Neoantigen-Derived Cancer Vaccines

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Cancers are driven by genetic instabilities that rapidly accumulate somatic mutations and eventually alter cell properties. Cancer immunotherapy has achieved multiple clinical benefits and has become an indispensable component of cancer treatment. Targeting tumor-specific antigens, also known as neoantigens, plays a crucial role in cancer immunotherapy. T cells of adaptive immunity that recognize neoantigens, but do not induce unwanted off-target effects, have demonstrated high efficacy and low side effects in cancer immunotherapy.

Keywords: cancer ; vaccine ; neoantigens

1. Tumor Lysates and Allogeneic Tumor-Cell-Based Vaccine

Autologous tumor lysates or allogeneic tumor cells obtained from patients were the earliest developed cancer vaccines. By administering either inactivated resected tumor lysates or allogeneic tumor-cell lysates with additional components such as adjuvants and cytokines, these cancer vaccines could present epitopes of tumor antigens to activate both $CD4^+$ and $CD8^+$ T cells in the human body [1][2][3].

An autologous tumor-lysate vaccine from Vaccinogen Inc, OncoVax, which uses Bacillus Calmette-Guerin (BCG) as an adjuvant, was shown to extend the recurrence-free period and reduce the risk for recurrences in surgically resected patients with stage II colon cancer. Their phase Ⅲ trial (NTC02448173) evaluating further clinical benefits of OncoVax is ongoing [4]. GVAX (Cell Genesys, Inc., South San Francisco, CA, USA) is an allogeneic whole-tumor-cell vaccine that consists of two prostate-cancer cell lines, LNCaP and PC-3, transfected with a human granulocyte-macrophage-stimulating factor (GM-CSF) gene. Phase I/II studies demonstrated its safety and clinical activity; however, it failed to reach clinical efficacy in a phase III trial of advanced prostate cancer [5]. To improve the overall survival rate, GVAX was recently used with chemotherapy agents and ipilimumab to treat metastatic pancreatic cancer in the trial stage [6]. Other studies on tumor-cell vaccines include melacine (an allogenic melanoma tumor-cell-lysate vaccine) [7], canvaxin (an antigen-rich allogeneic whole-cell vaccine developed from three melanoma cell lines) [8], and TRIMELVax (a heat-shocked melanoma-cell-lysate vaccine) [9]. Although all epitopes are included in this type of vaccine, the contents of neoantigens are quite low, and most are wild-type endogenous peptides, which might dilute the expected immune responses and increase the risk of adverse reactions. Research on optimizing this approach, such as combination therapy and optimized carriers to transport the cells, might address the current limitations of tumor lysates or allogeneic tumor-cell-based vaccines.

2. DNA-Based Vaccines

DNA vaccines can be introduced into cells and tissues via non-viral or viral gene-delivery systems. After being introduced into the cytoplasm, DNA migrates to the nucleus and initiates the production of antigens. Physical forces mainly represent the non-viral methods of facilitating intracellular gene transfection by transiently loosening the cell-membrane structure. These systems include electroporation, microinjection, and a gene gun to transfect plasmid DNA into the tissue [10]. Although the physical delivery system offers highly efficient gene transfection, tissue damage resulting from the applied physical forces may cause low activity [11]. GNOS-PV02, a neoantigen-DNA vaccine with plasmid-encoded IL-12 administered by electroporation and intradermal injection, entered a phase I/II clinical study with the combination of pembrolizumab for the treatment of advanced hepatocellular carcinoma. The up-to-date result revealed that the objective response rate (ORR) was 25% without reported dose-limiting toxicities (DLTs). Post-vaccination TCR-repertoire analysis identified novel expanded T-cell clones in both peripheral blood and tumor tissue, which potentially mediated the observed regression of tumors [12].

DNA vaccines can also be delivered by viral carriers such as adenoviruses, modified vaccinia viruses, lentiviruses, and retroviruses. The adenovirus is a non-envelope, double-stranded DNA virus commonly used as a viral vector among these viruses. Adenoviral-vector vaccines replace genes that enable replication of transgenes or other genes of interest, making

