survival (PFS) versus pharmacokinetic exposure. The PFS of evaluable patients receiving Compound 1 was compared against Compound 1 exposure above or below 1.6uM for at least 4 hours.

[00103] Figure 24 is a graph that illustrates the desirable PK pattern for improved safety and efficacy.

[00104] Figure 25 is a photograph illustrating that patients achieved prolong stable disease (>16 weeks) during BBI608 treatment have high levels of p-STAT3 in their tumor tissues prior to the treatment.

DETAILED DESCRIPTION OF THE INVENTION

[00105] Embodiments of the invention are discussed in detail below. In describing embodiments, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected. A person skilled in the relevant art will recognize that other equivalent components can be employed and other methods developed without parting from the spirit and scope of the invention. All references cited herein are incorporated by reference as if each had been individually incorporated.

[00106] In this text, a "substantial fraction" of a set of particles can be at least about 99%, at least about 95%, at least about 90%, at least about 85%, at least about 80%, at least about 75%, at least about 70%, at least about 60%, or at least about 50% of the total number of particles in the set.

[00107] The anti-cancer stem cell activity of a composition can be determined *in vitro* or *in vivo*. For example, antitumor activity of a composition can be determined *in vitro* by administering the compound and measuring the self-renewal and survival of cancer stem cells, For example, the antitumor activity of a compound can be assessed *in vitro* by comparing the behavior of tumor cells to which the compound has been administered with the behavior of tumor cells to which the compound has not been administered (a control). For example, antitumor activity of a composition can be determined *in vivo* by measuring, in an animal to which the compound has been administered, the change in volume of a tumor, by applying a metastatic model, and/or by applying an orthotopic model. For example, the antitumor activity of a compound can be assessed *in vivo* by comparing an animal to which the compound has been administered to an animal to which the compound has not been administered (a control).

WHAT IS CLAIMED IS:

1. A polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 2.

2. A polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray diffraction pattern including one or more peaks from the group consisting of peaks at least at about 10.2, 11.9, 14.1, 14.5, 17.3, 22.2, and 28.1 degrees 2θ.

3. A polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 3.

4. A polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray diffraction pattern including one or more peaks selected from the group consisting of peaks at least at about 7.5, 9.9, 12.3, 15, 23, 23.3, 24.6, and 28.4 degrees 2θ.

5. The polymorph of claim 2, wherein the polymorph is a polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray diffraction pattern including two or more peaks from a peak at least at about 10.2 degrees 2θ, a peak at least at about 11.9 degrees 2θ, a peak at least at about 14.1 degrees 2θ, a peak at least at about 14.5 degrees 2θ, a peak at least at about 17.3 degrees 2θ, a peak at least at about 22.2 degrees 2θ, and a peak at least at about 28.1 degrees 2θ and any combinations thereof.

6. The polymorph of claim 4, wherein the polymorph is a polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray diffraction pattern including two or more peaks from a peak at least at about 7.5 degrees 2θ, a peak at least at about 9.9 degrees 2θ, a peak at least at about 12.3 degrees 2θ, a peak at least at about 15 degrees 2θ, a peak at least at about 23 degrees 2θ, a peak at least at about 23.3 degrees 2θ, a peak at least at about 24.6 degrees 2θ, and a peak at least at about 28.4 degrees 2θ and any combinations thereof.

7. A polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione according to any one of claims 1 to 6, wherein the polymorph is in a particle form, and wherein the particle has a diameter in the range of about 0.02 to about 20 micrometers.

8. A polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione according to any one of claims 1 to 6, wherein the polymorph is in a pharmaceutical composition comprising a population of particles of the polymorph, and wherein a fraction of the cumulative total of the particles have a diameter in the range of 0.2 μm to 20 μm.

9. The pharmaceutical composition of claim 8, wherein the fraction is at least about 1%, about 5%, about 10%, about 20%, about 50%, or about 90% of the cumulative total of the particles.

10. A polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione according to any one of claims 1 to 6, wherein the polymorph is in a pharmaceutical composition comprising a population of particles of the polymorph, and wherein 50% of the cumulative total of the particles (D50) have a diameter of about 2 μm.

