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 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;

(b) an effective amount of a checkpoint inhibitor; and

(c) instructions for using the bosentan, or a pharmaceutically acceptable salt thereof and the checkpoint inhibitor according to the use disclosed herein.

[0012f] In another aspect of the present disclosure, there is provided a method of determining an effective amount of an agent that decompresses blood vessels in a subject with a solid tumor, wherein:

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

(b) an effective amount of an agent that decompresses blood vessels is to be administered to the subject; and

(c) the blood flow and/or stiffness of the solid tumor is measured after the agent that decompresses blood vessels is administered, wherein an increase in blood flow and/or a decrease in stiffness following administration of the agent that decompresses blood vessels to the subject indicates that the amount administered was an effective amount.

[0012g] In a further aspect of the present disclosure, there is provided a use of a chemotherapeutic agent 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 an agent that decompresses blood vessels is to be administered to the subject;

(c) the blood flow and/or stiffness of the solid tumor is measured after the agent that decompresses blood vessels is administered; and

(d) the chemotherapeutic agent 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 agent that decompresses blood vessels is administered.

[0012h] In another aspect of the present disclosure, there is provided a use of a chemotherapeutic agent 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 an agent that decompresses blood vessels is to be administered to the subject;
(c) the blood flow and/or stiffness of the solid tumor is measured after the agent that decompresses blood vessels is administered;
(d) the subject is determined to be responsive to the chemotherapeutic agent based on an increase in the blood flow of the solid tumor or a decrease in the stiffness of the solid tumor after the agent that decompresses blood vessels is administered; and
(e) the chemotherapeutic agent is to be administered to the subject who has been determined to be responsive to the chemotherapeutic agent based on the increase in the blood flow of the solid tumor or the decrease in the stiffness of the solid tumor after the agent that decompresses blood vessels is administered.

[0012i] In a further aspect of the present disclosure, there is provided a method for predicting response to treatment with a chemotherapeutic agent, wherein:
(a) the blood flow and/or stiffness of the solid tumor is measured;
(b) an effective amount of an agent that decompresses blood vessels is to be administered to the subject;
(c) the blood flow and/or stiffness of the solid tumor is measured after the agent that decompresses blood vessels 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 agent that decompresses blood vessels is administered indicates that the subject is likely to respond to treatment with the chemotherapeutic agent.

[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

subject an effective amount of bosentan, or a pharmaceutically acceptable salt thereof, in combination with a checkpoint inhibitor, wherein increasing blood flow of the solid tumor enhances the effect of the checkpoint inhibitor. In some ~~embodiment~~examples, blood flow is measured using ultrasound-based blood flow measurements or using histological techniques to measure hypoxia. In some ~~embodiment~~examples, blood flow is measured using ultrasound-based blood flow measurements. In some ~~embodiment~~examples, blood flow is measured using histological techniques to measure hypoxia. In some ~~embodiment~~examples, blood flow is measured using histological techniques to measure hypoxia in a biopsy from the solid tumor. Also provided herein is a method of improving the delivery or efficacy of a checkpoint inhibitor in a subject comprising administering an effective amount of bosentan, or a pharmaceutically acceptable salt thereof, in combination with the checkpoint inhibitor, wherein the subject has a solid tumor, thereby improving the delivery or efficacy of the therapy in the subject. In some ~~embodiment~~examples, administering bosentan, or pharmaceutically acceptable salt thereof, increases the number of anti-tumor T cells that colocalize with the solid tumor. In some ~~embodiment~~examples, administering bosentan, or pharmaceutically acceptable salt thereof, reduces the tissue stiffness of the solid tumor. In some ~~embodiment~~examples, the tissue stiffness of the solid tumor is measured using ultrasound elastography. In some ~~embodiment~~examples, administering bosentan, or pharmaceutically acceptable salt thereof, decreases the levels of an extracellular matrix protein in the solid tumor. In some ~~embodiment~~examples, the extracellular matrix protein is collagen I or hyaluronan binding protein (HABP). In some ~~embodiment~~examples, administering bosentan, or pharmaceutically acceptable salt thereof, reduces hypoxia in the solid tumor. In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, the checkpoint inhibitor is a CTLA-4, PD-L1, PD-L2, or PD-1 inhibitor. In some ~~embodiment~~examples, the checkpoint inhibitor is an anti-PD-1 antibody, anti-PD-L1 antibody, or anti-CTLA4 antibody. In some ~~embodiment~~examples, the checkpoint inhibitor is selected from the group consisting of MEDI0680, AMP-224, nivolumab, pembrolizumab, pidilizumab, MEDI4736, atezolizumab, ipilimumab, tremelimumab, and BMS-936559. In some ~~embodiment~~examples, the checkpoint inhibitor is a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject once per day. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject twice per day. In some ~~embodiment~~examples, the bosentan, or

