

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.

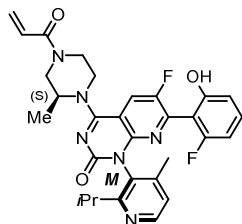
SUMMARY

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 for treating cancer, wherein at least one additional pharmaceutically active agent is carboplatin, an anti-PD-1 antibody, a MEK inhibitor, an EGFR inhibitor, an mTOR inhibitor, a SHP2 inhibitor, a PI3K inhibitor, or an AKT inhibitor.

30 In another 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)-1-piperazinyl)pyrido[2,3-*d*]pyrimidin-2(1*H*)-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, wherein at least one additional pharmaceutically active agent is carboplatin, an anti-PD-1 antibody, a MEK inhibitor, an EGFR inhibitor, an mTOR inhibitor, a SHP2 inhibitor, a PI3K inhibitor, or an AKT inhibitor. 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

thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and at least one chemotherapeutic agent.

2. In another example of the present disclosure, the present disclosure comprises a method of treating colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and at least one chemotherapeutic agent.

3. In another example of the present disclosure, the present disclosure comprises the method of example 2 wherein the colon cancer has a *KRAS p.G12C* mutation.

4. In another example of the present disclosure, the present disclosure comprises a method of treating lung cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a chemotherapeutic agent.

In some such examples, the lung cancer is non-small cell lung carcinoma.

5. In another example of the present disclosure, the present disclosure comprises the method of example 1, wherein the pancreatic cancer has a *KRAS p.G12C* mutation.

6. In another example of the present disclosure, the present disclosure comprises the method of any one of examples 1-5, wherein the chemotherapeutic agent is carboplatin.

7. In another example of the present disclosure, the present disclosure comprises a method of treating pancreatic cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a MEK inhibitor.

8. In another example of the present disclosure, the present disclosure comprises a method of treating colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a MEK inhibitor.

9. In another example of the present disclosure, the present disclosure comprises a method of treating lung cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a MEK inhibitor.

10. In another example of the present disclosure, the present disclosure comprises the method of example 9 wherein the lung cancer has a *p.KRAS G12C* mutation.

11. In another example of the present disclosure, the present disclosure comprises the method of any one of examples 7-10 wherein the MEK inhibitor is trametinib.

12. In another example of the present disclosure, the present disclosure comprises the method of any one of examples 7-10 wherein the MEK inhibitor is pimasertib, PD-325901, MEK162, TAK-733, GDC-0973 or AZD8330.

13. In another example of the present disclosure, the present disclosure comprises a method of treating pancreatic cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and an EGFR inhibitor.

14. In another example of the present disclosure, the present disclosure comprises a method of treating colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a EGFR inhibitor.

15. In another example of the present disclosure, the present disclosure comprises a method of treating lung cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a EGFR inhibitor.

16. In another example of the present disclosure, the present disclosure comprises the method of any one of examples 13-15 wherein the EGFR inhibitor is afatinib.

17. In another example of the present disclosure, the present disclosure comprises the method of any one of examples 13 and 15 wherein the EGFR inhibitor is erlotinib.

18. In another example of the present disclosure, the present disclosure comprises the method of example 15 wherein the EGFR inhibitor is lapatinib.

19. In another example of the present disclosure, the present disclosure comprises a method of treating pancreatic cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a SHP2 inhibitor.

20. In another example of the present disclosure, the present disclosure comprises a method of treating colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a SHP2 inhibitor.

21. In another example of the present disclosure, the present disclosure comprises a method of treating lung cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a SHP2 inhibitor.

22. In another example of the present disclosure, the present disclosure comprises the method of any one of examples 19-21 wherein the SHP2 inhibitor is selected from is RMC-4550

23. In another example of the present disclosure, the present disclosure comprises the method of example 22 wherein the SHP2 inhibitor is RMC 4550.

24. In another example of the present disclosure, the present disclosure comprises a method of treating pancreatic cancer, the method comprising administering to a patient in
5 need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a PI3K inhibitor.

25. In another example of the present disclosure, the present disclosure comprises a method of treating colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a PI3K inhibitor.

26. In another example of the present disclosure, the present disclosure comprises
10 a method of treating lung cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a PI3K inhibitor.

27. In another example of the present disclosure, the present disclosure comprises the method of any one of examples 24-26 wherein the PI3K inhibitor is AMG 511.

28. In another example of the present disclosure, the present disclosure comprises
15 the method of example 26 wherein the PI3K inhibitor is buparlisib.

