~~BRIEF~~ SUMMARY ~~OF THE INVENTION~~

[0011] The ~~invention~~ disclosure provides combination therapy methods of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising nanoparticles comprising a taxane (such as paclitaxel) and a carrier protein (such as albumin), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell (also referred herein as an "epigenetic modifier" or "the other agent").

[0011a] In one aspect, there is provided use of a composition comprising nanoparticles comprising a taxane and a carrier protein in the manufacture of a medicament for treating a cancer in an individual, wherein the medicament is to be administered intravenously in combination with an effective amount of azacitidine, wherein the azacitidine is to be administered orally.

In some embodiments, the disclosure~~invention~~ provides a method of treating a proliferative disease (such as cancer) in an individual comprising administering to the individual a) an effective amount of a composition comprising nanoparticles comprising paclitaxel coated with an albumin (such as Abraxane® or "nab-paclitaxel"), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the other agent modifies (such as inhibits) DNA methylation. In some embodiments, the other agent modifies histone modification, which includes, but is not limited to, histone acetylation, histone methylation, histone sumoylation, and histone phosphorylation. In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine).In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as vorinostat).

[0012] In some embodiments, the proliferative disease is resistant or refractory to the treatment of taxane when administered alone or in conjunction with an agent other than the epigenetic modifier. In some embodiments, the proliferative disease is resistant or refractory to the treatment when the epigenetic modifier is administered alone or in conjunction with an agent other than the nanoparticle composition (such as a non-nanoparticle composition of a taxane including paclitaxel).

[0013] In some embodiments, the composition comprising nanoparticles (also referred to as "nanoparticle composition") and the other agent are administered simultaneously, either in the same composition or in separate compositions. In some embodiments, the nanoparticle composition and the other agent are administered sequentially, i.e., the nanoparticle composition is administered either prior to or after the administration of the other agent.

[0014] In some embodiments, the administration of the nanoparticle composition and the other agent is concurrent, i.e., the administration period of the nanoparticle

a carrier protein (such as albumin), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, there is provided a method of treating breast cancer in an individual, wherein the individual is negative for ER, PR, and HER2, comprising administering to the individual a) an effective amount of a composition comprising nanoparticles comprising a taxane (such as paclitaxel) and a carrier protein (such as albumin), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the method further comprises conducting definitive surgery within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 following the preoperative therapy.

[0019] The methods of the disclosure~~invention~~ generally comprise administration of a composition comprising nanoparticles comprising a taxane (such as paclitaxel) and a carrier protein. In some embodiments, the nanoparticle composition comprises nanoparticles comprising paclitaxel and an albumin. In some embodiments, the nanoparticles in the composition described herein have an average diameter of no greater than about 200 nm, including for example no greater than about any one of 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, or 60 nm. In some embodiments, at least about 50% (for example at least about any one of 60%, 70%, 80%, 90%, 95%, or 99%) of all the nanoparticles in the composition have a diameter of no greater than about 200 nm, including for example no greater than about any one of 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, or 60 nm. In some embodiments, at least about 50% (for example at least any one of 60%, 70%, 80%, 90%, 95%, or 99%) of all the nanoparticles in the composition fall within the range of about 20 to about 400, including for example about 20 to about 200 nm, about 30 to about 180 nm, and any one of about 40 to about 150, about 50 to about 120, and about 60 to about 100 nm.

[0020] In some embodiments, the carrier protein has sulfhydral groups that can form disulfide bonds. In some embodiments, at least about 5% (including for example at least about any one of 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%) of the carrier protein in the nanoparticle portion of the composition are crosslinked (for example crosslinked through one or more disulfide bonds).

