pancreatic neuroendocrine tumors, advanced renal cell carcinoma, and subependymal giant cell astrocytoma (SEGA) associated with Tuberous Sclerosis. The mode of action of sirolimus is to bind the cytosolic protein FK-binding protein 12 (FKBP12), and the sirolimus-FKBP12 complex in turn inhibits the mTOR pathway by directly binding to the mTOR Complex 1 (mTORC1).

[0005] Albumin-based nanoparticle compositions have been developed as a drug delivery system for delivering substantially water insoluble drugs. *See*, for example, U. S. Pat. Nos.5,916,596; 6,506,405; 6,749,868, and 6,537,579, 7,820,788, and 7,923,536. Abraxane®, an albumin stabilized nanoparticle formulation of paclitaxel, was approved in the United States in 2005 and subsequently in various other countries for treating metastatic breast cancer. It was recently approved for treating non-small cell lung cancer in the United States, and has also shown therapeutic efficacy in various clinical trials for treating difficult-to-treat cancers such as bladder cancer and melanoma. Albumin derived from human blood has been used for the manufacture of Abraxane® as well as various other albumin-based nanoparticle compositions.

[0006] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

SUMMARY

[0006a] In a first aspect, there is provided use of an effective amount of a composition comprising nanoparticles comprising an mTOR inhibitor and an albumin in the preparation of a medicament for treating a solid tumor in an individual, wherein the nanoparticle composition is prepared to be administered with an effective amount of a second therapeutic agent, wherein the second therapeutic agent is selected from the group consisting of pomalidomide, lenalidomide, an immune checkpoint inhibitor, romidepsin, panobinostat, ricolinostat, belinostat, nilotinib, sorafenib, and a cancer vaccine.

[0007] The present disclosure provides methods of treating a solid tumor (such as bladder cancer, renal cell carcinoma, or melanoma) in an individual, comprising administering to the individual a) an effective amount of a composition comprising nanoparticles comprising an mTOR inhibitor (such as a limus drug, *e.g.*, sirolimus or a derivative thereof) and an albumin; and b) an effective amount of a second therapeutic agent. In some embodiments, the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) and the second therapeutic agent act synergistically to inhibit cell proliferation. In some embodiments, the mTOR inhibitor is a limus drug. In some embodiments, the mTOR inhibitor is sirolimus or a derivative thereof. In some embodiments, the mTOR inhibitor is sirolimus. In some embodiments, the albumin is human albumin (such as human serum albumin). In some embodiments, the nanoparticles comprise sirolimus or a derivative thereof associated (*e.g.*, coated) with albumin. In some embodiments, the nanoparticles comprise sirolimus or a derivative thereof coated with albumin. In some embodiments, the average particle size of the nanoparticles in the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin

CLAIMS

What is claimed is:

1. Use of an effective amount of a composition comprising nanoparticles comprising an mTOR inhibitor and an albumin in the preparation of a medicament for treating a solid tumor in an individual, wherein the nanoparticle composition is prepared to be administered with an effective amount of a second therapeutic agent, wherein the second therapeutic agent is selected from the group consisting of pomalidomide, lenalidomide, an immune checkpoint inhibitor, romidepsin, panobinostat, ricolinostat, belinostat, nilotinib, sorafenib, and a cancer vaccine.
2. The use of claim 1, wherein the solid tumor is bladder cancer, renal cell carcinoma, or melanoma.
3. The use of claim 1 or 2, wherein the solid tumor is relapsed or refractory to a standard therapy for the solid tumor.
4. The use of any one of claims 1-3, wherein the amount of the mTOR inhibitor in the mTOR inhibitor nanoparticle composition is from 10 mg/m^2 to 150 mg/m^2.
5. The use of claim 4, wherein the amount of the mTOR inhibitor in the mTOR inhibitor nanoparticle composition is 45 mg/m^2 to 100 mg/m^2.
6. The use of claim 4, wherein the amount of the mTOR inhibitor in the mTOR inhibitor nanoparticle composition is 75 mg/m^2 to 100 mg/m^2.
7. The use of any one of claims 1-6, wherein the mTOR inhibitor nanoparticle composition is prepared to be administered weekly.
8. The use of any one of claims 1-6, wherein the mTOR inhibitor nanoparticle composition is prepared to be administered 3 out of every 4 weeks.
9. The use of any one of claims 1-8, wherein the mTOR inhibitor nanoparticle composition is prepared to be administered with the second therapeutic agent sequentially to the individual.
10. The use of any one of claims 1-8, wherein the mTOR inhibitor nanoparticle composition is prepared to be administered with the second therapeutic agent simultaneously to the individual.
11. The use of any one of claims 1-10, wherein the mTOR inhibitor is a limus drug.
12. The use of claim 11, wherein the limus drug is sirolimus.
13. The use of any one of claims 1-12, wherein the average diameter of the nanoparticles in the composition is no greater than 150 nm.