29. In another example of the present disclosure, the present disclosure comprises a method of treating pancreatic cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and an AKT inhibitor.

30. In another example of the present disclosure, the present disclosure comprises
20 a method of treating lung cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a AKT inhibitor.

31. In another example of the present disclosure, the present disclosure comprises the method of any one of examples 29-30 wherein the AKT inhibitor is AZD5363.

32. In another example of the present disclosure, the present disclosure comprises
25 a method of treating colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and a EGFR antibody.

33. In another example of the present disclosure, the present disclosure comprises the method of example 32 wherein the EGFR antibody is cetuximab.

32. In another example of the present disclosure, the present disclosure comprises a method of treating colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and an anti-PD-1 antibody.

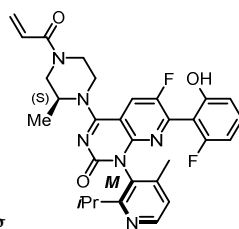
33. In another example of the present disclosure, the present disclosure comprises the method of example 32 wherein the anti-PD-1 antibody is selected from AMG 404, pembrolizumab and nivolumab.

34. In another example of the present disclosure, the present disclosure comprises the method of example 33 wherein the anti-PD-1 antibody is pembrolizumab.

35. In another example of the present disclosure, the present disclosure comprises the method of example 33 wherein the anti-PD-1 antibody is AMG 404.

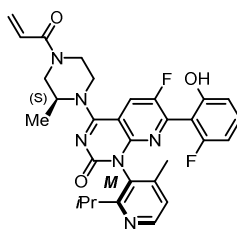
36. In another example of the present disclosure, the present disclosure comprises the method of example 33 wherein the anti-PD-1 antibody is nivolumab.

37. In another example of the present disclosure, the present disclosure comprises



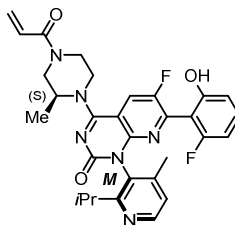
a pharmaceutical composition comprising , or a pharmaceutically acceptable salt thereof; carboplatin; and a pharmaceutically acceptable excipient.

38. In another example of the present disclosure, the present disclosure comprises



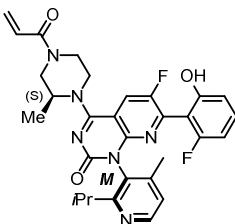
a pharmaceutical composition comprising , or a pharmaceutically acceptable salt thereof; trametinib; and a pharmaceutically acceptable excipient.

39. In another example of the present disclosure, the present disclosure comprises



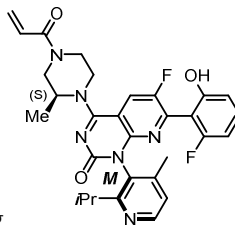
a pharmaceutical composition comprising: , or a pharmaceutically acceptable salt thereof; afatinib; and a pharmaceutically acceptable excipient.

40. In another example of the present disclosure, the present disclosure comprises



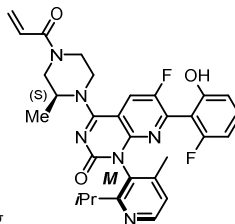
5 a pharmaceutical composition comprising , or a pharmaceutically acceptable salt thereof; erlotinib; and a pharmaceutically acceptable excipient.

41. In another example of the present disclosure, the present disclosure comprises



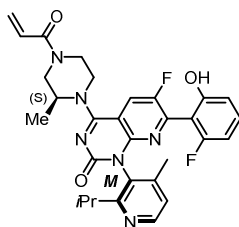
a pharmaceutical composition comprising , or a pharmaceutically acceptable salt thereof; lapatinib; and a pharmaceutically acceptable excipient.

10 42. In another example of the present disclosure, the present disclosure comprises



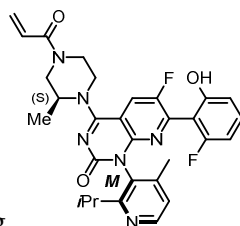
a pharmaceutical composition comprising , or a pharmaceutically acceptable salt thereof; RMC-4550; and a pharmaceutically acceptable excipient.

43. In another example of the present disclosure, the present disclosure comprises



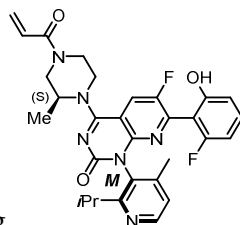
a pharmaceutical composition comprising , or a pharmaceutically acceptable salt thereof; AMG 511; and a pharmaceutically acceptable excipient.

