

due to inhibition of MAPK signaling in normal cells. This might limit the utility for combining such agents with standard-of-care or immunotherapy. Thus, there exists a significant unmet need for the development of tumor-selective therapies that do not introduce liabilities for normal cells.

5 *KRAS p.G12C* is present in approximately 13% of lung adenocarcinoma, 3% of colorectal cancer, and 2% of other solid tumors. The mutant cysteine of *KRAS*^{G12C} resides adjacent to a pocket (P2) present in the inactive GDP-bound form of *KRAS*. The proximity of P2 and a mutant cysteine led to a broad search for covalent inhibitors. The first reported electrophile screen of *KRAS*^{G12C} led to the eventual identification of ARS-1620, which
10 demonstrates in vivo efficacy in preclinical *KRAS p.G12C* models. While Araxes Pharma's ARS-1620 was a milestone for proof-of-concept, mutant-selective *KRAS* inhibition, it was positioned as a tool compound for preclinical studies. The scientists at Amgen, Inc. identified a series of novel acrylamide-based molecules that utilize a previously unexploited surface groove in *KRAS*^{G12C} to substantially enhance potency and selectivity. Intensive electrophile-
15 screening and structure-based design culminated in the discovery of AMG 510, the first *KRAS*^{G12C} inhibitor to reach clinical testing in humans (See www.clinicaltrials.gov NCT03600883). The present invention comprises the compelling preclinical activity of AMG 510, its ability to enhance tumor-cell killing as monotherapy or when combined with other therapies, and the dramatic impact on immune cell infiltration which renders the tumor
20 microenvironment exquisitely sensitive to immunotherapy. Preliminary evidence for clinical efficacy is also presented herein.

SUMMARY

In one aspect, the present disclosure refers to the use of (1*M*)-6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2*S*)-2-methyl-4-(2-propenoyl)-
25 1-piperazinyl)pyrido[2,3-*d*]pyrimidin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof, and at least one additional pharmaceutically active agent in the manufacture of a ~~pharmaceutical composition~~medicament for treating cancer mediated by a *KRAS* G12C mutation in an adult patient, wherein at least one additional pharmaceutically active agent is

- 30 (a) Carboplatin;
 (b) An anti-PD-1 antibody, wherein the anti-PD-1 antibody is perbrolizumab or nivolumab;
 (c) a MEK inhibitor, wherein the MEK inhibitor is trametinib;

(d) an EGFR inhibitor, wherein the EGFR inhibitor is afatinib, erlotinib, lapatinib, cetuximab, or panitumumab; ~~an mTOR inhibitor,~~

(e) a SHP2 inhibitor, wherein the SHP2 inhibitor is RMC 4550;

(f) a PI3K inhibitor, wherein the PI3K inhibitor is AMG511 or buparlisib; or

(g) an AKT inhibitor, wherein the AKT inhibitor is AZD5353.

In another aspect, the present disclosure refers to the use of (1M)-6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a first medicament and at least one additional pharmaceutically active agent in the manufacture of at least one further medicament wherein the first and the at least one further medicament are to be used in combination therapy for treating cancer mediated by a KRAS G12C mutation in an adult patient, wherein at least one additional pharmaceutically active agent is

(a) carboplatin;

(b) an anti-PD-1 antibody, wherein the anti-PD-1 antibody is pembrolizumab or nivolumab;

(c) a MEK inhibitor, wherein the MEK inhibitor is trametinib;

(d) an EGFR inhibitor, wherein the EGFR inhibitor is afatinib, erlotinib, lapatinib, cetuximab, or panitumumab; ~~an mTOR inhibitor,~~

(e) a SHP2 inhibitor, wherein the SHP2 inhibitor is RMC 4550;

(f) a PI3K inhibitor, wherein the PI3K inhibitor is AMG511 or buparlisib; or

(g) an AKT inhibitor, wherein the AKT inhibitor is AZD5353.

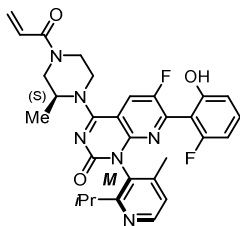
In yet another aspect, the present disclosure refers to the use of (1M)-6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one, or a pharmaceutically acceptable salt thereof, and at least one additional pharmaceutically active agent in the manufacture of a medicament for treating cancer mediated by a KRAS G12C mutation, wherein the at least one additional pharmaceutically active agent is a SHP2 inhibitor and wherein the SHP2 inhibitor is RMC 4630.

