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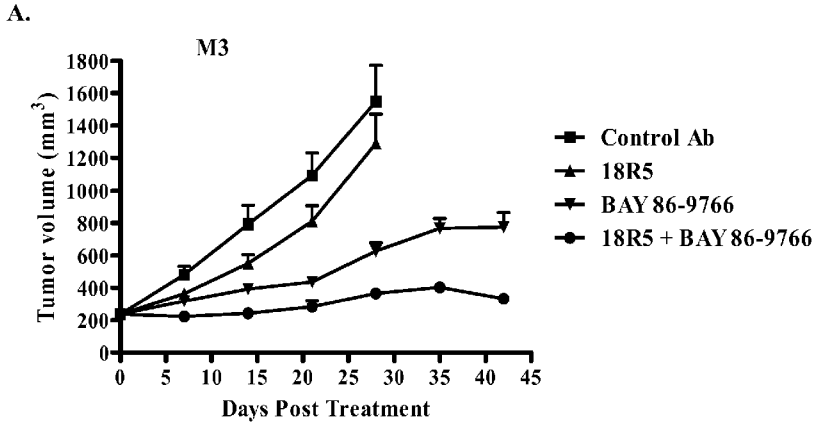
(54) Title: COMBINATION THERAPY FOR TREATMENT OF CANCER

Figure 1 A



(57) Abstract: The present invention provides methods comprising combination therapy for treating cancer. In particular, the present invention provides Wnt pathway inhibitors in combination with MAPK pathway inhibitors for the treatment of cancer and other diseases. In some embodiments, the MAPK pathway signaling activation is due to a mutation in a MAPK pathway component. In some embodiments, the MAPK pathway signaling component is Ras, Raf, MEK, or ERK.

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AMENDED CLAIMS
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1. A method of treating cancer in a subject comprising: administering to the subject a therapeutically effective amount of a Wnt pathway inhibitor in combination with a therapeutically effective amount of a mitogen-activated protein kinase (MAPK) pathway inhibitor.

2. A method of inhibiting tumor growth in a subject comprising: administering to the subject a therapeutically effective amount of a Wnt pathway inhibitor in combination with a therapeutically effective amount of a MAPK pathway inhibitor.

3. A method of inhibiting tumor growth comprising: contacting tumor cells with an effective amount of a Wnt pathway inhibitor in combination with an effective amount of a MAPK pathway inhibitor.

4. The method according to any one of claims 1-3, wherein the Wnt pathway inhibitor is:
   (a) an antibody;
   (b) an antibody that specifically binds at least one frizzled (FZD) protein or portion thereof; or
   (c) a soluble receptor.

5. The method of claim 4, wherein the antibody specifically binds:
   (a) at least one FZD protein selected from the group consisting of: FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, and FZD10;
   (b) FZD1, FZD2, FZD5, FZD7, and/or FZD8; or
   (c) FZD1, FZD2, FZD5, FZD7, and FZD8

6. The method of claim 4 or claim 5, wherein the antibody comprises:
   (a) a heavy chain CDR1 comprising GFTFSHYTLS (SEQ ID NO:5), a heavy chain CDR2 comprising VISGDGSYTYYADSVKG (SEQ ID NO:6), and a heavy chain CDR3 comprising NFIKYVFAN (SEQ ID NO:7), and
   (b) a light chain CDR1 comprising SGDNIGSFYVH (SEQ ID NO:8), a light chain CDR2 comprising DKSNRPSG (SEQ ID NO:9), and a light chain CDR3 comprising QSYANTLSL (SEQ ID NO:10).

7. The method according to any one of claims 4-6, wherein the antibody comprises:
   (a) a heavy chain variable region having at least 90% sequence identity to SEQ ID NO:3; and/or
   (b) a light chain variable region having at least 90% sequence identity to SEQ ID NO:4.

8. The method according to any one of claims 4-6, wherein the antibody comprises:
   (a) a heavy chain variable region comprising SEQ ID NO:3; and/or

(b) a light chain variable region comprising SEQ ID NO:4.

9. The method according to any one of claims 4-6, wherein the antibody comprises:
   (a) a heavy chain consisting essentially of SEQ ID NO:1 or SEQ ID NO:60; and
   (b) a light chain consisting essentially of SEQ ID NO:2 or SEQ ID NO:61.

10. The method according to any one of claims 4-6, wherein the antibody is 18R5.

11. The method according to any one of claims 1-3, wherein the Wnt pathway inhibitor is a Wnt-binding agent.

12. The method of claim 11, wherein the Wnt-binding agent is:
   (a) an antibody;
   (b) an antibody that specifically binds at least one Wnt protein selected from the group consisting of: Wnt1, Wnt2, Wnt2b, Wnt3, Wnt3a, Wnt7a, Wnt7b, Wnt8a, Wnt8b, Wnt10a, and Wnt10b; or
   (c) a soluble receptor.

13. The method according to any one of claims 4-9 or 12, wherein the antibody is a monoclonal antibody, a recombinant antibody, a chimeric antibody, a humanized antibody, a human antibody, an antibody fragment comprising an antigen-binding site, a bispecific antibody, an IgG1 antibody or an IgG2 antibody.