44. In another example of the present disclosure, the present disclosure comprises



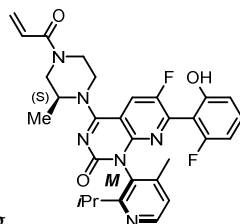
5 a pharmaceutical composition comprising , or a pharmaceutically acceptable salt thereof; buparlisib; and a pharmaceutically acceptable excipient.

45. In another example of the present disclosure, the present disclosure comprises



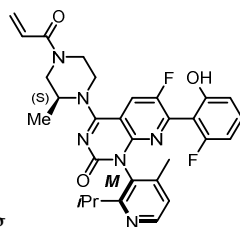
a pharmaceutical composition comprising , or a pharmaceutically acceptable salt thereof; AZD5363; and a pharmaceutically acceptable excipient.

10 46. In another example of the present disclosure, the present disclosure comprises



a pharmaceutical composition comprising , or a pharmaceutically acceptable salt thereof; cetuximab; and a pharmaceutically acceptable excipient.

47. In another example of the present disclosure, the present disclosure comprises



60. In another example of the present disclosure, the present disclosure comprises a combination of an KRAS^{G12C} inhibitor medicament and an EGFR inhibitor medicament for treating a solid tumor.

61. In another example of the present disclosure, the present disclosure comprises a combination of an KRAS^{G12C} inhibitor medicament and an EGFR inhibitor medicament for treating lung cancer.

62. In another example of the present disclosure, the present disclosure comprises a combination of an KRAS^{G12C} inhibitor medicament and an EGFR inhibitor medicament for treating colon cancer.

63. In another example of the present disclosure, the present disclosure comprises a combination of an KRAS^{G12C} inhibitor medicament and an EGFR inhibitor medicament for treating pancreatic cancer.

64. In another example of the present disclosure, the present disclosure comprises a combination of an KRAS^{G12C} inhibitor medicament and an anti-PD-1 antibody medicament for treating a solid tumor.

65. In another example of the present disclosure, the present disclosure comprises a combination of an KRAS^{G12C} inhibitor medicament and an anti-PD-1 antibody medicament for treating lung cancer.

66. In another example of the present disclosure, the present disclosure comprises a combination of an KRAS^{G12C} inhibitor medicament and an anti-PD-1 antibody medicament for treating colon cancer.

67. In another example of the present disclosure, the present disclosure comprises a combination of an KRAS^{G12C} inhibitor medicament and an anti-PD-1 antibody medicament for treating pancreatic cancer.

68. In another example of the present disclosure, the present disclosure comprises a use of an KRAS^{G12C} inhibitor in combination with a chemotherapeutic agent for manufacture of a medicament for the management or treatment of pancreatic cancer, lung cancer, or colon cancer in a subject.

69. In another example of the present disclosure, the present disclosure comprises a use of an KRAS^{G12C} inhibitor in combination with a MEK inhibitor for manufacture of a

medicament for the management or treatment of pancreatic cancer, lung cancer, or colon cancer in a subject.

70. In another example of the present disclosure, the present disclosure comprises a use of an KRAS^{G12C} inhibitor in combination with a EGFR inhibitor for manufacture of a medicament for the management or treatment of pancreatic cancer, lung cancer, or colon cancer in a subject.

71. In another example of the present disclosure, the present disclosure comprises a use of an KRAS^{G12C} inhibitor in combination with an anti-PD-1 antibody for manufacture of a medicament for the management or treatment of pancreatic cancer, lung cancer, or colon cancer in a subject.

72. In another example of the present disclosure, the present disclosure comprises an isolated cell line comprising two KRAS^{G12C} alleles.

73. In another example of the present disclosure, the present disclosure comprises the cell line of example 68, wherein the cell line is CT-26 *KRAS p.G12C*.

74. In another example of the present disclosure, the present disclosure 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.

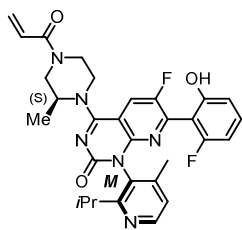
75. In another example of the present disclosure, the present disclosure comprises the method of example 70, wherein the CRISPR construct comprises a sequence CTTGTGATGGTTGGAGCTGA (SEQ ID NO.: 21).

76. In another example of the present disclosure, the present disclosure comprises a method of treating cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an KRAS^{G12C} inhibitor and at least one additional chemotherapeutic agent.

