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.

[0010] 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.

[0011] 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.

[0012] 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

[0012a] In an aspect of the present disclosure, there is provided a use of an effective amount of bosentan, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a solid tumor in a subject in need thereof, wherein the medicament is to be administered in combination with a checkpoint inhibitor.

[0012b] In another aspect of the present disclosure, there is provided a use of a checkpoint inhibitor in the manufacture of a medicament for treating a solid tumor in a subject in need thereof, wherein the medicament is to be administered in combination with bosentan, or a pharmaceutically acceptable salt thereof.

[0012c] In a further aspect of the present disclosure, there is provided a use of bosentan, or a pharmaceutically acceptable salt thereof, in the manufacture of a first medicament and use of a checkpoint inhibitor in the manufacture of a second medicament, wherein the first and

second medicaments are to be used in combination therapy to treat a solid tumor in a subject in need thereof.

[0012d] In another aspect of the present disclosure, there is provided a use of bosentan, or a pharmaceutically acceptable salt thereof, and a checkpoint inhibitor in the manufacture of a medicament for combination therapy to treat a solid tumor in a subject in need thereof.

[0012e] In a further aspect of the present disclosure, there is provided a kit comprising:

(a) an effective amount of bosentan, 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 bosentan, or a pharmaceutically acceptable salt thereof with the checkpoint inhibitor according to the use disclosed herein.

[0012f] In a further aspect of the present disclosure, there is provided a use of a checkpoint inhibitor in the manufacture of a medicament for treating a solid tumor in a subject in need thereof, wherein:

(a) the blood flow and/or stiffness of the solid tumor is measured;

(b) an effective amount of bosentan is to be administered to the subject;

(c) the blood flow and/or stiffness of the solid tumor is measured after bosentan is administered; and

(d) the checkpoint inhibitor is to be administered if the blood flow of the solid tumor is increased and/or the stiffness of the solid tumor is decreased after the bosentan is administered.

[0012g] In another aspect of the present disclosure, there is provided a use of a checkpoint inhibitor in the manufacture of a medicament for treating a solid tumor in a subject in need thereof, wherein:

(a) the blood flow and/or stiffness of the solid tumor is measured;

(b) an effective amount of bosentan is to be administered to the subject;

(c) the blood flow and/or stiffness of the solid tumor is measured after bosentan is administered;

(d) the subject is determined to be responsive to the checkpoint inhibitor based on an increase in the blood flow of the solid tumor or a decrease in the stiffness of the solid tumor after bosentan is administered; and

(e) the checkpoint inhibitor is to be administered to the subject who has been determined to be responsive to the checkpoint inhibitor based on the increase in the blood flow of the solid tumor or the decrease in the stiffness of the solid tumor after bosentan is administered.

[0012h] In a further aspect of the present disclosure, there is provided a method for predicting response to treatment with a checkpoint inhibitor, wherein:

(a) the blood flow and/or stiffness of the solid tumor is measured;

(b) an effective amount of bosentan is to be administered to the subject;

(c) the blood flow and/or stiffness of the solid tumor is measured after bosentan is administered,

wherein an increase in the blood flow of the solid tumor or a decrease in the stiffness of the solid tumor after the bosentan is administered indicates that the subject is likely to respond to treatment with the checkpoint inhibitor.

[0013] Provided herein is a method for treating a solid tumor in a subject in need thereof comprising administering to the subject an effective amount of bosentan, or a pharmaceutically acceptable salt thereof, in combination with a checkpoint inhibitor. Also provided herein is a method 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 bosentan, or a pharmaceutically acceptable salt thereof, in combination with a checkpoint inhibitor, wherein the subject has a solid tumor. Also provided herein is a method for potentiating the effects of a checkpoint inhibitor in a subject in need thereof comprising administering to the subject an effective amount of bosentan, or a pharmaceutically acceptable salt thereof, in combination with a checkpoint inhibitor, wherein the subject has a solid tumor. Also provided herein is method of increasing blood flow of a solid tumor in a subject comprising administering to the

CLAIMS

What is claimed is:

1. Use of an effective amount of bosentan, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a solid tumor in a subject in need thereof, wherein the medicament is to be administered in combination with a checkpoint inhibitor.

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

3. Use of bosentan, or a pharmaceutically acceptable salt thereof, in the manufacture of a first medicament and use of a checkpoint inhibitor in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat a solid tumor in a subject in need thereof.

4. Use of bosentan, or a pharmaceutically acceptable salt thereof, and a checkpoint inhibitor in the manufacture of a medicament for combination therapy to treat a solid tumor in a subject in need thereof.

5. The use of any one of claims 1-4, wherein:

(i) bosentan, or the pharmaceutically acceptable salt thereof, increases the number of anti-tumor T cells that colocalize with the solid tumor;

(ii) bosentan, or the pharmaceutically acceptable salt thereof, reduces the tissue stiffness of the solid tumor, optionally wherein the tissue stiffness of the solid tumor is measured using ultrasound elastography;

(iii) bosentan, or the pharmaceutically acceptable salt thereof, decreases the levels of an extracellular matrix protein in the solid tumor, optionally wherein the extracellular matrix protein is collagen I or hyaluronan binding protein (HABP); and/or

(iv) bosentan, or the pharmaceutically acceptable salt thereof, reduces hypoxia in the solid tumor.

6. The use of any one of claims 1-5, 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, optionally wherein the checkpoint inhibitor is an anti-PD-1 antibody, anti-PD-L1 antibody, or anti-CTLA4 antibody.

