THERAPEUTIC RNA FOR LUNG CANCER

This disclosure relates to the field of RNA to treat lung cancer, in particular non-small-cell lung carcinoma (NSCLC). Lung cancer is the third most frequent malignancy in women and the second most frequent malignancy in men. NSCLC accounts for about 85% of all lung cancers.

Disclosed herein are compositions, uses, and methods for treatment of lung cancers. Administration of therapeutic RNAs to a patient having lung cancer disclosed herein can reduce tumor size, prolong time to progressive disease, and/or protect against metastasis and/or recurrence of the tumor and ultimately extend survival time.

Summary

The present disclosure generally embraces the immunotherapeutic treatment of a subject comprising the administration of RNA, i.e., vaccine RNA, encoding a set of amino acid sequences, i.e., vaccine antigens, each of said amino acid sequences comprising a tumor antigen, an immunogenic variant thereof, or an immunogenic fragment of the tumor antigen or the immunogenic variant thereof, i.e., an antigenic peptide or protein. Thus, the vaccine antigen comprises an epitope of a tumor antigen for inducing an immune response against the tumor antigen in the subject. RNA encoding vaccine antigen is administered to provide (following expression of the polynucleotide by appropriate target cells) antigen for induction, i.e., stimulation, priming and/or expansion, of an immune response which is targeted to target antigen (tumor antigen) or a procession product thereof. In one example, the immune response which is to be induced according to the present disclosure is a T cell-mediated immune response. In one example, the immune response is an anti-cancer, in particular anti-lung cancer immune response such as an anti-non-small-cell lung carcinoma (NSCLC) immune response. The vaccine RNA treatment described herein is combined with additional treatments comprising administration of a further therapeutic agent other than the vaccine RNA described herein. In certain examples, such further therapeutic agent comprises one

or more immune checkpoint inhibitors, one or more chemotherapeutic agents, or a combination thereof.

The vaccine described herein comprises as the active principle single-stranded RNA that may be translated into the respective protein upon entering cells of a recipient. In addition to wildtype or codon-optimized sequences encoding the antigen sequence, the RNA may contain one or more structural elements optimized for maximal efficacy of the RNA with respect to stability and translational efficiency (5' cap, 5' UTR, 3' UTR, poly(A)-tail). In one example, the RNA contains all of these elements. In one example, beta-S-ARCA(D1) ($m_2^{7,2'\text{-}O}$GppSpG) may be utilized as specific capping structure at the 5'-end of the RNA drug substances. As 5'-UTR sequence, the 5'-UTR sequence of the human alpha-globin mRNA, optionally with an optimized 'Kozak sequence' to increase translational efficiency may be used. As 3'-UTR sequence, a combination of two sequence elements (FI element) derived from the "amino terminal enhancer of split" (AES) mRNA (called F) and the mitochondrial encoded 12S ribosomal RNA (called I) placed between the coding sequence and the poly(A)-tail to assure higher maximum protein levels and prolonged persistence of the mRNA may be used. These were identified by an *ex vivo* selection process for sequences that confer RNA stability and augment total protein expression (see WO 2017/060314, herein incorporated by reference). Furthermore, a poly(A)-tail measuring 110 nucleotides in length, consisting of a stretch of 30 adenosine residues, followed by a 10 nucleotide linker sequence (of random nucleotides) and another 70 adenosine residues may be used. This poly(A)-tail sequence was designed to enhance RNA stability and translational efficiency.

In one example, a vaccine antigen described herein comprises an amino acid sequence which breaks immunological tolerance. The amino acid sequence which breaks immunological tolerance may be fused to the C-terminus of the vaccine sequence, i.e., antigenic peptide or protein, either directly or separated by a linker. Optionally, the amino acid sequence which breaks immunological tolerance may link the antigenic peptide or protein and a MITD as further described below. The amino acid sequence which breaks immunological tolerance may be RNA encoded. In one example, the antigen-targeting RNAs are applied together with RNA coding for an amino acid sequence which breaks immunological tolerance. This RNA coding for an amino acid sequence which breaks immunological tolerance may contain

structural elements optimized for maximal efficacy of the RNA with respect to stability and translational efficiency (5' cap, 5' UTR, 3' UTR, poly(A)-tail) described above for the antigen-encoding RNA.

In one example, the amino acid sequence which breaks immunological tolerance comprises helper epitopes. In one example, the helper epitopes may be tetanus toxoid-derived, e.g., P2P16 amino acid sequences derived from the tetanus toxoid (TT) of Clostridium tetani. These sequences may support to overcome self-tolerance mechanisms for efficient induction of immune responses to self-antigens by providing tumor-unspecific T-cell help during priming. The tetanus toxoid heavy chain includes epitopes that can bind promiscuously to MHC class II alleles and induce CD4+ memory T cells in almost all tetanus vaccinated individuals. In addition, the combination of TT helper epitopes with tumor-associated antigens is known to improve the immune stimulation compared to the application of tumor-associated antigen alone by providing CD4+ mediated T-cell help during priming. To reduce the risk of stimulating CD8+ T cells, two peptide sequences known to contain promiscuously binding helper epitopes may be used to ensure binding to as many MHC class II alleles as possible, e.g., P2 and P16.

Furthermore, sec (secretory signal peptide) and/or MITD (MHC class I trafficking domain) may be fused to the antigen-encoding regions and/or helper epitope-encoding regions in a way that the respective elements are translated as N- or C-terminal tag, respectively. Fusion-protein tags derived from the sequence encoding the human MHC class I complex (HLA-B51, haplotype A2, B27/B51, Cw2/Cw3), have been shown to improve antigen processing and presentation. Sec may correspond to the 78 bp fragment coding for the secretory signal peptide, which guides translocation of the nascent polypeptide chain into the endoplasmatic reticulum. MITD may correspond to the transmembrane and cytoplasmic domain of the MHC class I molecule, also called MHC class I trafficking domain. Antigens such as CLDN6 having their own secretory signal peptide and transmembrane domain may not require addition of fusion tags. Sequences coding for short linker peptides predominantly consisting of the amino acids glycine (G) and serine (S), as commonly used for fusion proteins may be used as GS/Linkers.

The vaccine RNA may be complexed with liposomes to generate serum-stable RNA-lipoplexes (RNA(LIP)) for intravenous (i.v.) administration. If a combination of different RNAs is used, the RNAs may be separately complexed with liposomes to generate serum-stable RNA-lipoplexes (RNA(LIP)) for intravenous (i.v.) administration. RNA(LIP) targets antigen-presenting cells (APCs) in lymphoid organs which results in an efficient stimulation of the immune system.