the vector unable to generate their genome copies after delivery. This property also provides the virus with a higher package capacity to incorporate large transgene sequences [13]. Compared to other virus-based vectors, adenoviral vectors have less potential genotoxicity and have been applied to infectious diseases such as COVID-19 [14], Ebola virus [15], and malaria [16]. Nous-209 is a virus-based cancer vaccine encoding 209 commonly shared frameshift mutations of microsatellite instability tumors and uses the Great Ape Adenoviruses vectors for priming and Modified Vaccinia Ankara vectors for boosting. The preliminary results of the phase I study combined with pembrolizumab showed no DLTs. Seven out of the twelve enrolled patients had confirmed partial responses (PRs), and two patients had stable disease (SD), suggesting that Nous-209 is safe and immunogenic and may contribute to early clinical outcomes [17]. PRGN-2009, a human papillomavirus (HPV) therapeutic vaccine encoding 35 non-HLA-restricted epitopes of HPV 16 and 18 by a novel gorilla adenoviral vector, increased the number of T cells targeting HPV 16 or HPV 18 after vaccination in all six recruited patients in a phase I study without observed DLTs [18]. However, pre-existing immunity against particular virus serotypes prevents the efficacy of virus-based vaccines [19]. This problem may be overcome using viral vectors derived from other species [20]. Nonetheless, it remains to be determined whether existing immunity will decrease the immunization potential for a repeated dose of vaccine constructed in the same or similar serotype virus.

In addition to viral vectors, microbes are also candidates for carrying target antigens. Lm-platform technology is an antigen delivery platform via *Listeria monocytogenes* developed by ADVAXIS. Attenuated *Listeria monocytogenes* carrying the bacterial vector expresses fusion proteins containing adjuvant parts and target antigens to T cells after phagocytosis. ADXS-503 is a phase I study of pembrolizumab plus the Lm vaccine targeting 11 common hotspot mutations and 11 TAAs of metastatic non-small-cell lung carcinoma (NSCLC). Antigen-specific T cells were found in all patients with a transient release of pro-inflammatory cytokines. Seven of the nine recruited patients also showed antigen spreading. The ORR was 11%, and the disease-control rate (DCR) was 44%, with one achieving a PR and three achieving SD. The vaccine was well-tolerated without reported immune-related adverse events (irAEs) [21]. Another phase I study, ADXS-NEO-2, targeted personalized neoantigens for each cancer patient. Preliminary findings included immune-cell proliferation, antigen-specific T-cell response, and antigen spreading in one patient at 108 colony-forming units (CFUs). However, two patients had manageable DLTs at an initial dose of 109 CFUs, and the current state of this trial remains unclear [22]. The neoantigen-DNA-vaccine trials currently in the active or completed stages are listed in **Table 1**.

Table 1. Clinical trials of neoantigen-DNA vaccines.

Trial No. (Brand Name)	Target	Indication	Format/Route of Administration	Combination Therapy	Status
NCT03122106	Personalized NeoAg + Mesothelin	Pancreatic Cancer	Plasmid DNA/Electroporation + IM injection	N/A	Phase 1, Active, Not Recruiting
NCT04015700 (GNOS-PV01)	Personalized NeoAg	Unmethylated Glioblastoma	Plasmid DNA/Electroporation + IM injection	Pembrolizumab, Plasmid encoded IL-12 (INO-9012)	Phase 1, Recruiting
NCT04251117 (GNOS-PV02)	Personalized NeoAg + Mesothelin	HCC	Plasmid DNA/Electroporation + IM injection	Pembrolizumab, Plasmid encoded IL-12 (INO-9012)	Phase 1/2a, Recruiting
NCT04990479 (Nous-PEV)	Personalized NeoAg	Melanoma, NSCLC	Adenovirus vector + Vaccinia virus vector/IM injection	Pembrolizumab	Phase 1, Recruiting
NCT04041310 (Nous-209)	Personalized NeoAg	MSI-H CRC, gastric, G-E junction tumors	Adenovirus vector + vaccinia virus vector/IM injection	Pembrolizumab	Phase 1/2, Active, Not Recruiting
NCT05018273 (VB10.NEO)	Personalized NeoAg	Solid Tumors	Plasmid DNA/IM injection	Atezolizumab	Phase 1b, Recruiting
NCT02348320	Personalized NeoAg	Triple-Negative Breast Cancer	Plasmid DNA/Electroporation + IM injection	N/A	Phase 1, Completed
NCT03953235 (SLATE)	Shared Neoantigen	Shared neoantigen positive tumors	Adenovirus vector + RNA vector/Not specific	Nivolumab, Ipilimumab	Phase 1/2, Recruiting

Trial No. (Brand Name)	Target	Indication	Format/Route of Administration	Combination Therapy	Status
NCT03265080 (ADXS-NEO)	Personalized NeoAg	Colon Cancer, Head & Neck Cancer, NSCLC, Urothelial Carcinoma, Melanoma	*Lm*-based vector/I.V. infusion	Pembrolizumab (selectively)	Phase 1, Active, Not Recruiting
NCT03847519 (ADXS-503)	Personalized NeoAg	NSCLC, Metastatic SCC, Metastatic NSCLC	*Lm*-based vector/I.V. infusion	Pembrolizumab (selectively)	Phase 1/2, Recruiting

