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Clinical advances and ongoing trials of mRNA vaccines for cancer treatment

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Years of research exploring mRNA vaccines for cancer treatment in preclinical and clinical trials have set the stage for the rapid development of mRNA vaccines during the COVID-19 pandemic. Therapeutic cancer vaccines based on mRNA are well tolerated, and the inherent advantage in ease of production, which rivals the best available conventional vaccine manufacture methods, renders mRNA vaccines a promising option for cancer immunotherapy. Technological advances have optimised mRNA-based vaccine stability, structure, and delivery methods, and multiple clinical trials investigating mRNA vaccine therapy are now enrolling patients with various cancer diagnoses. Although therapeutic mRNA-based cancer vaccines have not yet been approved for standard treatment, encouraging results from early clinical trials with mRNA vaccines as monotherapy and in combination with checkpoint inhibitors have been obtained. This Review summarises the latest clinical advances in mRNA-based vaccines for cancer treatment and reflects on future perspectives and challenges for this new and promising treatment approach.

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Introduction

The COVID-19 pandemic has directed worldwide focus towards mRNA-based vaccines. Indeed, the foundation for the rapid COVID-19 vaccine development and production was based on years of research exploring mRNA vaccines as a therapeutic strategy against cancer in preclinical and clinical trials.[1] mRNA brings several benefits to a vaccine setting (panel). Firstly, mRNA-based vaccines are well tolerated, easily degraded, and do not integrate into the host genome.[2–4] Secondly, mRNA molecules are non-infectious, and mRNA vaccines have the potential to induce both humoral and cell-mediated immunity (figure).[5,6] Lastly, the production of mRNA vaccines is fast and inexpensive.[7]

In 1996, the first mRNA-based cancer vaccine study tested dendritic cells pulsed with RNA in vitro.[8] Nowadays, technological advances have led to optimised mRNA structure, stability, and delivery methods, and multiple clinical trials are now enrolling patients with cancer for mRNA-based vaccine treatments (tables 1, 2).[2,3] mRNA vaccine administration routes include intradermal, subcutaneous, intranasal, intranodal, intramuscular, intratumoural, and intravenous delivery.[9] The ex-vivo engineering of autologous dendritic cells with mRNA has been the method of choice for tumour antigen delivery, but most mRNA vaccine approaches focus on direct mRNA administration using lipid nanoparticulate formulation carriers (table 1).

The clinical efficacy and immunogenicity of mRNA vaccines have been evaluated across cancer diagnoses and administration methods (table 3). A few trials have reported durable objective responses in patients with cancer after mRNA-based vaccine treatment, without unmanageable toxic effects.[10,14–16,19] mRNA vaccines are promising therapeutic candidates for future cancer treatments, especially in combination with additional immunotherapies.[14,19,20] However, no phase 3 studies are ongoing, and, at the time of writing, the US Food and Drug Administration (FDA) has not yet approved a therapeutic mRNA-based cancer vaccine.[21]

This Review summarises the latest clinical advances in therapeutic mRNA-based cancer vaccines, with a focus on direct mRNA administration methods.

mRNA-based cancer vaccine trials

The aim of mRNA-based vaccination is to induce or boost an effective anti-tumour immune response.[22] Synthetic mRNA encoding tumour-associated or tumour-specific antigens is delivered through autologous dendritic cells engineered with mRNA ex vivo or through formulated or non-formulated mRNA injections.[23] After vaccination and cellular uptake by antigen-presenting cells, mRNA is transported to the cytoplasm and undergoes antigen processing and enters the MHC presentation cascade. Thus, antigen-presenting cells present tumour-associated antigens on MHC class I and MHC class II to activate $CD8^+$ and $CD4^+$ T cells. In addition, $CD4^+$ T cells can co-activate antigen-specific B cells and induce a humoral immune response. B cells that function as antigen-presenting cells can conversely activate $CD4^+$ T cells after internalisation of extracellular proteins and presentation on B cells' MHC class II (figure).[9,24]

Several clinical trials (eg, NCT04534205, NCT03313778, and NCT04503278) are enrolling patients for various mRNA-based cancer vaccine therapy studies with the

***Panel*: Advantages of mRNA vaccines for the treatment of cancer**

- Well tolerated: adverse events are generally manageable and transient
- No genome integration: eliminates the risk of insertional mutagenesis
- Non-infectious: no pathogenic viral agents are used
- Easily degraded: reduces risk of toxicity
- Humoral and cellular immunity: necessary for activating and sustaining anti-tumour responses
- Fast and inexpensive production: laboratory-based and cell-free production