In yet another aspect, the present disclosure refers to the use of (1M)-6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a first medicament and at least one additional

pharmaceutically active agent in the manufacture of at least one further medicament wherein the first and the at least one further medicament are to be used in combination therapy for treating cancer mediated by a KRAS G12C mutation, wherein the at least one additional pharmaceutically active agent is a SHP2 inhibitor and wherein the SHP2 inhibitor is RMC 4630.

The present disclosure also refers to the following:

The present disclosure comprises a pharmaceutical composition comprising



AMG 510, or a pharmaceutically acceptable salt thereof; and one or more therapeutic or pharmaceutically active agents; and a pharmaceutically acceptable excipient.

The present disclosure further comprises a method of treating cancers, such as solid tumors, including but not limited to lung, colon and pancreatic cancer with a combination of AMG 510, or a pharmaceutically acceptable salt, and at least one therapeutic agent, wherein the therapeutic agent is selected from an anti-PD-1 antibody, a chemotherapeutic agent, a MEK inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, PI3K inhibitor, and an AKT inhibitor.

The present disclosure further comprises an isolated cell line comprising two KRAS^{G12C} alleles, wherein the cell line is CT-26 *KRAS p.G12C*.

The present disclosure further comprises a method of generating a cell line comprising two KRAS^{G12C} alleles, the method comprising:

a) incubating a cell line comprising two KRAS^{G12D} alleles with a CRISPR construct that induces the replacement of a nucleotide on both the two KRAS alleles such that two KRAS^{G12C} alleles are formed; and

b) isolating the cell line comprising the two KRAS^{G12C} alleles.

FIRST SET OF EXAMPLES

1. In one example of the present disclosure, the present disclosure comprises a method of treating pancreatic cancer, the method comprising administering to a patient in need

CLAIMS

What is claimed is:

1. Use of (1M)-6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one, or a pharmaceutically acceptable salt thereof, and at least one additional pharmaceutically active agent in the manufacture of a medicament~~pharmaceutical composition~~ for treating cancer mediated by a KRAS G12C mutation in an adult patient, wherein the at least one additional pharmaceutically active agent is
 - (a) carboplatin;
 - (b) an anti-PD-1 antibody, wherein the anti-PD-1 antibody is pembrolizumab or nivolumab;
 - (c) a MEK inhibitor, wherein the MEK inhibitor is trametinib;
 - (d) an EGFR inhibitor, wherein the EGFR inhibitor is afatinib, erlotinib, lapatinib, cetuximab, or panitumumab;
 - (e) ~~an mTOR inhibitor~~, a SHP2 inhibitor, wherein the SHP2 inhibitor is RMC 4550;
 - (f) a PI3K inhibitor, wherein the PI3K inhibitor is AMG 511 or buparlisib; or
 - (g) an AKT inhibitor, wherein the AKT inhibitor is AZD5363.
2. -Use of (1M)-6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a first medicament and at least one additional pharmaceutically active agent in the manufacture of at least one further medicament wherein the first and the at least one further medicament are to be used in combination therapy for treating cancer mediated by a KRAS G12C mutation in an adult patient, wherein the at least one additional pharmaceutically active agent is
 - (a) carboplatin;
 - (b) an anti-PD-1 antibody, wherein the anti-PD-1 antibody is pembrolizumab or nivolumab;
 - (c) a MEK inhibitor, wherein the MEK inhibitor is trametinib;
 - (d) an EGFR inhibitor, wherein the EGFR inhibitor is afatinib, erlotinib, lapatinib, cetuximab, or panitumumab;
 - (e) ~~an mTOR inhibitor~~, a SHP2 inhibitor, wherein the SHP2 inhibitor is RMC 4550;
 - (f) a PI3K inhibitor, wherein the PI3K inhibitor is AMG 511 or buparlisib; or

(g) an AKT inhibitor, wherein the AKT inhibitor is AZD5363.

3. Use of (1M)-6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one, or a pharmaceutically acceptable salt thereof, and at least one additional pharmaceutically active agent in the manufacture of a medicament for treating cancer mediated by a KRAS G12C mutation, wherein the at least one additional pharmaceutically active agent is a SHP2 inhibitor and wherein the SHP2 inhibitor is RMC 4630.

4. Use of (1M)-6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a first medicament and at least one additional pharmaceutically active agent in the manufacture of at least one further medicament wherein the first and the at least one further medicament are to be used in combination therapy for treating cancer mediated by a KRAS G12C mutation, wherein the at least one additional pharmaceutically active agent is a SHP2 inhibitor and wherein the SHP2 inhibitor is RMC 4630.

53. The use of any one of claims 1 to 4 ~~claim 1 or 2~~, wherein the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, appendix cancer, endometrial cancer, ~~esophageal cancer~~, gastric cancer, small intestine cancer, nasal cavity cancer, ~~paranasal sinus cancer~~, bile duct cancer, ~~or~~ skin cancer, ~~or intraocular melanoma~~.

