SUMMARY

[0005] Disclosed herein include methods of treating cancer, including a metastatic cancer. The method for treating cancer can, in some examples, comprise administering a PLK1 inhibitor and an anti-angiogenics to a subject with a metastatic cancer, thereby reducing or inhibiting progression of the metastatic cancer, where the subject has not received any prior treatment comprising inhibiting angiogenesis. The method for treating cancer can, in some examples, comprises administering a PLK1 inhibitor and an anti-angiogenics to the subject, thereby reducing or inhibiting progression of the metastatic cancer, wherein the subject has not received any prior cancer treatment or the subject has not received any prior treatment comprising inhibiting angiogenesis. The method for treating cancer can, in some examples, comprise administering a PLK1 inhibitor and an anti-angiogenics to the subject, thereby reducing or inhibiting progression of the metastatic cancer, where the subject is known to have not received any prior cancer treatment or the subject is known to have not received any prior treatment comprising inhibiting angiogenesis. The method for treating cancer can, in some examples, comprises identifying a subject having a metastatic cancer and has not received any prior cancer treatment; and administering a PLK1 inhibitor and an anti-angiogenics to the subject, thereby reducing or inhibiting progression of the metastatic cancer. The method, in some examples, comprises: identifying a subject having a metastatic cancer and has not received any prior treatment comprising inhibiting angiogenesis; and administering a PLK1 inhibitor and an anti-angiogenics to the subject, thereby reducing or inhibiting progression of the metastatic cancer.

[0006] In some examples, the method comprises administering the subject with a chemotherapy, the PLK1 inhibitor and the anti-angiogenics. In some examples, the subject has not been received prior chemotherapy treatment. In some examples, the subject has not been received prior chemotherapy treatment for the metastatic cancer. The chemotherapy can comprise a treatment using FOLFIRI, abiraterone, FOLFOX, an anti-EGFR agent, a KRAS directed inhibitor, gemcitabine, abraxane, nanoliposomal irinotecan, 5-FU, FOLFIRINOX, FOLFOXIRI, or a combination thereof.

[0007] In some examples, administering the PLK1 inhibitor and the anti-angiogenics synergistically reduces or inhibits progression of the metastatic cancer relative to the PLK1 inhibitor treatment alone, the anti-angiogenics treatment alone, and/or the additive effect of the PLK1 inhibitor treatment alone and the anti-angiogenics treatment alone. In some examples, administering the PLK1 inhibitor and the anti-angiogenics improves one or more therapeutic effects in the subject relative to a control or a baseline. In some examples, administering the PLK1 inhibitor and the anti-angiogenics reduces oncogenic allelic burden in

the subject relative to subjects who have received prior treatment comprising inhibiting angiogenesis.

[0008] Also disclosed herein includes methods of improving objective response rate (ORR), progression free survival (PFS), or both in treating a metastatic cancer. The method, in some examples, comprises administering a PLK1 inhibitor and an anti-angiogenics to subjects suffering from a metastatic cancer, thereby improving the ORR and/or the PFS of the subjects, wherein the subjects have not received any prior cancer treatment or the subjects have not received any prior treatment comprising inhibiting angiogenesis. The method, in some examples, comprises administering a PLK1 inhibitor and an anti-angiogenics to subjects suffering from a metastatic cancer, thereby improving the ORR and/or the PFS of the subjects, wherein the subjects are known to have not received any prior cancer treatment or the subjects are known to have not received any prior treatment comprising inhibiting angiogenesis. In some examples, the method comprises identifying the subjects have the metastatic cancer and have not received any prior cancer treatment. In some examples, the method comprises identifying the subjects have the metastatic cancer and have not received any prior treatment comprising inhibiting angiogenesis. In some examples, administering the PLK1 inhibitor and the anti-angiogenics synergistically improves the ORR and/or the PFS of the subjects relative to the PLK1 inhibitor treatment alone, the anti-angiogenics treatment alone, and/or the additive effect of the PLK1 inhibitor treatment alone and the anti-angiogenics treatment alone. In some examples, administering the PLK1 inhibitor and the anti-angiogenics improves one or more therapeutic effects in the subjects relative to a control or a baseline; and optionally the one or more therapeutic effects comprise size of a tumor derived from the metastatic cancer, objective response rate (ORR), duration of response, time to response, progression free survival (PFS), overall survival (OS), disease control rate (DCR), oncogenic allelic burden, or a combination thereof. In some examples, administering the PLK1 inhibitor and the anti-angiogenics improves the ORR in the subjects, improves PFS in the subjects, improves OS in the subjects, improves DCR in the subjects, reduces oncogenic allelic burden in the subjects, or a combination thereof, relative to subjects who have received prior treatment comprising inhibiting angiogenesis. In some examples, administering the PLK1 inhibitor and the anti-angiogenics improves the ORR, the PFS or both in the subjects by at least 50% relative to subjects who have received prior treatment comprising inhibiting angiogenesis. In some examples, administering the PLK1 inhibitor and the anti-angiogenics to the subjects results in an ORR difference of 50%, 55%, 65%, 70%, 75%, or more, or a number or a range between any two of these values in the subjects. In some examples, administering the PLK1 inhibitor and the anti-angiogenics to the subjects results in an mPFS of 11 months, 12 months, 13 months,