[0021] In some embodiments, the nanoparticles comprise the taxane (such as paclitaxel) coated with a carrier protein, such as albumin (e.g., human serum albumin). In some embodiments, the composition comprises taxane in both nanoparticle and non-nanoparticle form, wherein at least about any one of 50%, 60%,

treating lung cancer (such as NSCLC), comprising: a) intravenously administering about 80 to about 200 mg/m^2 (such as about 90 or 100 mg/m^2) of Abraxane® to the individual, and b) intravenously administering about 1 mg/m^2 to about 15 mg/m^2 (such as 4.5 mg/m^2) of decitabine to the individual.

[0030] In some embodiments, there is provided a method of treating lung cancer (such as NSCLC), comprising: a) intravenously administering about 80 to about 200 mg/m^2 (such as about 100 mg/m^2) of Abraxane® to the individual, and b) intravenously administering about 5 mg/m^2 to about 100 mg/m^2 (such as 15 mg/m^2) of decitabine to the individual.

[0031] In some embodiments, there is provided a method of treating lung cancer (such as NSCLC), comprising: a) intravenously administering about 80 to about 200 mg/m^2 (such as about 90 or 100 mg/m^2) of Abraxane® to the individual for five consecutive days, and b) intraperitoneally administering about 1 mg/m^2/day to about 15 mg/m^2/day (such as 4.5 mg/m^2/day) of decitabine to the individual twice a day for five consecutive days.

[0032] In some embodiments, there is provided a method of treating lung cancer (such as NSCLC), comprising: a) intravenously administering about 80 to about 200 mg/m^2 (such as about 100 mg/m^2) of Abraxane® to the individual for weekly, and b) intravenously administering about 5 mg/m^2 to about 100 mg/m^2 (such as 15 mg/m^2) of decitabine to the individual every eight hours for three consecutive days. In some embodiments, the decitabine treatment is repeated every six weeks for four or more cycles.

[0033] In some embodiments, there is provided a method of treating lung cancer (such as NSCLC), comprising: a) intravenously administering about 80 to about 200 mg/m^2 (such as about 100 mg/m^2) of Abraxane® to the individual for weekly, and b) intravenously administering about 5 mg/m^2 to about 100 mg/m^2 (such as 20 mg/m^2) of decitabine to the individual daily for five consecutive days. In some embodiments, the decitabine treatment is repeated every four weeks for four or more cycles.

[0034] Also provided are kits and compositions useful for methods described herein.

[0034a] In one aspect, there is provided a kit comprising: a) a composition comprising nanoparticles comprising a taxane and a carrier protein, and b) an effective amount of at least one other agent, wherein the other agent is azacitidine, wherein the azacitidine is to be administered orally.

[0034b] In one aspect, there is provided a medicine comprising: a) a composition comprising nanoparticles comprising a taxane and a carrier protein, and b) an effective amount of at least one other agent, wherein the other agent is azacitidine, wherein the azacitidine is to be administered orally.

[0035] The methods of the present application are useful for the treatment of various diseases, including, for example, breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia,

lymphoma, and multiple myeloma. In some embodiments, the proliferative disease is solid tumor. In some embodiments, the proliferative disease is liquid tumor.

[0036] These and other ~~aspects~~ embodiments and advantages of the present disclosure~~invention~~ will become apparent from the subsequent detailed description and the appended claims.
It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present disclosure~~invention~~.

BRIEF DESCRIPTION OF FIGURES

[0037] Figure 1 shows the study design for the treatment with carboplatin and *nab*-paclitaxel with or without vorinostat in patients with HER2-negative primary operable breast cancer.

[0038] Figure 2 shows FDG-PET results prior to neoadjuvant therapy and D7 post neoadjuvant therapy from 2 patients. Patient 1 (top) shows FDG-PET prior to neoadjuvant therapy (left) documenting a right-sided breast mass (SUV of 12.4) and D7 post neoadjuvant therapy (right) revealing a reduction in SUV to 6.7. Patient 1 had a partial response to therapy. Patient 2 (bottom) shows FDG-PET prior to neoadjuvant therapy (left) documenting a left-sided breast mass (SUV of 31) and D7 post neoadjuvant therapy (right) revealing a reduction in SUV to 9.9. Patient 2 had a complete response to therapy.