14. The use of claim 13, wherein the average diameter of the nanoparticles in the composition is no greater than 120 nm.
15. The use of any one of claims 1-14, wherein the weight ratio of the albumin to the mTOR inhibitor in the nanoparticle composition is no greater than 9:1.
16. The use of any one of claims 1-15, wherein the nanoparticles comprise the mTOR inhibitor associated with the albumin.
17. The use of claim 16, wherein the nanoparticles comprise the mTOR inhibitor coated with the albumin.
18. The use of any one of claims 1-17, wherein the mTOR inhibitor nanoparticle composition is prepared to be administered intravenously, intraarterially, intraperitoneally, intravesicularly, subcutaneously, intrathecally, intrapulmonarily, intramuscularly, intratracheally, intraocularly, transdermally, orally, or by inhalation.
19. The use of claim 18, wherein the mTOR inhibitor nanoparticle composition is prepared to be administered intravenously.
20. The use of any one of claims 1-19, wherein the individual is human.
21. The use of any one of claims 1-20, further comprising selecting the individual for treatment based on the presence of at least one mTOR-activating aberration.
22. The use of claim 21, wherein the mTOR-activating aberration comprises a mutation in an mTOR-associated gene.
23. The use of claim 21 or 22, wherein the mTOR-activating aberration is in at least one mTOR-associated gene selected from the group consisting of AKT1, FLT-3, MTOR, PIK3CA, PIK3CG, TSC1, TSC2, RHEB, STK11, NF1, NF2, TP53, FGFR4, BAP1, KRAS, NRAS and PTEN.
24. The use of any one of claims 1-23, wherein the second therapeutic agent is an immune checkpoint inhibitor.
25. The use of claim 24, wherein the immune checkpoint inhibitor is an immune checkpoint inhibitor antagonistic antibody, an anti-CTLA4 antibody, Ipilimumab, Tremelimumab, an anti-PD-1 antibody, RMP1-14, Nivolumab, Pidilizumab, Pembrolizumab, an anti-PD-L1 antibody, MPDL3280A, BMS-936559, MEDI4736, Avelumab, an anti-PD-L2 antibody, an anti-LAG3 antibody, BMS-986016, C9B7W, an anti-B7-1 antibody, an anti-B7-H3 antibody, MGA271, an anti-B7-H4 antibody, an anti-TIM3 antibody, an anti-BTLA antibody, an anti-VISTA antibody, an anti-KIR antibody, Lirilumab, IPH2101, an anti-A2aR antibody, an anti-CD52 antibody, alemtuzumab, an anti-IL-10 antibody, an anti-FasL antibody, an anti-IL-35 antibody, an anti-TGB-β antibody, or fresolumimab.
26. The use of any one of claims 1-23, wherein the second therapeutic agent is selected from the group consisting of pomalidomide and lenalidomide.
27. The use of any one of claims 24-26, further comprising selecting the individual for treatment based on the presence of at least one biomarker indicative of favorable response to treatment with an immunomodulator.

28. The use of claim 27, wherein the at least one biomarker comprises a mutation in an immunomodulator-associated gene.
29. The use of any one of claims 1-23, wherein the second therapeutic agent is selected from the group consisting of romidepsin, panobinostat, ricolinostat, and belinostat.
30. The use of claim 29, further comprising selecting the individual for treatment based on the presence of at least one biomarker indicative of favorable response to treatment with a histone deacetylase inhibitor (HDACi).
31. The use of claim 30, wherein the at least one biomarker comprises a mutation in an HDACi-associated gene.
32. The use of any one of claims 1-23, wherein the second therapeutic agent is selected from the group consisting of nilotinib and sorafenib.
33. The use of claim 32, further comprising selecting the individual for treatment based on the presence of at least one biomarker indicative of favorable response to treatment with a kinase inhibitor.
34. The use of claim 33, wherein the at least one biomarker comprises a mutation in a kinase inhibitor-associated gene.
35. The use of any one of claims 1-23, wherein the second therapeutic agent is a cancer vaccine.
36. The use of claim 35, wherein the cancer vaccine is selected from the group consisting of a vaccine prepared from autologous tumor cells, a vaccine prepared from allogeneic tumor cells, and a vaccine prepared from at least one tumor-associated antigen.
37. The use of claim 35 or 36, further comprising selecting the individual for treatment based on the presence of at least one biomarker indicative of favorable response to treatment with a cancer vaccine.
38. The use of claim 37, wherein the at least one biomarker comprises a mutation in a cancer vaccine-associated gene.
39. The use of any one of claims 1-38, wherein the solid tumor is bladder cancer.
40. The use of any one of claims 1-38, wherein the solid tumor is renal cell carcinoma.
41. The use of any one of claims 1-38, wherein the solid tumor is melanoma.