat Commun. 2023;14(1):3650. doi:10.1038/s41467-023-39196-9.
50. Sonpavde GP, Maughan BL, McGregor BA, Wei XX, Kilbridge KL, Lee RJ, et al. Phase II trial of CV301 vaccine combined with atezolizumab in advanced urothelial carcinoma. Cancer Immunol Immunother. 2023;72(3):775-82. doi:10.1007/s00262-022-03274-6.

51. D'Alise AM, Leoni G, Cotugno G, Siani L, Vitale R, Ruzza V, et al. Phase I trial of viral vector-based personalized vaccination elicits robust neoantigen-specific antitumor T-cell responses. Clin Cancer Res. 2024;30(11):2412-23. doi:10.1158/1078-0432.CCR-23-3940.
52. Tan TJ, Ang WXG, Wang W, Chong H, Tan SH, Cheong R, et al. A phase I study of an adenoviral vector delivering a MUC1/CD40-ligand fusion protein in patients with advanced adenocarcinoma. Nat Commun. 2022;13(1):6453. doi:10.1038/s41467-022-33834-4.
53. Lassoued W, Madan RA, Xue E, Burnett D, Canubas KD, Bailey S, et al. Programmed death-1 inhibition increases vaccine-induced T-cell infiltration in patients with prostate cancer. J Immunother Cancer. 2025;13(6). doi:10.1136/jitc-2024-010851.
54. Singh P, Pal SK, Alex A, Agarwal N. Development of PROSTVAC immunotherapy in prostate cancer. Future Oncol. 2015;11(15):2137-48. doi:10.2217/fon.15.120.
55. Madan RA, Bilusic M, Stein MN, Donahue RN, Arlen PM, Karzai F, et al. Flutamide with or without PROSTVAC in non-metastatic castration resistant (M0) prostate cancer. Oncologist. 2023;28(7):642-e561. doi:10.1093/oncolo/oyad058.
56. Rajan A, Gray JE, Devarakonda S, Birhiray R, Korchin B, Menius E, et al. Phase 1 trial of CV301 in combination with anti-PD-1 therapy in nonsquamous non-small cell lung cancer. Int J Cancer. 2023;152(3):447-57. doi:10.1002/ijc.34267.
57. Redenti A, Im J, Redenti B, Li F, Rouanne M, Sheng Z, et al. Probiotic neoantigen delivery vectors for precision cancer immunotherapy. Nature. 2024;635(8038):453-61. doi:10.1038/s41586-024-08033-4.
58. Luo Y, Zhou S, Wu S, Jin H, Lovell JF. Emerging strategies for advancing peptide vaccines. Cell Rep Phys Sci. 2026;7(2):103096. doi:10.1016/j.xcrp.2026.103096.