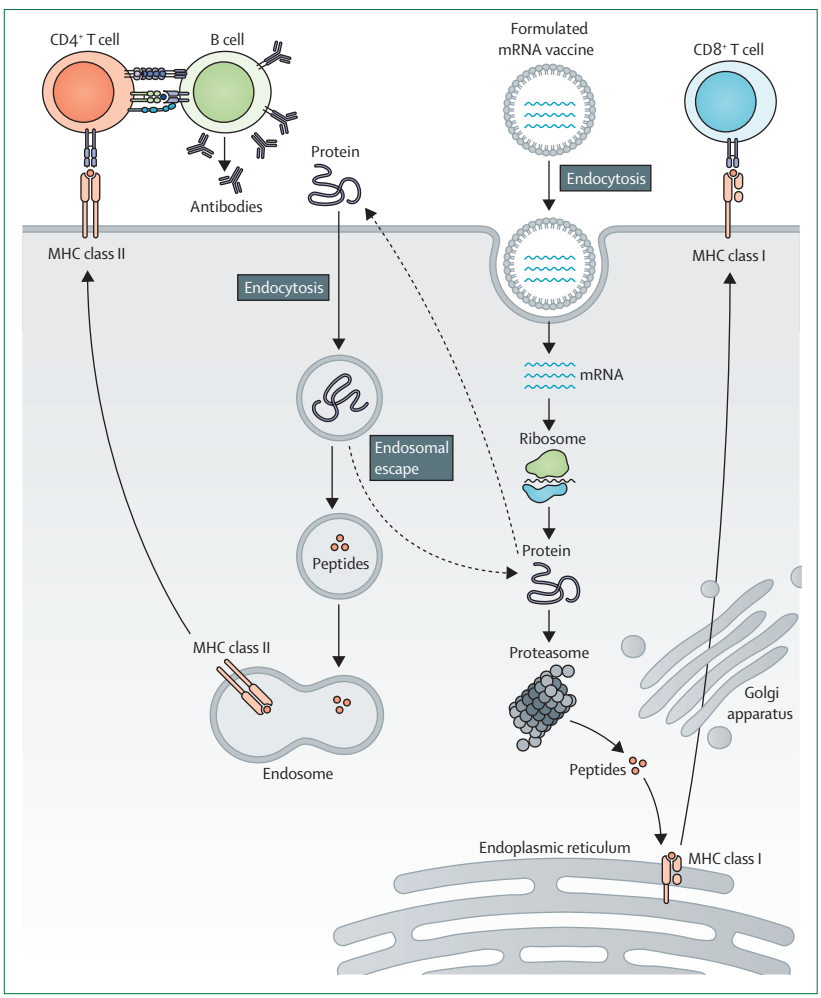

Figure: **mRNA-based vaccine mode of action**
mRNA is taken up by antigen-presenting cells and peptides are loaded on MHC class I for antigen-specific CD8+ T-cell activation. Extracellular proteins are cross-presented on MHC class I or loaded on MHC class II for CD4+ T-cell activation. CD4+ T cells can co-activate protein-specific B cells, and B cells can activate CD4+ T cells after B-cell receptor-mediated antigen internalisation.

aim of inducing an mRNA-based anti-tumour response (tables 1, 2).

Non-formulated (naked) mRNA-based cancer vaccines

Naked or non-formulated mRNA vaccines contain mRNA molecules in a buffer solution.[10] The non-formulated vaccines are administered either intradermally or intranodally.[10,25] The administration of non-formulated mRNA intranodally enables the delivery of antigens to antigen-presenting cells at the actual location of T-cell activation, thereby avoiding the requirement for antigen-presenting cell migration.[26] Several studies have shown that dendritic cells can take up intranodally injected non-formulated mRNA and induce potent anti-tumour T-cell responses.[7,10]

Only a few clinical trials have treated patients with cancer with non-formulated mRNA vaccines in the past 5 years (table 3). In a phase 1 clinical trial, non-formulated mRNA vaccines were administered intranodally in 13 patients with stage III or IV melanoma with stable disease, partial response, or complete response after previous treatment. This neoepitope-targeting vaccine encoded a unique and individualised tumour mutation signature with ten selected neoepitopes for each patient. All patients developed T-cell responses against numerous vaccine-encoded neoepitopes, and vaccine-related clinical responses were observed in two (40%) of the five patients with stage IV melanoma.[10] In a recently concluded phase 1 clinical trial (NCT03394937), 20 patients with resected melanoma (stages IIc, III, and IV) received an intranodally injected non-formulated mRNA vaccine (ECI-006). The vaccine included mRNAs encoding three dendritic cell-activating molecules (TriMix) and five tumour-associated antigens (table 3).[11] In a second study cohort (NCT03394937), patients with metastatic melanoma with stable disease after 3–12 months of standard treatment received the ECI-006 vaccine in combination with standard anti-PD-1 therapy; results are not yet published. No clinical trials registered at ClinicalTrials.gov are currently recruiting patients for non-formulated mRNA cancer vaccine treatment.

Formulated mRNA-based cancer vaccines

Non-formulated mRNA is easily degraded by extracellular RNases.[27] Consequently, several nanocarrier pharmaceutical systems, generally containing polymers such as peptides or lipids, have been developed to optimise mRNA preservation and facilitate mRNA uptake by antigen-presenting cells.[3,28,29]

Protamine-formulated mRNA-based cancer vaccines

Protamines are positively charged polycationic peptides that form complexes with negatively charged mRNA and protect the molecules from degradation.[30] Protamine-formulated mRNA vaccines have been evaluated in diverse clinical trials in the form of RNActive vaccines.[12–14] RNActive vaccines incorporate nucleotide modified mRNA molecules complexed with protamine to enhance protein expression and immunogenicity.[31] At the time of writing, no clinical trials registered at ClinicalTrials.gov are recruiting patients for protamine-formulated mRNA cancer vaccine studies.