77. In another example of the present disclosure, the present disclosure comprises a combination of an KRAS^{G12C} inhibitor medicament and an anti-PD-1 antibody medicament for treating a solid tumor.

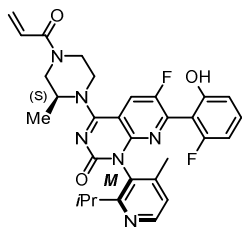
78. In another example of the present disclosure, the present disclosure comprises a use of an KRAS^{G12C} inhibitor in combination with at least one additional chemotherapeutic agent for the manufacture of a medicament for the management or treatment of pancreatic cancer, lung cancer, or colon cancer in a subject.

5 79. In another example of the present disclosure, the present disclosure comprises the method of example 76, wherein the KRAS^{G12C} inhibitor is



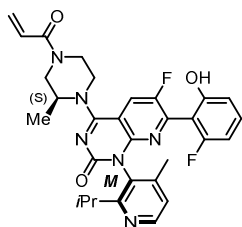
, or a pharmaceutically acceptable salt thereof.

80. In another example of the present disclosure, the present disclosure comprises the combination of example 77, wherein the KRAS^{G12C} inhibitor is



10 , or a pharmaceutically acceptable salt thereof.

81. In another example of the present disclosure, the present disclosure comprises the use of example 78, wherein the KRAS^{G12C} inhibitor is



, or a pharmaceutically acceptable salt thereof.

82. In another example of the present disclosure, the present disclosure comprises
15 the use of example 78, wherein the lung cancer is a non-small cell lung carcinoma (NSCLC).

SECOND SET OF EXAMPLES

1. In another example of the present disclosure, the present disclosure relates to a method of treating cancer, the method comprising administering to a patient in need thereof a

inhibitor, an EGFR inhibitor, TOR inhibitor, SHP2 inhibitor, a PI3K inhibitor or an AKT inhibitor.

13. In a further example, the method of example 12, wherein the at least one additional pharmaceutically active agent is carboplatin.

5 14. In a further example, the method of example 12, wherein the at least one additional pharmaceutically active agent is an anti-PD-1 inhibitor.

15. In a further example, the method of example 14, wherein the anti-PD-1 inhibitor is selected from AMG 404, pembrolizumab, and nivolumab.

10 16. In a further example, the method of example 15 wherein the anti-PD-1 inhibitor is pembrolizumab.

17. In a further example, the method of example 15 wherein the anti-PD-1 inhibitor is AMG 404.

18. In a further example, the method of example 15 wherein the anti-PD-1 inhibitor is nivolumab.

15 19. In a further example, the method of example 12, wherein the at least one additional pharmaceutically active agent is a MEK inhibitor.

20. In a further example, the method of example 19, wherein the MEK inhibitor is trametinib, pimasertib, PD-325901, MEK162, TAK-733, GDC-0973 or AZD8330.

20 21. In a further example, the method of example 20, wherein the MEK inhibitor is trametinib.

22. In a further example, the method of example 12, wherein the at least one additional pharmaceutically active agent is an EGFR inhibitor.

23. In a further example, the method of example 22, wherein the EGFR inhibitor is afatinib, erlotinib, lapatinib, or cetuximab.

25 24. In a further example, the method of example 23, wherein the EGFR inhibitor is afatinib.

25. In a further example, the method of example 23, wherein the EGFR inhibitor is cetuximab.

26. In a further example, the method of example 12, wherein the at least one additional pharmaceutically active agent is a SHP2 inhibitor.

27. In a further example, the method of example 26, wherein the SHP2 inhibitor is RMC 4550.

5 28. In a further example, the method of example 26, wherein the SHP2 inhibitor is RMC 4630.

29. In a further example, the method of example 12, wherein the at least one additional pharmaceutically active agent is a PI3K inhibitor.

30. In a further example, the method of example 29, wherein the PI3K inhibitor is
10 AMG 511 or buparlisib.

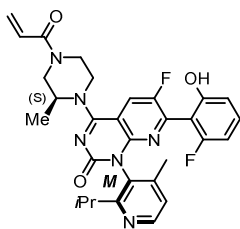
31. In a further example, the method of example 30, wherein the PI3K inhibitor is AMG 511.

32. In a further example, the method of example 30, wherein the PI3K inhibitor is buparlisib.

15 33. In a further example, the method of example 12, wherein the at least one additional pharmaceutically active agent is an AKT inhibitor.