14. The method of claim 4 or claim 12, wherein the soluble receptor comprises a Fri domain of a human FZD protein.

15. The method of claim 14, wherein the Fri domain of the human FZD protein comprises the Fri domain of FZD1, Fri domain of FZD2, Fri domain of FZD3, Fri domain of FZD4, Fri domain of FZD5, Fri domain of FZD6, Fri domain of FZD7, Fri domain of FZD8, Fri domain of FZD9, or Fri domain of FZD10.

16. The method of claim 15, wherein the Fri domain of the human FZD protein consists essentially of the Fri domain of FZD8.

17. The method of claim 14, wherein the Fri domain of the human FZD protein comprises a sequence selected from the group consisting of: SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID

NO:20, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and SEQ ID NO:58.

18. The method of claim 17, wherein the Fri domain of the human FZD protein consists essentially of SEQ ID NO:18 or SEQ ID NO:58.

19. The method according to any one of claims 14-18, wherein the Fri domain of the human FZD protein is directly linked to a non-FZD polypeptide, or is connected to a non-FZD polypeptide by a linker.

20. The method of claim 19, wherein the non-FZD polypeptide comprises a human Fc region.

21. The method of claim 19 or claim 20, wherein the non-FZD polypeptide consists essentially of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:59.

22. The method of claim 11, wherein the Wnt-binding agent comprises:
    (a) a first polypeptide consisting essentially of SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, or SEQ ID NO:58; and
    (b) a second polypeptide consisting essentially of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:59;
    wherein the first polypeptide is directly linked to the second polypeptide, or the first polypeptide is connected to the second polypeptide by a linker.

23. The method of claim 22, wherein the first polypeptide consists essentially of SEQ ID NO:18 or SEQ ID NO:58.

24. The method of claim 22, wherein the first polypeptide consists essentially of SEQ ID NO:18, and wherein the second polypeptide consists essentially of SEQ ID NO:22, SEQ ID NO:23, or SEQ ID NO:59.

25. The method of claim 22, wherein the first polypeptide consists essentially of SEQ ID NO:58, and wherein the second polypeptide consists essentially of SEQ ID NO:22, SEQ ID NO:23, or SEQ ID NO:59.

26. The method of claim 11, wherein the Wnt-binding agent comprises SEQ ID NO:25, SEQ ID NO:26, or SEQ ID NO:27.

27. The method of claim 11, wherein the Wnt-binding agent comprises SEQ ID NO:27.

28. The method of claim 11, wherein the Wnt-binding agent is 54F28.

29. The method according to any one of claims 1-28, wherein the MAPK pathway inhibitor is selected from a group consisting of: a MEK inhibitor, a Ras inhibitor, a Raf inhibitor, and a ERK inhibitor.

30. The method of claim 29, wherein the MAPK pathway inhibitor is a MEK inhibitor.

31. The method of claim 30, wherein the MEK inhibitor is selected from the group consisting of: BAY 86-9766 (RDEA119), PD0325901, CI-1040, PD98059, PD318088, GSK1120212 (JTP-74057), AZD8330 (ARRY-424704), AZD6244 (ARRY-142886), ARRY-162, ARRY-300, AS703026, U0126, CH4987655, and TAK-733.

32. The method of claim 31, wherein the MEK inhibitor is BAY 86-9766.

33. The method of claim 29, wherein the MAPK pathway inhibitor is a Raf inhibitor.

34. The method of claim 33, wherein the Raf inhibitor is selected from the group consisting of: GDC-0879, PLX-4720, PLX-4032 (vemurafenib), RAF265, BAY 73-4506, BAY 43-9006 (sorafenib), SB590885, XL281 (BMS-908662), and GSK 2118436436.

35. The method according to any one of claims 1-34, wherein the tumor/cancer is selected from the group consisting of melanoma, colon tumor/cancer, pancreatic tumor/cancer, lung tumor/cancer, liver tumor/cancer, and breast tumor/cancer.

36. The method according to any one of claims 1-34, wherein the tumor or cancer expresses wild type Raf, mutant Raf, wild type Ras, or mutant Ras.

37. The method according to any one of claim 1-35, wherein the tumor or cancer comprises a wild type B-Raf.

38. The method according to any one of claim 1-35, wherein the tumor or cancer comprises a B-Raf mutation.

39. The method of claim 38, wherein the B-Raf mutation is a valine to glutamate mutation at amino acid position 600 ($B\text{-}Raf^{V600E}$).

40. The method according to any one of claim 1-35, wherein the tumor or cancer comprises a N-Ras mutation or a K-Ras mutation.

41. The method according to any one of claims 36-40, wherein the Raf and Ras status is detected in a sample by a PCR-based assay or nucleotide sequencing.

42. The method of claim 41, wherein the sample is a fresh sample, a frozen sample, or a formalin-fixed paraffin-embedded sample.

43. The method according to any one claims 1-40, wherein the tumor or cancer is substantially non-responsive to at least one B-Raf kinase inhibitor.