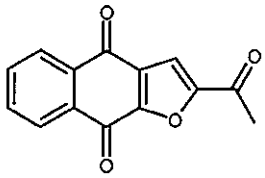
11. A composition comprising a purified form of a polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione according to any one of claims 1 to 9, wherein the composition has a purity greater than or equal to 95.0% as determined by high performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR) or both HPLC and NMR, and wherein the composition comprises less than or equal to 5% impurities.

12. The composition of claim 11, wherein the composition has a purity greater than or equal to 99% as determined by HPLC, NMR or both HPLC and NMR.

13. The composition of claim 11, wherein the composition comprises less than or equal to 0.2% of each single impurity.

14. The composition of claim 11, wherein the impurities comprising a residual solvent selected from the group consisting of ethyl acetate (EtOAc), toluene, Ethanol, methanol, chloroform, and CH_2Cl_2/hexane.

15. A composition comprising a purified form of compound 1, a salt, solvate, hydrate, or prodrug thereof,



(1)

wherein the composition has a purity greater than or equal to 95.0% as determined by high performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR) or both HPLC and NMR,

and wherein the composition comprises less than or equal to 5% impurities.

16. The composition of claim 15, wherein the composition has a purity greater than or equal to 99% as determined by HPLC, NMR or both HPLC and NMR.

17. The composition of claim 15, wherein the composition comprises less than or equal to 0.2% of each single impurity.

18. The composition of claim 15, wherein the impurities comprising a residual solvent selected from the group consisting of ethyl acetate (EtOAc), toluene, Ethanol, methanol, chloroform, and CH_2Cl_2/hexane.

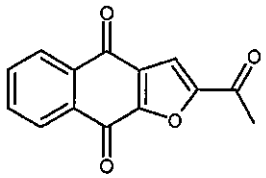
19. The composition of claim 15, wherein the particles comprise the compound in a crystalline state.

20. The composition of claim 15, wherein the pharmaceutical composition comprises the compound in at least two different polymorph states.

21. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition comprises the compound in an amorphous state.

22. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition comprises the compound is in a crystalline and the compound in an amorphous state.

23. A compound having the structure shown below, a salt, solvate, hydrate, or prodrug thereof,



wherein the compound is in a particle form, and wherein the particle has a diameter of less than or equal to about 20 micrometers.

24. A pharmaceutical composition comprising a population of particles of the compound of claim 23, wherein a fraction of the cumulative total of the particles have a diameter in the range of 0.2 μm to 20 μm.

25. A pharmaceutical composition comprising a population of particles of the compound of claim 23, wherein 50% of the cumulative total of the particles (D50) have a diameter of about 2 μm.

26. The pharmaceutical composition of claim 24 or claim 25, wherein the particles comprise the compound in a crystalline state, an amorphous state or at least two different polymorph states.

27. The pharmaceutical composition of claim 24 or claim 25, wherein the particles comprise the compound in a crystalline and the compound in an amorphous state.

28. The pharmaceutical composition of claim 24 or claim 2523, further comprising a pharmaceutically acceptable excipient.

29. A process of preparing a polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 2 comprising the steps of:

(a) reacting 3-butene-2-one with Br_2 to form 3,4-dibromobutene-2-one;

(b) debrominating 3,4-dibromobutene-2-one to form 3-bromobutene-2-one;

(c) reacting 3-bromobutene-2-one with 2-hydroxy-1,4-naphthoquinone to form a polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione;

(d) crystallizing the polymorph to generate a polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 2.

30. A process of preparing a polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 3 comprising the steps of:

(a) reacting 3-butene-2-one with Br_2 to form 3,4-dibromobutene-2-one;

(b) debrominating 3,4-dibromobutene-2-one to form 3-bromo-3-buten-2-one;

(c) reacting 3-bromo-3-buten-2-one with 2-hydroxy-1,4-naphthoquinone to form 2-acetyl-2,3-dihydropnaphtho[2,3-n]furan-4,9-dione;

(d) reacting 2-acetyl-2,3-dihydropnaphtho[2,3-n]furan-4,9-dione with MnO_2 and toluene to form 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione;

(e) crystallizing the 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione; and

(f) slurrying 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione in ethyl acetate to form a polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione.

