various cell lines and animal models. Other limus drugs, such as analogs of rapamycin, have been designed to improve the pharmacokinetic and pharmacodynamic properties of sirolimus. For example, Temsirolimus was approved in the United States and Europe for the treatment of renal cell carcinoma. Everolimus was approved in the U.S. for treatment of advanced breast cancer, pancreatic neuroendocrine tumors, advanced renal cell carcinoma, and subependymal giant cell astrocytoma (SEGA) associated with Tuberous Sclerosis. The mode of action of rapamycin 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).

[0006] However, the roles of TSC1/2 and mTOR mutations in responding to rapalogs remain controversial. For example, although it has been reported that mutations in TSC1/2 and mTOR are more frequent in renal cell carcinoma (RCC) patients who respond well to rapalogs, the majority of rapalog responders have no mutations in mTOR pathway. In Kwiatkowski *et al*, only 2/32 (6.25%) patients with TSC1 mutations or copy number loss and 0% patients with TSC2 mutations or copy number loss that were treated with an mTOR inhibitor (e.g., temsirolimus or everolimus) responded. In addition, in another study (Kwiatkowski, NCT02201212) only 2/30 (7%) responses were seen in patients with TSC1 or TSC2 mutations that were treated with everolimus. *See* Kwiatkowski *et al. Clin Cancer Res*. 2016;22:2445–52.

[0007] Moreover, rapalogs usually arrest cell proliferation but do not induce apoptosis. Despite the initial response, tumors frequently develop resistance to these agents. *See* Hua *et al.*, *J Hematol Oncol* 12, 71 (2019).

[0008] 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

[0009] The present application provides methods of treating cancer in an individual comprising administering to the individual an effective amount of a composition comprising nanoparticles comprising an mTOR inhibitor (such as a limus drug) and a carrier protein (such as albumin), wherein the individual is selected for treatment on the basis of having an mTOR-activating aberration. In some examples, the mTOR-activating aberration comprises an aberration at one or more genes (such as 1, 2, 3, 4, 5, 6 or more) selected from the group consisting of *TSC1*, *TSC2*, *RPS6*, *PTEN*, *TP53*, *RB1*, *ATRX*, and *FAT1*.

[0009a] In one aspect, the present disclosure refers to use of a composition comprising nanoparticles comprising sirolimus and an albumin in the manufacture of a medicament for treating a cancer in an individual, wherein the individual is selected for treatment on the basis of a) having an mTOR inactivating mutation at *TSC1* or *TSC2,* b) having an aberration at any of the genes selected from the group consisting of VHL, RB1, PBRM1, KDM6A, RET, SETD2, ARID1A, BAP1, BRCA2, TP53, RB1, ATRX, FLT1, NTRK1, TLX3, KDM6A, CDH4, CDKN2C, DAXX, ERBB3, GNAS, IL7R, PDGFRB, PMS2, PTEN. SMARCA4, and YY1AP1.

[0010] In one example of the present application, there is provided a method of treating a cancer in an individual, comprising administering to the individual an effective amount of a composition comprising nanoparticles comprising an mTOR inhibitor and a carrier protein, wherein the individual is selected for treatment based on having an mTOR-activating aberration at *TSC2* or *RPS6*. In some examples, the individual is selected for treatment based on having an mTOR-activating aberration at *TSC2* and *RPS6*.

[0011] In some examples according to any one of the methods described above, the mTOR-activating aberration at *TSC2* comprises a mutation in *TSC2*.

[0012] In some examples according to any one of the methods described above, the mTOR-activating aberration at *TSC2* comprises a single-nucleotide variant (SNV). In some examples, the SNV comprises a mutation selected from the group consisting of C1503T, C2743G, C5383T, C3755G, G760T, C3442T, G880A, T707C, A4949G, or a deletion of any one or more of the amino acids at the position of 1405-1409, 1960-1970, 4999, 5002, 3521, 5208, 5238-5255.

[0013] In some examples according to any one of the methods described above, the mTOR-activating aberration at *TSC2* comprises a copy number variation of *TSC2*.