The RNA lipoplex particles may be prepared using liposomes that may be obtained by injecting a solution of lipids in ethanol into water or a suitable aqueous phase. In one example, the aqueous phase has an acidic pH. In one example, the aqueous phase comprises acetic acid, e.g., in an amount of about 5 mM. Liposomes may be used for preparing RNA lipoplex particles by mixing the liposomes with RNA. In one example, the liposomes and RNA lipoplex particles comprise at least one cationic lipid and at least one additional lipid. In one example, the at least one cationic lipid comprises 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA). In one example, the at least one additional lipid comprises 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine (DOPE). In one example, the at least one cationic lipid comprises 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) and the at least one additional lipid comprises 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine (DOPE). In one example, the liposomes and RNA lipoplex particles comprise 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) and 1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine (DOPE). In one example, the molar ratio of the at least one cationic lipid to the at least one additional lipid is about 2:1. In one example, at physiological pH, the charge ratio of positive charges to negative charges in the RNA lipoplex particles is from about 1.6:2 to about 1:2, or about 1.6:2 to about 1.1:2. In specific examples, the charge ratio of positive charges to negative charges in the RNA lipoplex particles at physiological pH is about 1.6:2.0, about 1.5:2.0, about 1.4:2.0, about 1.3:2.0, about 1.2:2.0, about 1.1:2.0, or about 1:2.0.

In one example, vaccine RNA is co-formulated as lipoplex particles with an RNA encoding an amino acid sequence which breaks immunological tolerance.

In one aspect, the disclosure provides for a composition or medical preparation comprising: (a) at least one RNA, wherein the at least one RNA encodes the following amino acid sequences: (i) an amino acid sequence comprising claudin 6 (CLDN6), an immunogenic variant thereof, or an immunogenic fragment of the CLDN6 or the immunogenic variant thereof; (ii) an amino acid sequence comprising Kita-kyushu lung cancer antigen 1 (KK-LC-1), an immunogenic variant thereof, or an immunogenic fragment of the KK-LC-1 or the immunogenic variant thereof; (iii) an amino acid sequence comprising Melanoma antigen A3 (MAGE-A3), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A3 or the immunogenic variant thereof; (iv) an amino acid sequence comprising Melanoma antigen 4 (MAGE-A4), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A4 or the immunogenic variant thereof; (v) an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), an immunogenic variant thereof, or an immunogenic fragment of the PRAME or the immunogenic variant thereof; and (vi) an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof; and (b) a further therapeutic agent selected from an immune checkpoint inhibitor, a chemotherapeutic agent, or a combination thereof, optionally wherein the composition or medical preparation comprises: (i) RNA encoding an amino acid sequence comprising claudin 6 (CLDN6), an immunogenic variant thereof, or an immunogenic fragment of the CLDN6 or the immunogenic variant thereof; (ii) RNA encoding an amino acid sequence comprising Kita-kyushu lung cancer antigen 1 (KK-LC-1), an immunogenic variant thereof, or an immunogenic fragment of the KK-LC-1 or the immunogenic variant thereof; (iii) RNA encoding an amino acid sequence comprising Melanoma antigen A3 (MAGE-A3), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A3 or the immunogenic variant thereof; (iv) RNA encoding an amino acid sequence comprising Melanoma antigen 4 (MAGE-A4), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A4 or the immunogenic variant thereof; (v) RNA encoding an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), an immunogenic variant thereof, or an immunogenic fragment of the PRAME or the immunogenic variant thereof; and (vi) RNA encoding an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof. In one example, the disclosure relates to a composition or medical preparation comprising:

(a) at least one RNA, wherein the at least one RNA encodes the following amino acid sequences:

(i) an amino acid sequence comprising claudin 6 (CLDN6), an immunogenic variant thereof, or an immunogenic fragment of the CLDN6 or the immunogenic variant thereof;

(ii) an amino acid sequence comprising Kita-kyushu lung cancer antigen 1 (KK-LC-1), an immunogenic variant thereof, or an immunogenic fragment of the KK-LC-1 or the immunogenic variant thereof;

(iii) an amino acid sequence comprising Melanoma antigen A3 (MAGE-A3), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A3 or the immunogenic variant thereof;

(iv) an amino acid sequence comprising Melanoma antigen 4 (MAGE-A4), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A4 or the immunogenic variant thereof; and

(v) an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), an immunogenic variant thereof, or an immunogenic fragment of the PRAME or the immunogenic variant thereof; and

(b) a further therapeutic agent selected from an immune checkpoint inhibitor, a chemotherapeutic agent, or a combination thereof.

In one example, the at least one RNA further encodes one or both of the following amino acid sequences:

(vi) an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof; and

(vii) an amino acid sequence comprising New York esophageal squamous cell carcinoma-1 (NY-ESO-1), an immunogenic variant thereof, or an immunogenic fragment of the NY-ESO-1 or the immunogenic variant thereof.

In one example, the at least one RNA further encodes:

(vi) an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof.

In one example, the at least one RNA encodes:
(i) an amino acid sequence comprising claudin 6 (CLDN6), an immunogenic variant thereof, or an immunogenic fragment of the CLDN6 or the immunogenic variant thereof;
(ii) an amino acid sequence comprising Kita-kyushu lung cancer antigen 1 (KK-LC-1), an immunogenic variant thereof, or an immunogenic fragment of the KK-LC-1 or the immunogenic variant thereof;
(iii) an amino acid sequence comprising Melanoma antigen A3 (MAGE-A3), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A3 or the immunogenic variant thereof;
(iv) an amino acid sequence comprising Melanoma antigen 4 (MAGE-A4), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A4 or the immunogenic variant thereof;
(v) an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), an immunogenic variant thereof, or an immunogenic fragment of the PRAME or the immunogenic variant thereof; and
(vi) an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof.

In one example, each of the amino acid sequences under (i), (ii), (iii), (iv), (v), (vi), or (vii) is encoded by a separate RNA.

In one example,
(i) the RNA encoding the amino acid sequence under (i) comprises the nucleotide sequence of SEQ ID NO: 3 or 4, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 3 or 4; and/or

(ii) the amino acid sequence under (i) comprises the amino acid sequence of SEQ ID NO: 1 or 2, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 1 or 2.

In one example,

(i) the RNA encoding the amino acid sequence under (ii) comprises the nucleotide sequence of SEQ ID NO: 7 or 8, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 7 or 8; and/or

(ii) the amino acid sequence under (ii) comprises the amino acid sequence of SEQ ID NO: 5 or 6, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 5 or 6.

In one example,

(i) the RNA encoding the amino acid sequence under (iii) comprises the nucleotide sequence of SEQ ID NO: 11 or 12, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 11 or 12; and/or

(ii) the amino acid sequence under (iii) comprises the amino acid sequence of SEQ ID NO: 9 or 10, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 9 or 10.

In one example,

(i) the RNA encoding the amino acid sequence under (iv) comprises the nucleotide sequence of SEQ ID NO: 15 or 16, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 15 or 16; and/or

(ii) the amino acid sequence under (iv) comprises the amino acid sequence of SEQ ID NO: 13 or 14, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 13 or 14.

In one example,

(i) the RNA encoding the amino acid sequence under (v) comprises the nucleotide sequence of SEQ ID NO: 19 or 20, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 19 or 20; and/or

(ii) the amino acid sequence under (v) comprises the amino acid sequence of SEQ ID NO: 17 or 18, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 17 or 18.

In one example,

(i) the RNA encoding the amino acid sequence under (vi) comprises the nucleotide sequence of SEQ ID NO: 23 or 24, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 23 or 24; and/or

(ii) the amino acid sequence under (vi) comprises the amino acid sequence of SEQ ID NO: 21 or 22, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 21 or 22.