pharmaceutically acceptable salt thereof, is administered to the subject at a dose from about 0.01 mg/kg to about 5 mg/kg. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject at a dose from about 100 mg to about 1200 mg. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject at a dose from about 125 mg to about 500 mg. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject at a dose of about 125 mg. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject at a dose of about 500 mg. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject prior to the subject being administered the checkpoint inhibitor. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject beginning at least 1 day prior to the subject being administered the checkpoint inhibitor. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject beginning at least 2 days prior to the subject being administered the checkpoint inhibitor. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject beginning at least 3 days prior to the subject being administered the checkpoint inhibitor. In some ~~embodiment~~examples, the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject beginning at least 5 days prior to the subject being administered the checkpoint inhibitor. In some ~~embodiment~~examples, 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 administered the checkpoint inhibitor. In some ~~embodiment~~examples, the administration of bosentan, or pharmaceutically acceptable salt thereof, to the subject is maintained for the entire period of time the subject is administered the checkpoint inhibitor. In some ~~embodiment~~examples, one or more therapeutic effects in the subject is improved after administration of the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor relative to a baseline. In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, the size of a tumor derived from the cancer is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% relative to the size of the tumor derived from the cancer before administration of the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor. In some

~~embodiment~~examples, the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%. In some ~~embodiment~~examples, the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor. In some ~~embodiment~~examples, the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor. In some ~~embodiment~~examples, the duration of response to the antibody-drug conjugate is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor. In some ~~embodiment~~examples, 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.. In some ~~embodiment~~examples, the solid tumor is breast cancer. In some ~~embodiment~~examples, the breast cancer is triple negative breast cancer. In some ~~embodiment~~examples, the subject is a human.

[0014] Also provided herein is a kit comprising an effective amount of bosentan, or a pharmaceutically acceptable salt thereof, an effective amount of a checkpoint inhibitor, and

instructions for using the bosentan, or a pharmaceutically acceptable salt thereof and the checkpoint inhibitor according to any of the methods described herein.

[0015] Also provided herein is a method of determining an effective amount of an agent that decompresses blood vessels in a subject with a solid tumor comprising (a) measuring the blood flow and/or stiffness of the solid tumor; (b) administering to the subject an effective amount of an agent that decompresses blood vessels; and (c) measuring the blood flow and/or stiffness of the solid tumor after administering the agent that decompresses blood vessels, wherein an increase in blood flow and/or a decrease in stiffness following administration of the agent that decompresses blood vessels to the subject indicates that the amount administered was an effective amount. Also provided herein is a method for treating a solid tumor in a subject in need thereof comprising (a) measuring the blood flow and/or stiffness of the solid tumor; (b) administering to the subject an effective amount of an agent that decompresses blood vessels; (c) measuring the blood flow and/or stiffness of the solid tumor after administering the agent that decompresses blood vessels; and (d) administering a chemotherapeutic agent if the blood flow of the solid tumor is increased and/or the stiffness of the solid tumor is decreased after administering the agent that decompresses blood vessels. Also provided herein is a method for treating a solid tumor in a subject in need thereof comprising (a) measuring the blood flow and/or stiffness of the solid tumor; (b) administering to the subject an effective amount of an agent that decompresses blood vessels; (c) measuring the blood flow and/or stiffness of the solid tumor after administering the agent that decompresses blood vessels; (d) determining that the subject is responsive to a chemotherapeutic agent based on an increase in the blood flow of the solid tumor or a decrease in the stiffness of the solid tumor after administering the agent that decompresses blood vessels; and (e) administering the chemotherapeutic agent to the subject who has been determined to be responsive to the chemotherapeutic agent based on the increase in the blood flow of the solid tumor or the decrease in the stiffness of the solid tumor after administering the agent that decompresses blood vessels. Also provided herein is a method for predicting response to treatment with a chemotherapeutic agent comprising (a) measuring the blood flow and/or stiffness of the solid tumor; (b) administering to the subject an effective amount of an agent that decompresses blood vessels; (c) measuring the blood flow and/or stiffness of the solid tumor after administering the agent that decompresses blood vessels, wherein an increase in the blood flow of the solid tumor or a decrease in the stiffness of the solid tumor after administering the agent that decompresses blood vessels indicates that the subject is likely to respond to treatment with the chemotherapeutic agent. In some ~~embodiment~~example~~s~~, the