31. A compound according to any one of claims 1 to 6, 15 or 23, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a human subject.

32. The compound or pharmaceutically acceptable salt of claim 31, wherein the cancer is selected from the group consisting of colorectal adenocarcinoma, breast cancer, ovarian cancer, head and neck cancer, melanoma, angiosarcoma, gastric adenocarinoma, and adrenocorticoid.

33. The compound or pharmaceutically acceptable salt of claim 31, wherein the cancer is colorectal adenocarcinoma.

34. The compound or pharmaceutically acceptable salt of claim 31, wherein the cancer is ovarian cancer.

35. The compound or pharmaceutically acceptable salt of claim 31, wherein the cancer is breast cancer.

36. The compound or pharmaceutically acceptable salt of claim 31, wherein the cancer is lung cancer.

37. The compound or pharmaceutically acceptable salt of claim 31, wherein the cancer is refractory cancer.

38. The compound or pharmaceutically acceptable salt of claim 31, wherein the cancer is recurrent cancer.

39. The compound or pharmaceutically acceptable salt of claim 31, wherein the cancer is metastatic cancer.

40. The compound or pharmaceutically acceptable salt of claim 31, wherein the cancer is associated with overexpression of STAT3.

41. A compound according to any one of claims 1 to 6, 15 or 23, or a pharmaceutically acceptable salt thereof, for use in prolonging progression free survival (PFS) in a cancer patient.

42. The compound or pharmaceutically acceptable salt of claim 41, wherein the cancer is selected from the group consisting of colorectal adenocarcinoma, breast cancer, ovarian cancer, head and neck cancer, melanoma, angiosarcoma, gastric adenocarinoma, and adrenocorticoid.

43. The compound or pharmaceutically acceptable salt of claim 41, wherein the cancer is colorectal adenocarcinoma.

44. The compound or pharmaceutically acceptable salt of claim 41, wherein the cancer is ovarian cancer.

45. The compound or pharmaceutically acceptable salt of claim 41, wherein the cancer is breast cancer.

46. The compound or pharmaceutically acceptable salt of claim 41, wherein the cancer is lung cancer.

47. The compound or pharmaceutically acceptable salt of claim 41, wherein the cancer is refractory cancer.

48. The compound or pharmaceutically acceptable salt of claim 41, wherein the cancer is recurrent cancer.

49. The compound or pharmaceutically acceptable salt of claim 41, wherein the cancer is metastatic cancer.

50. The compound or pharmaceutically acceptable salt of claim 41, wherein the cancer is associated with overexpression of STAT3.

51. Use of a therapeutically effective amount of a compound according to any one of claims 1 to 6, 15 or 23, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer in a human subject.

52. The use according to claim 51, wherein the cancer is selected from the group consisting of colorectal adenocarcinoma, breast cancer, ovarian cancer, head and neck cancer, melanoma, angiosarcoma, gastric adenocarinoma, and adrenocorticoid.

53. The use according to claim 51, wherein the cancer is colorectal adenocarcinoma.

54. The use according to claim 51, wherein the cancer is ovarian cancer.

55. The use according to claim 51, wherein the cancer is breast cancer.

56. The use according to claim 51, wherein the cancer is lung cancer.

57. The use according to claim 51, wherein the cancer is refractory cancer.

58. The use according to claim 51, wherein the cancer is recurrent cancer.

59. The use according to claim 51, wherein the cancer is metastatic cancer.

60. The use according to claim 51, wherein the cancer is associated with overexpression of STAT3.

61. Use of a therapeutically effective amount of a compound according to any one of claims 1 to 6, 15 or 23, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for prolonging progression free survival (PFS) in a cancer patient.

62. The use according to claim 61, wherein the cancer is selected from the group consisting of colorectal adenocarcinoma, breast cancer, ovarian cancer, head and neck cancer, melanoma, angiosarcoma, gastric adenocarinoma, and adrenocorticoid.