In one example,

(i) the RNA encoding the amino acid sequence under (vii) comprises the nucleotide sequence of SEQ ID NO: 27 or 28, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 27 or 28; and/or

(ii) the amino acid sequence under (vii) comprises the amino acid sequence of SEQ ID NO: 25 or 26, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 25 or 26.

In one example, at least one amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), or (vii) comprises an amino acid sequence which breaks immunological tolerance and/or at least one RNA is co-administered with RNA encoding an amino acid sequence which breaks

immunological tolerance. In one example, each amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), or (vii) comprises an amino acid sequence which breaks immunological tolerance and/or each RNA is co-administered with RNA encoding an amino acid sequence which breaks immunological tolerance. In one example, the amino acid sequence which breaks immunological tolerance comprises helper epitopes, preferably tetanus toxoid-derived helper epitopes. In one example,

(i) the RNA encoding the amino acid sequence which breaks immunological tolerance comprises the nucleotide sequence of SEQ ID NO: 34, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 34; and/or

(ii) the amino acid sequence which breaks immunological tolerance comprises the amino acid sequence of SEQ ID NO: 33, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 33.

In one example, at least one of the amino acid sequences under (i), (ii), (iii), (iv), (v), (vi), or (vii) is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence. In one example, each of the amino acid sequences under (i), (ii), (iii), (iv), (v), (vi), or (vii) is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence.

In one example, at least one RNA is a modified RNA, in particular a stabilized mRNA. In one example, at least one RNA comprises a modified nucleoside in place of at least one uridine. In one example, at least one RNA comprises a modified nucleoside in place of each uridine. In one example, each RNA comprises a modified nucleoside in place of at least one uridine. In one example, each RNA comprises a modified nucleoside in place of

each uridine. In one example, the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).

In one example, at least one RNA comprises the 5' cap $m_2^{7,2'\text{-}O}Gpp_sp(5')G$. In one example, each RNA comprises the 5' cap $m_2^{7,2'\text{-}O}Gpp_sp(5')G$.

In one example, at least one RNA comprises a 5' UTR comprising the nucleotide sequence of SEQ ID NO: 35, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 35. In one example, each RNA comprises a 5' UTR comprising the nucleotide sequence of SEQ ID NO: 35, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 35.

In one example, at least one amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), or (vii) comprises an amino acid sequence enhancing antigen processing and/or presentation. In one example, each amino acid sequence under (iii), (iv), (v), (vi), or (vii) comprises an amino acid sequence enhancing antigen processing and/or presentation. In one example, each amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), or (vii) comprises an amino acid sequence enhancing antigen processing and/or presentation. In one example, the amino acid sequence enhancing antigen processing and/or presentation comprises an amino acid sequence corresponding to the transmembrane and cytoplasmic domain of a MHC molecule, preferably a MHC class I molecule. In one example,

(i) the RNA encoding the amino acid sequence enhancing antigen processing and/or presentation comprises the nucleotide sequence of SEQ ID NO: 32, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 32; and/or

(ii) the amino acid sequence enhancing antigen processing and/or presentation comprises the amino acid sequence of SEQ ID NO: 31, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 31.

In one example, the amino acid sequence enhancing antigen processing and/or presentation further comprises an amino acid sequence coding for a secretory signal peptide. In one example,

(i) the RNA encoding the secretory signal peptide comprises the nucleotide sequence of SEQ ID NO: 30, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 30; and/or

(ii) the secretory signal peptide comprises the amino acid sequence of SEQ ID NO: 29, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 29.

In one example, at least one RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 36, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 36. In one example, each RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 36, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 36.

In one example, at least one RNA comprises a poly-A sequence. In one example, each RNA comprises a poly-A sequence. In one example, the poly-A sequence comprises at least 100 nucleotides. In one example, the poly-A sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 37.

In one example, the RNA is formulated as a liquid, formulated as a solid, or a combination thereof. In one example, the RNA is formulated for injection. In one example, the RNA is formulated for intravenous administration.

In one example, the RNA is formulated or is to be formulated as lipoplex particles. In one example, the RNA lipoplex particles are obtainable by mixing the RNA with liposomes. In one example, at least one RNA encoding an amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), and/or (vii) is co-formulated or is to be co-formulated as lipoplex particles with RNA

encoding an amino acid sequence which breaks immunological tolerance. In one example, each RNA encoding an amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), and/or (vii) is co-formulated or is to be co-formulated as lipoplex particles with RNA encoding an amino acid sequence which breaks immunological tolerance. In one example, the RNA encoding an amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), and/or (vii) is co-formulated or is to be co-formulated as lipoplex particles with the RNA encoding an amino acid sequence which breaks immunological tolerance at a ratio of about 4:1 to about 16:1, about 6:1 to about 14:1, about 8:1 to about 12:1, or about 10:1.

In one example, the composition or medical preparation comprises:
(i) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 2;
(ii) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 6;
(iii) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 10;
(iv) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 14;
(v) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 18; and
(vi) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 22.

In one example, the composition or medical preparation comprises:
(i) RNA comprising the nucleotide sequence of SEQ ID NO: 4;
(ii) RNA comprising the nucleotide sequence of SEQ ID NO: 8;
(iii) RNA comprising the nucleotide sequence of SEQ ID NO: 12;
(iv) RNA comprising the nucleotide sequence of SEQ ID NO: 16;
(v) RNA comprising the nucleotide sequence of SEQ ID NO: 20; and
(vi) RNA comprising the nucleotide sequence of SEQ ID NO: 24.

In certain examples, the composition or medical preparation comprises one or more chemotherapeutic agents. In certain examples, the composition or medical preparation comprises a taxane such as docetaxel and/or paclitaxel, a folate antimetabolite such as pemetrexed, a platinum compound such as cisplatin and/or carboplatin, or a combination thereof. In certain examples, the composition or medical preparation comprises docetaxel. In certain examples, the composition or medical preparation comprises docetaxel and ramucirumab. In certain examples, the composition or medical preparation comprises docetaxel and nintedanib. In certain examples, the composition or medical preparation comprises paclitaxel. In certain exmamples, the composition or medical preparation comprises paclitaxel and a platinum compound such as cisplatin and/or carboplatin. In certain examples, the composition or medical preparation comprises pemetrexed. In certain examples, the composition or medical preparation comprises pemetrexed and a platinum compound such as cisplatin and/or carboplatin. In certain examples, the composition or medical preparation comprises comprises cisplatin. In certain examples, the composition or medical preparation comprises carboplatin.

In certain examples, the composition or medical preparation comprises one or more immune checkpoint inhibitors. In certain examples, the composition or medical preparation comprises an antibody selected from an anti-PD-1 antibody, an anti-PD-L1 antibody and a combination thereof. In certain examples, the composition or medical preparation comprises an anti-PD-1 antibody. In certain examples, the composition or medical preparation comprises cemiplimab (LIBTAYO, REGN2810), nivolumab (OPDIVO; BMS-936558), pembrolizumab (KEYTRUDA; MK-3475), pidilizumab (CT-011), spartalizumab (PDR001), MEDI0680 (AMP-514), dostarlimab (TSR-042), cetrelimab (JNJ 63723283), toripalimab (JS001), AMP-224 (GSK-2661380), PF-06801591, tislelizumab (BGB-A317), ABBV-181, BI 754091, or SHR-1210. In certain examples, the composition or medical preparation comprises cemiplimab. In certain examples, the composition or medical preparation comprises an anti-PD-L1 antibody. In certain examples, the composition or medical preparation comprises atezolizumab (TECENTRIQ; RG7446; MPDL3280A; R05541267),

durvalumab (MEDI4736), BMS-936559, avelumab (bavencio), lodapolimab (LY3300054), CX-072 (Proclaim-CX-072), FAZ053, KN035, or MDX-1105.