[0014] In some examples according to any one of the methods described above, the mTOR-activating aberration at *TSC2* is a loss of function mutation.

[0015] In some examples according to any one of the methods described above, the mTOR-activating aberration at *TSC2* comprises an aberrant expression level of *TSC2*.

[0016] In some examples according to any one of the methods described above, the mTOR-activating aberration at *TSC2* comprises an aberrant activity level of a protein encoded by *TSC2*.

[0017] In some examples according to any one of the methods described above, the mTOR-activating aberration at *TSC2* comprises a loss of heterozygosity of *TSC2*.

[0018] The present application in another example provides a method of treating a cancer in an individual comprising administering to the individual an effective amount of a composition comprising nanoparticles comprising an mTOR inhibitor and a carrier protein, wherein the individual is selected for treatment on the basis of having an mTOR-activating aberration at *TSC1* or *RPS6*.

[0019] In some examples according to any one of the methods described above, the mTOR-activating aberration at *RPS6* comprises an aberrant phosphorylation level of the protein encoded by *RPS6.*

[0020] In some examples according to any one of the methods described above, the mTOR-activating aberration at *RPS6* comprises an aberrant expression level of *RPS6*.

[0021] In some examples according to any one of the methods described above, the cancer is advanced and/or malignant.

[0022] In some examples according to any one of the methods described above, the cancer is a solid tumor.

[0023] In some examples according to any one of the methods described above, the cancer is a hematologic cancer.

[0024] In some examples according to any one of the methods described above, the cancer is selected from the group consisting of pancreatic neuroendocrine cancer, endometrial cancer, breast cancer, lymphangioleiomyomatosis (LAM), prostate cancer, hepatocellular carcinoma, melanoma, renal cell carcinoma, bladder cancer, endometrial cancer, ovary cancer, gynecologic cancer, sarcoma, perivascular epithelioid cell neoplasms (PEComa), Hodgkin's lymphoma and multiple myeloma.

[0025] In some examples according to any one of the methods described above, the nanoparticles in the composition comprises the mTOR inhibitor associated with the carrier protein.

[0026] In some examples according to any one of the methods described above, the nanoparticles in the composition have an average diameter of no greater than about 200 nm.

[0027] In some examples according to any one of the methods described above, the ratio of the mTOR inhibitor to the carrier protein in the nanoparticles is from about 1:1 to about 9:1.

[0028] In some examples according to any one of the methods described above, the carrier protein is an albumin. In some examples, the albumin is human serum albumin.

[0029] In some examples according to any one of the methods described above, the mTOR inhibitor is a limus drug. In some examples, the limus drug is rapamycin.

[0030] In some examples according to any one of the methods described above, the dose of the mTOR inhibitor in the composition for each administration is from about 10 mg/m^2 to about 100 mg/m^2.

[0031] In some examples according to any one of the methods described above, nanoparticle composition is administered at a frequency of about once a week to about once every two weeks.

[0032] In some examples according to any one of the methods described above, the method comprises administering the nanoparticle composition to the individual weekly for about two weeks followed by a rest period of about one week.

[0033] In some examples according to any one of the methods described above, the individual is resistant or refractory to a prior therapy.

[0034] In some examples according to any one of the methods described above, the method further comprises administering a second agent.

[0035] In some examples according to any one of the methods described above, the individual is a human.

[0036] In some examples according to any one of the methods described above, the individual does not comprise a mutation in *TSC1*.

[0037] In some examples according to any one of the methods described above, the method further comprises assessing the mTOR-activating aberration at *TSC1, TSC2,* or *RPS6* in the individual.