[0039] Figure 3 shows representative examples of a methylation-specific PCR assay for SPARC in NSCLC cell lines and NSCLC xenografts. H460 cells were treated with decitabine (5 μM) in vitro for 3 days (H460 w/ DEC). PCR products were visualized on 1.5% agarose gels. Me represents methylated and UM represents unmethylated.

[0040] Figure 4 shows a western blot analysis demonstrating that SPARC expression in xenografts and NSCLC cell lines is up-regulated on treatment with decitabine. Panel A shows a western blot of NSCLC cell lines A549, H460, and H157, treated with 5 μM decitabine for 3 days in vitro and then harvested for RT-PCR. Panel B shows PD NSCLC xenografts and H460 xenografts treated with or without decitabine at 1.5 mg/kg/d. Xenografts were harvested for SPARC expression analysis. GAPDH was used as the endogenous control. GAPDH is glyceraldehyde-3-phosphate dehydrogenase.

CLAIMS

What is claimed is:

1. A method of treating a proliferative disease in an individual comprising administering to the individual:
a) an effective amount of a composition comprising nanoparticles comprising a taxane and a carrier protein, and
b) an effective amount of at least one other agent that modifies the epigenetics in a cell.

2. The method according to claim 1, wherein said other agent is an inhibitor of histone deacetylase.

3. The method according to claim 2, wherein said other agent is vorinostat.

4. The method according to claim 3, further comprising administering to said individual a platinum-based agent.

5. The method according to claim 1, wherein said other agent is an inhibitor of DNA methytransferase.

6. The method according to claim 5, wherein the other agent is azacitidine.

7. The method according to claim 5, wherein the other agent is decitabine.

8. The method according to any one of claims 1-7, wherein the proliferative disease is cancer.

9. The method according to claim 8, wherein the cancer is breast cancer.

10. The method according to claim 9, wherein the individual is negative for ER, PR, or HER2.

11. The method according to claim 10, wherein the individual is negative for ER, PR, and HER2.

12. The method according to claim 8, wherein the cancer is ovarian cancer.

13. The method according to claim 8, wherein the cancer is non-small lung cancer.

14. The method according to any one of claims 1-13, wherein the composition comprising nanoparticles comprising taxane and albumin and the other agent are administered simultaneously.

15. The method according to any one of claims 1-13, wherein the composition comprising nanoparticles of taxane and albumin and the other agent are administered sequentially.

16. The method according to any one of claims 1-13, wherein the composition comprising nanoparticles of taxane and albumin and the other agent are administered concurrently.

17. The method according to any one of claims 1-16, wherein the taxane is paclitaxel.

18. The method according to any one of claims 1-17, wherein the average diameter of the nanoparticles in the composition is no greater than about 200 nm.

19. The method according to any one of claims 1-18, wherein the carrier protein is albumin.

20. The method according to claim 19, wherein the weight ratio of the albumin and the taxane in the nanoparticle composition is less than about 1:1 to about 18:1.

21. The method according to claim 20, wherein the weight ratio of the albumin and the taxane in the nanoparticle composition is less than about 1:1 to about 9:1.

22. The method according to any one of claims 1-21, wherein the individual is a human.

23. A kit comprising: a) a composition comprising nanoparticles comprising a taxane and a carrier protein, and b) an effective amount of at least one other agent that modifies the epigenetics in a cell.

24. A medicine comprising: a) a composition comprising nanoparticles comprising a taxane and a carrier protein, and b) an effective amount of at least one other agent that modifies the epigenetics in a cell.

CLAIMS

What is claimed is:

1. Use of a composition comprising nanoparticles comprising a taxane and a carrier protein in the manufacture of a medicament for treating a cancer in an individual, wherein the medicament is to be administered intravenously in combination with an effective amount of azacitidine, wherein the azacitidine is to be administered orally.