In certain examples, the composition or medical preparation comprises one or more chemotherapeutic agents and one or more immune checkpoint inhibitors. In certain examples, the composition or medical preparation comprises cisplatin and an immune checkpoint inhibitor. In certain examples, the composition or medical preparation comprises carboplatin and an immune checkpoint inhibitor. In certain examples, the composition or medical preparation comprises a combination of paclitaxel and cisplatin and/or carboplatin (e.g., a combination of paclitaxel and cisplatin, a combination of paclitaxel and carboplatin, or a combination of paclitaxel, cisplatin and carboplatin) and an immune checkpoint inhibitor. In certain examples, the composition or medical preparation comprises a combination of pemetrexed and cisplatin and/or carboplatin (e.g., a combination of pemetrexed and cisplatin, a combination of pemetrexed and carboplatin, or a combination of pemetrexed, cisplatin and carboplatin) and an immune checkpoint inhibitor. In certain examples, the immune checkpoint inhibitor comprises an antibody selected from an anti-PD-1 antibody, an anti-PD-L1 antibody and a combination thereof. In certain examples, the the immune checkpoint inhibitor comprises an anti-PD-1 antibody. In certain examples, the immune checkpoint inhibitor comprises cemiplimab (LIBTAYO, REGN2810), nivolumab (OPDIVO; BMS-936558), pembrolizumab (KEYTRUDA; MK-3475), pidilizumab (CT-011), spartalizumab (PDR001), MEDI0680 (AMP-514), dostarlimab (TSR-042), cetrelimab (JNJ 63723283), toripalimab (JS001), AMP-224 (GSK-2661380), PF-06801591, tislelizumab (BGB-A317), ABBV-181, BI 754091, or SHR-1210. In certain examples, the immune checkpoint inhibitor comprises cemiplimab. In certain examples, the immune checkpoint inhibitor comprises an anti-PD-L1 antibody. In certain examples, the immune checkpoint inhibitor comprises atezolizumab (TECENTRIQ; RG7446; MPDL3280A; R05541267), durvalumab (MEDI4736), BMS-936559, avelumab (bavencio), lodapolimab (LY3300054), CX-072 (Proclaim-CX-072), FAZ053, KN035, or MDX-1105.

In certain examples, the composition or medical preparation comprises one or more chemotherapeutic agents and cemiplimab. In certain examples, the composition or medical preparation comprises cisplatin and cemiplimab. In certain examples, the composition or medical preparation comprises carboplatin and cemiplimab. In certain examples, the composition or medical preparation comprises a combination of paclitaxel and cisplatin and/or carboplatin (e.g., a combination of paclitaxel and cisplatin, a combination of paclitaxel and carboplatin, or a combination of paclitaxel, cisplatin and carboplatin) and cemiplimab. In certain examples, the composition or medical preparation comprises a combination of pemetrexed and cisplatin and/or carboplatin (e.g., a combination of pemetrexed and cisplatin, a combination of pemetrexed and carboplatin, or a combination of pemetrexed, cisplatin and carboplatin) and cemiplimab.

In certain examples, cemiplimab comprises an antibody selected from:

(i) an antibody comprising a heavy chain and a light chain sequence, wherein:

(a) the heavy chain comprises the amino acid sequence:

EVQLLESGGV LVQPGGSLRL SCAASGFTFS NFGMTWVRQA PGKGLEWVSG ISGGGRDTYF ADSVKGRFTI SRDNSKNTLY LQMNSLKGED TAVYYCVKWG NIYFDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK (SEQ ID NO:62), and

(b) the light chain comprises the amino acid sequence:

DIQMTQSPSS LSASVGDSIT ITCRASLSIN TFLNWYQQKP GKAPNLLIYA ASSLHGGVPS RFSGSGSGTD FTLTIRTLQP EDFATYYCQQ SSNTPFTFGP GTVVDFRRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC (SEQ ID NO:63);

(iii) an antibody comprising the six CDR sequences from SEQ ID NO:62 and SEQ ID NO:63 (*e.g.*, the three heavy chain CDRs from SEQ ID NO:62 and the three light chain CDRs from SEQ ID NO:63);
(iv) an antibody comprising the heavy chain variable domain from SEQ ID NO:62 and the light chain variable domain from SEQ ID NO:63;
(v) an antibody comprising: (a) a heavy chain variable region (VH) that comprises a CDR-1 comprising the amino acid sequence FTFSNFG, a CDR-2 comprising the amino acid sequence ISGGGRDT, and a CDR-3 comprising the amino acid sequence VKWGNIYFDY, and (b) a light chain variable region (VL) that comprises a CDR-1 comprising the amino acid sequence LSINTF, a CDR-2 comprising the amino acid sequence AAS, and a CDR-3 comprising the amino acid sequence QQSSNTPFT.

In one aspect, the disclosure provides for the composition or medical preparation as described herein, which is a pharmaceutical composition, optionally wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients. In one example, the composition or medical preparation is a pharmaceutical composition. In one example, the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

In one aspect, the disclosure provides for the composition or medical preparation as described herein, wherein the medical preparation is a kit, optionally wherein the RNAs and the further therapeutic agent are in separate vials, further optionally comprising instructions for use of the composition or medical preparation for treating or preventing lung cancer. In one example, the medical preparation is a kit. In one example, the RNAs and the further therapeutic agent are in separate vials.

In one example, the composition or medical preparation further comprises instructions for use of the composition or medical preparation for treating or preventing lung cancer.

In one aspect, the disclosure provides for the composition or medical preparation as described herein for pharmaceutical use, optionally wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder. In one example, the composition or medical preparation is for pharmaceutical use. In one example, the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder. In one aspect, the disclosure provides for a use of the composition or medical preparation as described herein in the manufacture of a medicament for the treatment or prevention of lung cancer, optionally for the treatment or prevention of lung cancer in a human. In one example, the therapeutic or prophylactic treatment of a disease or disorder comprises treating or preventing lung cancer. In one example, the composition or medical preparation is for administration to a human.