14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, or more, or a number or a range between any two of these values in the subjects. As described herein, administering the PLK1 inhibitor and the anti-angiogenics to the subjects can comprises administering the PLK1 inhibitor, the anti-angiogenics and one or more anti-cancer therapeutics or therapies (e.g., one or more chemotherapies) to the subject.

[0009] Non-limiting examples of the metastatic cancer include metastatic colorectal cancer, metastatic bladder cancer, metastatic breast cancer, metastatic kidney cancer, metastatic lung cancer, metastatic ovarian cancer, metastatic pancreatic cancer, metastatic prostate cancer, metastatic stomach cancer, metastatic thyroid cancer, metastatic uterine cancer, metastatic renal cancer, metastatic cervical cancer, metastatic recurrent glioblastoma, or a combination thereof.

[0010] In some examples, the PLK1 inhibitor is selective and/or specific for PLK1. In some examples, the PLK1 inhibitor is onvansertib, BI2536, Volasertib (BI 6727), GSK461364, AZD1775, CYC140, HMN-176, HMN-214, rigosertib (ON-01910), MLN0905, TKM-080301, TAK-960, or Ro3280. In some examples, the subject has not received any prior treatment comprising administration of an angiogenesis inhibitor, and optionally wherein the angiogenesis inhibitor is the same as the anti-angiogenics. In some examples, the anti-angiogenics is bevacizumab. In some examples, the angiogenesis inhibitor is bevacizumab.

[0011] The PLK1 inhibitor and the anti-angiogenics can be administered simultaneously or sequentially. In some examples, the PLK1 inhibitor is administered prior to the administration of the anti-angiogenics, and optionally wherein the PLK1 inhibitor is administered prior to the administration of the anti-angiogenics every day on which the subject is administered with the PLK1 inhibitor and the anti-angiogenics. In some examples, the PLK1 inhibitor is administered about 30 minutes to about 5 hours prior to the administration of the anti-angiogenics on a given day. In some examples, the administration of the PLK1 inhibitor is oral administration, and the administration of the anti-angiogenics is intravenous administration or oral administration. In some examples, the anti-angiogenics and the PLK1 inhibitor are each administered to the subject in a cycle of at least twice or at least five times within a week. In some examples, the anti-angiogenics, the PLK1 inhibitor, or both are administered in a cycle of at least 7 days; optionally each cycle of treatment is at least about 21 days; and further optionally each cycle of treatment is from about 21 days to about 28 days.

[0012] In some examples, the PLK1 inhibitor is administered on at least four days in the cycle. In some examples, the PLK1 inhibitor is not administered on at least one day in the cycle. In some examples, the anti-angiogenics is administered daily, weekly, bi-weekly, every three weeks, every four weeks, or every month. In some examples, the subject undergoes at least two cycles of the administration of the anti-angiogenics and the PLK1

inhibitor. In some examples, the anti-angiogenics is bevacizumab and the PLK1 inhibitor is onvansertib. Onvansertib can be administered at, for example, 12 mg/m^2 – 90 mg/m^2. Bevacizumab can be administered at, for example, about 1 mg/kg – 20 mg/kg; optionally wherein bevacizumab is administered at about 5 mg/kg, about 7.5 mg/kg, about 10 mg/kg, or about 15 mg/kg.

[0013] In some examples, the subject has received at least one prior cancer treatment, and optionally wherein the prior treatment does not comprise the use of an anti-angiogenics, a PLK1 inhibitor, or both. In some examples, the subject or the subjects had a prior remission for cancer. The prior remission can be complete remission (CR) or partial remission (PR).

[0014] In some examples, the method further comprises one or more of (1) determining cancer status of the subject or the subjects, (2) determining responsiveness of the subject or the subjects to a PLK1 inhibitor treatment, and (3) administering to the subject or the subjects one or more cancer therapeutics or therapies. The subject or the subjects can be human.

