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 an immunomodulator, a histone deacetylase inhibitor, and a kinase inhibitor.

[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

nanoparticle composition) is no greater than about 150 nm (such as no greater than about 120 nm). In some embodiments, the average particle size of the nanoparticles in the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) is no more than about 120 nm. In some embodiments, the nanoparticles in the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) are sterile filterable. In some embodiments, the mTOR inhibitor nanoparticle composition comprises the albumin stabilized nanoparticle formulation of sirolimus (*nab*-sirolimus, a formulation of sirolimus stabilized by human albumin USP, where the weight ratio of human albumin and sirolimus is about 8:1 to about 9:1). In some embodiments, the mTOR inhibitor nanoparticle composition is *nab*-sirolimus. In some embodiments, the mTOR inhibitor nanoparticle composition is administered intravenously, intraarterially, intraperitoneally, intravesicularly, subcutaneously, intrathecally, intrapulmonarily, intramuscularly, intratracheally, intraocularly, transdermally, orally, or by inhalation. In some embodiments, the mTOR inhibitor nanoparticle composition is administered intravenously. In some embodiments, the mTOR inhibitor nanoparticle composition is administered subcutaneously. In some embodiments, the individual is a human.

[0008] In some embodiments, according to any of the use or methods described above, the second therapeutic agent is selected from the group consisting of an immunomodulator (such as an immunostimulator or an immune checkpoint inhibitor), a histone deacetylase inhibitor, a kinase inhibitor (such as a tyrosine kinase inhibitor), and a cancer vaccine (such as a vaccine prepared using tumor cells or at least one tumor-associated antigen). In some embodiments, the second therapeutic agent is an immunomodulator. In some embodiments, the immunomodulator is an IMiDs® compound (small molecule immunomodulator, such as lenalidomide or pomalidomide). In some embodiments, the second therapeutic agent is an immunomodulator that stimulates the immune system (hereinafter also referred to as an "immunostimulator"). In some embodiments, the immunomodulator is an agonistic antibody that targets an activating receptor (including co-stimulatory receptors) on an immune cell (such as a T cell). In some embodiments, the immunomodulator is an immune checkpoint inhibitor. In some embodiments, the immune checkpoint inhibitor is an antagonistic antibody that targets an immune checkpoint protein. In some embodiments, the second therapeutic agent is an immunomodulator selected from the group consisting of pomalidomide and lenalidomide. In some embodiments, the immunomodulator is small molecule or antibody-based IDO inhibitor. In some embodiments, the second therapeutic agent is a histone deacetylase inhibitor. In some embodiments, the histone

deacetylase inhibitor is selected from the group consisting of romidepsin, panobinostat, ricolinostat, and belinostat. In some embodiments, the second therapeutic agent is a kinase inhibitor. In some embodiments, the kinase inhibitor is selected from the group consisting of nilotinib and sorafenib. In some embodiments, the second therapeutic agent is a cancer vaccine. In some embodiments, the cancer vaccine is a vaccine prepared from a tumor cell or a vaccine prepared from at least one tumor-associated antigen.

[0009] In some embodiments, according to any of the use or methods described above, the solid tumor is selected from the group consisting of bladder cancer, renal cell carcinoma, and melanoma. In some embodiments, the solid tumor is a relapsed solid tumor. In some embodiments, the solid tumor is refractory to a standard therapy for the solid tumor.

[0010] In some embodiments, according to any of the use or methods described above, the solid tumor is bladder cancer, and the second therapeutic agent is selected from the group consisting of an immunomodulator (such as an immunostimulator or an immune checkpoint inhibitor), a histone deacetylase inhibitor, a kinase inhibitor (such as a tyrosine kinase inhibitor), and a cancer vaccine. In some embodiments, the solid tumor is renal cell carcinoma, and the second therapeutic agent is selected from the group consisting of an immunomodulator (such as an immunostimulator or an immune checkpoint inhibitor), a histone deacetylase inhibitor, a kinase inhibitor (such as a tyrosine kinase inhibitor), and a cancer vaccine. In some embodiments, the solid tumor is melanoma, and the second therapeutic agent is selected from the group consisting of an immunomodulator (such as an immunostimulator or an immune checkpoint inhibitor), a histone deacetylase inhibitor, a kinase inhibitor (such as a tyrosine kinase inhibitor), and a cancer vaccine.