In a further example, the disclosure relates to a method of treating lung cancer in a subject comprising administering:

(a) at least one RNA to the subject, wherein the at least one RNA encodes the following amino acid sequences:

(i) an amino acid sequence comprising claudin 6 (CLDN6), an immunogenic variant thereof, or an immunogenic fragment of the CLDN6 or the immunogenic variant thereof;

(ii) an amino acid sequence comprising Kita-kyushu lung cancer antigen 1 (KK-LC-1), an immunogenic variant thereof, or an immunogenic fragment of the KK-LC-1 or the immunogenic variant thereof;

(iii) an amino acid sequence comprising Melanoma antigen A3 (MAGE-A3), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A3 or the immunogenic variant thereof;

(iv) an amino acid sequence comprising Melanoma antigen 4 (MAGE-A4), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A4 or the immunogenic variant thereof; and

(v) an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), an immunogenic variant thereof, or an immunogenic fragment of the PRAME or the immunogenic variant thereof; and

(b) a further therapeutic agent selected from an immune checkpoint inhibitor, a chemotherapeutic agent, or a combination thereof.

In one example, the at least one RNA further encodes one or both of the following amino acid sequences:

(vi) an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof; and

(vii) an amino acid sequence comprising New York esophageal squamous cell carcinoma-1 (NY-ESO-1), an immunogenic variant thereof, or an immunogenic fragment of the NY-ESO-1 or the immunogenic variant thereof.

In one example, the at least one RNA further encodes:

(vi) an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof.

In one example, the at least one RNA encodes:
(i) an amino acid sequence comprising claudin 6 (CLDN6), an immunogenic variant thereof, or an immunogenic fragment of the CLDN6 or the immunogenic variant thereof;
(ii) an amino acid sequence comprising Kita-kyushu lung cancer antigen 1 (KK-LC-1), an immunogenic variant thereof, or an immunogenic fragment of the KK-LC-1 or the immunogenic variant thereof;
(iii) an amino acid sequence comprising Melanoma antigen A3 (MAGE-A3), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A3 or the immunogenic variant thereof;
(iv) an amino acid sequence comprising Melanoma antigen 4 (MAGE-A4), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A4 or the immunogenic variant thereof;
(v) an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), an immunogenic variant thereof, or an immunogenic fragment of the PRAME or the immunogenic variant thereof; and
(vi) an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof.

In one example, each of the amino acid sequences under (i), (ii), (iii), (iv), (v), (vi), or (vii) is encoded by a separate RNA.

In one example,
(i) the RNA encoding the amino acid sequence under (i) comprises the nucleotide sequence of SEQ ID NO: 3 or 4, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 3 or 4; and/or

(ii) the amino acid sequence under (i) comprises the amino acid sequence of SEQ ID NO: 1 or 2, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 1 or 2.

In one example,

(i) the RNA encoding the amino acid sequence under (ii) comprises the nucleotide sequence of SEQ ID NO: 7 or 8, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 7 or 8; and/or

(ii) the amino acid sequence under (ii) comprises the amino acid sequence of SEQ ID NO: 5 or 6, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 5 or 6.

In one example,

(i) the RNA encoding the amino acid sequence under (iii) comprises the nucleotide sequence of SEQ ID NO: 11 or 12, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 11 or 12; and/or

(ii) the amino acid sequence under (iii) comprises the amino acid sequence of SEQ ID NO: 9 or 10, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 9 or 10.

In one example,

(i) the RNA encoding the amino acid sequence under (iv) comprises the nucleotide sequence of SEQ ID NO: 15 or 16, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 15 or 16; and/or

(ii) the amino acid sequence under (iv) comprises the amino acid sequence of SEQ ID NO: 13 or 14, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 13 or 14.

In one example,

(i) the RNA encoding the amino acid sequence under (v) comprises the nucleotide sequence of SEQ ID NO: 19 or 20, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 19 or 20; and/or

(ii) the amino acid sequence under (v) comprises the amino acid sequence of SEQ ID NO: 17 or 18, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 17 or 18.

In one example,

(i) the RNA encoding the amino acid sequence under (vi) comprises the nucleotide sequence of SEQ ID NO: 23 or 24, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 23 or 24; and/or

(ii) the amino acid sequence under (vi) comprises the amino acid sequence of SEQ ID NO: 21 or 22, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 21 or 22.

In one example,

(i) the RNA encoding the amino acid sequence under (vii) comprises the nucleotide sequence of SEQ ID NO: 27 or 28, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 27 or 28; and/or

(ii) the amino acid sequence under (vii) comprises the amino acid sequence of SEQ ID NO: 25 or 26, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 25 or 26.

In one example, at least one amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), or (vii) comprises an amino acid sequence which breaks immunological tolerance and/or at least one RNA is co-administered with RNA encoding an amino acid sequence which breaks

immunological tolerance. In one example, each amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), or (vii) comprises an amino acid sequence which breaks immunological tolerance and/or each RNA is co-administered with RNA encoding an amino acid sequence which breaks immunological tolerance. In one example, the amino acid sequence which breaks immunological tolerance comprises helper epitopes, preferably tetanus toxoid-derived helper epitopes. In one example,

(i) the RNA encoding the amino acid sequence which breaks immunological tolerance comprises the nucleotide sequence of SEQ ID NO: 34, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 34; and/or

(ii) the amino acid sequence which breaks immunological tolerance comprises the amino acid sequence of SEQ ID NO: 33, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 33.

In one example, at least one of the amino acid sequences under (i), (ii), (iii), (iv), (v), (vi), or (vii) is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence. In one example, each of the amino acid sequences under (i), (ii), (iii), (iv), (v), (vi), or (vii) is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence.

In one example, at least one RNA is a modified RNA, in particular a stabilized mRNA. In one example, at least one RNA comprises a modified nucleoside in place of at least one uridine. In one example, at least one RNA comprises a modified nucleoside in place of each uridine. In one example, each RNA comprises a modified nucleoside in place of at least one uridine. In one example, each RNA comprises a modified nucleoside in place of

each uridine. In one example, the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).

In one example, at least one RNA comprises the 5' cap $m_2^{7,2'\text{-}O}Gpp_sp(5')G$. In one example, each RNA comprises the 5' cap $m_2^{7,2'\text{-}O}Gpp_sp(5')G$.

In one example, at least one RNA comprises a 5' UTR comprising the nucleotide sequence of SEQ ID NO: 35, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 35. In one example, each RNA comprises a 5' UTR comprising the nucleotide sequence of SEQ ID NO: 35, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 35.

In one example, at least one amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), or (vii) comprises an amino acid sequence enhancing antigen processing and/or presentation. In one example, each amino acid sequence under (iii), (iv), (v), (vi), or (vii) comprises an amino acid sequence enhancing antigen processing and/or presentation. In one example, each amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), or (vii) comprises an amino acid sequence enhancing antigen processing and/or presentation. In one example, the amino acid sequence enhancing antigen processing and/or presentation comprises an amino acid sequence corresponding to the transmembrane and cytoplasmic domain of a MHC molecule, preferably a MHC class I molecule. In one example,

(i) the RNA encoding the amino acid sequence enhancing antigen processing and/or presentation comprises the nucleotide sequence of SEQ ID NO: 32, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 32; and/or

(ii) the amino acid sequence enhancing antigen processing and/or presentation comprises the amino acid sequence of SEQ ID NO: 31, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 31.

In one example, the amino acid sequence enhancing antigen processing and/or presentation further comprises an amino acid sequence coding for a secretory signal peptide. In one example,

(i) the RNA encoding the secretory signal peptide comprises the nucleotide sequence of SEQ ID NO: 30, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 30; and/or

(ii) the secretory signal peptide comprises the amino acid sequence of SEQ ID NO: 29, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 29.

