it is now estimated to benefit less than 20% of cancer patients. Increasing the fraction of patients responding and the length of their response is an urgent unmet clinical need. Accordingly, there is a need to develop methods and combination therapies to initiate or enhance the effectiveness of the checkpoint inhibitors in both the nonresponding subject population and the responding subject population.

[0011] Anti-tumor T cells must circulate into tumors through blood vessels, bind the endothelium, and pass across the vessel wall and migrate through cancer-associated fibroblasts (CAFs) and extracellular matrix (ECM) before encountering cancer cells. However, because up to 80% of intratumoral blood vessels lack perfusion, the area of vessel wall for T cells to migrate across is limited.

[0012] Compressed blood vessels impair blood flow and oxygen delivery to tumors, resulting in increased hypoxia in the tumors and resistance to immunotherapy through numerous mechanisms. Strategies that decompress vessels potentiate the efficacy of ICB in ICB-resistant mouse models of metastatic breast cancer. If there was a way to decompress tumor vessels while also facilitating vessel adhesion and transmigration of T cells into the tumor parenchyma, the fraction of cancer patients that respond to ICB could increase.

[0013] All references cited herein, including patent applications, patent publications, and scientific literature, are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY

[0013a] In an aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising ketotifen, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a solid tumor in a subject in need thereof, wherein the pharmaceutical composition is to be administered in combination with a checkpoint inhibitor.

[0013b] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising a checkpoint inhibitor, in the manufacture of a medicament for the treatment of a solid tumor in a subject in need thereof, wherein the pharmaceutical composition is to be administered in combination with ketotifen, or a pharmaceutically acceptable salt thereof.

[0013c] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising a combination of ketotifen, or a pharmaceutically acceptable salt thereof, and a checkpoint inhibitor, in the manufacture of a medicament for

the treatment of a solid tumor in a subject in need thereof, wherein the pharmaceutical composition is to be administered to the subject in need thereof.

[0013d] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising ketotifen, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for increasing blood flow of a solid tumor in a subject, wherein the pharmaceutical composition is to be administered in combination with a checkpoint inhibitor.

[0013e] In a further aspect of the present disclosure, there is provided a kit comprising:

(a) an effective amount of ketotifen, or a pharmaceutically acceptable salt thereof, and an effective amount of a checkpoint inhibitor as a combined pharmaceutical formulation for use as disclosed herein; and

(b) a package insert comprising instructions for using the ketotifen, or a pharmaceutically acceptable salt thereof, with the checkpoint inhibitor according to the use disclosed herein.

[0014] Provided herein are methods for treating a solid tumor in a subject in need thereof comprising administering to the subject an effective amount of ketotifen, or a pharmaceutically acceptable salt thereof, in combination with a checkpoint inhibitor. Also provided herein are methods for initiating, enhancing or prolonging the effects of a checkpoint inhibitor, or enabling a subject to respond to a checkpoint inhibitor in a subject in need thereof comprising administering to the subject an effective amount of ketotifen, or a pharmaceutically acceptable salt thereof, in combination with a checkpoint inhibitor, wherein the subject has a solid tumor. Also provided herein are methods for potentiating the effects of a checkpoint inhibitor in a subject in need thereof comprising administering to the subject an effective amount of ketotifen, or a pharmaceutically acceptable salt thereof, in combination with a checkpoint inhibitor, wherein the subject has a solid tumor. Also provided herein are methods for increasing blood flow of a solid tumor in a subject comprising administering to

CLAIMS

What is claimed is:

1. Use of a pharmaceutical composition comprising ketotifen, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a solid tumor in a subject in need thereof, wherein the pharmaceutical composition is to be administered in combination with a checkpoint inhibitor.

2. Use of a pharmaceutical composition comprising a checkpoint inhibitor, in the manufacture of a medicament for the treatment of a solid tumor in a subject in need thereof, wherein the pharmaceutical composition is to be administered in combination with ketotifen, or a pharmaceutically acceptable salt thereof.

3. Use of a pharmaceutical composition comprising a combination of ketotifen, or a pharmaceutically acceptable salt thereof, and a checkpoint inhibitor, in the manufacture of a medicament for the treatment of a solid tumor in a subject in need thereof, wherein the pharmaceutical composition is to be administered to the subject in need thereof.

4. Use of a pharmaceutical composition comprising ketotifen, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for increasing blood flow of a solid tumor in a subject, wherein the pharmaceutical composition is to be administered in combination with a checkpoint inhibitor.

