CLAIMS

1. Use of an effective amount of RNAs comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and RNA encoding a GM-CSF protein, in the manufacture of a medicament for treating a subject having a solid tumor cancer, wherein the subject has failed, or become intolerant, resistant, or refractory to an anti-programmed cell death 1 (PD-1) or anti-programmed cell death 1 ligand 1 (PD-L1) therapy.
2. The use of claim 1, wherein:
   i. the subject has anti-PD-1 and/or anti-PD-L1 resistant solid tumor cancer; or
   ii. the subject has a solid tumor cancer with acquired resistance to anti-PD-1 and/or anti-PD-L1 therapy; or
   iii. the subject has a solid tumor cancer with innate resistance to anti-PD-1 and/or anti-PD-L1 therapy; or
   iv. the subject has an advanced-stage, unresectable, or metastatic solid tumor cancer; or
   v. the refractory or resistant cancer is one that does not respond to a specified treatment; or
   vi. the refraction occurs from the very beginning of treatment; or
   vii. the refraction occurs during treatment; or
   viii. the cancer is resistant before treatment begins; or
   ix. the subject has a cancer that does not respond to the anti-programmed cell death 1 (PD-1) and/or anti-programmed cell death 1 ligand 1 (PD-L1) therapy; or
   x. the subject has a cancer that is becoming refractory or resistant to a specified treatment, wherein the specified treatment is as an anti-PD1 or anti-PD-L1 therapy; or
   xi. the subject has become less responsive to the therapy since first receiving it; or
   xii. the subject has not received the therapy, but has a type of cancer that does not typically respond to the therapy.
3. The use of claim 1 or 2, wherein the use further comprises selecting a subject that has failed, or become intolerant, resistant, or refractory to an anti-programmed cell death 1 (PD-1) or anti-programmed cell death 1 ligand 1 (PD-L1) therapy.
4. The use of any one of claims 1-3, wherein the subject is human.

5. The use of any one of claims 1-4, wherein one or more of the following (i)-(viii) is met:
    i. the subject has a metastatic solid tumor;
    ii. the subject has an unresectable solid tumor;
    iii. the subject has not been treated previously with an anti-PD-1 or anti-PD-L1 therapy;
    iv. the subject is without other treatment options;
    v. the subject has two or three tumor lesions;
    vi. the subject has measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria;
    vii. the subject has a life expectancy of more than 3 months; or
    viii. the subject is at least 18 years of age.
6. The use of any one of claims 1-5, wherein the subject has a cancer cell comprising a partial or total loss of beta-2-microglobulin (B2M) function.
7. The use of claim 6, wherein the cancer cell has a partial loss of B2M function or a total loss of B2M function.
8. The use of claim 6 or 7,
    wherein the subject comprises a cell comprising a mutation in the B2M gene, wherein the mutation is a substitution, insertion, or deletion or the mutation is a frameshift mutation, wherein the frameshift mutation is in exon 1 of B2M or the frameshift mutation comprises p.Leu13fs and/or p.Ser14fs.
9. The use of any one of claims 6-8, wherein the B2M gene comprises a loss of heterozygosity (LOH).
10. The use of any one of claims 6-9, wherein the subject has a reduced level of B2M protein as compared to a subject without a partial or total loss of B2M function.
11. The use of any one of claims 1-10, wherein the subject has a reduced level of surface expressed major histocompatibility complex class I (MHC I) as compared to a control, optionally wherein the control is a non-cancerous sample from the same subject.
12. The use of any one of claims 1-11, wherein the solid tumor cancer is an epithelial tumor, prostate tumor, ovarian tumor, renal cell tumor, gastrointestinal tract tumor, hepatic tumor, colorectal tumor, tumor with vasculature, mesothelioma tumor, pancreatic tumor, breast tumor, sarcoma tumor, lung tumor, colon tumor, melanoma tumor, small cell lung

tumor, non-small cell lung cancer, neuroblastoma tumor, testicular tumor, carcinoma tumor, adenocarcinoma tumor, seminoma tumor, retinoblastoma, cutaneous squamous cell carcinoma (CSCC), squamous cell carcinoma for the head and neck (HNSCC), head and neck cancer, osteosarcoma tumor, kidney tumor, thyroid tumor, anaplastic thyroid cancer (ATC), liver tumor, colon tumor, or other solid tumors amenable to intratumoral injection.