In one example, at least one RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 36, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 36. In one example, each RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 36, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 36.

In one example, at least one RNA comprises a poly-A sequence. In one example, each RNA comprises a poly-A sequence. In one example, the poly-A sequence comprises at least 100 nucleotides. In one example, the poly-A sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 37.

In one example, the RNA is administered by injection. In one example, the RNA is administered by intravenous administration.

In one example, the RNA is formulated as lipoplex particles. In one example, the RNA lipoplex particles are obtainable by mixing the RNA with liposomes. In one example, at least one RNA encoding an amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), and/or (vii) is co-formulated as lipoplex particles with RNA encoding an amino acid sequence which breaks immunological tolerance. In one example, each RNA encoding an amino acid sequence

under (i), (ii), (iii), (iv), (v), (vi), and/or (vii) is co-formulated as lipoplex particles with RNA encoding an amino acid sequence which breaks immunological tolerance. In one example, the RNA encoding an amino acid sequence under (i), (ii), (iii), (iv), (v), (vi), and/or (vii) is co-formulated as lipoplex particles with the RNA encoding an amino acid sequence which breaks immunological tolerance at a ratio of about 4:1 to about 16:1, about 6:1 to about 14:1, about 8:1 to about 12:1, or about 10:1.

In one example, the method comprises administering:
(i) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 2;
(ii) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 6;
(iii) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 10;
(iv) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 14;
(v) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 18; and
(vi) RNA encoding an amino acid sequence comprising the amino acid sequence of SEQ ID NO: 22.

In one example, the method comprises administering:
(i) RNA comprising the nucleotide sequence of SEQ ID NO: 4;
(ii) RNA comprising the nucleotide sequence of SEQ ID NO: 8;
(iii) RNA comprising the nucleotide sequence of SEQ ID NO: 12;
(iv) RNA comprising the nucleotide sequence of SEQ ID NO: 16;
(v) RNA comprising the nucleotide sequence of SEQ ID NO: 20; and
(vi) RNA comprising the nucleotide sequence of SEQ ID NO: 24.

In certain examples, the method comprises administering one or more chemotherapeutic agents. In certain examples, the method comprises administering a taxane such as docetaxel and/or paclitaxel, a folate antimetabolite such as pemetrexed, a platinum compound such as cisplatin and/or carboplatin, or a combination thereof. In certain examples, the method comprises administering docetaxel. In certain examples, the method comprises administering docetaxel and ramucirumab. In certain examples, the method comprises administering docetaxel and nintedanib. In certain examples, the method comprises administering paclitaxel. In certain examples, the method comprises administering paclitaxel and a platinum compound such as cisplatin and/or carboplatin. In certain examples, the method comprises administering pemetrexed. In certain examples, the method comprises administering pemetrexed and a platinum compound such as cisplatin and/or carboplatin. In certain examples, the method comprises administering comprises cisplatin. In certain examples, the method comprises administering carboplatin.

In certain examples, the method comprises administering one or more immune checkpoint inhibitors. In certain examples, the method comprises administering an antibody selected from an anti-PD-1 antibody, an anti-PD-L1 antibody and a combination thereof. In certain examples, the method comprises administering an anti-PD-1 antibody. In certain examples, the method comprises administering cemiplimab (LIBTAYO, REGN2810), nivolumab (OPDIVO; BMS-936558), pembrolizumab (KEYTRUDA; MK-3475), pidilizumab (CT-011), spartalizumab (PDR001), MEDI0680 (AMP-514), dostarlimab (TSR-042), cetrelimab (JNJ 63723283), toripalimab (JS001), AMP-224 (GSK-2661380), PF-06801591, tislelizumab (BGB-A317), ABBV-181, BI 754091, or SHR-1210. In certain examples, the method comprises administering cemiplimab. In certain examples, the method comprises administering an anti-PD-L1 antibody. In certain examples, the method comprises administering atezolizumab (TECENTRIQ; RG7446; MPDL3280A; R05541267), durvalumab (MEDI4736), BMS-936559, avelumab (bavencio), lodapolimab (LY3300054), CX-072 (Proclaim-CX-072), FAZ053, KN035, or MDX-1105.

In certain examples, the method comprises administering one or more chemotherapeutic agents and one or more immune checkpoint inhibitors. In certain examples, the method comprises administering cisplatin and an immune checkpoint inhibitor. In certain examples, the method comprises administering carboplatin and an immune checkpoint inhibitor. In certain examples, the method comprises administering a combination of paclitaxel and cisplatin and/or carboplatin (e.g., a combination of paclitaxel and cisplatin, a combination of paclitaxel and carboplatin, or a combination of paclitaxel, cisplatin and carboplatin) and an immune checkpoint inhibitor. In certain examples, the method comprises administering a combination of pemetrexed and cisplatin and/or carboplatin (e.g., a combination of pemetrexed and cisplatin, a combination of pemetrexed and carboplatin, or a combination of pemetrexed, cisplatin and carboplatin) and an immune checkpoint inhibitor. In certain examples, the immune checkpoint inhibitor comprises an antibody selected from an anti-PD-1 antibody, an anti-PD-L1 antibody and a combination thereof. In certain examples, the the immune checkpoint inhibitor comprises an anti-PD-1 antibody. In certain examples, the immune checkpoint inhibitor comprises cemiplimab (LIBTAYO, REGN2810), nivolumab (OPDIVO; BMS-936558), pembrolizumab (KEYTRUDA; MK-3475), pidilizumab (CT-011), spartalizumab (PDR001), MEDI0680 (AMP-514), dostarlimab (TSR-042), cetrelimab (JNJ 63723283), toripalimab (JS001), AMP-224 (GSK-2661380), PF-06801591, tislelizumab (BGB-A317), ABBV-181, BI 754091, or SHR-1210. In certain examples, the immune checkpoint inhibitor comprises cemiplimab. In certain examples, the immune checkpoint inhibitor comprises an anti-PD-L1 antibody. In certain examples, the immune checkpoint inhibitor comprises atezolizumab (TECENTRIQ; RG7446; MPDL3280A; R05541267), durvalumab (MEDI4736), BMS-936559, avelumab (bavencio), lodapolimab (LY3300054), CX-072 (Proclaim-CX-072), FAZ053, KN035, or MDX-1105.

In certain examples, the method comprises administering one or more chemotherapeutic agents and cemiplimab. In certain examples, the method comprises administering cisplatin and cemiplimab. In certain examples, the method comprises administering carboplatin and cemiplimab. In certain examples, the method comprises administering a combination of paclitaxel and cisplatin and/or carboplatin (e.g., a combination of paclitaxel

and cisplatin, a combination of paclitaxel and carboplatin, or a combination of paclitaxel, cisplatin and carboplatin) and cemiplimab. In certain examples, the method comprises administering a combination of pemetrexed and cisplatin and/or carboplatin (e.g., a combination of pemetrexed and cisplatin, a combination of pemetrexed and carboplatin, or a combination of pemetrexed, cisplatin and carboplatin) and cemiplimab.

