

CLAIMS

Claims

1. A crystalline form of the sulfate salt of 5-bromo-2,6-di(1*H*-pyrazol-1-yl)pyrimidin-4-amine characterized by an X-ray powder diffraction (XRPD) pattern comprising a representative peak, in terms of $^{\circ}2\theta$, at $9.4 \pm 0.2^{\circ}2\theta$, when measured using CuK α radiation with a wavelength of 1.5418 Å and at a temperature of about 22°C.
2. A crystalline form of the free form of 5-bromo-2,6-di(1*H*-pyrazol-1-yl)pyrimidin-4-amine characterized by an X-ray powder diffraction (XRPD) pattern comprising a peak at $8.2 \pm 0.2^{\circ}2\theta$, when measured using CuK α radiation with a wavelength of 1.5418 Å and at a temperature of about 22°C.
3. A crystalline form of the free form of 5-bromo-2,6-di(1*H*-pyrazol-1-yl)pyrimidin-4-amine according to claim 2 wherein the X-ray powder diffraction pattern further comprises one or more additional peaks chosen from $24.9 \pm 0.2^{\circ}2\theta$, $25.7 \pm 0.2^{\circ}2\theta$ and $26.5 \pm 0.2^{\circ}2\theta$, when measured using CuK α radiation with a wavelength of 1.5418 Å and at a temperature of about 22°C.
4. A crystalline form according to claim 3 wherein the X-ray powder diffraction pattern further comprises one or more additional peaks chosen from $16.4 \pm 0.2^{\circ}2\theta$, $30.8 \pm 0.2^{\circ}2\theta$, and $11.5 \pm 0.2^{\circ}2\theta$, when measured using CuK α radiation with a wavelength of 1.5418 Å and at a temperature of about 22°C.
5. A crystalline form according to claim 2, 3 or 4 wherein said crystalline form is Form F.
6. A crystalline form according to claim 5 wherein said Form F is substantially phase pure.
7. A pharmaceutical composition comprising a crystalline form according to any one of claims 1 to 6, and a pharmaceutically acceptable excipient.
8. A pharmaceutical composition comprising a crystalline form of the free form of 5-bromo-2,6-

di(1*H*-pyrazol-1-yl)pyrimidin-4-amine according to any one of claims 2 to 5 and further comprising at least one other solid state form of the free form of 5-bromo-2,6-di(1*H*-pyrazol-1-yl)pyrimidin-4-amine.

9. A pharmaceutical composition comprising a crystalline form of the free form of 5-bromo-2,6-di(1*H*-pyrazol-1-yl)pyrimidin-4-amine according to any one of claims 2 to 5 and further comprising an amorphous form of 5-bromo-2,6-di(1*H*-pyrazol-1-yl)pyrimidin-4-amine or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical combination comprising a therapeutically effective amount of a crystalline form according to any one of claims 1 to 6, and one or more immunotherapeutic agents.

11. A method of treating cancer, in a subject in need thereof, comprising: administering to a subject in need thereof, a therapeutically effective amount of a crystalline form according to any one of claims 1 to 6, or a pharmaceutical composition according to any one of claims 7 to 9, alone or in combination with one or more immunotherapeutic agents.

12. The use of a crystalline form according to any one of claims 1 to 6, alone or in combination with one or more immunotherapeutic agents, for the treatment of cancer.

13. A crystalline form according to any one of claims 1 to 6, or a pharmaceutical composition according to any one of claims 7 to 9, for use in the treatment of cancer.

14. A combination of a crystalline form according to any one of claims 1 to 6, and one or more immunotherapeutic agents, for use in the treatment of cancer.

15. A method of inhibiting adenosine A2a receptor, in a subject in need thereof comprising: administering to a subject a therapeutically effective amount of a crystalline form according to any one of claims 1 to 6, or a pharmaceutical composition according to any one of claims 7 to 9.

16. A method according to claim 11, a use according to claim 12, a crystalline form for use

according to claim 13, or a combination for use according to claim 14, wherein the cancer is selected from wherein the cancer is selected from a lung cancer, a melanoma, a renal cancer, a liver cancer, a myeloma, a prostate cancer, a breast cancer, a colorectal cancer, a pancreatic cancer, a head and neck cancer, anal cancer, gastro-esophageal cancer, thyroid cancer, cervical cancer, a lymphoproliferative disease or a hematological cancer, T-cell lymphoma, B-cell lymphoma, a non-Hodgkin lymphoma, or a leukemia.

17. The method, use or combination for use of claim 16 wherein the cancer is carcinomas, specifically lung cancer and more specifically non-small cell lung cancer.