63. The use according to claim 61, wherein the cancer is colorectal adenocarcinoma.

64. The use according to claim 61, wherein the cancer is ovarian cancer.

65. The use according to claim 61, wherein the cancer is breast cancer.

66. The use according to claim 61, wherein the cancer is lung cancer.

67. The use according to claim 61, wherein the cancer is refractory cancer.

68. The use according to claim 61, wherein the cancer is recurrent cancer.

69. The use according to claim 61, wherein the cancer is metastatic cancer.

70. The use according to claim 61, wherein the cancer is associated with overexpression of STAT3.

survival (PFS) versus pharmacokinetic exposure. The PFS of evaluable patients receiving Compound 1 was compared against Compound 1 exposure above or below 1.6uM for at least 4 hours.

[00103] Figure 24 is a graph that illustrates the desirable PK pattern for improved safety and efficacy.

[00104] Figure 25 is a photograph illustrating that patients achieved prolong stable disease (>16 weeks) during BBI608 treatment have high levels of p-STAT3 in their tumor tissues prior to the treatment.

DETAILED DESCRIPTION OF THE INVENTION

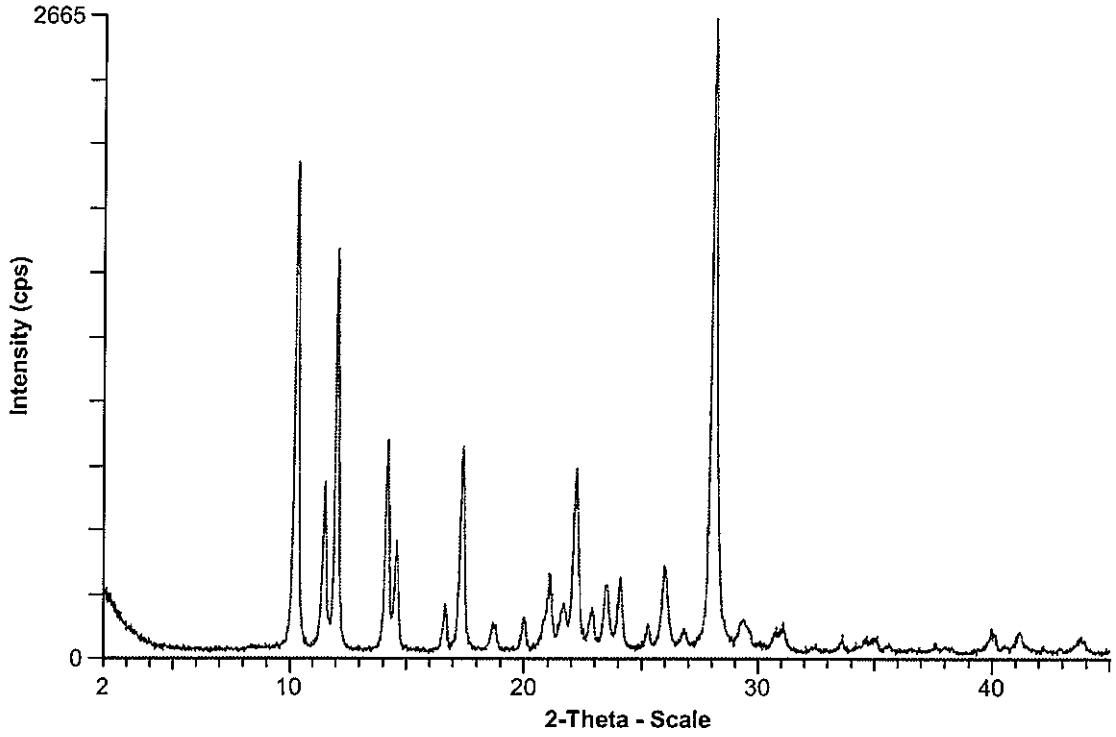
[00105] Embodiments of the invention are discussed in detail below. In describing embodiments, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected. A person skilled in the relevant art will recognize that other equivalent components can be employed and other methods developed without parting from the spirit and scope of the invention.