Abbreviations: CRC, colorectal cancer. HCC, hepatocellular carcinoma. I.V., intravascular infusion. I.M., intramuscular injection. *Lm*, *Listeria monocytogenes*. MSI-H, high microsatellite instability. NSCC, small-cell lung cancer. NSCLC, non-small-cell lung cancer

3. mRNA-Based Vaccines

Additionally, mRNA vaccines have shown substantial potential against diseases during the COVID-19 pandemic [23]. Theoretically, mRNA vaccines are internalized in the cytoplasm, and antigens of interest can be translated without mutagenesis concerns. The magnitude and rate of mRNA translation are typically higher than those of DNA vaccines. Currently, mRNA can be rapidly produced using in vitro transcription (IVT) methods, making it feasible for scale-up manufacturing. These characteristics make mRNA vaccines powerful tools for responding to emergent needs.

The significant clinical breakthrough of the application of mRNA cancer vaccines was first published by Sahin et al. [24]. Thirteen patients with stage III and IV melanoma received at least eight doses of personalized neoantigen vaccines percutaneously into the inguinal lymph nodes. Each patient's five–ten mutations were selected based on the predicted high-affinity binding to autologous HLA class I and HLA class II. Not only were de novo immune responses observed, but pre-existing immune responses against predicted neoantigens were also augmented in all patients. Eight patients remained recurrence-free during the follow-up period. One patient experienced a complete response of metastases, which contributed to neoantigen-vaccine monotherapy. Another patient had a rapid, complete response within two months with PD1-blockade combination therapy. These results translated into sustained progression-free survival (PFS) and significantly reduced the cumulative sum of metastatic events compared to those before vaccine treatment. Notably, immune escape was observed in one patient who initially had a PR but suffered from metastasis two months after 12 vaccinations and follow-up surgeries. Loss of β-2 microglobulin was observed in autologous tumor cells, leading to HLA-class-I dysfunction [24].

Additionally, mRNA-4157 is the neoantigen-mRNA-vaccine trial of Moderna and is currently under phase I evaluation for solid tumors. From the updated outcome, the vaccine's safety was acceptable, with only mild-related adverse events reported [25]. Remarkably, the response rate was 50% for HPV-negative head and neck squamous-cell carcinoma combined with pembrolizumab, and the median PFS was compared favorably to pembrolizumab monotherapy. In addition, 14 of 16 patients with resected solid tumors receiving vaccine monotherapy remained disease free. The trial is ongoing for efficacy analysis [26]. However, the other trial of neoantigen-mRNA vaccines, mRNA-4650, did not proceed because no clinical response was observed. Neoepitopes for each patient were selected by HLA-I prediction and validated by TIL–APC coculture, plus any mutations in the hot driver genes of Kirsten rat sarcoma virus (KRAS), tumor protein p53 (TP53), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA). Despite the suboptimal clinical results, T-cell reactivity against several predicted neoepitopes was found in the post-vaccination PBMC of some patients. TCR analysis revealed neoantigen-specific clonotypes capable of recognizing designed neoantigens, suggesting that a combination of immune-checkpoint inhibitors (ICIs) or immune-cell therapy could have clinical benefits [27].

Naked RNA is vulnerable to extracellular RNAse and can undergo rapid degradation that limits the internalization of the vaccine. Improved mRNA-delivery systems facilitate vaccine protection, distribution, and release. For instance, ionizable lipid nanoparticles (LNPs) are self-assembled particles commonly used for RNA delivery. LNPs are stable at physiological pH, but the ionizable coated lipid can interact with the ionic endosomal membrane in an acidic endosomal microenvironment, thus promoting membrane fusion and RNA release. Moreover, mRNA has intrinsic immunogenicity, recognized mostly by toll-like receptor-7 and -8, and activates downstream interferon pathways and pro-inflammatory cytokine release. Although this might augment adaptive-immune responses, it could also dampen the antigen