44. A method of treating a human subject, comprising:
    (a) determining if the subject has a tumor or cancer comprising a mutation in the MAPK pathway; and
    (b) administering to the subject a therapeutically effective amount of a Wnt pathway inhibitor in combination with a therapeutically effective amount of a MAPK pathway inhibitor.

45. A method of treating a human subject, comprising:
    (a) selecting a subject for treatment based, at least in part, on the subject having a tumor or cancer that comprises a wild-type B-Raf or a B-Raf mutation; and
    (b) administering to the subject a therapeutically effective amount of a Wnt pathway inhibitor in combination with a therapeutically effective amount of a MAPK pathway inhibitor.

46. A method of treating a human subject who has a tumor or cancer comprising a wild-type B-Raf, comprising administering to the subject a therapeutically effective amount of a Wnt pathway inhibitor in combination with a therapeutically effective amount of a MAPK pathway inhibitor.

47. A method of treating a human subject who has a tumor or cancer which is substantially non-responsive to at least one B-Raf inhibitor, comprising administering to the subject a therapeutically effective amount of a Wnt pathway inhibitor in combination with a therapeutically effective amount of a MAPK pathway inhibitor.

48. A method of treating a human subject, comprising:

(a) selecting a subject for treatment based, at least in part, on the subject having a tumor or cancer which is substantially non-responsive to at least one B-Raf inhibitor; and

(b) administering to the subject a therapeutically effective amount of a Wnt pathway inhibitor in combination with a therapeutically effective amount of a MAPK pathway inhibitor.

49. A method of treating a human subject who has tumor or cancer comprising a B-Raf mutation, comprising administering to the subject a therapeutically effective amount of a Wnt pathway inhibitor in combination with a therapeutically effective amount of a MAPK pathway inhibitor.

50. The method according to any one of claims 44-49, wherein the Wnt pathway inhibitor is an antibody comprising:

(a) a heavy chain CDR1 comprising GFTFSHYTLS (SEQ ID NO:5), a heavy chain CDR2 comprising VISGDGSYTYYADSVKG (SEQ ID NO:6), and a heavy chain CDR3 comprising NFIKYVFAN (SEQ ID NO:7), and

(b) a light chain CDR1 comprising SGDNIGSFYVH (SEQ ID NO:8), a light chain CDR2 comprising DKSNRPSG (SEQ ID NO:9), and a light chain CDR3 comprising QSYANTLSL (SEQ ID NO:10).

51. The method according to any one of claims 44-49, wherein the Wnt pathway inhibitor is a soluble receptor comprising:

(a) a first polypeptide consisting essentially of SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, or SEQ ID NO:58; and

(b) a second polypeptide consisting essentially of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, or SEQ ID NO:59;
wherein the first polypeptide is directly linked to the second polypeptide, or
the first polypeptide is connected to the second polypeptide by a linker.

52. The method according to any one of claims 44-49, wherein the Wnt pathway inhibitor is a soluble receptor comprising SEQ ID NO:27, SEQ ID NO: 26, or SEQ ID NO:25.

53. The method according to any one of claims 44-49, wherein the Wnt pathway inhibitor is a soluble receptor comprising SEQ ID NO:27.

54. The method according to any one of claims 44-49, wherein the Wnt pathway inhibitor is soluble receptor 54F28.

55. The method according to any one of claims 44-54, wherein the MAPK pathway inhibitor is selected from the group consisting of: a MEK inhibitor, a Ras inhibitor, a Raf inhibitor, and a ERK inhibitor.

56. The method of claim 55, wherein the MAPK pathway inhibitor is a MEK inhibitor.

57. The method of claim 56, wherein the MEK inhibitor is selected from the group consisting of: BAY 86-9766 (RDEA119), PD0325901, CI-1040, PD98059, PD318088, GSK1120212 (JTP-74057), AZD8330 (ARRY-424704), AZD6244 (ARRY-142886), ARRY-162, ARRY-300, AS703026, U0126, CH4987655, and TAK-733.

58. The method of claim 55, wherein the MAPK pathway inhibitor is a Raf inhibitor.

59. The method of claim 58, wherein the Raf inhibitor is selected from the group consisting of: GDC-0879, PLX-4720, PLX-4032 (vemurafenib), RAF265, BAY 73-4506, BAY 43-9006 (sorafenib), SB590885, XL281 (BMS-908662), and GSK 2118436436.

60. A method of inhibiting growth of a melanoma tumor in a subject, comprising administering to the subject a therapeutically effective amount of an anti-FZD antibody in combination with a MEK inhibitor.

61. A method of inhibiting growth of a melanoma tumor in a subject, comprising administering to the subject a therapeutically effective amount of anti-FZD antibody 18R5 in combination with MEK inhibitor BAY 86-9766.

62. A method of inhibiting growth of a melanoma tumor in a subject, comprising administering to the subject a therapeutically effective amount of a FZD-Fc soluble receptor in combination with a MEK inhibitor.

63. A method of inhibiting growth of a melanoma tumor in a subject, comprising administering to the subject a therapeutically effective amount of a FZD8-Fc soluble receptor in combination with MEK inhibitor BAY 86-9766.

64. The method according to any one of claims 1-63, which further comprises administering an additional therapeutic agent.