34. In a further example, the method of example 33, wherein the AKT inhibitor is AZD5363.

35. In a further example, a pharmaceutical composition comprising



20 , or a pharmaceutically acceptable salt thereof; at least one additional pharmaceutically active agent; and a pharmaceutically acceptable excipient.

36. In a further example, the composition of example 35, wherein at least one additional pharmaceutically active agent is carboplatin, an anti-PD-1 inhibitor, a MEK inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, a PI3K inhibitor or an AKT
25 inhibitor.

37. In a further example, the composition of example 36, wherein at least one additional pharmaceutically active agent is carboplatin.

38. In a further example, the composition of example 36, wherein the at least one additional pharmaceutically active agent is an anti-PD-1 inhibitor.
39. In a further example, the composition of example 38, wherein the anti-PD-1 inhibitor is selected from AMG 404, pembrolizumab, and nivolumab.
- 5 40. In a further example, the composition of example 39 wherein the anti-PD-1 inhibitor is pembrolizumab.
41. In a further example, the composition of example 39 wherein the anti-PD-1 inhibitor is AMG 404.
42. In a further example, the composition of example 39 wherein the anti-PD-1
10 inhibitor is nivolumab.
43. In a further example, the composition of example 36, wherein the at least one additional pharmaceutically active agent is a MEK inhibitor.
44. In a further example, the composition of example 43, wherein the MEK inhibitor is trametinib, pimasertib, PD-325901, MEK162, TAK-733, GDC-0973 or AZD8330.
- 15 45. In a further example, the composition of example 44, wherein the MEK inhibitor is trametinib.
46. In a further example, the composition of example 36, wherein the at least one additional pharmaceutically active agent is an EGFR inhibitor.
47. In a further example, the composition of example 46, wherein the EGFR
20 inhibitor is afatinib, erlotinib, lapatinib, or cetuximab.
48. In a further example, the composition of example 47, wherein the EGFR inhibitor is afatinib.
49. In a further example, the composition of example 47, wherein the EGFR inhibitor is cetuximab.
- 25 50. In a further example, the composition of example 36, wherein the at least one additional pharmaceutically active agent is a SHP2 inhibitor.
51. In a further example, the composition of example 50, wherein the SHP2 inhibitor is RMC 4550.

52. In a further example, the composition of example 50, wherein the SHP2 inhibitor is RMC 4630.

53. In a further example, the composition of example 36, wherein the at least one additional pharmaceutically active agent is a PI3K inhibitor.

5 54. In a further example, the composition of example 53, wherein the PI3K inhibitor is AMG 511 or buparlisib.

55. In a further example, the composition of example 54, wherein the PI3K inhibitor is AMG 511.

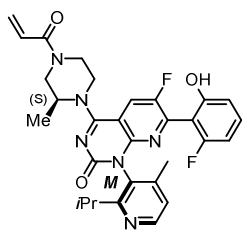
56. In a further example, the composition of example 54, wherein the PI3K inhibitor
10 is buparlisib.

57. In a further example, the composition of example 36, wherein the at least one additional pharmaceutically active agent is an AKT inhibitor.

58. In a further example, the composition of example 57, wherein the AKT inhibitor is AZD5363.

15 59. In a further example, a kit, the kit comprising: a KRAS^{G12C} inhibitor, or a pharmaceutically acceptable salt thereof; and at least one additional pharmaceutically active agent.

60. In a further example, the kit of example 59, wherein the KRAS^{G12C} inhibitor is



, or the pharmaceutically acceptable salt thereof.

20 61. In a further example, the kit of example 59, wherein at least one additional pharmaceutically active agent is carboplatin, an anti-PD-1 inhibitor, a MEK inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, a PI3K inhibitor or an AKT inhibitor.

62. In a further example, the kit of example 59, wherein at least one additional pharmaceutically active agent is carboplatin.

25 63. In a further example, the kit of example 59, wherein the at least one additional pharmaceutically active agent is an anti-PD-1 inhibitor.