5. The use of claim 4, wherein blood flow is measured using ultrasound-based blood flow measurements or using histological techniques to measure hypoxia.

6. The use of any one of claims 1-5, wherein the ketotifen, or pharmaceutically acceptable salt thereof, increases the number of anti-tumor T cells that colocalize with the solid tumor.

7. The use of any one of claims 1-6, wherein the ketotifen, or pharmaceutically acceptable salt thereof, reduces the tissue stiffness of the solid tumor.

8. The use of claim 7, wherein the tissue stiffness of the solid tumor is measured using ultrasound elastography.

9. The use of any one of claims 1-8, wherein the ketotifen, or pharmaceutically acceptable salt thereof, decreases the levels of an extracellular matrix protein in the solid tumor.

10. The use of claim 9, wherein the extracellular matrix protein is collagen I or hyaluronan binding protein (HABP).

11. The use of any one of claims 1-10, wherein administering ketotifen, or pharmaceutically acceptable salt thereof, reduces hypoxia in the solid tumor.

12. The use of any one of claims 1-11, wherein the checkpoint inhibitor inhibits a checkpoint protein selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-L2, B7-H3, B7-H4, BMA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK1, CHK2, A2aR, and B-7 family ligands or a combination thereof.

13. The use of claim 12, wherein the checkpoint inhibitor is an anti-PD-1 antibody, anti-PD-L1 antibody, anti-CTLA4 antibody, or a combination thereof.

14. The use of any one of claims 1-13, wherein the ketotifen, or pharmaceutically acceptable salt thereof, is to be administered to the subject once per day.

15. The use of any one of claims 1-14, wherein the ketotifen, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose from 0.01 mg/kg to 5 mg/kg.

16. The use of any one of claims 1-15, wherein the ketotifen, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose from 100 mg to 1200 mg.

17. The use of any one of claims 1-16, wherein the ketotifen, or pharmaceutically acceptable salt thereof, is to be administered to the subject prior to the subject being administered the checkpoint inhibitor.

18. The use of any one of claims 1-17, wherein the administration of ketotifen, or pharmaceutically acceptable salt thereof, to the subject is maintained for at least a portion of the time the subject is to be administered the checkpoint inhibitor.

19. The use of any one of claims 1-18, wherein one or more therapeutic effects in the subject is improved after administration of the ketotifen, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor relative to a baseline, wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival and overall survival.

20. The use of any one of claims 1-19, wherein the size of a tumor derived from the cancer is reduced by at least 10% relative to the size of the tumor derived from the cancer before administration of the ketotifen, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor.

21. The use of any one of claims 1-20, wherein the objective response rate is at least 20%.

22. The use of any one of claims 1-21, wherein the subject exhibits progression-free survival of at least 1 month after administration of the ketotifen, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor.

23. The use of any one of claims 1-22, wherein the subject exhibits overall survival of at least 1 month after administration of the ketotifen, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor.

24. The use of any one of claims 1-23, wherein the duration of response is at least 1 month after administration of the ketotifen, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor.

25. The use of any one of claims 1-24, wherein the solid tumor is selected from the group consisting of mesothelioma, breast cancer, breast cancer lung metastases, sarcoma, pancreatic cancer, ovarian cancer, liver metastases, prostate cancer, brain cancer, melanoma, renal cell carcinoma, colorectal cancer, hepatocellular carcinoma, lung cancer, squamous cell carcinoma of the head and neck, urothelial carcinoma, esophageal squamous cell carcinoma, gastric cancer, esophageal cancer, cervical cancer, Merkel cell carcinoma, endometrial carcinoma, and cutaneous squamous cell carcinoma.

26. The use of any one of claims 1-25, wherein the subject is a human.

27. The use of any one of claims 1-26, wherein an additional chemotherapeutic agent is to be further administered.

28. The use of claim 27, wherein the additional chemotherapeutic agent is doxorubicin or an analogue or derivative thereof.

29. A kit comprising:

(a) an effective amount of ketotifen, or a pharmaceutically acceptable salt thereof and an effective amount of a checkpoint inhibitor as a combined pharmaceutical formulation for use according to any one of claims 1-28; and

(b) a package insert comprising instructions for using the ketotifen, or a pharmaceutically acceptable salt thereof, with the checkpoint inhibitor according to the use of any one of claims 1-28.

30. The use of any one of claims 1-28 or the kit of claim 29, wherein the subject is selected for the treatment based on increased blood flow and/or decreased stiffness of the solid tumor in response to ketotifen, or a pharmaceutically acceptable salt thereof.