An RNActive vaccine encoding six prostate cancer-specific antigens (CV9104) was investigated in a placebo-controlled phase 1/2 study in patients with metastatic castration-resistant prostate cancer. The vaccine was clinically safe for the patients but did not improve overall survival and progression-free survival compared with the placebo.[12]

The RNActive immunisation technology was also investigated in a phase 1/2 dose-escalation trial in patients with non-small-cell lung cancer (NSCLC). Patients had reached stable disease after first-line therapy before receiving the protamine-formulated mRNA

	Trial phase	Target antigen	Cancer type	Combination	Vaccine route of administration	Sponsor
Lipid nanoparticle formulation						
NCT03948763	1	mRNA-5671 (KRAS gene driver mutations)	Non-small-cell lung, pancreatic, and colorectal neoplasms	With pembrolizumab	Intramuscular	Merck Sharp & Dohme
NCT03313778	1	mRNA-4157 (personalised cancer vaccine encoding several neoantigens)	Solid tumours (resected)	With pembrolizumab	Intramuscular	Moderna
NCT03897881	2	mRNA-4157 (personalised cancer vaccine encoding 20 different mutated neoepitopes)	Melanoma	With pembrolizumab	Intramuscular	Moderna
NCT04573140	1	Formulation with pp65 LAMP and tumour mRNA	Glioblastoma	None	Intravenous	University of Florida (Gainesville, FL, USA)
Lipoplex formulation						
NCT02410733	1	BNT111 (NY-ESO-1 [CTAG1A], tyrosinase, MAGE-A3, and TPTE)	Melanoma	None	Intravenous	BioNTech
NCT04526899	2	BNT111 (NY-ESO-1, tyrosinase, MAGE-A3, and TPTE)	Melanoma	With cemiplimab	Intravenous	BioNTech
NCT04382898	1/2	BNT112 (PAP, PSA, and three undisclosed antigens)	Prostate	With cemiplimab	Intravenous	BioNTech
NCT04534205	2	BNT113 (HPV16 E6 and E7 oncoproteins)	Head and neck squamous cell carcinoma	With pembrolizumab	Intravenous	BioNTech
NCT03418480	1/2	BNT113 (HPV16 E6 and E7 oncoproteins)	HPV16-positive solid tumours	With anti-CD40 antibodies	Intravenous	University of Southampton (Southampton, UK)
NCT05142189	1	BNT116 (non-small-cell lung cancer tumour-associated antigens)	Non-small-cell lung cancer	With cemiplimab plus docetaxel	Intravenous	BioNTech
NCT04486378	2	BNT122 (personalised cancer vaccine encoding individual tumour mutations)	Colorectal	None	Intravenous	BioNTech
NCT02316457	1	BNT-114 plus BNT-122 (personalised set of pre-manufactured non-mutated shared tumour-associated antigens plus a personalised cancer vaccine encoding individual tumour mutations)	Triple-negative breast cancer	None	Intravenous	BioNTech
NCT04163094	1	BNT115 (ovarian cancer tumour-associated antigens)	Ovarian	With carboplatin plus paclitaxel	Intravenous	University Medical Center Groningen (Groningen, Netherlands)
NCT04161755	1	BNT122 (personalised cancer vaccine encoding individual tumour mutations)	Pancreatic	With oxaliplatin, irinotecan, fluorouracil, leucovorin, and atezolizumab	Intravenous	Memorial Sloan Kettering Cancer Center (New York, NY, USA)
NCT03815058	2	BNT122 (personalised cancer vaccine encoding individual tumour mutations)	Advanced melanoma	With pembrolizumab	Intravenous	Genentech
NCT03289962	1	BNT122 (personalised cancer vaccine encoding individual tumour mutations)	Solid tumours	With atezolizumab	Intravenous	Genentech
NCT04503278	1/2	CARVac (CLDN6)	Solid tumours	With chimeric antigen receptor therapy	Intravenous	BioNTech and Gene Therapies

Trials with recruitment status "not yet recruiting," "recruiting," and "active, not recruiting" were found on ClinicalTrials.gov with the search terms "cancer" and "RNA, vaccine" on Feb 7, 2022, and through a PubMed search (see Search strategy and selection criteria panel). HPV=human papillomavirus.

