SUMMARY

[0011] The 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 proliferative disease in an individual, wherein the medicament is to be administered in combination with an effective amount of azacitidine, wherein the azacitidine is to be administered orally.

In some embodiments, the disclosure 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

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 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 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,

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 proliferative disease in an individual, wherein the medicament is to be administered 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 proliferative disease is cancer.

3. The use according to claim 2, 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 2, wherein the cancer is ovarian cancer.

7. The use according to claim 2, wherein the cancer is non-small lung cancer.

8. The use according to claim 2, wherein the cancer is endometrial cancer.

9. The use according to claim 2, wherein the cancer is cervical cancer.

10. The use according to claim 2, wherein the cancer is pancreatic cancer.

11. The use according to claim 2, wherein the cancer is melanoma.

12. The use according to claim 2, wherein the cancer is bladder cancer.

13. The use according to claim 2, 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 the 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 the 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 the 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 less than 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 less than 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 the 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 the 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 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 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.