[0011] In some embodiments, according to any of the use or methods described above, the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) and the second therapeutic agent are administered simultaneously. In other embodiments, the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) and the second therapeutic agent are not administered simultaneously. In some embodiments, the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) and the second therapeutic agent are administered sequentially.

[0012] In some embodiments, according to any of the use or methods described above, the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) and the second therapeutic agent are present in amounts that produce a synergistic effect in the treatment

of a solid tumor (such as bladder cancer, renal cell carcinoma, or melanoma) in an individual in need thereof.

[0013] In some embodiments, according to any of the use or methods described above, the use or method is carried out in a neoadjuvant setting. In some embodiments, the use or method is carried out in an adjuvant setting.

[0014] In some embodiments, according to any of the use or methods described above, the solid tumor is refractory to a standard therapy or recurrent after the standard therapy. In some embodiments, the treatment is first line treatment. In some embodiments, the treatment is second line treatment.

[0015] In some embodiments, according to any of the use or methods described above, the individual has progressed from an earlier therapy for a solid tumor. In some embodiments, the individual is refractory to an earlier therapy for a solid tumor. In some embodiments, the individual has recurrent solid tumor.

[0016] In some embodiments, according to any of the use or methods described above, the amount of the nanoparticles in the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) is about 10 mg/m^2 to about 200 mg/m^2 (such as about any of 10, 20, 30, 45, 75, 100, 150, or 200 mg/m^2, including any range between these values). In some embodiments, the amount of the nanoparticles in the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) is about 45 mg/m^2. In some embodiments, the amount of the nanoparticles in the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) is about 75 mg/m^2. In some embodiments, the amount of the nanoparticles in the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) is about 100 mg/m^2. In some embodiments, the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) is administered weekly (such as 3 out of 4 weeks). In some embodiments, the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) is administered at least twice (such as at least 2, 3, or 4 times) in a 28-day cycle for at least one (such at least 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) cycle. In some embodiments, the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin nanoparticle composition) is administered at least twice (such as at least 2, 3, or 4 times) at weekly intervals in a 28-day cycle (such as on days 1, 8, and 15 of the 28-day cycle) for at least one (such at least 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) cycle. In some embodiments, the mTOR inhibitor nanoparticle composition (such as sirolimus/albumin

nanoparticle composition) is administered three times in a 28-day cycle (such as on days 1, 8, and 15 of the 28-day cycle) for at least one (such at least 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) cycle.

[0017] Also provided are methods of treating a solid tumor according to any of the use or methods described above, wherein the treatment is based on the level of at least one biomarker. In some embodiments, the use or method further comprises selecting the individual for treatment based on the presence of at least one mTOR-activating aberration. In some embodiments, the mTOR-activating aberration comprises a mutation in an mTOR-associated gene. In some embodiments, the mTOR-activating aberration is in at least one mTOR-associated gene selected from the group consisting of protein kinase B (PKB/Akt), fms-like tyrosine kinase 3 internal tandem duplication (FLT-3ITD), mechanistic target of rapamycin (mTOR), phosphoinositide 3-kinase (PI3K), TSC1, TSC2, RHEB, STK11, NF1, NF2, Kirsten rat sarcoma viral oncogene homolog (KRAS), neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) and PTEN. In some embodiments, the treatment is based on the presence of at least one genetic variant in a gene selected from the group consisting of drug metabolism genes, cancer genes, and drug target genes.

[0018] In some embodiments, according to any of the use or methods described above, the use or method further comprises selecting the individual for treatment based on the presence of at least one biomarker indicative of favorable response to treatment with an immunomodulator. In some embodiments, the at least one biomarker comprises a mutation in an immunomodulator-associated gene.

[0019] In some embodiments, according to any of the use or methods described above, the use or method further comprises 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). In some embodiments, the at least one biomarker comprises a mutation in an HDACi-associated gene.

[0020] In some embodiments, according to any of the use or methods described above, the use or method further comprises selecting the individual for treatment based on the presence of at least one biomarker indicative of favorable response to treatment with a kinase inhibitor. In some embodiments, the at least one biomarker comprises a mutation in a kinase inhibitor-associated gene.

