cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death 1 receptor (PD-1), can facilitate the treatment of a disease or disorder described herein (*e.g.*, abnormal cell growth, *e.g.*, cancer (*e.g.*, a cancer described herein)). CTLA-4 and PD-1 can function as negative regulators and have non-redundant roles in modulating immune responses. They are expressed on tumor-specific T-cells and can lead to compromised activation and suppressed effector functions *e.g.*, profileration, cytokine secretion, and tumor cell lysis. CTLA-4 can attenuate the early activation of naïve and memory T-cells. PD-1 is involved in modulating T-cell activity in *e.g.*, peripheral tissues, *e.g.*, via interaction with its ligands, i.e., PD-L1 and PD-L2. Blockers of the immune checkpoint pathway (*e.g.* anti-PD-1, anti-PD-L1, anti-CTLA-4,) can enhance antitumor immunity and provide opportunities to treat a disease or disorder described herein (*e.g.*, abnormal cell growth, *e.g.*, cancer (*e.g.*, a cancer described herein)), *e.g.*, provide more effective treatment for subjects suffering from cancer.

Although durable responses to single agent immune checkpoint inhibitors have been reported, additional approaches are needed to extend this therapeutic benefit to a greater proportion of cancer patients. Accordingly, substantial efforts are ongoing to identify agents that can augment T-cell mediated killing of tumor cells and potentiate the effects of checkpoint inhibitors. Focal Adhesion Kinase (FAK) and the closely related family member PYK2 are potentially valuable targets in this regard due to the roles of these enzymes in regulating key cellular populations in the tumor microenvironment. FAK inhibitors may increase cytotoxic T-cells (CD8+ expressing cytotoxic T-cells) in tumors, and decrease the immune cell populations that suppress the host anti-tumor immune response (T-regs, M2 tumor associated macrophages, myeloid-derived suppressor cells). FAK inhibitors can turn up the PD-1/PD-L1 immune checkpoint pathway and may augment anti-tumor efficacy of various anti-tumor immunotherapies. A combination of a cancer therapy (*e.g.*, a FAK inhibitor) with a cancer immunotherapy (*e.g.* anti-PD-1, anti-PD-L1, anti-CTLA-4), may enhance the generation and effectiveness of tumor-specific cytotoxic lymphocytes and provide a promising approach for more effectively treating a disease or disorder described herein (*e.g.*, abnormal cell growth, *e.g.*, cancer (*e.g.*, a cancer described herein)). The compounds described herein, *e.g.*, FAK inhibitors, may be used in combination with an immunotherapy described herein, to prevent and treat a disease or disorder described herein, *e.g.*, abnormal cell growth (*e.g.*, a cancer described herein).

SUMMARY OF THE INVENTION

In an aspect, there is provided the use of a FAK inhibitor in the manufacture of a medicament, for treating a human subject suffering from a disease or disorder described herein (*e.g.*, abnormal cell growth, *e.g.*, cancer (*e.g.*, a cancer described herein)), wherein the FAK inhibitor is to be administered in combination with an immunotherapeutic agent or procedure (e.g., wherein the immunotherapeutic agent

is a compound that inhibits the immune checkpoint blockade pathway). Described herein is a method for treating a human subject suffering from a disease or disorder described herein (*e.g.*, abnormal cell growth, *e.g.*, cancer (*e.g.*, a cancer described herein)), comprising administering a FAK inhibitor in combination with an immunotherapeutic agent or procedure

CLAIMS

1. Use of a FAK inhibitor in the manufacture of a medicament, for treating a human subject suffering from a disease or disorder described herein (*e.g.*, abnormal cell growth, *e.g.*, cancer (*e.g.*, a cancer described herein)), wherein the FAK inhibitor is to be administered in combination with an immunotherapeutic agent or procedure (e.g., wherein the immunotherapeutic agent is a compound that inhibits the immune checkpoint blockade pathway).

2. The use of claim 1, wherein the cancer is a solid tumor, soft tissue tumor, metastasis, or non-solid cancer.

3. The use of claim 2, wherein the cancer is solid tumor.

4. The use of claim 3, wherein the solid tumor is a malignancy (*e.g.*, sarcomas, adenocarcinomas, and carcinomas) of an organ (*e.g.*, of lung, breast, lymphoid, gastrointestinal (*e.g.*, colon), and genitourinary (*e.g.*, renal, urothelial, or testicular tumors) tracts, pharynx, prostate, and ovary).

5. The use of claim 1, wherein the cancer is a mesothelioma; neurofibromatosis; *e.g.*, neurofibromatosis type 2, neurofibromatosis type 1; renal cancer; lung cancer, non small cell lung cancer; liver cancer; thyroid cancer; ovarian; breast cancer; a nervous system tumor; schwannoma; meningioma; schwannomatosis; neuroma acoustic; adenoid cystic carcinoma; ependymoma; or ependymal tumors.

6. The use of claim 1, wherein the cancer is mesothelioma (*e.g.,* malignant pleural mesothelioma, *e.g.,* surgical resectable malignant pleural mesothelioma), breast cancer (*e.g.,* triple negative breast cancer), ovarian cancer (*e.g.,* advanced ovarian cancer), lung cancer (*e.g.,* non-small cell lung cancer (NSCLC), *e.g.,* KRAS mutant NSCLC)), or a non-hematolotic malignancy.