Table 1: **ClinicalTrials.gov-registered mRNA-based cancer vaccine trials by type of formulation**

vaccine (CV9201) encoding five NSCLC tumour-associated antigens. Seven patients with stage IIIb NSCLC and 39 patients with stage IV NSCLC received five intradermal injections of CV9201. The vaccines were well tolerated, and T-cell responses against at least one tumour-associated antigen were detected in 19 (63%) of 30 evaluable patients, but the therapy did not improve overall survival when compared with historical controls.[13] A third phase 1b clinical trial evaluated an RNActive vaccine treatment in combination with local irradiation in patients with stage IV NSCLC. In this trial, RNActive encoding six tumour-associated antigens (CV9202; the five tumour-associated antigens used in CV9201 plus MUC-1) was administered to patients intradermally. The patients were divided into three strata according to their NSCLC pathology. Two of the three patient strata continued chemotherapy or tyrosine-kinase inhibitor treatment. The vaccine therapy was well tolerated, and CV9202 antigen-specific immunity was detected in 21 (84%) of 25 evaluable patients. One (3·8%) patient had a partial response and 12 (46·2%) of 26 evaluable patients reached stable disease across the three patient strata.[14] The CV9202 vaccine was also evaluated in a recently completed two-arm phase 1/2 study (NCT03164772), in which patients with metastatic NSCLC received CV9202 in combination with either durvalumab (a PD-L1 antibody), or durvalumab plus tremelimumab (anti-CTLA-4 antibody); results are not yet published.

	Trial phase	Target antigen	Cancer type	Combination	Vaccine route of administration	Sponsor
NCT05000801	Not described	WT1, hTERT, and survivin-loaded dendritic cells	Acute myeloid leukaemia	With follow-up care	Not described	Affiliated Hospital to Academy of Military Medical Sciences (Beijing, China)
NCT01686334	2	WT1	Acute myeloid leukaemia	With follow-up care	Intradermal	Antwerp University Hospital (Antwerp, Belgium)
NCT02649829	1/2	WT1	Pleural mesothelioma	With standard therapy	Intradermal	Antwerp University Hospital
NCT04911621	1/2	WT1	High-grade glioma and diffuse intrinsic pontine glioma	With chemoradiation (with or without standard therapy)	Intradermal	Antwerp University Hospital
NCT02649582	1/2	WT1	Glioblastoma multiforme	With temozolomide	Intradermal	Antwerp University Hospital
NCT04157127	1	Pancreatic adenocarcinoma mRNA and lysate	Pancreatic adenocarcinoma	With standard therapy	Intradermal	Baylor College of Medicine (Houston, TX, USA)
NCT00639639	1	Cytomegalovirus pp65-LAMP	Glioblastoma multiforme	With autologous lymphocyte transfer and Td	Intradermal	Duke University (Durham, NC, USA)
NCT03688178	2 (randomised)	Cytomegalovirus pp65-FLLAMP	Glioblastoma multiforme	With temozolomide, varlilumab, and Td	Intradermal	Duke University
NCT04335890	1	Autologous tumour RNA with gp100, tyrosinase, PRAME, MAGE-A3, IDO, and different driver mutations	Uveal melanoma	With standard therapy	Intravenous	Hasumi International Research Foundation
NCT02465268	2 (randomised)	HCMV pp65-shLAMP or pp65-FLLAMP	Glioblastoma multiforme	With temozolomide, GM-CSF, and Td	Not described	Immunomic Therapeutics
NCT01995708	1	CT7, MAGE-A3, and WT1 (Langerhans-type dendritic cells)	Multiple myeloma	With standard treatment	Intradermal	Memorial Sloan Kettering Cancer Center (New York, NY, USA)
NCT01456104	1	Trp2 (Langerhans-type dendritic cells)	Melanoma	None	Not described	Memorial Sloan Kettering Cancer Center
NCT01197625	1/2	hTERT, survivin, and mRNA from primary prostate cancer tissue	Prostate cancer	None	Not described	Oslo University Hospital (Oslo, Norway)
NCT03548571	2/3	hTERT, survivin, and mRNA from autologous tumour stem cells	Glioblastoma multiforme	With temozolomide	Intradermal	Oslo University Hospital
NCT01983748	3 (randomised)	Autologous tumour RNA	Uveal melanoma	None	Intravenous	University Hospital Erlangen (Erlangen, Germany)
NCT03083054	1/2	WT1	Myelodysplastic syndromes, acute myeloid leukaemia	None	Not described	University of Campinas (Campinas, Brazil)
NCT04963413	1	Cytomegalovirus pp65-FLLAMP	Glioblastoma multiforme	With temozolomide, GM-CSF, and Td	Not described	University of Florida (Gainesville, FL, USA)
NCT03396575	1	TTRNA	Brainstem gliomas	With cyclophosphamide, fludarabine, temozolomide, TTRNA-xALT, autologous haematopoietic stem cells, GM-CSF, and Td	Intradermal	University of Florida
NCT01326104	1/2	TTRNA	Medulloblastoma, neuroectodermal tumour	With TTRNA-xALT	Intradermal	University of Florida

Trials with recruitment status: "not yet recruiting," "recruiting," and "active, not recruiting" were found on ClinicalTrial.gov with the search terms: "cancer" and "RNA, vaccine" on Feb 7, 2022, and through a PubMed search (see Search strategy and selection criteria panel). Td=tetanus-diphtheria toxoid vaccine. TTRNA=tumour mRNA-pulsed autologous dendritic cells. TTRNA-xALT=tumour-specific autologous lymphocyte transfer.