effective amount of an agent that decompresses blood vessels is determined by measuring the change in blood flow and/or stiffness of the solid tumor following administration of the agent that decompresses blood vessels to the subject, wherein an increase in blood flow and/or a decrease in stiffness following administration of the agent that decompresses blood vessels to the subject indicates that the amount administered was an effective amount. In some ~~embodiment~~examples, the method comprises measuring the blood flow of the solid tumor and the blood flow of the solid tumor is increased after administering the agent that decompresses blood vessels. In some ~~embodiment~~examples, the method comprises measuring the stiffness of the solid tumor and the stiffness of the solid tumor is decreased after administering the agent that decompresses blood vessels. In some ~~embodiment~~examples, the agent that decompresses blood vessels is administered for at least 1 day, at least 2 days, at least 3 days, at least 4 days, or at least 5 days prior to the administration of the chemotherapeutic agent. In some ~~embodiment~~examples, the agent that decompresses blood vessels is administered at a dose that increases the blood flow of the solid tumor and/or decreases the stiffness of the solid tumor. In some ~~embodiment~~examples, the agent that decompresses blood vessels is bosentan, or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, blood flow and/or stiffness of the solid tumor is measured using ultrasound. In some ~~embodiment~~examples, blood flow of the solid tumor is measured using histological techniques to measure hypoxia. In some ~~embodiment~~examples, the chemotherapeutic agent is a checkpoint inhibitor. In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, the checkpoint inhibitor is a CTLA-4, PD-L1, PD-L2, or PD-1 inhibitor. In some ~~embodiment~~examples, the checkpoint inhibitor is an anti-PD-1 antibody, anti-PD-L1 antibody, or anti-CTLA4 antibody. In some ~~embodiment~~examples, the checkpoint inhibitor is selected from the group consisting of MEDI0680, AMP-224, nivolumab, pembrolizumab, pidilizumab, MEDI4736, atezolizumab, ipilimumab, tremelimumab, and BMS-936559. In some ~~embodiment~~examples, the checkpoint inhibitor is a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody. In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, the solid tumor is breast cancer. In some ~~embodiment~~examples, the breast cancer is triple negative breast cancer. In some ~~embodiment~~examples, the subject is a human.

[0016] It is to be understood that one, some, or all of the properties of the various ~~embodiment~~examples described herein may be combined to form other ~~embodiment~~examples of the present ~~invention~~disclosure. These and other ~~aspect~~examples of the ~~invention~~disclosure will become apparent to one of skill in the art. These and other ~~embodiment~~examples of the ~~invention~~disclosure are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIGS. 1A-1L is a series of images and graphs showing that bosentan normalizes the tumor mechanical microenvironment. FIG. 1A: Ultrasound elastography heat maps of control treated (top) and 1 mg/kg bosentan treated E0771 tumors on day 10 after treatment, with lower kPa indicating compliant tissue and higher kPa indicating stiff tissue. The dashed black line denotes the tumor border. FIG. 1B: Longitudinal quantification of elasticity in E0771 tumors. Symbol indicates $P < 0.05$. FIG. 1C: Longitudinal quantification of elasticity in 4T1 tumors. Symbol indicates $P < 0.05$. FIG. 1D: Young's modulus quantification of atomic force microscopy measurements in E0771 tumors. Symbol indicates $P < 0.05$. FIG. 1E: Representative atomic force microscopy stiffness fingerprint histogram of a control treated E0771 tumor. The peak on the left side of the graph is the contribution from compliant cancer cells, while the tail in the box is the contribution of stiffer components like collagen. FIG. 1F: Representative atomic force microscopy stiffness fingerprint histogram of a 1 mg/kg bosentan treated E0771 tumor. FIG. 1G: Representative atomic force microscopy stiffness fingerprint histogram of a 10 mg/kg bosentan treated E0771 tumor. FIG. 1H: Quantification of interstitial fluid pressure in E0771 tumors. Symbol indicates $P < 0.05$. FIG. 1I: Representative images of pico sirius red staining, αSMA immunofluorescence staining, and hyaluronan binding protein (HABP) immunofluorescence staining in E0771 tumors. FIG. 1J: Quantification of pico sirius red staining in E0771 tumors. Symbol indicates $P < 0.05$. FIG. 1K: Quantification of αSMA staining in 4T1 tumors. Symbol indicates $P < 0.05$. FIG. 1L Quantification of HABP staining in E0771 tumors.