In certain examples, cemiplimab comprises an antibody selected from:

(i) an antibody comprising a heavy chain and a light chain sequence, wherein:

(a) the heavy chain comprises the amino acid sequence:

EVQLLESGGV LVQPGGSLRL SCAASGFTFS NFGMTWVRQA PGKGLEWVSG ISGGGRDTYF ADSVKGRFTI SRDNSKNTLY LQMNSLKGED TAVYYCVKWG NIYFDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK (SEQ ID NO:62), and

(b) the light chain comprises the amino acid sequence:

DIQMTQSPSS LSASVGDSIT ITCRASLSIN TFLNWYQQKP GKAPNLLIYA ASSLHGGVPS RFSGSGSGTD FTLTIRTLQP EDFATYYCQQ SSNTPFTFGP GTVVDFRRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC (SEQ ID NO:63);

(iii) an antibody comprising the six CDR sequences from SEQ ID NO:62 and SEQ ID NO:63 (*e.g.*, the three heavy chain CDRs from SEQ ID NO:62 and the three light chain CDRs from SEQ ID NO:63);

(iv) an antibody comprising the heavy chain variable domain from SEQ ID NO:62 and the light chain variable domain from SEQ ID NO:63;

(v) an antibody comprising: (a) a heavy chain variable region (VH) that comprises a CDR-1 comprising the amino acid sequence FTFSNFG, a CDR-2 comprising the amino acid sequence ISGGGRDT, and a CDR-3 comprising the amino acid sequence VKWGNIYFDY, and (b) a light

chain variable region (VL) that comprises a CDR-1 comprising the amino acid sequence LSINTF, a CDR-2 comprising the amino acid sequence AAS, and a CDR-3 comprising the amino acid sequence QQSSNTPFT.

In one example, the subject is a human.

In one example, provided herein is RNA described herein, e.g.,
(i) RNA encoding an amino acid sequence comprising claudin 6 (CLDN6), an immunogenic variant thereof, or an immunogenic fragment of the CLDN6 or the immunogenic variant thereof;
(ii) RNA encoding an amino acid sequence comprising Kita-kyushu lung cancer antigen 1 (KK-LC-1), an immunogenic variant thereof, or an immunogenic fragment of the KK-LC-1 or the immunogenic variant thereof;
(iii) RNA encoding an amino acid sequence comprising Melanoma antigen A3 (MAGE-A3), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A3 or the immunogenic variant thereof;
(iv) RNA encoding an amino acid sequence comprising Melanoma antigen 4 (MAGE-A4), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A4 or the immunogenic variant thereof; and
(v) RNA encoding an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), an immunogenic variant thereof, or an immunogenic fragment of the PRAME or the immunogenic variant thereof;
and optionally one or more of:
(vi) RNA encoding an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof; and/or
(vii) RNA encoding an amino acid sequence comprising New York esophageal squamous cell carcinoma-1 (NY-ESO-1), an immunogenic variant thereof, or an immunogenic fragment of the NY-ESO-1 or the immunogenic variant thereof,
for use in a method described herein.

Examples of the RNA for the use are as described herein, e.g., in respect of the composition or medical preparation or the method of the disclosure.

Claims

1. A composition or medical preparation comprising:

(a) at least one RNA, wherein the at least one RNA encodes the following amino acid sequences:

(i) an amino acid sequence comprising claudin 6 (CLDN6), an immunogenic variant thereof, or an immunogenic fragment of the CLDN6 or the immunogenic variant thereof;

(ii) an amino acid sequence comprising Kita-kyushu lung cancer antigen 1 (KK-LC-1), an immunogenic variant thereof, or an immunogenic fragment of the KK-LC-1 or the immunogenic variant thereof;

(iii) an amino acid sequence comprising Melanoma antigen A3 (MAGE-A3), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A3 or the immunogenic variant thereof;

(iv) an amino acid sequence comprising Melanoma antigen 4 (MAGE-A4), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A4 or the immunogenic variant thereof;

(v) an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), an immunogenic variant thereof, or an immunogenic fragment of the PRAME or the immunogenic variant thereof; and

(vi) an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof; and

(b) a further therapeutic agent selected from an immune checkpoint inhibitor, a chemotherapeutic agent, or a combination thereof, optionally wherein the composition or medical preparation comprises:

(i) RNA encoding an amino acid sequence comprising claudin 6 (CLDN6), an immunogenic variant thereof, or an immunogenic fragment of the CLDN6 or the immunogenic variant thereof;

(ii) RNA encoding an amino acid sequence comprising Kita-kyushu lung cancer antigen 1 (KK-LC-1), an immunogenic variant thereof, or an immunogenic fragment of the KK-LC-1 or the immunogenic variant thereof;

(iii) RNA encoding an amino acid sequence comprising Melanoma antigen A3 (MAGE-A3), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A3 or the immunogenic variant thereof;
(iv) RNA encoding an amino acid sequence comprising Melanoma antigen 4 (MAGE-A4), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-A4 or the immunogenic variant thereof;
(v) RNA encoding an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), an immunogenic variant thereof, or an immunogenic fragment of the PRAME or the immunogenic variant thereof; and
(vi) RNA encoding an amino acid sequence comprising Melanoma antigen C1 (MAGE-C1), an immunogenic variant thereof, or an immunogenic fragment of the MAGE-C1 or the immunogenic variant thereof.

2. The composition or medical preparation of claim 1, wherein each of the amino acid sequences under (i), (ii), (iii), (iv), (v), or (vi) is encoded by a separate RNA.

3. The composition or medical preparation of claim 1 or 2, wherein
A
(i) the RNA encoding the amino acid sequence under (i) comprises the nucleotide sequence of SEQ ID NO: 3 or 4, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 3 or 4; and/or
(ii) the amino acid sequence under (i) comprises the amino acid sequence of SEQ ID NO: 1 or 2, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 1 or 2; and/or
B
(i) the RNA encoding the amino acid sequence under (ii) comprises the nucleotide sequence of SEQ ID NO: 7 or 8, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 7 or 8; and/or
(ii) the amino acid sequence under (ii) comprises the amino acid sequence of SEQ ID NO: 5 or 6, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 5 or 6; and/or
C

(i) the RNA encoding the amino acid sequence under (iii) comprises the nucleotide sequence of SEQ ID NO: 11 or 12, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 11 or 12; and/or

(ii) the amino acid sequence under (iii) comprises the amino acid sequence of SEQ ID NO: 9 or 10, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 9 or 10; and/or

D

(i) the RNA encoding the amino acid sequence under (iv) comprises the nucleotide sequence of SEQ ID NO: 15 or 16, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 15 or 16; and/or

(ii) the amino acid sequence under (iv) comprises the amino acid sequence of SEQ ID NO: 13 or 14, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 13 or 14; and/or

E

(i) the RNA encoding the amino acid sequence under (v) comprises the nucleotide sequence of SEQ ID NO: 19 or 20, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 19 or 20; and/or

(ii) the amino acid sequence under (v) comprises the amino acid sequence of SEQ ID NO: 17 or 18, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 17 or 18.