[00106] In this text, a "substantial fraction" of a set of particles can be at least about 99%, at least about 95%, at least about 90%, at least about 85%, at least about 80%, at least about 75%, at least about 70%, at least about 60%, or at least about 50% of the total number of particles in the set.

[00107] The anti-cancer stem cell activity of a composition can be determined *in vitro* or *in vivo*. For example, antitumor activity of a composition can be determined *in vitro* by administering the compound and measuring the self-renewal and survival of cancer stem cells, For example, the antitumor activity of a compound can be assessed *in vitro* by comparing the behavior of tumor cells to which the compound has been administered with the behavior of tumor cells to which the compound has not been administered (a control). For example, antitumor activity of a composition can be determined *in vivo* by measuring, in an animal to which the compound has been administered, the change in volume of a tumor, by applying a metastatic model, and/or by applying an orthotopic model. For example, the antitumor activity of a compound can be assessed *in vivo* by comparing an animal to which the compound has been administered to an animal to which the compound has not been administered (a control).

CLAIM

1. A crystalline form of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray powder diffraction pattern that is the same as the X-ray powder diffraction pattern set forth herein:



2. A crystalline form of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray powder diffraction pattern including one or more peaks from the group consisting of peaks at 10.2, 11.9, 14.1, 14.5, 17.3, 22.2, and 28.1 degrees 2θ.

3. The crystalline form of claim 2, wherein the crystalline form is a crystalline form of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray powder diffraction pattern including two or more peaks from a peak at 10.2 degrees 2θ, a peak at 11.9 degrees 2θ, a peak at 14.1 degrees 2θ, a peak at 14.5 degrees 2θ, a peak at 17.3 degrees 2θ, a peak at 22.2 degrees 2θ, and a peak at 28.1 degrees 2θ and any combinations thereof.

4. A crystalline form of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione according to any one of claims 1 to 3, wherein the crystalline form is in a particle form, and wherein the particle has a diameter in the range of 0.02 to 20 micrometers.

5. A crystalline form of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione according to any one of claims 1 to 3, wherein the crystalline form is in a pharmaceutical composition comprising a population of particles of the crystalline form, and wherein a fraction of the cumulative total of the particles have a diameter in the range of 0.2 μm to 20 μm.

6. The crystalline form of claim 5, wherein the fraction is 1%, 5%, 10%, 20%, 50%, or 90% of the cumulative total of the particles.

7. A crystalline form of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione according to any one of claims 1 to 3, wherein the crystalline form is in a pharmaceutical composition comprising a population of particles of the crystalline form, and wherein 50% of the cumulative total of the particles (D50) have a diameter of 2 μm.

8. A composition comprising a purified form of a crystalline form of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione according to any one of claims 1 to 6, wherein the composition has a purity greater than or equal to 95.0% as determined by high performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR) or both HPLC and NMR, and wherein the composition comprises less than or equal to 5% impurities.

9. The composition of claim 8, wherein the composition has a purity greater than or equal to 99% as determined by HPLC, NMR or both HPLC and NMR.

10. The composition of claim 8, wherein the composition comprises less than or equal to 0.2% of each single impurity.

11. The composition of claim 8, wherein the impurities comprising a residual solvent selected from the group consisting of ethyl acetate (EtOAc), toluene, Ethanol, methanol, chloroform, and CH_2Cl_2/hexane.

12. A process of preparing a crystalline form of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray powder diffraction pattern that is the same as the X-ray powder diffraction pattern set forth in claim 1 comprising the steps of:

(a) reacting 3-butene-2-one with Br_2 to form 3,4-dibromobutene-2-one;

(b) debrominating 3,4-dibromobutene-2-one to form 3-bromobutene-2-one;

(c) reacting 3-bromobutene-2-one with 2-hydroxy-1,4-naphthoquinone to form a polymorph of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione;

(d) crystallizing the polymorph to generate a crystalline form of 2-acetyl-4H, 9H-naphtho[2,3-b]furan-4,9-dione characterized by an X-ray powder diffraction pattern that is the same as the X-ray powder diffraction pattern set forth in claim 1.

13. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof for use in the treatment of cancer in a human subject.