Table 2: **mRNA-based dendritic cell cancer vaccines**

mRNA-based lipoplex vaccines

The mRNA lipoplex vaccine is a hybrid carrier combining a complex of mRNA with a polycationic component, within a lipid shell.[32] Positively charged cationic lipids naturally form complexes with negatively charged mRNA and facilitate antigen-presenting cell endocytosis,[33] and are therefore often used for the construction of lipoplexes.[34] Ongoing mRNA lipoplex vaccine trials are listed in table 1. Clinical trial results are listed in table 3.

A phase 1 dose-escalation trial (NCT02410733) evaluated the safety and efficacy of an mRNA lipoplex vaccine (BNT111) encoding four melanoma tumour-associated antigens in patients with advanced melanoma expressing at least one of the four antigens. BNT111 was the first in the series of fixed combinations of shared cancer antigens (FixVac) mRNA vaccines that included a fixed combination of shared tumour-associated antigens. Immune responses against one or more tumour-associated antigens were detected in over 39 (75%) of 50 patients, and BNT111 induced both $CD4^+$ and $CD8^+$ T-cell responses. 17 patients received BNT111 plus standard anti-PD-1 therapy; six (35%) of these patients had a partial response and two (12%) patients

	Trial phase	Target antigen	Cancer type	Patients, n	Combination	Immune response	Clinical response
Non-formulated (naked)							
NCT02035956	1	An individualised tumour mutation signature with ten selected neoepitopes for each patient	Melanoma (stages III and IV)	13	None	T-cell responses against numerous vaccine neoepitopes	One (8%) patient had complete response and another patient (8%) had partial response[10]
NCT03394937	1	CD40L, CD70, caTLR4; tumour-associated antigens: tyrosinase, gp100, MAGE-A3, MAGE-C2, and PRAME	Resected melanoma (stages IIc, III, and IV)	20	None	Vaccine-induced immune responses in four (40%) of ten patients (low dose) and three (33%) of nine patients (high dose)	Not reported[11]
Protamine formulation							
NCT01817738	1/2	PSA, PSMA, PSCA, STEAP1, PAP, and MUC1	Metastatic castration-resistant prostate cancer	197	None	Not reported	No significant differences in progression-free survival[12]
NCT00923312	1/2	MAGE-C1, MAGE-C2, NY-ESO-1, survivin, and 5T4	Non-small-cell lung cancer (stages IIIb and IV)	46	None	T-cell responses against at least one tumour-associated antigen in 19 (63%) patients	No objective responses; progression-free survival and overall survival not improved[13]
NCT01915524	1	MAGE-C1, MAGE-C2, NY-ESO-1, survivin, 5T4, and MUC-1	Non-small-cell lung cancer (stage IV)	26	With local irradiation (with or without pemetrexed and with or without EGFR tyrosine-kinase inhibitor)	Detectable antigen-specific immunity in 21 (84%) patients	One (4%) patient had partial response in combination with chemotherapy treatment, and 12 (46%) patients had stable disease[14]
Lipoplex formulation							
NCT02410733	1	NY-ESO-1, tyrosinase, MAGE-A3, and TPTE	Melanoma	25 (monotherapy); 17 (combination)	With or without standard PD-1 therapy	Immune responses against a minimum of one tumour-associated antigen in 39 (75%) patients	mRNA vaccine with anti-PD-1 therapy: six (35%) patients had partial response and two (12%) had stable disease; mRNA vaccine monotherapy: three (12%) patients had partial response, and seven (28%) had stable disease[15]
NCT04503278	1/2	CLDN6 (CARVac)	Solid tumours (CLDN6 CAR T cells with CARVac)	7	With CLDN6 CAR T cells	Engraftment of CAR T cells in all patients	Four (57%) patients had partial response and one (14%) patient had stable disease at the 6-week evaluation[16,17]
Lipid nanoparticle formulation							
NCT03480152	1/2	Neoantigen-specific mRNA	Gastrointestinal cancer	4	None	Mutation-specific $CD4^+$ and $CD8^+$ T-cell responses against predicted neoepitopes in three (75%) of four patients	No objective clinical responses[18]
NCT03313778	1	Personalised cancer vaccine encoding several neoantigens	Solid tumours (resected)	13 (monotherapy); 19 (combination)	With pembrolizumab	Detectable neoantigen T-cell responses	Vaccine monotherapy: 12 patients were cancer-free on study treatment with a median follow-up of 8 months; combination treatment: one patient had complete response before vaccination, two patients had partial response, five patients had stable disease, five had disease progression, and two had unconfirmed disease progression[19]

CAR=chimeric antigen receptor.

Table 3: **A summary of the published results (2017–22) from mRNA cancer vaccine trials by type of formulation**

reached stable disease. 25 patients were given single-agent BNT111, with three (12%) patients reaching partial response and seven (28%) patients reaching stable disease.[15] FixVac BNT111 is being evaluated in a randomised phase 2 trial (NCT04526899), alone or in combination with the anti-PD-1 antibody cemiplimab, in patients with anti-PD-1-refractory or relapsed unresectable stage III and IV melanoma.