[0038] In some examples according to any one of the methods described above, the method further comprises selecting the individual for treatment based on the individual having the mTOR-activating aberration at *TSC1, TSC2* or *RPS6.*

[0039] In some examples according to any one of the methods described above, the composition comprises: (a) nanoparticles comprising rapamycin and albumin, and (b) a non-nanoparticle portion comprising albumin and rapamycin. In some examples, the nanoparticles comprise a core comprising rapamycin and a coating comprising albumin. In some examples, about 70% to about 85% of the albumin in the nanoparticles is in the form of monomeric albumin. In some examples, about 5% to about 15% of the albumin in the nanoparticles is in the form of polymeric albumin (or trimeric albumin). In some examples, about 9% to about 20% of the albumin in the nanoparticles is in the form of dimeric albumin. In some examples, about 0.5% to about 5% of the albumin in the non-nanoparticle portion is in the form of polymeric albumin (or trimeric albumin). In some examples, about 80% to about 95% of the albumin in the non-nanoparticle portion is in the form of monomeric albumin. In some examples, about 4% to about 14% of the albumin in the non-nanoparticle portion is in the form of dimeric albumin. In some examples, about 0.5% to about 5% of total albumin in the composition is in the form of polymeric albumin (or trimeric albumin). In some examples, about 80% to about 95% of total albumin in the composition is in the form of monomeric albumin. In some examples, about 4% to about 15% of total albumin in the composition is in the form of dimeric albumin.

In some examples, the percentage of polymeric albumin (or trimeric albumin), dimeric albumin, or monomeric albumin is determined using size-exclusion chromatography. In some examples, the percentage of polymeric albumin (or trimeric albumin), dimeric albumin, or monomeric albumin is determined using size-exclusion chromatography using a saline mobile phase coupled with a multiple angle light scattering (MALS) detector. In some examples, the volume weighted mean particle size of the nanoparticles is about 200 nm or less. In some examples, the volume weighted mean particle size of the nanoparticles is about 50 nm to about 200 nm. In some examples, the Z-average particle size of the nanoparticles is about 200 nm or less. In some examples, the Z-average particle size of the nanoparticles is about 50 nm to about 200 nm. In some examples, the polydispersity index of the nanoparticles is less than 0.2. In some examples, the polydispersity index of the nanoparticles is about 0.03 to about 0.2. In some examples, the span of particle size distribution ((D_v95-D_v5)/D_v50) of the nanoparticles is about 0.8 to about 1.2. In some examples, the weight percentage of the albumin in the nanoparticles is about 25% to about 45%. In some examples, the weight percentage of rapamycin in the nanoparticles is about 55% to about 75%. In some examples, the weight ratio of the albumin to the rapamycin in the nanoparticles is about 1:1 to about 1:4. In some examples, the weight ratio of the albumin to the rapamycin in the composition is about 1:1 to about 10:1. In some examples, about 90% or more of the albumin in the composition is in the non-nanoparticle portion. In some examples, about 90% or more of the rapamycin in the composition is in the nanoparticles. In some examples, the nanoparticle composition is a nanoparticle suspension. In some examples, the concentration of albumin in the composition is about 30 mg/mL to about 100 mg/mL. In some examples, the concentration of albumin in the composition that is in the non-nanoparticle portion is about 30 mg/mL to about 100 mg/mL. In some examples, the concentration of albumin in the nanoparticle composition that is in the nanoparticles is about 1 mg/mL to about 5 mg/mL. In some examples, the concentration of rapamycin in the nanoparticle composition is about 1 mg/mL to about 100 mg/mL. In some examples, the concentration of rapamycin in the composition that is in the non-nanoparticle portion is about 20 μg/mL to about 55 μg/mL. In some examples, the concentration of rapamycin in the composition that is in the nanoparticles is about 1 mg/mL to about 15 mg/mL. In some examples, the osmolality of the composition is about 300 mOsm/kg to about 350 mOsm/kg. In some examples, the viscosity of the composition is about 1.2 cP to about 1.5 cP. In some examples, the composition is stable at 25 °C for at least 24 hours. In some examples, the composition is