7. The use of claim 5, wherein the checkpoint inhibitor is selected from the group consisting of MEDI0680, AMP-224, nivolumab, pembrolizumab, pidilizumab, MEDI4736, atezolizumab, ipilimumab, tremelimumab, and BMS-936559.

8. The use of claim 6 or claim 7, wherein the checkpoint inhibitor is a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody.

9. The use of any one of claims 1-8, wherein:

(i) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject once per day;

(ii) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject twice per day;

(iii) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose from 0.01 mg/kg to 5 mg/kg;

(iv) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose from 100 mg to 1200 mg;

(v) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose from 125 mg to 500 mg;

(vi) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose of 125 mg;

(vii) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose of 500 mg;

(viii) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject before the checkpoint inhibitor is to be administered, optionally wherein the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at least 1 day before the checkpoint inhibitor is to be administered;

(ix) the administration of bosentan, 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, optionally wherein the administration of bosentan, or pharmaceutically

acceptable salt thereof, to the subject is maintained for the entire period of time the subject is to be administered the checkpoint inhibitor.

10. The use of any one of claims 1-9, wherein one or more therapeutic effects in the subject is improved relative to a baseline after the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor are to be administered, optionally 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.

11. The use of any one of claims 1-10, wherein:

(i) the size of a tumor derived from the cancer is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, or at least 80% relative to the size of the tumor derived from the cancer before the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor are to be administered;

(ii) the objective response rate is at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, or at least 80%;

(iii) the subject exhibits progression-free survival of at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least eighteen months, at least two years, at least three years, at least four years, or at least five years after the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor are to be administered;

(iv) the subject exhibits overall survival of at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least eighteen months, at least two years, at least three years, at least four years, or at least five years after the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor are to be administered;

(v) the duration of response is at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least eighteen months, at least two years, at least three years, at least four years, or at least five years after

the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor are to be administered.

12. The use of any one of claims 1-11, wherein the solid tumor is selected from the group consisting of breast cancer, breast cancer lung metastases, sarcoma, pancreatic cancer, ovarian cancer, liver metastases, prostate cancer, brain cancer, melanoma, mesothelioma, 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, optionally wherein the cancer is breast cancer that is triple negative breast cancer.

13. The use of any one of claims 1-12, wherein the subject is a human.

14. A kit comprising:

(a) an effective amount of bosentan, 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 1-13; and

(b) a package insert comprising instructions for using the bosentan, or a pharmaceutically acceptable salt thereof with the checkpoint inhibitor according to the use of any one of claims 1-13.

15. Use of a checkpoint inhibitor in the manufacture of a medicament for treating a solid tumor in a subject in need thereof, wherein:

(a) the blood flow and/or stiffness of the solid tumor is measured;

(b) an effective amount of bosentan is to be administered to the subject;

(c) the blood flow and/or stiffness of the solid tumor is measured after bosentan is administered; and

(d) the checkpoint inhibitor is to be administered if the blood flow of the solid tumor is increased and/or the stiffness of the solid tumor is decreased after the bosentan is administered.

16. Use of a checkpoint inhibitor in the manufacture of a medicament for treating a solid tumor in a subject in need thereof, wherein:

(a) the blood flow and/or stiffness of the solid tumor is measured;

(b) an effective amount of bosentan is to be administered to the subject;

(c) the blood flow and/or stiffness of the solid tumor is measured after bosentan is administered;

(d) the subject is determined to be responsive to the checkpoint inhibitor based on an increase in the blood flow of the solid tumor or a decrease in the stiffness of the solid tumor after bosentan is administered; and

(e) the checkpoint inhibitor is to be administered to the subject who has been determined to be responsive to the checkpoint inhibitor based on the increase in the blood flow of the solid tumor or the decrease in the stiffness of the solid tumor after the bosentan is administered.

17. A method for predicting response to treatment with a checkpoint inhibitor, wherein:

(a) the blood flow and/or stiffness of the solid tumor is measured;

(b) an effective amount of bosentan is to be administered to the subject;

(c) the blood flow and/or stiffness of the solid tumor is measured after bosentan is administered,

wherein an increase in the blood flow of the solid tumor or a decrease in the stiffness of the solid tumor after the bosentan is administered indicates that the subject is likely to respond to treatment with the checkpoint inhibitor.

18. The use of claim 15 or claim 16 or the method of claim 17, wherein the effective amount of bosentan is determined by measuring the change in blood flow and/or stiffness of the solid tumor following administration of bosentan to the subject, wherein an increase in blood flow and/or a decrease in stiffness following administration of bosentan to the subject indicates that the amount administered was an effective amount.

19. The method or use of any one of claims 15-16 or 18, wherein:

(i) blood flow and/or stiffness of the solid tumor is measured using ultrasound;

(ii) blood flow of the solid tumor is measured using histological techniques to measure hypoxia;

(iii) 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, further optionally wherein the checkpoint inhibitor is a CTLA-4, PD-L1, PD-L2, or PD-1 inhibitor, further optionally wherein the checkpoint inhibitor is an anti-PD-1 antibody, anti-PD-L1 antibody, or anti-CTLA4 antibody, further optionally wherein the checkpoint inhibitor is selected from the group consisting of MEDI0680, AMP-224, nivolumab, pembrolizumab, pidilizumab, MEDI4736, atezolizumab, ipilimumab, tremelimumab, and BMS-936559, further optionally wherein the checkpoint inhibitor is a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody;

(iv) the solid tumor is selected from the group consisting of 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, mesothelioma, and cutaneous squamous cell carcinoma, optionally wherein the solid tumor is breast cancer that is triple negative breast cancer; and/or

(v) the subject is a human.