[0015] In some examples, reducing or inhibiting progression of the cancer comprises inhibition of growth of one or more tumors in the subject or the subjects and/or reducing the number of cancer cells detected in the subject or the subjects by at least about 25%, 30%, 40%, 50%, 60%, or 70% relative to an untreated subject. In some examples, reducing or inhibiting progression of the cancer comprises inhibition of growth of one or more tumors in the subject or the subjects and/or reducing the number of cancer cells detected in the subject or the subjects by at least about 25%, 30%, 40%, 50%, 60%, or 70% relative to the subject or the subjects prior to administration of the PLK1 inhibitor and the anti-angiogenics. In some examples, the growth of at least one of the one or more tumors in the subject or the subjects is reduced by at least about 25%, 30%, 40%, 50%, 60%, or 70% following one or more cycles of treatment. In some examples, the size/volume of at least one of the one or more tumors in the subject or the subjects is reduced by at least about 25%, 30%, 40%, 50%, 60%, or 70% following one or more cycles of treatment.

[0016] In some examples, the one or more cancer therapeutics or therapies comprise FOLFIRI, abiraterone, FOLFOX, an anti-EGFR agent, a KRAS directed inhibitor, gemcitabine, abraxane, nanoliposomal irinotecan, 5-FU, or a combination thereof; wherein the anti-EGFR agents is optionally cetuximab, and KRAS directed inhibitor is optionally a G12C inhibitor, a G12D inhibitor, or a combination thereof. In some examples, determining the responsiveness of the subject or the subjects comprises determining if the subject is a responder of the treatment, if the subject or the subjects is or is going to be in complete recovery (CR), or if the subject or the subjects is or is going to be in partial remission (PR). In some examples,

determining the responsiveness of the subjects comprises determining objective response rate (ORR), duration of response, time to response, progression free survival (PFS), overall survival (OS), disease control rate (DCR), oncogenic allelic burden, or a combination thereof of the subjects. In some examples, determining the responsiveness of the subject or the subjects comprises determining if the subject or the subjects have a partial response to the treatment, if the subject have a complete response to the treatment, if the subject has a stable disease (SD) status, or if the subject has a progressive disease (PD) status.

[0017] Also disclosed herein incudes kits. The kit, in some examples, comprises a PLK1 inhibitor; and a manual providing instructions for administrating the PLK1 inhibitor with an anti-angiogenics to a subject having a metastatic cancer, wherein the subject has not received any prior cancer treatment or the subject has not received any prior treatment comprising inhibiting angiogenesis. The kit, in some examples, comprises a PLK1 inhibitor; and a manual providing instructions for administrating the PLK1 inhibitor with an anti-angiogenics to a subject having a metastatic cancer, wherein the subject is known to have not received any prior cancer treatment or the subject is known to have not received any prior treatment comprising inhibiting angiogenesis.

[0018] In some examples, the instructions comprise instructions for administrating the PLK1 inhibitor and the anti-angiogenics simultaneously. In some examples, the instructions comprise instructions for administrating the PLK1 inhibitor and the anti-angiogenics sequentially. In some examples, the instructions comprise (1) instructions for administering of the PLK1 inhibitor orally, (2) instructions for administrating the anti-angiogenics orally, (3) instructions for administrating the anti-angiogenics intravenously, or any combination thereof. In some examples, the instructions comprise instructions wherein the subject has not received any prior treatment comprising administration of an angiogenesis inhibitor, and optionally wherein the angiogenesis inhibitor is the same as the anti-angiogenics. In some examples, the instructions comprise instructions for administering each of the anti-angiogenics and the PLK1 inhibitor to the subject in a cycle of at least twice or at least five times within a week. In some examples, the instructions comprise instructions for administering the anti-angiogenics, the PLK1 inhibitor, or both are in a cycle of at least 7 days; and optionally wherein each cycle of treatment is at least about 21 days, and further optionally each cycle of treatment is from about 21 days to about 28 days. In some examples, the instructions comprise instructions for administering the PLK1 inhibitor on at least four days in the cycle. In some examples, the instructions comprise instructions for not administering the PLK1 inhibitor on at least one day in the cycle.

[0019] In some examples, the instructions comprise instructions for

administrating the anti-angiogenics daily, weekly, bi-weekly, every three weeks, every four weeks, or monthly. In some examples, the instructions comprise instructions for administrating the anti-angiogenics and the PLK1 inhibitor for at least two cycles. The anti-angiogenics can be bevacizumab. The PLK1 inhibitor can be onvansertib. In some examples, the instructions comprise instructions for administering onvansertib at 12 mg/m^2 – 90 mg/m^2. In some examples, the kit further comprises the anti-angiogenic.

[0019a] In one aspect, the present disclosure provides use of an effective amount of onvansertib in the manufacture of a medicament for the treatment of a KRAS-mutated metastatic colorectal cancer in combination with bevacizumab and a chemotherapy containing fluorouracil; wherein a patient having a KRAS-mutated metastatic colorectal cancer is selected for the treatment, the patient not having received any prior treatment for the metastatic colorectal cancer and not having received any prior treatment with bevacizumab; and wherein onvansertib is to be administered in multiple doses and bevacizumab is to be administered in multiple doses to the patient during a treatment cycle.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIG. 1 depicts an exemplary Kaplan-Meir survival curve of cancer patients treated using the methods and compositions provided herein, with or without prior anti-angiogenics treatments.

