

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 microenvironment exquisitely
20 sensitive to immunotherapy. Preliminary evidence for clinical efficacy is also presented herein.

SUMMARY

In one aspect, the present disclosure refers to the use of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one, or a pharmaceutically acceptable salt
25 thereof, and carboplatin in the manufacture of a medicament for treating cancer mediated by a KRAS G12C mutation in an adult patient

In another aspect, the present disclosure refers to the use of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof, in the manufacture of a first medicament and carboplatin 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 non-small cell lung cancer mediated by a KRAS G12C mutation in an adult patient.

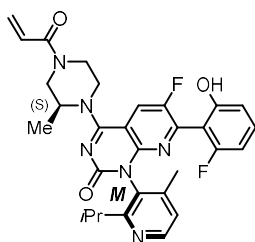
In yet another aspect, the present disclosure refers to the use of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof, and panitumumab in the manufacture of a medicament for treating colorectal cancer mediated by a KRAS G12C mutation in an adult patient.

In yet another aspect, the present disclosure refers to the use of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one, or a pharmaceutically acceptable

salt thereof in the manufacture of a first medicament and panitumumab 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 colorectal cancer mediated by a KRAS G12C mutation in an adult patient.

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 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof, and carboplatin in the manufacture of a medicament for treating non-small cell lung cancer mediated by a KRAS G12C mutation in an adult patient.
2. Use of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof, in the manufacture of a first medicament and carboplatin 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 non-small cell lung cancer mediated by a KRAS G12C mutation in an adult patient.
3. Use of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof, and panitumumab in the manufacture of a medicament for treating colorectal cancer mediated by a KRAS G12C mutation in an adult patient.
4. Use of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof, in the manufacture of a first medicament and panitumumab 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 colorectal cancer mediated by a KRAS G12C mutation in an adult patient.