[0018] FIGS. 2A-2F is a series of images and graphs showing that bosentan reduces hypoxia and increases T cell association with blood vessels. FIG. 2A: Representative images of pimonidazole (hypoxia) staining (top box) and colocalization of $CD3^+$ T cells and $CD31^+$

CLAIMS

What is claimed is:

1. ~~A method for treating a solid tumor in a subject in need thereof comprising administering to the subject~~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 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.

~~2. 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.~~

~~3. 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.~~

~~4. A method of increasing blood flow of a solid tumor in a subject comprising administering to the subject an effective amount of bosentan, or a pharmaceutically acceptable salt thereof, in combination with a checkpoint inhibitor, wherein increasing blood flow of the solid tumor enhances the effect of the checkpoint inhibitor.~~

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

~~6. A method of improving the delivery or efficacy of a checkpoint inhibitor in a subject comprising administering an effective amount of bosentan, or a pharmaceutically acceptable salt thereof, in combination with the checkpoint inhibitor, wherein the subject has a solid tumor, thereby improving the delivery or efficacy of the therapy in the subject.~~

~~7~~5. The ~~method~~ use of any one of claims 1-5~~6~~, wherein:

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

~~8. The method of any one of claims 1-7, wherein~~(ii) ~~administering~~ bosentan, or the pharmaceutically acceptable salt thereof, reduces the tissue stiffness of the solid tumor~~.~~

~~9. The method of claim 8~~, optionally wherein the tissue stiffness of the solid tumor is measured using ultrasound elastography;~~.~~

~~10. The method of any one of claims 1-9, wherein~~(iii) ~~administering~~ bosentan, or the pharmaceutically acceptable salt thereof, decreases the levels of an extracellular matrix protein in the solid tumor~~.~~

~~11. The method of claim 10~~, optionally wherein the extracellular matrix protein is collagen I or hyaluronan binding protein (HABP);~~.~~ and/or

~~12. The method of any one of claims 1-11, wherein~~(iv) ~~administering~~ bosentan, or the pharmaceutically acceptable salt thereof, reduces hypoxia in the solid tumor.

613. The usemethod of any one of claims 1-512, 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.

~~14. The method of claim 13, wherein the checkpoint inhibitor is a CTLA-4, PD-L1, PD-L2, or PD-1 inhibitor.~~

~~15. The method of claim 13~~, optionally wherein the checkpoint inhibitor is an anti-PD-1 antibody, anti-PD-L1 antibody, or anti-CTLA4 antibody.

716. The usemethod of claim 613, wherein the checkpoint inhibitor is selected from the group consisting of MEDI0680, AMP-224, nivolumab, pembrolizumab, pidilizumab, MEDI4736, atezolizumab, ipilimumab, tremelimumab, and BMS-936559.

817. The usemethod of any one of claim 6 or claim 713-16, wherein the checkpoint inhibitor is a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody.

918. The usemethod of any one of claims 1-817, wherein:

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

~~19. The method of any one of claims 1-17, wherein~~(ii) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject twice per day;.

~~20. The method of any one of claims 1-19, wherein~~(iii) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose from about 0.01 mg/kg to about 5 mg/kg;.

~~21. The method of any one of claims 1-19, wherein~~(iv) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose from about 100 mg to about 1200 mg;.