64. In a further example, the kit of example 63, wherein the anti-PD-1 inhibitor is selected from AMG 404, pembrolizumab, and nivolumab.
65. In a further example, the kit of example 64 wherein the anti-PD-1 inhibitor is pembrolizumab.
- 5 66. In a further example, the kit of example 64 wherein the anti-PD-1 inhibitor is AMG 404.
67. In a further example, the kit of example 64 wherein the anti-PD-1 inhibitor is nivolumab.
68. In a further example, the kit of example 61, wherein the at least one additional
10 pharmaceutically active agent is a MEK inhibitor.
69. In a further example, the kit of example 68, wherein the MEK inhibitor is trametinib, pimasertib, PD-325901, MEK162, TAK-733, GDC-0973 or AZD8330.
70. In a further example, the kit of example 69, wherein the MEK inhibitor is trametinib.
- 15 71. In a further example, the kit of example 61, wherein the at least one additional pharmaceutically active agent is an EGFR inhibitor.
72. In a further example, the kit of example 61, wherein the EGFR inhibitor is afatinib, erlotinib, lapatinib, or cetuximab.
73. In a further example, the kit of example 62, wherein the EGFR inhibitor is
20 afatinib.
74. In a further example, the kit of example 62, wherein the EGFR inhibitor is cetuximab.
75. In a further example, the kit of example 61, wherein the at least one additional pharmaceutically active agent is a SHP2 inhibitor.
- 25 76. In a further example, the kit of example 75, wherein the SHP2 inhibitor is RMC 4550.
77. In a further example, the kit of example 75, wherein the SHP2 inhibitor is RMC 4630.

78. In a further example, the kit of example 61, wherein the at least one additional pharmaceutically active agent is a PI3K inhibitor.
79. In a further example, the kit of example 78, wherein the PI3K inhibitor is AMG 511 or buparlisib.
- 5 80. In a further example, the kit of example 79, wherein the PI3K inhibitor is AMG 511.
81. In a further example, the kit of example 79, wherein the PI3K inhibitor is buparlisib.
82. In a further example, the kit of example 61, wherein the at least one additional
10 pharmaceutically active agent is an AKT inhibitor.
83. In a further example, the kit of example 82, wherein the AKT inhibitor is AZD5363.
84. In a further example, the kit of example 59, wherein the kit is for treating cancer.
85. In a further example, the kit of example 84, wherein the cancer a *KRAS p.G12C*
15 mutation.
86. In a further example, the kit of example 84, wherein the cancer is pancreatic, colorectal, lung, appendix, endometrial, or small intestine cancer.
87. In a further example, the kit of example 86, wherein the cancer is pancreatic cancer.
- 20 88. In a further example, the kit of example 86, wherein the cancer is colorectal cancer.
89. In a further example, the kit of example 86, wherein the cancer is lung cancer.
90. In a further example, the kit of example 89, wherein the lung cancer is non-small cell lung cancer (NSCLC).
- 25 91. In a further example, the kit of example 86, wherein the cancer is appendix cancer.
92. In a further example, the kit of example 86, wherein the cancer is endometrial cancer.

103. In a further example, the compound of example 102, wherein the lung cancer is non-small cell lung cancer (NSCLC).
104. In a further example, the compound of example 99, wherein the cancer is appendix cancer.
- 5 105. In a further example, the compound of example 99, wherein the cancer is endometrial cancer.
106. In a further example, the compound of example 99, wherein the cancer is small intestine cancer.
- 10 107. In a further example, the compound of example 96, wherein the at least one additional pharmaceutically active agent is carboplatin, an anti-PD-1 inhibitor, a MEK inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, a PI3K inhibitor or an AKT inhibitor.
108. In a further example, the compound of example 107, wherein the at least one additional pharmaceutically active agent is carboplatin.
- 15 109. In a further example, the compound of example 107, wherein the at least one additional pharmaceutically active agent is an anti-PD-1 inhibitor.
110. In a further example, the compound of example 109, wherein the anti-PD-1 inhibitor is selected from AMG 404, pembrolizumab, and nivolumab.
- 20 111. In a further example, the compound of example 110 wherein the anti-PD-1 inhibitor is pembrolizumab.
112. In a further example, the compound of example 110 wherein the anti-PD-1 inhibitor is AMG 404.
113. In a further example, the compound of example 110 wherein the anti-PD-1 inhibitor is nivolumab.
- 25 114. In a further example, the compound of example 107, wherein the at least one additional pharmaceutically active agent is a MEK inhibitor.
115. In a further example, the compound of example 114, wherein the MEK inhibitor is trametinib, pimasertib, PD-325901, MEK162, TAK-733, GDC-0973 or AZD8330.
- 30 116. In a further example, the compound of example 115, wherein the MEK inhibitor is trametinib.

