

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a KRAS nucleic acid inhibitor molecule and a pharmaceutically acceptable excipient.
2. The pharmaceutical composition of claim 1 further comprising an immunotherapy agent.
3. The pharmaceutical composition of claim 1 further comprising an MEK inhibitor.
4. The pharmaceutical composition of any one of claims 1-3 for use in the treatment of a KRAS-associated cancer in a subject.
5. The pharmaceutical composition of claim 3 or 4, wherein the MEK inhibitor is trametinib.
6. The pharmaceutical composition of claim 4 or 5, wherein the KRAS-associated cancer is resistant to treatment with the MEK inhibitor prior to the administration of the KRAS nucleic acid inhibitor molecule.
7. The pharmaceutical composition of claim 4, wherein prior to the administration of the KRAS nucleic acid inhibitor molecule, the KRAS-associated cancer is associated with a non-T cell inflamed phenotype that is resistant to immunotherapy and wherein using the KRAS nucleic acid inhibitor molecule converts the non-T cell inflamed phenotype into a T cell-inflamed phenotype that is responsive to an immunotherapeutic agent.
8. The pharmaceutical composition of any one of the preceding claims, further comprising an agent that reduces stromal markers in the tumor microenvironment.
9. The pharmaceutical composition of claim 8, wherein the agent that reduces stromal markers in the tumor microenvironment is a TGF- β inhibitor or a CSF1 inhibitor.
10. A pharmaceutical composition for use in the treatment of a KRAS-associated cancer in a subject comprising -

a therapeutically effective amount of a KRAS nucleic acid inhibitor molecule, and
a therapeutically effective amount of an immunotherapeutic agent.

11. The pharmaceutical composition of claim 2 or 10, wherein:
 - i) the immunotherapeutic agent is an antagonist of an inhibitory immune checkpoint molecule or an agonist of a co-stimulatory checkpoint molecule;
 - ii) the immunotherapeutic agent is an antagonist of an inhibitory check point, and the inhibitory check point is PD-1 or PD-L1; and
 - iii) the antagonist of the inhibitory immune checkpoint molecule or the agonist of the co-stimulatory checkpoint molecule is a monoclonal antibody.
12. The pharmaceutical composition of any one of claims 4-11, wherein the KRAS-associated cancer is pancreatic cancer.
13. The pharmaceutical composition of any one of the preceding claims, wherein the KRAS nucleic acid inhibitor molecule is a double stranded RNAi inhibitor molecule comprising a sense stand and an antisense strand and a region of complementarity between the sense strand and the antisense strand of about 15-45 base pairs.
14. The pharmaceutical composition of claim 13, wherein:
 - a) the sense strand is 26-36 nucleotides and contains a stem and a tetraloop, and the antisense strand is 18-24 nucleotides, wherein the sense strand and antisense strand form a duplex region of 18-24 nucleotides;
 - b) the sense strand is 34-36 nucleotides and contains a stem and a tetraloop, and the antisense strand is 18-24 nucleotides, wherein the sense strand and antisense strand form a duplex region of 18-24 nucleotides;
 - c) the sense strand is 34-36 nucleotides and contains a stem and a tetraloop, and the antisense strand is 18-24 nucleotides, wherein the sense strand and antisense strand form a duplex region of 18-24 nucleotides;
 - d) the sense strand is 25-35 nucleotides and contains a stem and a triloop, and the antisense strand is 18-24 nucleotides, wherein the sense strand and antisense strand form a duplex region of 18-24 nucleotides;
 - e) the sense strand is 25-40 nucleotides and contains a stem and a loop, the antisense strand is 18-24 nucleotides and optionally comprises a single-stranded overhang of

1-2 nucleotides at its 3'-terminus, wherein the sense strand and antisense strand form a duplex region of 18-24 base pairs; or

f) wherein the region of complementarity between the sense strand and the antisense strand is 21-26 nucleotides, wherein the sense strand is 21-26 nucleotides in length and wherein the antisense strand is 23-38 nucleotides in length and includes a single-stranded overhang of 1-2 nucleotides at its 3'-terminus; and

g) wherein the antisense strand further comprises a single-stranded overhang of 1-5 nucleotides at its 5'-terminus.