14. The compound or pharmaceutically acceptable salt of claim 13, wherein the cancer is selected from the group consisting of colorectal adenocarcinoma, breast cancer, ovarian cancer, head and neck cancer, melanoma, angiosarcoma, gastric adenocarcinoma, and adrenocorticoid.

15. The compound or pharmaceutically acceptable salt of claim 13, wherein the cancer is colorectal adenocarcinoma.

16. The compound or pharmaceutically acceptable salt of claim 13, wherein the cancer is ovarian cancer.

17. The compound or pharmaceutically acceptable salt of claim 13, wherein the cancer is breast cancer.

18. The compound or pharmaceutically acceptable salt of claim 3, wherein the cancer is lung cancer.

19. The compound or pharmaceutically acceptable salt of claim 13, wherein the cancer is refractory cancer.

20. The compound or pharmaceutically acceptable salt of claim 13, wherein the cancer is recurrent cancer.

21. The compound or pharmaceutically acceptable salt of claim 13, wherein the cancer is metastatic cancer.

22. The compound or pharmaceutically acceptable salt of claim 13, wherein the cancer is associated with overexpression of STAT3.

23. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof for use in prolonging progression free survival (PFS) in a cancer patient.

24. The compound or pharmaceutically acceptable salt of claim 23, wherein the cancer is selected from the group consisting of colorectal adenocarcinoma, breast cancer, ovarian cancer, head and neck cancer, melanoma, angiosarcoma, gastric adenocarcinoma, and adrenocorticoid.

25. The compound or pharmaceutically acceptable salt of claim 23, wherein the cancer is colorectal adenocarcinoma.

26. The compound or pharmaceutically acceptable salt of claim 23, wherein the cancer is ovarian cancer.

27. The compound or pharmaceutically acceptable salt of claim 23, wherein the cancer is breast cancer.

28. The compound or pharmaceutically acceptable salt of claim 23, wherein the cancer is lung cancer.

29. The compound or pharmaceutically acceptable salt of claim 23, wherein the cancer is refractory cancer.

30. The compound or pharmaceutically acceptable salt of claim 23, wherein the cancer is recurrent cancer.

31. The compound or pharmaceutically acceptable salt of claim 23, wherein the cancer is metastatic cancer.

32. The compound or pharmaceutically acceptable salt of claim 23, wherein the cancer is associated with overexpression of STAT3.

33. Use of a therapeutically effective amount of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer in a human subject.

34. The use according to claim 33, wherein the cancer is selected from the group consisting of colorectal adenocarcinoma, breast cancer, ovarian cancer, head and neck cancer, melanoma, angiosarcoma, gastric adenocarcinoma, and adrenocorticoid.

35. The use according to claim 33, wherein the cancer is colorectal adenocarcinoma.

36. The use according to claim 33, wherein the cancer is ovarian cancer.

37. The use according to claim 33, wherein the cancer is breast cancer.

38. The use according to claim 33, wherein the cancer is lung cancer.

39. The use according to claim 33, wherein the cancer is refractory cancer.

40. The use according to claim 33, wherein the cancer is recurrent cancer.

41. The use according to claim 33, wherein the cancer is metastatic cancer.

42. The use according to claim 33, wherein the cancer is associated with overexpression of STAT3.

43. Use of a therapeutically effective amount of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for prolonging progression free survival (PFS) in a cancer patient.

44. The use according to claim 43, wherein the cancer is selected from the group consisting of colorectal adenocarcinoma, breast cancer, ovarian cancer, head and neck cancer, melanoma, angiosarcoma, gastric adenocarcinoma, and adrenocorticoid.

45. The use according to claim 43, wherein the cancer is colorectal adenocarcinoma.

46. The use according to claim 43, wherein the cancer is ovarian cancer.

47. The use according to claim 43, wherein the cancer is breast cancer.

48. The use according to claim 43, wherein the cancer is lung cancer.

49. The use according to claim 43, wherein the cancer is refractory cancer.

50. The use according to claim 43, wherein the cancer is recurrent cancer.

51. The use according to claim 43, wherein the cancer is metastatic cancer.

52. The use according to claim 43, wherein the cancer is associated with overexpression of STAT3.