Multiple active clinical trials are assessing FixVac mRNA lipoplex vaccines. A phase 1/2, four-arm expansion trial (NCT04382898) is evaluating the cancer vaccine BNT112, encoding five tumour-associated antigens, alone or in combination with cemiplimab in patients with metastatic castration-resistant prostate cancer. The FixVac BNT115 encodes three ovarian-specific tumour-associated antigens and is being evaluated in a phase 1 study (NCT04163094), administered both before and in combination with adjuvant and neoadjuvant chemotherapies in patients with ovarian cancer. A randomised phase 2 clinical trial (NCT04534205) is evaluating the anti-human papillomavirus (HPV) -16-derived oncoprotein-encoding mRNA BNT113 in

combination with the PD-1 inhibitor pembrolizumab in patients with HPV16-positive and PD-L1-positive head and neck squamous cell carcinoma. BNT113 is also being evaluated in a two-arm, phase 1/2 vaccine dose-escalation study (NCT03418480) in patients with previously treated HPV16-positive head and neck squamous cell carcinoma or advanced HPV16-positive head and neck squamous cell carcinoma. A fifth clinical trial (NCT05142189) is evaluating the FixVac vaccine BNT116 in combination with cemiplimab or docetaxel in a phase 1 study in patients with advanced or metastatic NSCLC.

In addition to FixVac vaccines, several studies are exploring the mRNA lipoplex vaccine platform called individualised neoantigen-specific immunotherapy (iNeST) or BNT122. iNeST includes mRNA lipoplex vaccines that encode individual tumour mutations, and the treatment is being evaluated in clinical trials across multiple solid tumour diagnoses (NCT03289962, NCT03815058, NCT04486378, and NCT04161755). iNeST is also being assessed in combination with another lipoplex-formulated mRNA encoding tumour-associated antigens (BNT114) and RNA encoding p53 in patients with triple-negative breast cancer (NCT02316457). Finally, an ongoing phase 1/2 clinical study (NCT04503278) is investigating a CLDN6-encoding mRNA lipoplex vaccine, CARvac, in patients with relapsed or refractory CLDN6-positive advanced solid tumours. CARVac is administered intravenously in combination with an autologous CLDN6 targeting CAR T-cell therapy, BNT211, and aims to improve CAR T-cell therapy. Early data showed that four (57%) of seven evaluable patients treated with CLDN6 CAR T-cell therapy and CARVac together had partial response and one (14%) patient had stable disease at the 6-week evaluation; ongoing responses were reported at the 12-week evaluation. Efficacy data showed no dose-limiting, drug-related serious adverse events in the evaluated patients. Manageable, low-grade cytokine release syndrome was observed in eight patients in total.[16,17]

mRNA-based lipid nanoparticle vaccines

Lipid nanoparticle vaccines consist of ionisable lipids, cholesterol, phospholipids, and lipid-linked polyethylene glycol derivates.[3] Cholesterol and phospholipids increase stability and support the bilayer structure of the lipid nanoparticle vaccines.[35] Polyethylene glycol prevents mRNA-plasma protein binding, thereby increasing the nanoparticle's circulation period. Lipid nanoparticle vaccine properties are affected by changes in pH levels, which facilitate mRNA encapsulation and host-cell endocytosis.[34] The mRNA nanoparticle vaccine carrier system recently gained attention following the approval of the first two lipid nanoparticle SARS-CoV-2 vaccines.[36,37] Ongoing mRNA nanoparticle vaccine trials are listed in table 1 and clinical trial results are listed in table 3.

Two lipid nanoparticle mRNA cancer vaccines encoding several neoantigens (mRNA-4157) are being assessed in combination with pembrolizumab as adjuvant therapy in patients with high-risk cutaneous melanoma following complete resection (NCT03313778 and NCT03897881). The same vaccine template (mRNA-4157) was examined as a monotherapy in patients with completely resected solid tumours (NCT03313778), and in combination with pembrolizumab in patients with unresectable solid tumours. The treatment induced neoantigen-specific T cells and did not lead to serious adverse events (grade 3 or worse). 13 patients received mRNA-4157 monotherapy, and all patients except one remained free of cancer on study treatment, with a median follow-up of 8 months. Of the 19 evaluable patients receiving combination treatment, one (5%) patient had a complete response before vaccination, two (11%) patients had a partial response, five (36%) patients had stable disease, five (36%) had confirmed disease progression, and two (11%) had unconfirmed disease progression.[19] A phase 1/2 trial evaluated a neoantigen-specific mRNA nanoparticle vaccine in four patients with gastrointestinal cancer (table 3).[18] A phase 1 clinical trial (NCT03948763) is now evaluating the lipid nanoparticle-based mRNA cancer vaccine mRNA-5671, which targets four *KRAS* mutations. The mRNA vaccine is either administered as monotherapy or in combination with pembrolizumab in patients with *KRAS*-mutated NSCLC, colorectal cancer, or pancreatic cancer (table 1).

mRNA-based dendritic cell cancer vaccines

Dendritic cells have been of particular interest in immune therapy approaches because of their unique ability not only to initiate immunity, but also to control and regulate the type of immune response, making them attractive candidates as vehicles for mRNA delivery.[7,38] Over the past 30 years, research has focused on generating an ex-vivo population of antigen-loaded dendritic cells that are able to stimulate robust and long-lasting $CD8^+$ and $CD4^+$ T-cell responses in patients with cancer.[39] Of note, though, is the current inability to fully recapitulate the development of immunopotent dendritic cells ex vivo for effective anti-tumour immune responses.[40] Obtaining the source of dendritic cells and the ex-vivo manipulation of them in addition to antigen preparation and loading are laborious and time-consuming compared with the manufacture of formulated and non-formulated mRNA vaccines.[41] Ongoing mRNA dendritic cell vaccine clinical trials are listed in table 2.