2. The use according to claim 1, wherein the medicament is to be administered with a platinum-based agent.

3. The use according to claim 1, wherein the cancer is breast cancer.

4. The use according to claim 3, wherein the individual is negative for ER, PR, or HER2.

5. The use according to claim 4, wherein the individual is negative for ER, PR, and HER2.

6. The use according to claim 1, wherein the cancer is ovarian cancer.

7. The use according to claim 1, wherein the cancer is non-small lung cancer.

8. The use according to claim 1, wherein the cancer is endometrial cancer.

9. The use according to claim 1, wherein the cancer is cervical cancer.

10. The use according to claim 1, wherein the cancer is pancreatic cancer.

11. The use according to claim 1, wherein the cancer is melanoma.

12. The use according to claim 1, wherein the cancer is bladder cancer.

13. The use according to claim 1, wherein the cancer is head and neck cancer.

14. The use according to any one of claims 1-13, wherein the composition comprising nanoparticles comprising taxane and a carrier protein and azacitidine are to be administered simultaneously.

15. The use according to any one of claims 1-13, wherein the composition comprising nanoparticles of taxane and a carrier protein and azacitidine are to be administered sequentially.

16. The use according to any one of claims 1-13, wherein the composition comprising nanoparticles of taxane and a carrier protein and azacitidine are to be administered concurrently.

17. The use according to any one of claims 1-16, wherein the taxane is paclitaxel.

18. The use according to any one of claims 1-17, wherein the average diameter of the nanoparticles in the composition is no greater than about 200 nm.

19. The use according to any one of claims 1-18, wherein the carrier protein is albumin.

20. The use according to claim 19, wherein the albumin is human serum albumin.

21. The use according to claim 19, wherein the albumin is human albumin.

22. The use according to any of claims 19-21, wherein the weight ratio of the albumin and the taxane in the nanoparticle composition is about 1:1 to about 18:1.

23. The use according to any of claims 19-22, wherein the weight ratio of the albumin and the taxane in the nanoparticle composition is about 1:1 to about 9:1.

24. The use according to any one of claims 1-23, wherein the individual is a human.

25. The use according to any one of claims 1-24, wherein the nanoparticles in the composition are to be administered intravenously.

26. The use according to claim 25, wherein the amount of taxane in the composition is between about 80 mg/m^2 to about 150 mg/m^2.

27. The use according to claim 26, wherein the amount of taxane in the composition is between about 100 mg/m^2 to about 125 mg/m^2.

28. The use according to claim 1, wherein the effective amount of the azacitidine is between about 80 mg to about 1000 mg.

29. The use according to claim 28, wherein the effective amount of the azacitidine is between about 100 mg to about 200 mg.

30. A kit comprising: a) a composition comprising nanoparticles comprising a taxane and a carrier protein, and b) an effective amount of at least one other agent, wherein the other agent is azacitidine, wherein the azacitidine is to be administered orally.

31. The kit according to claim 30, wherein the taxane is paclitaxel.

32. The kit according to any one of claims 30-31, wherein the average diameter of the nanoparticles in the composition is no greater than about 200 nm.

33. The kit according to any one of claims 30-32, wherein the carrier protein is albumin.

34. The kit according to claim 33, wherein the albumin is human serum albumin.

35. The kit according to claim 33, wherein the albumin is human albumin.

36. A medicine comprising: a) a composition comprising nanoparticles comprising a taxane and a carrier protein, and b) an effective amount of at least one other agent, wherein the other agent is azacitidine, wherein the azacitidine is to be administered orally.

37. The medicine according to claim 36, wherein the taxane is paclitaxel.

38. The medicine according to any one of claims 36-37, wherein the average diameter of the nanoparticles in the composition is no greater than about 200 nm.

39. The medicine according to any one of claims 36-38, wherein the carrier protein is albumin.

40. The medicine according to claim 39, wherein the albumin is human serum albumin.

41. The medicine according to claim 39, wherein the albumin is human albumin.