~~22. The method of any one of claims 1-19, wherein~~(v) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose from about 125 mg to about 500 mg~~;~~.

~~23. The method of any one of claims 1-19, wherein~~(vi) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose of about 125 mg~~;~~.

~~24. The method of any one of claims 1-19, wherein~~(vii) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose of about 500 mg~~;~~.

~~25. The method of any one of claims 1-24, wherein~~(viii) the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject ~~prior to the subject being administered~~before the checkpoint inhibitor is to be administered~~.~~

~~26. The method of claim 25~~, optionally wherein the bosentan, or pharmaceutically acceptable salt thereof, is to be administered to the subject ~~beginning~~ at least 1 day ~~prior to the subject being administered~~ before the checkpoint inhibitor is to be administered~~;~~.

~~27. The method of claim 25, wherein the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject beginning at least 2 days prior to the subject being administered the checkpoint inhibitor.~~

~~28. The method of claim 25, wherein the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject beginning at least 3 days prior to the subject being administered the checkpoint inhibitor.~~

~~29. The method of claim 25, wherein the bosentan, or pharmaceutically acceptable salt thereof, is administered to the subject beginning at least 5 days prior to the subject being administered the checkpoint inhibitor.~~

~~30. The method of any one of claims 1-29, wherein~~(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~~.~~

~~31. The method of claim 30~~, 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.

1032. The use~~method~~ of any one of claims 1-931, wherein one or more therapeutic effects in the subject is improved relative to a baseline after ~~administration of~~ the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor are to be administered ~~relative to a baseline.~~

~~33. The method of claim 32~~, 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.

1134. The use~~method~~ of any one of claims 1-1033, wherein:

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

~~35. The method of any one of claims 1-34, wherein~~(ii) the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%;~~.~~

~~36. The method of any one of claims 1-35, wherein~~(iii) the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after

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

~~37. The method of any one of claims 1-36, wherein~~(iv) the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after ~~administration of~~ the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor are to be administered;~~.~~

~~38. The method of any one of claims 1-37, wherein~~(v) the duration of response to the antibody-drug conjugate is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after ~~administration of~~ the bosentan, or pharmaceutically acceptable salt thereof, and the checkpoint inhibitor are to be administered.

12~~39~~. The use~~method~~ of any one of claims 1-11~~38~~, 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~~.~~

~~40. The method of claim 39~~, optionally wherein the ~~solid tumor~~cancer is breast cancer~~.~~

~~41. The method of claim 40, wherein the breast cancer~~ that is triple negative breast cancer.

~~42~~13. The ~~method~~ use of any one of claims 1-12~~41~~, wherein the subject is a human.

1443. A kit comprising:

(a) an effective amount of bosentan, or a pharmaceutically acceptable salt thereof;

(b) an effective amount of a checkpoint inhibitor; and

(c) instructions for using the bosentan, or a pharmaceutically acceptable salt thereof and the checkpoint inhibitor according to the usemethod of any one of claims 1-1342.

1544. A method of determining an effective amount of an agent that decompresses blood vessels in a subject with a solid tumor, wherein comprising:

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

(b) administering to the subject an effective amount of an agent that decompresses blood vessels is to be administered to the subject; and

(c) measuring the blood flow and/or stiffness of the solid tumor is measured after administering the agent that decompresses blood vessels is administered, wherein an increase in blood flow and/or a decrease in stiffness following administration of the agent that decompresses blood vessels to the subject indicates that the amount administered was an effective amount.

4516. Use of a chemotherapeutic agent in the manufacture of a medicament A method for treating a solid tumor in a subject in need thereof, wherein comprising:

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

(b) administering to the subject an effective amount of an agent that decompresses blood vessels is to be administered to the subject;

(c) measuring the blood flow and/or stiffness of the solid tumor is measured after administering the agent that decompresses blood vessels is administered; and

(d) theadministering a chemotherapeutic agent 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 administering the agent that decompresses blood vessels is administered.