In general, mRNA-loaded dendritic cell vaccines induce modest T-cell responses and have low clinical efficacy.[42] However, some studies suggest that the mRNA-based dendritic vaccines can prevent or delay disease relapse and potentially prolong overall survival.[20,43] In the past 5 years of published trials, dendritic cell vaccines have been investigated in patients with various cancer diagnoses either as monotherapy or in combination with chemotherapy or immunotherapy. Patients with metastatic renal cell carcinoma were given dendritic cells loaded with amplified tumour RNA and mRNA encoding

CD40L in combination with the tyrosine-kinase inhibitor sunitinib in a phase 3 trial;[44] however, the vaccine did not significantly improve patient survival. In a phase 2 trial,[45] patients with metastatic castration-resistant prostate cancer were given dendritic cells loaded with mRNA encoding tumour-associated antigens, but the vaccine did not significantly improve patient survival either. In a phase 2 trial, patients with advanced melanoma were given TriMix dendritic cells with tumour-associated antigen-encoding mRNA in combination with the anti-CTLA-4 antibody ipilimumab. Of the 39 treated patients, 15 (38%) reached either a partial response or a complete response with the combination therapy, but no direct comparison was made between responses to the two treatments.[20] Patients with acute myeloid leukaemia in remission were vaccinated with dendritic cells loaded with a tumour-associated antigen-encoding mRNA. 5-year overall survival of the vaccinated patients compared favourably with historical controls, and prevention or delay of relapse was observed in 43% of patients.[43] Finally, patients with glioblastoma multiforme were given dendritic cells loaded with mRNA encoding a cytomegalovirus antigen in different phase 1 clinical studies (eg, NCT00639639, NCT00626483, and NCT02529072). The choice of antigen was based on the high expression of cytomegalovirus proteins in glioblastomas. Trial results indicate long-lasting overall survival compared with non-transfected dendritic cell vaccines and historical controls.[46,47] Six active clinical trials are evaluating mRNA-based dendritic cell vaccines in different treatment combinations in patients with glioblastoma multiforme (NCT03688178, NCT02465268, NCT00639639, NCT04963413, NCT02649582, and NCT03548571; table 2).

Challenges and future perspectives for mRNA-based cancer vaccines

The number of clinical trials with therapeutic mRNA cancer vaccines is rapidly expanding, taking advantage of recent research advances that have optimised mRNA delivery, simplified administration methods, and improved translational efficiency.[2,3] Despite substantial progress, several challenges to mRNA vaccine immunogenicity and efficacy remain. Thus, one of the most important advances in therapeutic clinical cancer vaccines is the ability to identify individual cancer neoantigens. However, identifying tumour-specific mutations or non-conforming sequences and predicting corresponding neoepitopes for individual HLA alleles remains difficulut.[48,49] Furthermore, the technological and regulatory hurdles that will arise from the need for rapid and large-scale good manufacturing practice production of individualised mRNA vaccines are future obstacles that will need to be addressed.

Another challenge is to validate the most feasible vaccine administration methods. The administration route determines mRNA distribution and influences vaccine efficacy. mRNA that is injected intradermally and subcutaneously is easily processed by regional antigen-presenting cells, but the administrations often induce considerable local injection-site reactions.[50] Intranasal administered mRNA reaches antigen-presenting cells in the peripheral lymph nodes, and intranodal injections reach lymphatic antigen-presenting cells directly, but the delivery methods are cumbersome and only allow for small injection volumes.[7,9] The same limitations apply to intratumoural injections, and this administration route primarily aims to induce local inflammation with mRNA encoding co-activating molecules.[51] Muscle tissue is highly vascularised, contains diverse immune cells for mRNA processing, and intramuscular injection induces fewer injection-site reactions in general. Intramuscular administration is, therefore, a common and feasible vaccination route, and the current approved mRNA SARS-CoV-2 vaccines are administered intramuscularly.[52,53] Intravenous injections allow mRNA to reach numerous lymphoid organs, and this administration method has been shown to induce a robust $CD8^+$ T-cell response compared with local injections.[40,54,55] $CD8^+$ T cells have a central role in anti-tumour responses, and intravenous injection is the most common direct administration route in active therapeutic mRNA cancer vaccine trials (table 1).

Most mRNA-based cancer vaccines are therapeutic rather than prophylactic, and require multiple administrations and substantial vaccine potency to induce a tumour response when given as monotherapy. Monotherapy mRNA-based vaccines could be an effective treatment for patients diagnosed with early-stage cancer or in an adjuvant setting, but it appears unlikely that the vaccines will succeed as a monotherapy treatment for advanced cancers because of challenges regarding the highly immunosuppressive tumour microenvironment of this setting.