117. In a further example, the compound of example 107, wherein the at least one additional pharmaceutically active agent is an EGFR inhibitor.
118. In a further example, the compound of example 117, wherein the EGFR inhibitor is afatinib, erlotinib, lapatinib, or cetuximab.
- 5 119. In a further example, the compound of example 118, wherein the EGFR inhibitor is afatinib.
120. In a further example, the compound of example 118, wherein the EGFR inhibitor is cetuximab.
121. In a further example, the compound of example 107, wherein the at least one
10 additional pharmaceutically active agent is a SHP2 inhibitor.
122. In a further example, the compound of example 121, wherein the SHP2 inhibitor is RMC 4550.
123. In a further example, the compound of example 121, wherein the SHP2 inhibitor is RMC 4630.
- 15 124. In a further example, the compound of example 107, wherein the at least one additional pharmaceutically active agent is a PI3K inhibitor.
125. In a further example, the compound of example 124, wherein the PI3K inhibitor is AMG 511 or buparlisib.
126. In a further example, the compound of example 125, wherein the PI3K inhibitor
20 is AMG 511.
127. In a further example, the compound of example 125, wherein the PI3K inhibitor is buparlisib.
128. In a further example, the compound of example 107, wherein the at least one additional pharmaceutically active agent is an AKT inhibitor.
- 25 129. In a further example, the compound of example 128, wherein the AKT inhibitor is AZD5363.
130. In a further example, the method of example 1, wherein the KRAS^{G12C} inhibitor and the at least one additional pharmaceutically active agent are administered simultaneously.

131. In a further example, the method of example 1, wherein the KRAS^{G12C} inhibitor and the at least one additional pharmaceutically active agent are administered separately.

A further example of the disclosure includes the use of a combination comprising an KRAS^{G12C} inhibitor with another therapeutic agent selected from a chemotherapeutic agent, a PD-1 inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, or an AKT inhibitor. A further example of the disclosure includes the use of a combination for treatment of cancer, the combination comprising an KRAS^{G12C} inhibitor with another therapeutic agent selected from a chemotherapeutic agent, a PD-1 inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, or an AKT inhibitor. A further example of the disclosure includes a method of using a combination comprising an KRAS^{G12C} inhibitor with another therapeutic agent selected from a chemotherapeutic agent, a PD-1 inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, or an AKT inhibitor, for the treatment of cancer. A further example of the disclosure includes the use of a combination for treatment of cancer, the combination comprising a KRAS^{G12C} inhibitor with another therapeutic agent selected from a chemotherapeutic agent, a PD-1 inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, or an AKT inhibitor, wherein the use comprises self-administering the combination.

A further example of the disclosure includes a method of treating cancer comprising prescribing a combination further comprising an KRAS^{G12C} inhibitor with another therapeutic agent selected from a chemotherapeutic agent, a PD-1 inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, or an AKT inhibitor. A further example of the disclosure includes a method of treating cancer comprising prescribing to a subject in need thereof, a combination further comprising an KRAS^{G12C} inhibitor with another therapeutic agent selected from a chemotherapeutic agent, a PD-1 inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, or an AKT inhibitor.

A further example of the disclosure includes a method of treating cancer using a combination comprising a KRAS^{G12C} inhibitor with another therapeutic agent selected from a chemotherapeutic agent, a PD-1 inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, or an AKT inhibitor, wherein such method further comprises listing said combination in a formulary and directing a patient in need of such cancer

A further example of the disclosure includes a method of using a combination comprising a KRAS^{G12C} inhibitor with another therapeutic agent selected from a chemotherapeutic agent, a PD-1 inhibitor, a MEK inhibitor, a PI3K a selective inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, or an AKT inhibitor, for the treatment of cancer, wherein such method comprises purchasing said combination for self-administration by a patient in need of such cancer treatment.

A further example of the disclosure includes a method of treating cancer comprising instructing a subject in need of such treatment to administer a combination comprising an KRAS^{G12C} inhibitor with another therapeutic agent selected from a chemotherapeutic agent, an anti-PD-1 inhibitor, a MEK inhibitor, a PI3K a selective inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, or an AKT inhibitor.

A further example of the disclosure includes a process of treating cancer comprising

A] prescribing

B] selling or advertising to sell,

C] purchasing,

D] instructing to self-administer, or

E] administering

of a combination described herein, wherein the combination has been approved by a regulatory agency for the treatment of cancer, to a subject in need of cancer treatment.