stable at 4 °C for at least 24 hours. In some examples, the nanoparticles had been resuspended from a dried composition. In some examples, the pH of the composition is about 6.0 to about 7.5. In some examples, the composition comprises less than 10 μg/mL *tert*-butanol. In some examples, the composition comprises *tert*-butanol. In some examples, the composition comprises less than 5 μg/mL chloroform. In some examples, the composition comprises chloroform. In some examples, the composition is a dried composition. In some examples, the zeta potential of the nanoparticles is about -25 mV to about -50 mV. In some examples, the composition has an amorphous morphology as determined by measuring crystallinity of a lyophilized form of the composition by X-ray diffraction. In some examples, the nanoparticles have an amorphous morphology as determined by separating the nanoparticles from the composition, lyophilizing the separated nanoparticles, and measuring crystallinity of the separated and lyophilized nanoparticles by X-ray diffraction. In some examples, the rapamycin in nanoparticles has an amorphous morphology as determined by Raman spectroscopy, polarized light microscopy, differential scanning calorimetry (DSC), modulated differential scanning calorimetry (mDSC), Fourier transform infrared (FTIR) spectroscopy, or nuclear magnetic resonance (NMR) spectroscopy. In some examples, the vinyl chain of the rapamycin in the nanoparticles interacts with the albumin in the nanoparticles. In some examples, at least a portion of the nanoparticles are non-spherical. In some examples, at least 20% of the nanoparticles in the composition are non-spherical. In some examples, seco-rapamycin is less than 3% by weight of the sum of seco-rapamycin and rapamycin in the nanoparticles. In some examples, seco-rapamycin is less than 3% by weight of the sum of seco-rapamycin and rapamycin in the composition. In some examples, seco-rapamycin is more than 0.2% by weight of the sum of seco-rapamycin and rapamycin in the nanoparticles. In some examples, seco-rapamycin is more than 0.2% by weight of the sum of seco-rapamycin and rapamycin in the composition.

[0040] In some examples according to any one of the methods described above, the composition comprises: (a) nanoparticles comprising rapamycin and albumin, and (b) a non-nanoparticle portion comprising albumin and rapamycin. In some examples, the nanoparticles comprise a core comprising rapamycin and a coating comprising albumin. In some examples, about 25% to about 50% of the albumin in the nanoparticles is in the form of monomeric albumin. In some examples, about 1% to about 4.5% of the albumin in the nanoparticles is in the form of oligomeric albumin. In some examples, about 42% to about 60% of the albumin in the nanoparticles is in the form of polymeric albumin (other

than oligomeric albumin). In some examples, about 5% to about 16% of the albumin in the nanoparticles is in the form of dimeric albumin. In some examples, about 0.5% to about 3% of the albumin in the non-nanoparticle portion is in the form of polymeric albumin (other than oligomeric albumin). In some examples, about 0.5% to about 4% of the albumin in the non-nanoparticle portion is in the form of oligomeric albumin. In some examples, about 80% to about 95% of the albumin in the non-nanoparticle portion is in the form of monomeric albumin. In some examples, about 4% to about 14% of the albumin in the non-nanoparticle portion is in the form of dimeric albumin. In some examples, about 2% to about 7% of total albumin in the composition is in the form of polymeric albumin (other than oligomeric albumin). In some examples, about 0.3% to about 3% of the total albumin in the composition is in the form of oligomeric albumin. In some examples, about 80% to about 95% of total albumin in the composition is in the form of monomeric albumin. In some examples, about 4% to about 15% of total albumin in the composition is in the form of dimeric albumin. In some examples, the percentage of polymeric albumin (other than oligomeric albumin), oligomeric albumin, dimeric albumin, or monomeric albumin is determined using size-exclusion chromatography. In some examples, the percentage of polymeric albumin (other than oligomeric albumin), oligomeric albumin, dimeric albumin, or monomeric albumin is determined using size-exclusion chromatography using a mobile phase containing an aqueous portion and a miscible portion (such as an aqueous buffer containing 7.5% methanol) coupled with a UV detector. In some examples, the volume weighted mean particle size of the nanoparticles is about 200 nm or less. In some examples, the volume weighted mean particle size of the nanoparticles is about 50 nm to about 200 nm. In some examples, the Z-average particle size of the nanoparticles is about 200 nm or less. In some examples, the Z-average particle size of the nanoparticles is about 50 nm to about 200 nm. In some examples, the polydispersity index of the nanoparticles is less than 0.2. In some examples, the polydispersity index of the nanoparticles is about 0.03 to about 0.2. In some examples, the span of particle size distribution ($(D_v95-D_v5)/D_v50$) of the nanoparticles is about 0.8 to about 1.2. In some examples, the weight percentage of the albumin in the nanoparticles is about 25% to about 45%. In some examples, the weight percentage of rapamycin in the nanoparticles is about 55% to about 75%. In some examples, the weight ratio of the albumin to the rapamycin in the nanoparticles is about 1:1 to about 1:4. In some examples, the weight ratio of the albumin to the rapamycin in the composition is about 1:1 to about 10:1. In some examples, about 90% or more of the albumin in the