4617. Use of a chemotherapeutic agent in the manufacture of a medicament A method for treating a solid tumor in a subject in need thereof, wherein comprising:

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

(b) ~~administering to the subject~~ an effective amount of an agent that decompresses blood vessels is to be administered to the subject;

(c) ~~measuring~~ the blood flow and/or stiffness of the solid tumor is measured after ~~administering~~ the agent that decompresses blood vessels is administered;

(d) ~~determining that~~ the subject is determined to be responsive to the~~a~~ chemotherapeutic agent based on an increase in the blood flow of the solid tumor or a decrease in the stiffness of the solid tumor after ~~administering~~ the agent that decompresses blood vessels is administered; and

(e) ~~administering~~ the chemotherapeutic agent is to be administered to the subject who has been determined to be responsive to the chemotherapeutic agent based on the increase in the blood flow of the solid tumor or the decrease in the stiffness of the solid tumor after ~~administering~~ the agent that decompresses blood vessels is administered.

18~~47~~. A method for predicting response to treatment with a chemotherapeutic agent, wherein ~~comprising~~:

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

(b) ~~administering to the subject~~ an effective amount of an agent that decompresses blood vessels is to be administered to the subject;

(c) ~~measuring~~ the blood flow and/or stiffness of the solid tumor is measured after ~~administering~~ the agent that decompresses blood vessels is administered,

wherein an increase in the blood flow of the solid tumor or a decrease in the stiffness of the solid tumor after ~~administering~~ the agent that decompresses blood vessels is administered indicates that the subject is likely to respond to treatment with the chemotherapeutic agent.

19~~48~~. The use of claim 16 or claim 17 or the method of claim 18~~any one of claims 45-47~~, wherein the effective amount of an agent that decompresses blood vessels is determined by measuring the change in blood flow and/or stiffness of the solid tumor following administration of the agent that decompresses blood vessels to the subject, wherein an increase in blood flow and/or a decrease in stiffness following administration of the agent that decompresses blood vessels to the subject indicates that the amount administered was an effective amount.

~~49. The method of any one of claims 44-48, wherein the method comprises measuring the blood flow of the solid tumor and the blood flow of the solid tumor is increased after administering the agent that decompresses blood vessels.~~

~~50. The method of any one of claims 44-48, wherein the method comprises measuring the stiffness of the solid tumor and the stiffness of the solid tumor is decreased after administering the agent that decompresses blood vessels.~~

~~51. The method of any one of claims 44-50, wherein the agent that decompresses blood vessels is administered for at least 1 day, at least 2 days, at least 3 days, at least 4 days, or at least 5 days prior to the administration of the chemotherapeutic agent.~~

~~52. The method of any one of claims 44-51, wherein the agent that decompresses blood vessels is administered at a dose that increases the blood flow of the solid tumor and/or decreases the stiffness of the solid tumor.~~

~~53~~20. The method or use of any one of claims ~~44-52~~16-17 or 19, wherein:

(i) the agent that decompresses blood vessels is bosentan, or a pharmaceutically acceptable salt thereof;~~.~~

~~54. The method of any one of claims 44-53, wherein~~(ii) blood flow and/or stiffness of the solid tumor is measured using ultrasound;~~.~~

~~55. The method of claim any one of claims 44-53, wherein~~(iii) blood flow of the solid tumor is measured using histological techniques to measure hypoxia;~~.~~

~~56. The method of any one of claims 45-55, wherein~~(iv) the chemotherapeutic agent is a checkpoint inhibitor~~.~~

~~57. The method of claim 56~~, optionally 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~~.~~

~~58. The method of claim 57~~, further optionally wherein the checkpoint inhibitor is a CTLA-4, PD-L1, PD-L2, or PD-1 inhibitor~~.~~

~~59. The method of claim 57~~, further optionally wherein the checkpoint inhibitor is an anti-PD-1 antibody, anti-PD-L1 antibody, or anti-CTLA4 antibody~~.~~

~~60. The method of claim 57~~, 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~~.~~

~~61. The method of any one of claim 57-60~~, further optionally wherein the checkpoint inhibitor is a combination of an anti-PD-1 antibody and an anti-CTLA-4 antibody;~~.~~

~~62. The method of any one of claims 44-61, wherein~~(v) 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~~.~~

~~63. The method of claim 62~~, optionally wherein the solid tumor is breast cancer~~.~~

~~64. The method of claim 63, wherein the breast cancer~~ that is triple negative breast cancer; and/or~~.~~

~~65. The method of any one of claims 44-64, wherein~~(vi) the subject is a human.