64. The use of any one of claims 1 to 53, wherein the cancer is pancreatic cancer.

75. The use of any one of claims 1 to 53, wherein the cancer is colorectal cancer.

86. The use of any one of claims 1 to 53, wherein the cancer is non-small cell lung cancer.

97. The use of any one of claims 1, 2 and 5 to 86, wherein the at least one additional pharmaceutically active agent is carboplatin.

108. The use of any one of claims 1, 2, and 5 to 8 ~~to 6~~, wherein the at least one additional pharmaceutically active agent is an anti-PD-1 ~~antibody inhibitor~~.

9. ~~The use of any one of claims 1 to 6 and 8, wherein the anti PD-1 inhibitor is AMG 404, pembrolizumab, and nivolumab.~~

1140. The use of ~~claim 10, any one of claims 1 to 6 and 8~~ wherein the anti-PD-1 ~~antibody inhibitor~~ is pembrolizumab.

1244. The use of ~~claim 10, any one of claims 1 to 6 and 8~~ wherein the anti-PD-1 ~~inhibitor antibody~~ is nivolumab.

12. ~~The use of any one of claims 1-6 and 8, wherein the anti PD-1 antibody comprises a heavy chain (HC) complementarity determining region (CDR) 1 amino acid sequence comprising SEQ ID NO: 1, an HC CDR2 amino acid sequence comprising SEQ ID NO: 2; an HC CDR3 amino acid sequence comprising SEQ ID NO: 3; a light chain (LC) CDR1 amino acid sequence comprising SEQ ID NO: 4; an LC CDR2 amino acid sequence comprising SEQ ID NO: 5; and an LC CDR3 amino acid sequence comprising SEQ ID NO: 6.~~
13. ~~The use of any one of claims 1-6 and 8, wherein the anti PD-1 antibody comprises the heavy chain variable region sequence of SEQ ID NO: 7 and the light chain variable region of SEQ ID NO: 8.~~
14. ~~The use of any one of claims 1-6 and 8, wherein the anti PD-1 antibody comprises the heavy chain sequence of SEQ ID NO: 9 and the light chain sequence of SEQ ID NO: 10.~~
15. ~~The use of any one of claims 1-6 and 8, wherein the anti PD-1 antibody is AMG 404.~~
1346. The use of any one of claims 1, 2, and 5-8-6, wherein the at least one additional pharmaceutically active agent is a MEK inhibitor and wherein the MEK inhibitor is trametinib.
17. ~~The use of claims 1-16, wherein the MEK inhibitor is trametinib, pimasertib, PD-325901, MEK162, TAK-733, GDC-0973 or AZD8330.~~
18. ~~The use of claim 17, wherein the MEK inhibitor is trametinib.~~
1419. The use of any one of claims 1, 2, and 5 to 8-6, wherein the at least one additional pharmaceutically active agent is an EGFR inhibitor.
1520. The use of claim 1419, wherein the EGFR inhibitor is afatinib, erlotinib, or lapatinib, ~~cetuximab, or panitumumab.~~
1621. The use of claim 1420, wherein the EGFR inhibitor is cetuximabafatinib.
1722. The use of claim 1420, wherein the EGFR inhibitor is panitumumab.
1823. The use of any one of claims 1, 2, and 5 to 8-6, wherein the at least one additional pharmaceutically active agent is a SHP2 inhibitor and wherein the SHP2 inhibitor is RMC 4550.
24. ~~The use of claim 23, wherein the SHP2 inhibitor is RMC 4550.~~
25. ~~The use of claim 23, wherein the SHP2 inhibitor is RMC 4630.~~
26. ~~The use of any one of claims 1-6, wherein the at least one additional pharmaceutically active agent is an mTOR inhibitor.~~
27. ~~The use of claim 26, wherein the mTOR inhibitor is everolimus.~~

1928. The use of any one of claims 1, 2, and 5 to 8-6, wherein the at least one additional pharmaceutically active agent is a PI3K inhibitor.

~~29. — The use of claim 28, wherein the PI3K inhibitor is AMG 511 or buparlisib.~~

2030. The use of claim 1929, wherein the PI3K inhibitor is AMG 511.

5 2134. The use of claim 1929, wherein the PI3K inhibitor is buparlisib.

2232. The use of any one of claims 1, 2, and 5 to 8-6, wherein the at least one additional pharmaceutically active agent is an AKT inhibitor and wherein the AKT inhibitor is AZD5363.

~~33. — The use of claim 32, wherein the AKT inhibitor is AZD5363.~~

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