A further example of the disclosure includes a method of supplying a combination comprising an KRAS^{G12C} inhibitor with another therapeutic agent selected from a chemotherapeutic agent, a PD-1 inhibitor, a MEK inhibitor, a PI3K a selective inhibitor, an EGFR inhibitor, a TOR inhibitor, a SHP2 inhibitor, or an AKT inhibitor for treating cancer, said method comprises reimbursing a physician, a formulary, a patient or an insurance company for the sale of said combination.

For clarity, the term “instructing” is meant to include information on a label approved by a regulatory agency, in addition to its commonly understood definition.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows AMG 510 in combination with carboplatin enhances the suppression of NCI-H358 NSCLC tumor growth.

Figure 2 shows AMG 510 combined with the MEK inhibitor PD-325901 results in enhanced efficacy in the NSCLC NCI-H358 xenograft model.

Figure 3 shows AMG 510 inhibits the *in vivo* growth of CT-26 *KRAS p.G12C* tumors.

Figure 4 shows AMG 510 combined with an anti-PD-1 antibody results in increased survival and durable cures in a mouse model of *KRAS p.G12C* mutant cancer.

Figure 5 shows AMG 510 treatment leads to increase in CD8+ and CD4+ T-cell infiltration in CT-26 G12C-H10 tumors.

Figure 6 shows AMG 510 treatment leads to increase in PD-L1 positive neutrophils in CT-26 G12C-H10 tumors.

Figure 7 shows the additivity excess matrix identifies regions of synergistic interaction.

Figure 8 shows the self-cross matrices model additivity experimentally.

Figure 9 shows AMG 510 synergizes with both RMC-4550 (SHP2i) and trametinib (MEKi) to achieve cell killing in NCI-H358 cell line.

Figure 10 shows the lack of single agent activity with afatinib or RMC-4550 may contribute to weaker synergy in MIA PaCA-2 cell line.

CLAIMS

What is claimed is:

1. 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 pharmaceutical composition for treating cancer, wherein at least one additional pharmaceutically active agent is carboplatin, an anti-PD-1 antibody, a MEK inhibitor, an EGFR inhibitor, an mTOR inhibitor, a SHP2 inhibitor, a PI3K inhibitor, or an AKT inhibitor.
2. 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, wherein at least one additional pharmaceutically active agent is carboplatin, an anti-PD-1 antibody, a MEK inhibitor, an EGFR inhibitor, an mTOR inhibitor, a SHP2 inhibitor, a PI3K inhibitor, or an AKT inhibitor.
3. The use of 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, skin cancer, or intraocular melanoma.
4. The use of any one of claims 1 to 3, wherein the cancer is pancreatic cancer.
5. The use of any one of claims 1 to 3, wherein the cancer is colorectal cancer.
6. The use of any one of claims 1 to 3, wherein the cancer is non-small cell lung cancer.
7. The use of any one of claims 1 to 6, wherein the at least one additional pharmaceutically active agent is carboplatin.
8. The use of any one of claims 1 to 6, wherein the at least one additional pharmaceutically active agent is an anti-PD-1 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.

10. The use of any one of claims 1 to 6 and 8 wherein the anti-PD-1 inhibitor is pembrolizumab.
11. The use of any one of claims 1 to 6 and 8 wherein the anti-PD-1 inhibitor is nivolumab.
- 5 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
10 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
15 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.
16. The use of any one of claims 1-6, wherein the at least one additional
20 pharmaceutically active agent is a MEK inhibitor.
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.
19. The use of any one of claims 1-6, wherein the at least one additional
25 pharmaceutically active agent is an EGFR inhibitor.
20. The use of claim 19, wherein the EGFR inhibitor is afatinib, erlotinib, lapatinib, cetuximab, or panitumumab.
21. The use of claim 20, wherein the EGFR inhibitor is afatinib.
22. The use of claim 20, wherein the EGFR inhibitor is panitumumab.
- 30 23. The use of any one of claims 1-6, wherein the at least one additional pharmaceutically active agent is a SHP2 inhibitor.
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.
28. The use of any one of claims 1-6, wherein the at least one additional
5 pharmaceutically active agent is a PI3K inhibitor.
29. The use of claim 28, wherein the PI3K inhibitor is AMG 511 or buparlisib.
30. The use of claim 29, wherein the PI3K inhibitor is AMG 511.
31. The use of claim 29, wherein the PI3K inhibitor is buparlisib.
32. The use of any one of claims 1-6, wherein the at least one additional
10 pharmaceutically active agent is an AKT inhibitor.
33. The use of claim 32, wherein the AKT inhibitor is AZD5363.