Therapeutic mRNA cancer vaccines are more likely to succeed in combination with other immunotherapeutic treatment methods such as immune checkpoint inhibitors, oncolytic viruses, and adoptive cell therapy. Indeed, patients receiving these combinations show encouraging clinical treatment responses across cancer diagnoses.[14,17,19,20] There is a need for new treatment combinations that increase response rates and progression-free survival without inducing severe side-effects, and an mRNA cancer vaccine with low toxicity is an obvious combination partner. Several trials are already combining mRNA vaccines with checkpoint inhibitors (tables 1–3). Moderna (MA, USA) has recently expanded its vaccine development programme with a new checkpoint-targeting cancer vaccine, mRNA-4359. The mRNA vaccine encodes indoleamine 2,3-dioxygenase and PD-L1 antigens, and will be administered to patients with NSCLC and advanced or metastatic cutaneous melanoma.[56] In addition, BioNTech (Mainz, Germany) combines the mRNA-based FixVac platform with cemiplimab for patients with various cancer diagnoses

Search strategy and selection criteria

References were found through searches on PubMed with the Medical Subject Headings terms "RNA" or "RNA, Messenger" and "cancer vaccines" for articles published between Jan 1, 2017, and Jan 1, 2022. For tables 1 and 2, trials with recruitment status "not yet recruiting," "recruiting," and "active, not recruiting" were found on ClinicalTrials.gov. with the search terms "cancer" and "RNA, vaccine" on Feb 7, 2022, and through a PubMed search. A 5-year period was chosen to focus solely on the most recent clinical studies and patient data. All human clinical trials published in English with a full journal text available were reviewed. The additional references were relevant references from the selected search results and applicable abstracts based on clinical mRNA cancer vaccine trials.

(ie, NCT04526899, NCT04382898, and NCT05142189). Together with Regeneron (NY, USA), BioNTech is now planning a phase 1/2 trial for a first-line treatment for late-stage NSCLC.[57]

The future for therapeutic mRNA-based cancer vaccines is promising. Many clinical trials of mRNA vaccines are still early phase studies, but the field is moving fast. For example, in November, 2021, BioNTech received an FDA Fast Track Designation for BNT111 in patients with stage III or IV melanoma on the basis of the phase 1 trial results listed in table 3 (NCT02410733).[15,58]

Conclusion

The rapid development and worldwide approval of mRNA vaccines against SARS-CoV-2 have showcased the vast potential of mRNA technology.[36,37] The response to the COVID-19 pandemic has leveraged data from years of research to improve the design of therapeutic mRNA cancer vaccines.[1] Results from early clinical trials have shown only modest indications of clinical efficacy. However, with the optimisation of mRNA vaccine structure, stability, and delivery methods, and with the associated advantages of personalised preparations, low manufacturing costs, and the fast and scalable production required for a patient group that often experiences rapid disease progression (panel), mRNA vaccines are reaching their potential as a future crucial strategy for cancer treatment.

Contributors

CLL did the literature and clinical trial searches, created the tables and figure, and wrote the original draft. JBH, ÖM, and IMS contributed to the writing of the original draft and revisions.

Declaration of interests

IMS reports having lectured for or having had advisory board relationships with Bristol Myers Squibb, MSD, Sanofi Aventis, Pierre Fabre, IO Biotech, Novartis, TILT Biotherapeutics, and Novo Nordisk; research grants from Bristol Myers Squibb, Adaptimmune, Lytix Biopharma, IO Biotech, and TILT Biotherapeutics; and is a co-founder and shareholder for IO Biotech, a company that is developing peptide vaccines targeting immune regulation. IO Biotech is a spin-out of Copenhagen University Hospital and has no approved products at the time of writing; an IDO and PD-L1 targeting peptide vaccine for melanoma has been granted Breakthrough Therapy designation by the FDA and is being tested in a phase 3 trial (NCT05155254). The same vaccine is also in phase 2 trials (NCT05077709 and NCT05280314) in other cancer types (including bladder cancer and head and neck cancer). An additional peptide vaccine targeting arginase is being tested in solid cancers in a phase 1 trial. IO Biotech has no interests in RNA vaccines. JBH reports research grants from Amgen, Asher Bio, BioNTech, Bristol Myers Squibb, MSD, and Novartis; had advisory board relationships with Achilles Therapeutics, BioNTech, Bristol Myers Squibb, Ipsen, Iovance Bio, Instil Bio, MSD, Merck Serono, Neogene Therapeutics, Novartis, Pfizer, PokeAcel, Roche, Sanofi, and T-Knife; and holds stock options in Neogene Therapeutics, a company that is developing T-cell receptor gene modified T cells targeting neoantigens. The first neoantigen-specific T-cell receptor gene therapy for the treatment of solid cancers is planned for testing in a phase 1 clinical trial. Neogene Therapeutics has no interests in RNA vaccines. CLL and ÖM declare no competing interests.

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