[0021] FIG. 2 depicts number of events and censoring (non-reporting) patients for the study described herein.

[0022] FIG. 3 depicts objective response rates for a cohort of patients treated using the methods and compositions provided herein, broken down by patients who had or had not received previous anti-angiogenics treatment. Numbers in boxes are the total number of patients in the indicated group.

[0023] FIGS. 4A-4B show best radiographic response and duration of response for 66 evaluable patients (as of June 16, 2023). * Radiographic response determined per RECIST 1.1. Waterfall plot and table reflect interim data as of June 16, 2023 from an ongoing trial and unlocked database. Patients 02-008 and 07-029 were categorized as bev naïve in the July 25, 2022 data, but are now determined to have been bev exposed. mDOR CI: "–" means not reached. After external review of the tumor measurements completed May 12, 2023, it was determined that patients 02-028 and 04-038 were confirmed PRs.

[0024] FIGS. 5A-5B are simmer plots showing responses of the 66 evaluable patients (as of June 16, 2023). * Swimmer plot / table reflect interim data as of June 16, 2023 from an ongoing trial and unlocked database. After external review of the tumor measurements

completed May 12, 2023, it was determined that patients 02-028 and 04-038 were confirmed PRs.

[0025] FIG. 6 depicts plots showing progression free survival of the 66 evaluable patients (as of June 16, 2023). * Onvansertib mPFS are interim data as of June 16, 2023 from an ongoing trial and unlocked database.

[0026] FIG. 7 shows plots showing changes in tumor size from baseline. *Spider plots reflect interim data as of June 16, 2023 from an ongoing trial and unlocked database.

[0027] FIG. 8 shows changes in tumor volume in KRAS-mutant xenograft models

WHAT IS CLAIMED IS:

1. Use of an effective amount of onvansertib in the manufacture of a medicament for the treatment of a KRAS-mutated metastatic colorectal cancer in combination with bevacizumab and a chemotherapy containing fluorouracil; wherein a patient having a KRAS-mutated metastatic colorectal cancer is selected for the treatment, the patient not having received any prior treatment for the metastatic colorectal cancer and not having received any prior treatment with bevacizumab; and wherein onvansertib is to be administered in multiple doses and bevacizumab is to be administered in multiple doses to the patient during a treatment cycle.

2. The use of claim 1, wherein the patient has not received a prior chemotherapy for the metastatic colorectal cancer.

3. The use of claim 2, wherein the prior chemotherapy comprises a treatment using FOLFIRI, abiraterone, FOLFOX, an anti-EGFR agent, a KRAS-directed inhibitor, gemcitabine, abraxane, nanoliposomal irinotecan, 5-fluorouuracil (5-FU), FOLFIRINOX, FOLFOXIRI, or a combination thereof.

4. The use of claim 1, wherein onvansertib is to be administered for at least four days and bevacizumab is to be administered weekly or biweekly in the treatment cycle; wherein the treatment cycle is 21 to 28 days; and wherein the patient is to undergo at least two treatment cycles.

5. The use of claim 1, wherein onvansertib and bevacizumab are to be administered to the patient simultaneously or sequentially.

6. The use of claim 1, wherein the administration of onvansertib is oral administration, and the administration of bevacizumab is intravenous administration or oral administration.

7. The use of claim 1, wherein onvansertib is to be administered at 12 mg/m^2 – 90 mg/m^2.

8. The use of claim 1, wherein bevacizumab is to be administered at 1 mg/kg – 20 mg/kg.

9. The use of claim 1, wherein the chemotherapy containing fluorouracil is FOLFIRI or FOLFOX.

10. The use of claim 1, wherein one or more additional cancer therapeutics or therapies is/are to be administered to the patient.

11. The use of claim 10, wherein the one or more additional cancer therapeutics or therapies comprise abiraterone, an anti-EGFR agent, a KRAS directed inhibitor, gemcitabine, abraxane, nanoliposomal irinotecan, 5-FU, or a combination thereof.

12. The use of claim 1, wherein the cancer status of the patient is pre-determined.

13. The use of claim 1, wherein onvansertib and bevacizumab synergistically improves objective response rate (ORR) and/or progression free survival (PFS) in the patient when compared to a patient who has received prior bevacizumab treatment.

14. The use of claim 13, wherein the patient achieves about 2-fold, 3-fold, 4-fold or 5-fold higher ORR, compared to patients who have received prior bevacizumab treatment.

15. The use of claim 13, wherein the patient achieves about 2-fold higher PFS, compared to patients who have received prior bevacizumab treatment.

16. The use of claim 1, wherein the patient is human.