composition is in the non-nanoparticle portion. In some examples, about 90% or more of the rapamycin in the composition is in the nanoparticles. In some examples, the nanoparticle composition is a nanoparticle suspension. In some examples, the concentration of albumin in the composition is about 30 mg/mL to about 100 mg/mL. In some examples, the concentration of albumin in the composition that is in the non-nanoparticle portion is about 30 mg/mL to about 100 mg/mL. In some examples, the concentration of albumin in the nanoparticle composition that is in the nanoparticles is about 1 mg/mL to about 5 mg/mL. In some examples, the concentration of rapamycin in the nanoparticle composition is about 1 mg/mL to about 100 mg/mL. In some examples, the concentration of rapamycin in the composition that is in the non-nanoparticle portion is about 20 μg/mL to about 55 μg/mL. In some examples, the concentration of rapamycin in the composition that is in the nanoparticles is about 1 mg/mL to about 15 mg/mL. In some examples, the osmolality of the composition is about 300 mOsm/kg to about 350 mOsm/kg. In some examples, the viscosity of the composition is about 1.2 cP to about 1.5 cP. In some examples, the composition is stable at 25 °C for at least 24 hours. In some examples, the composition is stable at 4 °C for at least 24 hours. In some examples, the nanoparticles had been resuspended from a dried composition. In some examples, the pH of the composition is about 6.0 to about 7.5. In some examples, the composition comprises less than 10 μg/mL *tert*-butanol. In some examples, the composition comprises *tert*-butanol. In some examples, the composition comprises less than 5 μg/mL chloroform. In some examples, the composition comprises chloroform. In some examples, the composition is a dried composition. In some examples, the zeta potential of the nanoparticles is about -25 mV to about -50 mV. In some examples, the composition has an amorphous morphology as determined by measuring crystallinity of a lyophilized form of the composition by X-ray diffraction. In some examples, the nanoparticles have an amorphous morphology as determined by separating the nanoparticles from the composition, lyophilizing the separated nanoparticles, and measuring crystallinity of the separated and lyophilized nanoparticles by X-ray diffraction. In some examples, the rapamycin in nanoparticles has an amorphous morphology as determined by Raman spectroscopy, polarized light microscopy, differential scanning calorimetry (DSC), modulated differential scanning calorimetry (mDSC), Fourier transform infrared (FTIR) spectroscopy, or nuclear magnetic resonance (NMR) spectroscopy. In some examples, the vinyl chain of the rapamycin in the nanoparticles interacts with the albumin in the nanoparticles. In some examples, at least a portion of the nanoparticles are non-spherical.

In some examples, at least 20% of the nanoparticles in the composition are non-spherical. In some examples, seco-rapamycin is less than 3% by weight of the sum of seco-rapamycin and rapamycin in the nanoparticles. In some examples, seco-rapamycin is less than 3% by weight of the sum of seco-rapamycin and rapamycin in the composition. In some examples, seco-rapamycin is more than 0.2% by weight of the sum of seco-rapamycin and rapamycin in the nanoparticles. In some examples, seco-rapamycin is more than 0.2% by weight of the sum of seco-rapamycin and rapamycin in the composition.

[0041] In some examples, about 3% or less of the rapamycin in the nanoparticle composition is free rapamycin.

BRIEF DESCRIPTION OF THE DRAWINGS

[0042] FIG. 1 depicts distributions of patients that have PEComa with various primary sites of diseases.

[0043] FIGS. 2A-2B depict duration of treatment, time-to-response, and progression-free survival of each evaluable individual patient up to May 2019.

[0044] FIG. 3 depicts longitudinal tumor size of each evaluable individual patient under independent radiology review up to May 2019.