[0021] In some embodiments, according to any of the use or methods described above, the use or method further comprises selecting the individual for treatment based on the presence of at least one biomarker indicative of favorable response to treatment with a cancer vaccine. In some

embodiments, the at least one biomarker comprises a tumor-associated antigen (TAA) expressed in tumor cells in the individual, such as an aberrantly expressed protein or a neo-antigen.

[0022] The use or methods described herein can be used for any one or more of the following purposes: alleviating one or more symptoms of a solid tumor, delaying progressing of a solid tumor, shrinking tumor size in a solid tumor patient, inhibiting solid tumor growth, prolonging overall survival, prolonging disease-free survival, prolonging time to tumor progression, preventing or delaying metastasis, reducing (such as eradicating) preexisting metastasis, reducing incidence or burden of preexisting metastasis, and preventing recurrence of solid tumor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1 shows the experimental design schema for a Phase I clinical study in pediatric patients of ABI-009 as a single agent and in combination with temozolomide and irinotecan.

DETAILED DESCRIPTION OF THE INVENTION

[0024] The present invention provides methods and compositions for treating a solid tumor (such as bladder cancer, renal cell carcinoma, or melanoma) in an individual by administering to the individual a composition comprising nanoparticles comprising an mTOR inhibitor (such as a limus drug, *e.g.*, sirolimus or a derivative thereof) and an albumin (hereinafter also referred to as an "mTOR inhibitor nanoparticle composition") in conjunction with a second therapeutic agent. The second therapeutic agent may be an immunomodulator (such as an immunostimulator or an immune checkpoint inhibitor), a histone deacetylase inhibitor, a kinase inhibitor (such as a tyrosine kinase inhibitor), or a cancer vaccine (such as a vaccine prepared from a tumor cell or a vaccine prepared from at least one tumor-associated antigen).

[0025] The present application thus provides methods of combination therapy. It is to be understood by a person of ordinary skill in the art that the combination therapy methods described herein requires that one agent or composition be administered in conjunction with another agent.

[0026] Also provided are compositions (such as pharmaceutical compositions), kits, and unit dosages useful for the methods described herein.

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 an immunomodulator, a histone deacetylase inhibitor, and a kinase inhibitor.
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 about 10 mg/m^2 to about 150 mg/m^2.
5. The use of claim 4, wherein the amount of the mTOR inhibitor in the mTOR inhibitor nanoparticle composition is about 45 mg/m^2 to about 100 mg/m^2.
6. The use of claim 4, wherein the amount of the mTOR inhibitor in the mTOR inhibitor nanoparticle composition is about 75 mg/m^2 to about 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 about 150 nm.

14. The use of claim 13, wherein the average diameter of the nanoparticles in the composition is no greater than about 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 about 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 immunomodulator.
25. The use of claim 24, wherein the immunomodulator is an IMiD® compound.
26. The use of claim 24, wherein the immunomodulator is an immune checkpoint inhibitor.
27. The use of claim 24, wherein the immunomodulator is selected from the group consisting of pomalidomide and lenalidomide.
28. The use of any one of claims 24-27, 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.

29. The use of claim 28, wherein the at least one biomarker comprises a mutation in an immunomodulator-associated gene.
30. The use of any one of claims 1-23, wherein the second therapeutic agent is a histone deacetylase inhibitor.
31. The use of claim 30, wherein the histone deacetylase inhibitor is selected from the group consisting of romidepsin, panobinostat, ricolinostat, and belinostat.
32. The use of claim 30 or 31, 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).
33. The use of claim 32, wherein the at least one biomarker comprises a mutation in an HDACi-associated gene.
34. The use of any one of claims 1-23, wherein the second therapeutic agent is a kinase inhibitor.
35. The use of claim 34, wherein the kinase inhibitor is selected from the group consisting of nilotinib and sorafenib.
36. The use of claim 34 or 35, 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.
37. The use of claim 36, wherein the at least one biomarker comprises a mutation in a kinase inhibitor-associated gene.
38. The use of any one of claims 1-23, wherein the second therapeutic agent is a cancer vaccine.
39. The use of claim 38, 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.
40. The use of claim 38 or 39, 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.
41. The use of claim 36, wherein the at least one biomarker comprises a mutation in a cancer vaccine-associated gene.
42. The use of any one of claims 1-41, wherein the solid tumor is bladder cancer.
43. The use of any one of claims 1-41, wherein the solid tumor is renal cell carcinoma.
44. The use of any one of claims 1-41, wherein the solid tumor is melanoma.