13. The use of any one of claims 1-12, wherein

(a) the solid tumor cancer is lymphoma; or

(b) the solid tumor cancer is melanoma; or

(c) the solid tumor cancer is uveal melanoma or mucosal melanoma; or

(d) the solid tumor cancer is melanoma comprising superficial, subcutaneous and/or lymph node metastases amenable for intratumoral injection; or

(e) the solid tumor cancer is HNSCC and/or mucosal melanoma with only mucosal sites; or

(f) the solid tumor cancer is not melanoma.

14. The use of claim 13, wherein the lymphoma is Non-Hodgkin lymphoma or Hodgkin lymphoma.
15. The use of any one of claims 1-14, wherein the RNAs are administered as monotherapy.
16. The use of any one of claims 1-15, wherein the subject has more than one solid tumor.
17. The use of claim 16, wherein at least one tumor is resistant, refractory, or intolerant to an anti-PD-1 or anti-PD-L1 therapy and at least one tumor is not.
18. The use of claim 17, wherein both resistant and non-resistant tumors are successfully treated.
19. The use of any one of claims 1-18, wherein one or more of the following (1)-(10) is met:

(1) the solid tumor cancer is stage III, subsets of stage III, stage IV, or subsets of stage IV;

(2) the solid tumor cancer is advanced-stage and unresectable;

(3) the solid tumor cancer has spread from its origin to another site in the subject;

(4) the solid tumor cancer has one or more cutaneous or subcutaneous lesions, optionally wherein the cancer is not a skin cancer;

(5) the solid tumor cancer is stage IIIB, stage IIIC, or stage IV melanoma;

(6) the solid tumor cancer is one in which an anti-PD-1 or anti-PD-L1 therapy is not routinely used;

(7) the solid tumor cancer is is not melanoma, non-small cell lung cancer, kidney cancer, head and neck cancer, breast cancer, or CSCC;

(8) the solid tumor cancer is one for which an anti-PD1 or anti-PD-L1 therapy is routinely used, but which has not been treated with the therapy yet;

(9) the solid tumor cancer is stage IIIB, IIIC, or unresectable stage IV melanoma that is resistant and/or refractory to anti-PD-1 or anti-PD-L1 therapy; or

(10) the solid tumor cancer comprises superficial or subcutaneous lesions and/or metastases.

20. The use of any one of claims 1-19, wherein
    i. the solid tumor cancer is not melanoma, CSCC, or HNSCC; and
    ii. an anti-PD-1 or anti-PD-L1 therapy is not routinely used; and
    iii. there are no other suitable treatment options.
21. Use of an effective amount of RNAs comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and RNA encoding a GM-CSF protein, in the manufacture of a medicament for treating a subject having an advanced-stage melanoma, wherein
    i. the subject is at least 18 years of age;
    ii. the subject has failed prior anti-PD1 or anti-PD-L1 therapies;
    iii. the subject has a minimum of 2 lesions; and
    iv. the melanoma comprises a tumor that is suitable for direct intratumoral injection.
22. The use of any one of claims 1-21, wherein
    i. the RNA encoding an IL-12sc protein comprises the nucleotide sequence of SEQ ID NO: 17 or 18, 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: 17 or 18; and/or
    ii. the IL-12sc protein comprises the amino acid sequence of SEQ ID NO: 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:14; and/or

iii. the RNA encoding an IL-12sc protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p40 portion of IL-12sc (nucleotides 1-984 of SEQ ID NO: 17 or 18) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p30 portion of IL-12sc (nucleotides 1027-1623 of SEQ ID NO: 17 or 18) and further comprises nucleotides between the p40 and p35 portions encoding a linker polypeptide.