[0045] FIG. 4 depicts maximum percentage of target lesion reduction of each evaluable individual patient. "+" or "-" indicates phosphorylation level of S6. Patients numbered 19-22, 26, 27, 29-31 had *TSC2* mutation; patients numbered 4, 9, 14, 18, and 28 had *TSC1* mutations; patients 1-3, 6, 8, 10, 11, 13, 16, 17, and 24 did not have either *TSC1* or *TSC2* mutation; patients numbered 5, 7, 12, 15, 23, and 25 had no evaluable sample for determining *TSC1* or *TSC2* mutational status. Patients' numbers in this Figure do not correspond to patients' numbers in Table 9.

[0046] FIGS. 5A-5B depict representative computed tomography images of tumors in patients with uterine primary PEComa before and after treatment. FIG. 5A is a representative image of a 67-year old female patient. She had uterine primary PEComa and the cancer had metastasized to spleen, colon, perigastric, and pulmonary area. Partial response occurred at the first restaging (6 weeks). The patient is currently on treatment (>1.5 years on therapy). FIG. 5B is a representative image of another 67-year old female patient. She also had uterine primary PEComa and the cancer had metastasized to pelvis and lung. Partial response

Claims

1. Use of a composition comprising nanoparticles comprising sirolimus and an albumin in the manufacture of a medicament for treating a cancer in an individual, wherein the individual is selected for treatment on the basis of a) having an mTOR inactivating mutation at *TSC1* or *TSC2,* b) having an aberration at any of the genes selected from the group consisting of VHL, RB1, PBRM1, KDM6A, RET, SETD2, ARID1A, BAP1, BRCA2, TP53, RB1, ATRX, FLT1, NTRK1, TLX3, KDM6A, CDH4, CDKN2C, DAXX, ERBB3, GNAS, IL7R, PDGFRB, PMS2, PTEN. SMARCA4, and YY1AP1.

2. The use of claim 1, wherein the individual has not been treated with an mTOR inhibitor.

3. The use of claim 1 or claim 2, wherein the individual has failed a prior therapy.

4. The use of claim 3, wherein the prior therapy comprises administration of a platinum-based agent, a chemotherapeutic agent, an angiogenesis inhibitor, a checkpoint inhibitor, a RANKL ligand inhibitor, or a first-line or standard therapy for the cancer.

5. The use of any one of claims 1-4, wherein the inactivating mutation in *TSC1* or *TSC2* comprises a homozygous deletion, bi-allelic mutations, a splice site mutation, a frameshift mutation, nonsense mutation in coding region, missense mutation with confirmed impact, or a loss or deletion of *TSC1* or *TSC2*.

6. The use of claim 5, wherein the inactivating mutation in *TSC1* or *TSC2* comprises bi-allelic mutations.

7. The use of any one of claims 1-6, wherein the individual is selected for treatment on the basis of having an aberration at any of the genes selected from the group consisting of TP53, RB1, ATRX, FLT1, NTRK1, TLX3, KDM6A, CDH4, CDKN2C, DAXX, ERBB3, GNAS, IL7R, PDGFRB, PMS2, PTEN. SMARCA4, and YY1AP1.

8. The use of any one of claims 1-7, wherein the individual is selected for treatment on the basis of having an inactivating mutation in *TSC1*.

9. The use of claim 8, wherein the individual is selected for treatment on the basis of having an aberration at any of the genes selected from the group consisting of NTRK1, RB1, TP53, and PBRM1.

10. The use of any one of claims 1-9, wherein the individual is selected for treatment on the basis of having an inactivating mutation in *TSC2*.

11. The use of claim 10, wherein the individual is selected for treatment on the basis of having an aberration at any of the genes selected from the group consisting of TP53, ATRX, DAXX, ERBB3, FLT1, GNAS, KDM6A, PMS2, PTEN, RB1, and TLX3.