presentation. Unwanted double-stranded RNA (dsRNA) produced during IVT can activate RNA-dependent protein kinase, phosphorylate eukaryotic elongation factor-2, and block mRNA translation [28]. Several strategies have been investigated to overcome this limitation. Baiersdörfer et al. presented a dsRNA-removal method using cellulose in an ethanol-containing buffer. Up to 90% of dsRNA contaminants can be removed, resulting in better translation efficacy in vivo [29]. CureVax AG developed an RNA/protamine complex that serves as a toll-like receptor 7/8 (TLR7/8) adjuvant, increasing antitumor immunity after vaccination [30]. Luo et al. reported a formulation of synthetic polymeric nanoparticles with an intrinsic activating property for the stimulator of interferon genes (STING), leading to the inhibition of tumor progression in three types of cancer models [31]. In addition, BioNTech developed an RNA-lipoplex cancer-vaccine platform, Lipo-MERIX, which can precisely target dendritic cells (DC) in the lymphoid compartment by systematic administration (intravenous injection) to induce a potent immune response [32]. Several trials evaluating Lipo-MERIX carrying TAA or TSA for different types of solid tumors are ongoing. A relative trial targeting TAA for advanced melanoma, BNT-111, has recently received FDA fast-track designation [33]. Active and completed neoantigen-mRNA-vaccine trials are listed in **Table 2**.

Table 2. Clinical trials of neoantigen RNA vaccines.

Trial No. (Brand Name)	Target	Indication	Format/Route of Administration	Combination Therapy	Status
RO7198457					
NCT03289962	**Personalized NeoAg**	**Solid tumors**	**RNA-Lipoplex/I.V.**	**Atezolizumab**	**Phase 1a/1b, Recruiting**
NCT03815058	**Personalized NeoAg**	**Advanced Melanoma**	**RNA-Lipoplex/I.V.**	**Pembrolizumab**	**Phase 2, Recruiting**
NCT04486378	**Personalized NeoAg**	**Colorectal Cancer Stage II, III**	**RNA-Lipoplex/I.V.**	**N/A**	**Phase 2, Recruiting**
NCT04161755	**Personalized NeoAg**	**Pancreatic Cancer**	**RNA-Lipoplex/I.V.**	**Atezolizumab, mFOLFIRINOX**	**Phase 1, Recruiting**
IVAC mutanome					
NCT02035956	**Personalized NeoAg**	**Melanoma**	**Not specific/Intra-nodal**	**RBL001/RBL002 (TAA RNA Vaccine)**	**Phase 1, Completed**
NCT02316457	**Personalized NeoAg**	**Breast Cancer (TNBC)**	**Nanoparticulate lipoplex RNA/I.V.**	**IVAC_W_bre1_uID (TAA RNA vaccine)**	**Phase 1, Active, Not Recruiting**
mRNA-4157					
NCT03897881	**Personalized NeoAg**	**Melanoma**	**lipid encapsulated RNA/I.M.**	**Pembrolizumab**	**Phase 2, Active, Not Recruiting**
NCT03313778	**Personalized NeoAg**	**Solid tumors**	**lipid encapsulated RNA/I.M.**	**Pembrolizumab**	**Phase 1, Recruiting**
mRNA-5671					
NCT03948763	**KRAS common mutations**	**Solid Tumors**	**lipid encapsulated RNA/I.M.**	**Pembrolizumab (selectively)**	**Phase 1, Recruiting**

Abbreviations: I.V., intravascular infusion. I.M., intramuscular injection. TAA, tumor-associated antigens. TNBC, triple-negative breast cancer.

4. Protein and Peptide Vaccines

Peptide-based vaccines use synthetic peptides to trigger peptide-specific immune responses against cancer. It is intuitive and cost-effective, and no intricate logistics are required for transport and restoration. As reviewed by Shemesh et al., neoantigen vaccines derived from peptides, along with mRNA, have undergone the most ongoing clinical trials [34]. The primary outcomes of peptide vaccines showed promising results in treating melanoma and brain malignancies in multiple trials [35][36].

Hilf et al. conducted the GAPVAC trial for glioblastoma by administering peptide vaccines containing the predicted neoantigens and glioma-related TAAs. Notably, Th1 cells were induced in 11 of 13 patients receiving the neoepitope vaccine. In one patient who had a complete response after vaccination but experienced recurrence two years afterward, high infiltration by T cells was found, with a favorable ratio of $CD8^+$/$FOXP3^+$ (forkhead box P3+) Treg cells from the re-resected tumor [37]. Similar results were reported by Keskin et al., who demonstrated that neoantigen-specific $CD4^+$ and $CD8^+$ T cells enriched in the memory phenotype were found after neoantigen-peptide administration. This research further proved that neoantigen-specific T cells triggered by the vaccine could migrate into intracranial glioblastoma tumors [35].