23. The use of any one of claims 1-22, wherein

i. the RNA encoding an IL-15 sushi protein comprises the nucleotide sequence of SEQ ID NO: 26, 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: 26; and/or

ii. the IL-15 sushi protein comprises the amino acid sequence of SEQ ID NO: 24, 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: 24; and/or

iii. the RNA encoding an IL-15 sushi protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the sushi domain of IL-15 receptor alpha (nucleotides 1-321 of SEQ ID NO: 26) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to mature IL-15 (nucleotides 382-729 of SEQ ID NO: 26) and optionally further comprises nucleotides between the sushi domain of IL-15 and the mature IL-15 encoding a linker polypeptide.

24. The use of any one of claims 1-23, wherein

i. the RNA encoding an IFNα protein comprises the nucleotide sequence of SEQ ID NO: 22 or 23, 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: 22 or 23 and/or

ii. the IFNα protein comprises the amino acid sequence of SEQ ID NO: 19, 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: 19.

25. The use of any one of claims 1-24, wherein

i. the RNA encoding a GM-CSF protein comprises the nucleotide sequence of SEQ ID NO: 29, 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: 29 and/or

ii. the GM-CSF protein comprises the amino acid sequence of SEQ ID NO: 27, 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: 27.

26. The use of any one of claims 1-25, wherein at least one RNA comprises a modified nucleoside in place of at least one uridine, optionally in place of each uridine.

27. The use of any one of claims 1-26, wherein each RNA comprises a modified nucleoside in place of at least one uridine, optionally in place of each uridine.

28. The use of claim 26 or 27, wherein the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$), and 5-methyl-uridine (m^5U).

29. The use of any one of claims 1-28, wherein at least one RNA comprises more than one type of modified nucleoside, wherein the modified nucleosides are independently selected from pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$), and 5-methyl-uridine (m^5U), optionally wherein the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

30. The use of any one of claims 1-29, wherein at least one RNA, optionally each RNA, comprises the 5' cap $m_2^{7,3'\text{-}O}Gppp(m_1^{2'\text{-}O})ApG$ or 3´-O-Me-m^7G(5')ppp(5')G.

31. The use of any one of claims 1-30, wherein at least one RNA, optionally each RNA, comprises a 5' UTR comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6.

32. The use of any one of claims 1-31, wherein at least one RNA, optionally each RNA, comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 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: 8.

33. The use of any one of claims 1-32, wherein at least one RNA, optionally each RNA, comprises a poly-A tail, optionally wherein the poly-A tail comprises at least 100 nucleotides or optionally wherein the poly-A tail comprises he poly-A tail shown in SEQ ID NO: 30.
34. The use of any one of claims 1-33, wherein one or more RNA comprises:
    i. a 5' cap comprising $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$ or 3´-O-Me-$m^7G(5')ppp(5')G$;
    ii. a 5' UTR comprising (i) a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or (ii) a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6;
    iii. a 3' UTR comprising (i) the nucleotide sequence of SEQ ID NO: 8, or (ii) a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO:8; and
    iv. a poly-A tail comprising at least 100 nucleotides.
35. The use of any one of claims 1-34, wherein treating the solid tumor cancer comprises reducing the size of a tumor or preventing cancer metastasis in a subject.
36. The use of any one of claims 1-35, wherein the RNAs are administered at the same time.
37. The use of any one of claims 1-36, wherein the RNAs are administered via injection.
38. The use of claim 36 or 37, wherein the RNAs are mixed together in liquid solution prior to injection.
39. The use of any one of claims 1-38, wherein the RNAs are administered in a neoadjuvant setting.