12. The use of any one of claim 1-11, wherein the individual has a tumor mutational burden less than about 10.

13. The use of any one of claims 1-12, wherein the individual has a stable microsatellite status.

14. The use of any one of claims 1-13, wherein the individual does not comprise any of a) a deletion mutation in *EGFR* exon 19; b) *EGFR* exon 21 L858R alteration; c) *EGFR* exon 20 T790M alteration; d) *ALK* rearrangement; e) *BRAF* V600E or V600K; f) *MET* single nucleotide variant or indel that leads to *MET* exon 14 skipping; g) *ERBB2* amplification; h) any of C420R, E542K, E545A, E545D, E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y in *PIK3CA*; i) BRCA1/2 alteration; j) a *FGFR2* fusion and/or rearrangement; and k) a mutation in any of *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* and *RAD54L*.

15. The use of any one of claims 1-14, wherein the individual has an mTOR-activating aberration at *RPS6.*

16. The use of claim 15, wherein the mTOR-activating aberration at *RPS6* comprises an aberrant phosphorylation level of the protein encoded by *RPS6* or an aberrant expression level of *RPS6*.

17. The use of any one of claims 1-16, wherein the cancer is advanced and/or malignant.

18. The use of any one of claims 1-17, wherein the cancer is a solid tumor.

19. The use of any one of claims 1-18, wherein the cancer is a hematologic cancer.

20. The use of any one of claims 1-19, wherein the cancer is selected from the group consisting of pancreatic neuroendocrine cancer, endometrial cancer, breast cancer, lymphangioleiomyomatosis (LAM), prostate cancer, hepatocellular carcinoma, melanoma,

renal cell carcinoma, bladder cancer, endometrial cancer, ovary cancer, gynecologic cancer, sarcoma, perivascular epithelioid cell neoplasms (PEComa), Hodgkin's lymphoma and multiple myeloma.

21. The use of any one of claims 1-20, wherein the nanoparticles in the composition comprises the mTOR inhibitor associated with the carrier protein.

22. The use of any one of claims 1-21, wherein the nanoparticles in the composition have an average diameter of no greater than about 200 nm.

23. The use of any one of claims 1-22, wherein the ratio of the mTOR inhibitor to the carrier protein in the nanoparticles is from about 1:1 to about 9:1.

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

25. The use of claim 24, wherein the composition is to be administered at a dose of about 30 mg/m^2 to about 100 mg/m^2 for two out of every three weeks a cycle for one or more cycles.

26. The use of claim 25, wherein the composition is to be administered for at least about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 cycles.

27. The use of any one of claims 1-26, wherein the composition is to be administered intravenously or subcutaneously.

28. The use of any one of claims 1-27, wherein the composition comprises (a) nanoparticles comprising rapamycin and albumin, and (b) a non-nanoparticle portion comprising albumin and rapamycin;

wherein about 80% to about 95% of the albumin in the composition is in the form of monomeric albumin, about 4% to about 15% of the albumin in the composition is in the form of dimeric albumin, and about 0.5% to about 5% of the albumin in the composition is in the form of polymeric albumin when the percentage of albumin in the composition that is in the form of monomeric albumin, dimeric albumin, or polymeric albumin is determined by subjecting the composition to size-exclusion chromatography (SEC) using a saline mobile phase coupled with a multiple angle light scattering (MALS) detector.

29. The use of any one of claims 1-29, wherein the nanoparticle composition comprising: (a) nanoparticles comprising rapamycin and albumin, and (b) a non-nanoparticle portion comprising albumin and rapamycin;
wherein about 42% to about 60% of the albumin in the nanoparticles is in the form of polymeric albumin other than oligomeric albumin when the percentage of albumin in the nanoparticles that is in the form of polymeric albumin other than oligomeric albumin is determined by separating the nanoparticles from the non-nanoparticle portion, dissolving the nanoparticles, and subjecting the dissolved nanoparticles to size-exclusion chromatography.

30. The use of any one of claims 1-29, wherein the medicament is to be further administered with a second agent.

31. The use of any one of claims 1-30, wherein the use further comprises assessing the mTOR-activating aberration at *TSC1* or *TSC2*.

32. The use of any one of claims 1-31, wherein the use further comprises assessing if the mTOR-activating aberration at *TSC1* or *TSC2* is pathogenic.