4. The composition or medical preparation of any one of claims 1 to 3, wherein

(i) the RNA encoding the amino acid sequence under (vi) comprises the nucleotide sequence of SEQ ID NO: 23 or 24, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 23 or 24; and/or

(ii) the amino acid sequence under (vi) comprises the amino acid sequence of SEQ ID NO: 21 or 22, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 21 or 22.

5. The composition or medical preparation of any one of claims 1 to 4, which comprises:
(i) RNA comprising the nucleotide sequence of SEQ ID NO: 4;
(ii) RNA comprising the nucleotide sequence of SEQ ID NO: 8;
(iii) RNA comprising the nucleotide sequence of SEQ ID NO: 12;
(iv) RNA comprising the nucleotide sequence of SEQ ID NO: 16;
(v) RNA comprising the nucleotide sequence of SEQ ID NO: 20; and
(vi) RNA comprising the nucleotide sequence of SEQ ID NO: 24.

6. The composition or medical preparation of any one of claims 1 to 5, wherein at least one amino acid sequence under (i), (ii), (iii), (iv), (v), or (vi) comprises an amino acid sequence which breaks immunological tolerance and/or at least one RNA is co-administered with RNA encoding an amino acid sequence which breaks immunological tolerance, or wherein each amino acid sequence under (i), (ii), (iii), (iv), (v), or (vi) comprises an amino acid sequence which breaks immunological tolerance and/or each RNA is co-administered with RNA encoding an amino acid sequence which breaks immunological tolerance.

7. The composition or medical preparation of claim 6, wherein the amino acid sequence which breaks immunological tolerance comprises helper epitopes, preferably tetanus toxoid-derived helper epitopes.

8. The composition or medical preparation of claim 6 or 7, wherein
(i) the RNA encoding the amino acid sequence which breaks immunological tolerance comprises the nucleotide sequence of SEQ ID NO: 34, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 34; and/or
(ii) the amino acid sequence which breaks immunological tolerance comprises the amino acid sequence of SEQ ID NO: 33, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 33.

9. The composition or medical preparation of any one of claims 1 to 8, wherein at least one of the amino acid sequences under (i), (ii), (iii), (iv), (v), or (vi) is encoded by a coding sequence

which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence, or wherein each of the amino acid sequences under (i), (ii), (iii), (iv), (v), or (vi) is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence.

10. The composition or medical preparation of any one of claims 1 to 9, wherein at least one RNA comprises the 5' cap $m_2^{7,2'-O}Gpp_sp(5')G$, or wherein each RNA comprises the 5' cap $m_2^{7,2'-O}Gpp_sp(5')G$.

11. The composition or medical preparation of any one of claims 1 to 10, wherein at least one RNA comprises a 5' UTR comprising the nucleotide sequence of SEQ ID NO: 35, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 35, or wherein each RNA comprises a 5' UTR comprising the nucleotide sequence of SEQ ID NO: 35, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 35.

12. The composition or medical preparation of any one of claims 1 to 11, wherein at least one amino acid sequence under (i), (ii), (iii), (iv), (v), or (vi) comprises an amino acid sequence enhancing antigen processing and/or presentation, or wherein each amino acid sequence under (i), (ii), (iii), (iv), (v), or (vi) comprises an amino acid sequence enhancing antigen processing and/or presentation, optionally wherein the amino acid sequence enhancing antigen processing and/or presentation comprises an amino acid sequence corresponding to the transmembrane and cytoplasmic domain of a MHC molecule, preferably a MHC class I molecule, further optionally wherein

(i) the RNA encoding the amino acid sequence enhancing antigen processing and/or presentation comprises the nucleotide sequence of SEQ ID NO: 32, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 32; and/or

(ii) the amino acid sequence enhancing antigen processing and/or presentation comprises the amino acid sequence of SEQ ID NO: 31, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 31.

13. The composition or medical preparation of any one of claims 1 to 12, wherein at least one RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 36, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 36, or wherein each RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 36, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 36.

14. The composition or medical preparation of any one of claims 1 to 13, wherein at least one RNA comprises a poly-A sequence, or wherein each RNA comprises a poly-A sequence, optionally wherein the poly-A sequence comprises at least 100 nucleotides, further optionally wherein the poly-A sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 37.

15. The composition or medical preparation of any one of claims 1 to 14, wherein the RNA is formulated as a liquid, formulated as a solid, or a combination thereof, or wherein the RNA is formulated for injection, or wherein the RNA is formulated for intravenous administration, or wherein the RNA is formulated or is to be formulated as lipoplex particles, optionally wherein the RNA lipoplex particles are obtainable by mixing the RNA with liposomes, further optionally wherein at least one RNA encoding an amino acid sequence under (i), (ii), (iii), (iv), (v), or (vi) is co-formulated or is to be co-formulated as lipoplex particles with RNA encoding an amino acid sequence which breaks immunological tolerance or wherein each RNA encoding an amino acid sequence under (i), (ii), (iii), (iv), (v), or (vi) is co-formulated or is to be co-formulated as lipoplex particles with RNA encoding an amino acid sequence which breaks immunological tolerance.

16. The composition or medical preparation of any one of claims 1 to 17, which comprises one or more chemotherapeutic agents, for example a taxane such as docetaxel and/or paclitaxel,

a folate antimetabolite such as pemetrexed, a platinum compound such as cisplatin and/or carboplatin, or a combination thereof.

17. The composition or medical preparation of any one of claims 1 to 16, which comprises docetaxel, docetaxel and ramucirumab, docetaxel and nintedanib, paclitaxel, paclitaxel and a platinum compound such as cisplatin and/or carboplatin, pemetrexed, pemetrexed and a platinum compound such as cisplatin and/or carboplatin, cisplatin, or carboplatin.

18. The composition or medical preparation of any one of claims 1 to 17, which comprises one or more immune checkpoint inhibitors such as an anti-PD-1 antibody.

19. The composition or medical preparation of any one of claims 1 to 18, which comprises cisplatin and an immune checkpoint inhibitor, carboplatin and an immune checkpoint inhibitor, a combination of paclitaxel and cisplatin and/or carboplatin (e.g., a combination of paclitaxel and cisplatin, a combination of paclitaxel and carboplatin, or a combination of paclitaxel, cisplatin and carboplatin) and an immune checkpoint inhibitor, or a combination of pemetrexed and cisplatin and/or carboplatin (e.g., a combination of pemetrexed and cisplatin, a combination of pemetrexed and carboplatin, or a combination of pemetrexed, cisplatin and carboplatin) and an immune checkpoint inhibitor.

20. The composition or medical preparation of any one of claims 1 to 19, wherein the immune checkpoint inhibitor comprises cemiplimab.

21. The composition or medical preparation of any one of claims 1 to 20, which is a pharmaceutical composition, optionally wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

22. The composition or medical preparation of any one of claims 1 to 21, wherein the medical preparation is a kit, optionally wherein the RNAs and the further therapeutic agent are in separate vials, further optionally comprising instructions for use of the composition or medical preparation for treating or preventing lung cancer.

23. The composition or medical preparation of any one of claims 1 to 22 for pharmaceutical use, optionally wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.

24. Use of the composition or medical preparation of any one of claims 1 to 22 in the manufacture of a medicament for the treatment or prevention of lung cancer, optionally for the treatment or prevention of lung cancer in a human.