15. The pharmaceutical composition of claim 13, wherein the region of complementarity between the sense strand and the antisense strand is 19 nucleotides, wherein the sense strand is 21 nucleotides in length and includes a single-stranded overhang of 2 nucleotides at its 3'-terminus and wherein the antisense strand is 21 nucleotides in length and includes a single-stranded overhang of 2 nucleotides at its 3'-terminus.

16. The pharmaceutical composition of claim 13, wherein the region of complementarity between the sense strand and the antisense strand is 21 nucleotides, wherein the sense strand is 21 nucleotides in length and wherein the antisense strand is 23 nucleotides in length and includes a single-stranded overhang of 2 nucleotides at its 3'-terminus.

17. The pharmaceutical composition of any one of the preceding claims, wherein the KRAS nucleic acid inhibitor molecule is formulated with a lipid nanoparticle; wherein the lipid nanoparticle comprises a cationic lipid and a pegylated lipid.

18. The pharmaceutical composition of claim 13, wherein the sense strand comprises or consists of the sequence of SEQ ID NO: 13; and wherein the antisense strand comprises or consists of the sequence of SEQ ID NO: 14 or SEQ ID NO: 18.

19. The pharmaceutical composition of claim 13, wherein the sense strand comprises or consists of the sequence of one of SEQ ID NO: 15; and wherein the antisense sense strand comprises or consists of the sequence of one of SEQ ID NO: 16 or 19.

20. The pharmaceutical composition of claim 14, wherein:

- (a) the sense strand comprises or consists of the sequence of SEQ ID NO: 3 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 4;
- (b) the sense strand comprises or consists of the sequence of SEQ ID NO: 1 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 2;
- (c) the sense strand comprises or consists of the sequence of SEQ ID NO: 5 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 6;
- (d) the sense strand comprises or consists of the sequence of SEQ ID NO: 7 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 8;
- (e) the sense strand comprises or consists of the sequence of SEQ ID NO: 9 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 10;
- (f) the sense strand comprises or consists of the sequence of SEQ ID NO: 11 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 12;
- (g) the sense strand comprises or consists of the sequence of SEQ ID NO: 7 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 17;
- (h) the sense strand comprises or consists of the sequence of SEQ ID NO: 13 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 18;
- (i) the sense strand comprises or consists of the sequence of SEQ ID NO: 15 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 19;
- (j) the sense strand comprises or consists of the sequence of SEQ ID NO: 13 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 14; or
- (k) the sense strand comprises or consists of the sequence of SEQ ID NO: 15 and the antisense sense strand comprises or consists of the sequence of SEQ ID NO: 16.

21. Use of the pharmaceutical composition of any one of claims 1-3, 5-9, 13-20, in the manufacture of a medicament for the treatment of a KRAS-associated cancer in a subject, wherein the medicament is to be administered to the subject.

22. Use of a therapeutically effective amount of a KRAS nucleic acid inhibitor molecule and a therapeutically effective amount of an immunotherapeutic agent in the manufacture of a medicament for the treatment of a KRAS-associated cancer in a subject, wherein the medicament is to be administered to the subject.

23. The use of claim 22 wherein:

- i) the immunotherapeutic agent is an antagonist of an inhibitory immune checkpoint molecule or an agonist of a co-stimulatory checkpoint molecule;
- ii) the immunotherapeutic agent is an antagonist of an inhibitory check point, and the inhibitory check point is PD-1 or PD-L1; and
- iii) the antagonist of the inhibitory immune checkpoint molecule or the agonist of the co-stimulatory checkpoint molecule is a monoclonal antibody.

24. The use of any one of claims 21-23 wherein the KRAS-associated cancer is pancreatic cancer.