7. The use of claim 1, wherein the cancer is melanoma (*e.g.,* N-Ras mutated locally advanced or metastasis malignant cutaneous melanoma), colorectal cancer (*e.g.*, metastatic colorectal cancer), leukemia (*e.g.*, acute myeloid leukemia), adenocarcinoma (*e.g.,* pancreatic adenocarcinoma), or a solid tumor (*e.g.,* locally advanced solid tumor, metastatic solid tumor, hepatocellular carcinoma).

8. The use of claim 1, wherein the FAK inhibitor is to be administered orally.

9. The use of claim 8, wherein the FAK inhibitor is VS-4718, VS-5095, VS-6062, VS-6063, BI 853520, or GSK2256098.

10. The use of claim 9, wherein the FAK inhibitor is VS-4718.

11. The use of claim 9, wherein the FAK inhibitor is VS-6063.

12. The use of claim 8, wherein the FAK inhibitor is to be administered at least once a day.

13. The use of claim 12, wherein the FAK inhibitor is to be administered once a day.

14. The use of claim 12, wherein the FAK inhibitor is to be administered twice a day.

15. The use of claim 8, wherein the FAK inhibitor is to be administered at about 100 mg to about 2000 mg.

16. The use of claim 8, wherein the FAK inhibitor is VS-6063 and the FAK inhibitor is to be administered at about 200 mg to about 600 mg twice a day.

17. The use of claim 8, wherein VS-6063 is to be administered before or after (e.g., immediately before or immediately after) consumption of food.

18. The use of claim 8, wherein the FAK inhibitor is VS-4718 and the FAK inhibitor is to be administered at about 300 mg to about 500 mg once a day.

19. The use of claim 18, wherein the FAK inhibitor is VS-4718 and the FAK inhibitor is to be administered at about 200 mg to about 400 mg twice a day.

20. The use of claim 1, wherein the immunotherapeutic agent is to be administered parenterally.

21. The use of claim 20, wherein the immunotherapeutic agent is an anti-CTLA-4 antibody (*e.g.*, ipilimumab, tremelimumab).

22. The use of claim 20, wherein the immunotherapeutic agent is an anti-PD-1 ligand (*e.g.*, PD-LI (*e.g.*, B7-HI or CD274); or PD-L2 (*e.g.*, B7-DC or CD273)).

23. The use of claim 20, wherein the immunotherapeutic agent is an anti-PD-1 antibody (*e.g.*, anti-PD-1 or anti-PD-L1, e.g., nivolumab (i.e., MDX-1106, BMS-936558, ONO-4538); CT-011; AMP-224; pembrolizumab; pidilizumab; or MK-3475).

24. The use of claim 20, wherein the immunotherapeutic agent is an anti-PD-L1 antibody (*e.g.*, BMS936559 (i.e., MDX-1105); MEDI4736; MSB0010718C (avelumab); or MPDL-3280A).

25. The use of claim 20, wherein the immunotherapeutic agent is a checkpoint blocking antibody (*e.g.*, IMP321, MGA271).

26. The use of claim 20, wherein the immunotherapeutic agent is an anti-CTLA-4 antibody (*e.g.*, ipilimumab, tremelimumab, anti-TIM3, anti-LAG3, anti-TIGIT).

27. The use of claim 20, wherein the immunotherapeutic agent is a cell-based therapy.

28. The use of claim 27, wherein the cell-based therapy is a CAR-T therapy.

29. The use of claim 20, wherein the immunotherapeutic agent is a co-stimulatory antibody (e.g., anti-4-1BB, anti-OX40, anti-GITR, anti-CD27, anti-CD40).

30. The use of claim 1, wherein an additional chemotherapeutic agent or radiation therapy is to be administered.

31. The use of claim 1, wherein a cytotoxic agent is to be administered.

32. The use of claim 31, wherein the cytotoxic agent is gemcitabine or paclitaxel (e.g., nab-paclitaxel).

33. The use of claim 1, wherein the additional therapeutic agent is selected from: Alkylating agents, Anti-metabolites, Antibiotics, Hormonal therapy agents, Plant derived anti-tumor substances, Cytotoxic topoisomerase inhibiting agents, Immunologicals, Biological response modifiers, Other anticancer agents, Other anti-angiogenic compounds, Platinum-coordinated compounds, Tyrosine kinase inhibitors, Antibodies, and Interferons.

34. The use of claim 1, wherein the FAK inhibitor is to be administered before the immunotherapeutic agent has been administered.

35. The use of claim 1, wherein the FAK inhibitor is to be administered after the immunotherapeutic agent has been administered.

36. The use of claim 1, wherein the FAK inhibitor is to be administered concurrently with the immunotherapeutic agent.

37. The use of claim 1, wherein the subject has been previously treated with a chemotherapeutic agent or with radiation therapy.

38. The use of claim 1, wherein the subject has failed (*e.g.*, relapsed from, insensitive to, received no or little benefit from) conventional or standard cancer treatment (*e.g.*, surgery, first-line therapy for cancer).

39. The use of claim 1, wherein the subject has failed (*e.g.*, relapsed from, insensitive to, received no or little benefit from) first-line treatment (*e.g.*, first-line therapy for cancer).

40. The use of claim 1, wherein the subject is identified to have high PD-L1 or PD-L2, e.g., high PD-L1 or PD-L2 in tumor cells.

41. The use of claim 1, wherein the subject is identified to have low PD-L1 or PD-L2, e.g., low PD-L1 or PD-L2 in tumor cells.

42. The use of claim 1, wherein the subject is identified to express interferon gamma-induced (IFN-γ) genes.