18. The method of claim 11, 16 or 17, a use according to claim 12, 16 or 17, or the combination for use according to claim 14, 16 or 17, wherein one or more immunotherapeutic agents are selected from the group consisting of anti-CTLA4 antibodies, anti-PD-1 antibodies and anti-PD-L1 antibodies.

19. The method of claim 11, 16 or 17, a use according to claim 12, 16 or 17, or the combination for use according to claim 14, 16 or 17, wherein the immunotherapeutic agent is selected from the group consisting of: Ipilimumab, Tremelimumab, Nivolumab, Pembrolizumab, Pidilizumab (CT-011), AMP-224, AMP-514 (MEDI0680-Medimmune), MPDL3280A (Genentech Roche), MEDI4736, MSB0010718C (Merck Serono), YW243.55.S70 and MDX-1105.

20. The method of claim 11, 16 or 17, a use according to claim 12, 16 or 17, or the combination for use according to claim 14, 16 or 17, wherein the immunotherapeutic agents is an anti-PD-1 antibody.

21. The method, the use or the combination for use according to claim 20, wherein the anti-PD-1 antibody comprises:

(a) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 4, a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a VLCDR1 amino

acid sequence of SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 15;

(b) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 1; a VHCDR2 amino acid sequence of SEQ ID NO: 2; and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12;

(c) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 41, a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 15; or

(d) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 41; a VHCDR2 amino acid sequence of SEQ ID NO: 2; and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 12.

22. The method, the use or the combination for use according to claim 20, wherein the anti-PD-1 comprises a VH comprising the amino acid sequence of SEQ ID NO: 6 and a VL comprising the amino acid sequence of SEQ ID NO: 20.

23. The method, the use or the combination for use according to claim 20, wherein the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 8 and a light chain comprising the amino acid sequence of SEQ ID NO: 22.

24. The method, the use or the combination for use according to claim 20, wherein the anti-PD-1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 6 and a VL comprising the amino acid sequence of SEQ ID NO: 16.

25. The method, the use or the combination for use according to claim 20, wherein the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 8 and a light chain comprising the amino acid sequence of SEQ ID NO: 18.

26. The method, the use or the combination for use according to any one of claims 20-25, wherein the anti-PD-1 antibody molecule is administered at a dose of about 300 mg once every three weeks.

27. The method, the use or the combination for use according to any one of claims 20-25, wherein the anti-PD-1 antibody molecule is administered at a dose of about 400 mg once every four weeks.

28. The method of claim 11, 16 or 17, a use according to claim 12, 16 or 17, or the combination for use according to claim 14, 16 or 17, wherein the immunotherapeutic agents is is an anti-PD-L1 antibody.

29. The method, the use or the combination for use according to claim 28, wherein the anti PD-L1 antibody molecule comprises:

(a) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 47, a VHCDR2 amino acid sequence of SEQ ID NO: 48, and a VHCDR3 amino acid sequence of SEQ ID NO: 46; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 52, a VLCDR2 amino acid sequence of SEQ ID NO: 53, and a VLCDR3 amino acid sequence of SEQ ID NO: 54;

(b) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 44; a VHCDR2 amino acid sequence of SEQ ID NO: 45; and a VHCDR3 amino acid sequence of SEQ ID NO: 46; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 49, a VLCDR2 amino acid sequence of SEQ ID NO: 50, and a VLCDR3 amino acid sequence of SEQ ID NO: 51;

(c) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 63, a VHCDR2 amino acid sequence of SEQ ID NO: 48, and a VHCDR3 amino acid sequence of SEQ ID NO: 46; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 52, a VLCDR2 amino acid sequence of SEQ ID NO: 53, and a VLCDR3 amino acid sequence of SEQ ID NO: 54; or

(d) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 63; a VHCDR2 amino acid sequence of SEQ ID NO: 45; and a VHCDR3 amino acid sequence of SEQ ID NO: 46; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 49, a VLCDR2 amino acid sequence of SEQ ID NO: 50, and a VLCDR3 amino acid sequence of SEQ ID NO: 51.

30. The method, the use or the combination for use according to claim 28, wherein the anti PD-L1 antibody molecule comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 55 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 58.

31. The method, the use or the combination for use according to any one of claims 18- 30, wherein immunotherapeutic agent is administered together in a single composition or administered separately in two or more different compositions forms.

32. The method, the use or the combination for use according to any one of claims 18-30 wherein the immunotherapeutic agent is administered concurrently with, prior to, or subsequent to, a crystalline form of the free form or sulfate salt of 5-bromo-2,6-di(1*H*-pyrazol-1-yl)pyrimidin-4-amine.