Recently, Platten et al. tested the safety and efficacy of a mutated isocitrate dehydrogenase 1 (IDH1) peptide vaccine in a phase I trial. Mutations in IDH1 are molecular characteristics of certain gliomas that contribute to the early stages of tumor development. Patients with the IDH1 R132H variant were recruited and treated with a 20-mer peptide containing a mutated spot. A mutant-specific T-cell response was found in over 90% of recruited patients with appropriate safety profiles [38]. In recent years, elongated $CD8^+$ T-cell epitopes have been thought to enhance epitope-specific anticancer immunity. Unlike the predicted short epitopes, long peptides are believed to only be processed and presented by professional APC, leading to robust T-cell induction. In the mutant IDH1 trial, a single LSP (long synthetic peptide) was presented across various MHC alleles and, therefore, could be applied as an off-the-shelf product.

Moreover, the combination of neoantigen-peptide vaccines and ICIs has been validated in several trials. The NEO-PV-01 phase Ib clinical trial of a personalized peptide vaccine plus anti-PD1 (anti-programmed death-1) agent was evaluated for safety and efficacy in patients with advanced melanoma, NSCLC, and bladder cancer. Persistent cytotoxic T-cell responses were identified post-vaccination, without severe adverse reactions, in all three cancer cohorts. The median ORR and PFS were favorably compared with historical results for anti-PD-1 monotherapy but could not firmly attribute these outcomes to the vaccine because it was a single-arm investigation [39]. The comparison of neoantigen-peptide-vaccine monotherapy or in combination with ICIs was validated in an ongoing trial, GEN-009 [40].

NeoVax is a personalized long-peptide vaccine plus poly-ICLC (polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose) (i.e., a TLR-3 and MDA5 (melanoma differentiation-associated protein 5) agonist) [36][39]. A long-term follow-up study revealed that all patients with resected metastatic melanoma who had previous NeoVax treatment were still alive up to four years after treatment. Six of the eight patients had no evidence of disease. T cells with reactivity against certain vaccinated neoantigens persisted in the circulating blood of patients during the priming, boosting, and post-vaccination stages (up to 4.5 years). After the vaccination period, these functional T cells shifted to the less exhausted memory phenotype. Encouragingly, T cells able to target non-vaccinated TAAs or neoantigens were identified only in the post-vaccination sample, suggesting that the neoantigen-peptide vaccine could induce epitope spreading [40]. Epitope spreading has also been observed in several neoantigen-peptide-vaccine trials, including the NEO-PV-01, GEN-009, and glioblastoma trials [35][37][39][40]. In the NeoVax follow-up study, enhanced epitope spreading was observed in one patient experiencing recurrence in the post-vaccination period, but no evidence of disease after pembrolizumab therapy was shown, indicating that the combination of the neoantigen vaccine and ICIs could further improve clinical outcomes [40].

5. Dendritic- Cell (DC)-Based Vaccines

The cell-based-vaccine approach exploits autologous dendritic-cell (DCs) loaded with tumor antigens in various formats, including tumor lysates, DNA, mRNA, or peptides. Encouraging results, including Sipuleucel-T, an autologous DC vaccine targeting prostatic-acid phosphatase (PAP), a TAA, have demonstrated a significant improvement in overall survival for men with metastatic castration-resistant prostate cancer and was approved by the FDA [41]. For the neoantigen-pulsed DC vaccine, Carreno et al. conducted a trial applying an in vitro matured autologous DC vaccine stimulated by personalized neoantigen peptides in three patients with advanced melanoma. TCR-sequencing results indicated diverse neoantigen-specific clonotypes induced by personalized DC vaccines, and increased immunity was observed in all patients [42]. Moreover, a patient with metastatic pancreatic cancer experienced regression of multiple metastatic lesions 2.5 months after DC-based-vaccine treatment. In this case, the selected neoepitope was an HLA-A*0201–restricted KRAS-G12D epitope, and the patient received a vaccine containing a neoantigen plus DC and neoantigen-reactive $CD8^+CD137^+$ T cells [43]. Similar research on patients with heavily treated lung cancer by administering a neoantigen-peptide-loaded DC vaccine demonstrated a 25% ORR and 75% DCR. Although none of the recruited patients achieved CR, the results were auspicious considering the initially poor prognosis of the study population. In addition, they noticed that the neoantigen-loaded DC vaccine could re-induce objective responses to ICIs in patients who had a relapse after previous ICI treatment.

This finding corresponds to that mentioned in the peptide-vaccine section, namely that the combination of cancer vaccines and ICMs could further provide synergetic therapeutic benefits [44].

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